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暨中国肿瘤标志物产业创新大会

论文集
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TBM 优秀论文

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壁报交流

TBM 优秀论文

1. 基于文献计量学分析盘状结构域受体 DDR1 与胃癌的研究关系

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目的： 盘状结构域受体 DDR1 在胃癌中发挥着关键作用。然而，关于盘状结构域受体 DDR1 与胃癌的文献计量学目前知之甚少。

方法：本文采用文献计量学方法，以 PubMed 文献数据库为基础，使用使用 citexs 网站（https://www.citexs.com/)进行文献计量分析，以 Discoidin domain receptor 1 与 Gastric cancer 为关键词搜索，时间为 2013-01 至 2023-10 进行文献大数据挖掘分析。

结果：（1）年度发文趋势分析：以 Discoidin domain receptor 1 和 gastric cancer 为关键词搜索，2013-01 至 2023-10 的文献有 7 篇，文献年均发文量 2 篇。其中，2018 达到年发文量顶峰 3 篇，2018 增长率最快为 200%，提示该领域的研究得到快速发展，处于快速上升阶段；

（2）研究国家分析：2013-01 至 2023-10，全球在 Discoidin domain receptor 1 和 gastric cancer 研究领域发文量前 7 的国家。其中， 在该领域发文量最多的国家是 China（3 篇，42.86%），South Korea（2 篇，28.57%）和 United States of America（2 篇，28.57%）位居第二和第三；

（3）研究机构分析：2013-01 至 2023-10，全球在 Discoidin domain receptor 1 和 gastric cancer 研究领域发文量前 13 的国家研究机构，其中 ajou university school of medicine 和 university of texas southwestern medical center 发文量占据前两名，分别发表了 2 篇和 2 篇，cancer hospital 发表了 1 篇，位于第三名；

（4）研究作者分析：2013-01 至 2023-10，全球在 Discoidin domain receptor 1 和 gastric cancer 研究领域发文量前 30 的作者。该领域产出文献最多的作者是 Dakeun Lee、Hoon Hur、Hye Jeong Oh、Hyejin Jin、In-Hye Ham、Rolf A Brekken、Sang-Uk Han、Young-Bae Kim，迄今为止一共发表 2 篇文献； Akhila B Rai、Anh T Le、Anke Baum、Cheong A Bae、Christian

Haslinger、D A B Rex、Danjie Pan、Davide Gianni、Emer Bourke、Frank Hilberg、G P Suchitha、Hidehiko Takigawa、Huaning Chen、James A L Brown、Ji Eun Kwon、Jiayang Liu、Jing Wang、Kazuaki Chayama、Ke Ding、Kristina Y Aguilera、Kudelaidi Kuerban、Li Chen 并列第二，发表了 1 篇文献；(声明：文献原始数据来源于 pubmed，由于其部分机构缺失和部分杂志未收录，造成文章数量偏少，排名仅供参考！)。

（5）发文期刊分析：2013-01 至 2023-10，以 Discoidin domain receptor 1 和 gastric cancer 为关键词搜索，检索出论文 7 篇，发文量排名前 7 的期刊见图 4，其中刊载文献量最多的期刊是 BMC Cancer（1 篇）；Front Cell Dev Biol 位居第二，刊载文献量 1 篇；Front Immunol 位居第三，刊载文献量 1 篇；

（6）关键词热点词频分析：论文关键词是对研究目的、研究对象、研究方法进行高度凝练与概括。基于关键词的分析能够反映某一研究领域某一时间段内主题演变趋势和研究热点。把 Discoidin domain receptor 1 和 gastric cancer 作为关键词搜索，时间跨度为 2013-01 至 2023-10，其中，出现频次前 5 的关键词分别是： cancer，prognosis，breast，cancer stroma，ddr1；

（7）关联基因分析:2013-01 至 2023-10，以 Discoidin domain receptor 1 和 gastric cancer 为关键词搜索，检索出论文 7 篇，采用 BioBERT 生物医学言语表示模型对 7 篇文章的摘要中基因的实体词挖掘并统计分析。其中，其中文献量最多的 DDR1（4 篇）；6030432F18 位居第二，文献量为 3 篇；COX8A 位居第三，文献量 3 篇。

结论:尽快胃癌与盘状结构域受体 DDR1 之间的研究目前较少，但是，该领域的研究仍处于快速上升阶段。

关键字：胃癌；盘状结构域受体 DDR1；大数据

2. CDKN3 在宫颈癌中的表达水平及与其预后的关系

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目的:研究 CDKN3 在宫颈癌组织中的表达水平及临床意义，并分析与宫颈癌预后的关系。

方法:免疫组织化学法检测 CDKN3 在 105 例宫颈癌患者组织中的表达水平，卡方检验分析 CDKN3 的表达水平与宫颈癌临床病理学特征之间的关系，Cox 风险模型和 Kaplan-Meier 生存分析用于评估 CDKN3 的表达与宫颈癌预后的关系。P＜0.05 被认为差异具有统计学意义。

结果:通过免疫组织化学染色，与癌旁正常宫颈组织相比， CDKN3 在宫颈癌症组织中高表达（78/105，74.3%），差异有统计学意义（P＜0.05），宫颈癌组织中 CDKN3 的阳性表达与宫颈癌 FIGO 分期相关（P＜0.05）。分析比较宫颈癌患者 CDKN3 低表达水平及高表达水平组的 5 年生存率，与 CDKN3 低表达的患者相比，CDKN3 高表达的宫颈癌患者总生存率显著降低，差异有统计学意义（P<0.05）。多因素分析表明，CDKN3 的表达水平和 FIGO 分期是影响宫颈癌总生存期的独立危险因素。高水平的 CDKN3 表达与宫颈癌不良预后风险增加相关（HR，2.216；P=0.010）。结论:宫颈癌组织中 CDKN3 的阳性表达与宫颈癌 FIGO 分期相关，且 CDKN3 的表达水平是影响宫颈癌总生存期的独立危险因素，未来可作为宫颈癌预后评估的新的指标。

关键字：宫颈癌，CDKN3，预后

3. C18ORF54 作为肝细胞癌的潜在生物标志物促进免疫浸润和不良预后

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目的:肝细胞癌(HCC)的发病率逐年上升。 本研究的目的是利用生物信息学方法研究 HCC 上调基因的分子机制，从而发现新的潜在生物标志物。

方法:从 HCC 数据集挖掘基因表达综合数据库(GEO database),筛选中枢基因并进行(基因本体论)GO 和(京都基因和基因组百科全书)KEGG 富集分析。 根据受试者操作特征(ROC)和甲基化水平分析中枢基因。 中枢基因的验证通过基于中枢基因的蛋白质和基因表达水平的基本病理学改变来完成。 基于数据库 Timer 2.0 分析基因与 HCC 免疫浸润的相关性，并使用 R studio 软件分析 HCC hub 基因的预后和存活率。 最后，我们对 HCC 的潜在治疗靶点进行了基因组合药物分析。

结果:通过差异分析筛选出表达上调的基因，这些基因主要富集于细胞周期和 DNA 复制途径。 使用蛋白质相互作用网络(PPI)鉴定了 5 个枢纽基因，BRCA1 相关环域 1 (BARD1)、错配修复蛋白(MSH2)、重组 H2A 组蛋白家族、成员 X (H2AFX)、重组 H2A 组蛋白家族、成员 z (H2AFZ)和 18 号染色体开放阅读框 54 (C18orf54)。 在综合分析 ROC 曲线和甲基化基因突变位点后，通过基础实验对 C18orf54 进行定位，从而验证 C18orf54 在 HCC 上调。基于在线数据库 Timer 2.0，分析了 C18orf54 基因在 HCC 的免疫浸润，发现其与 HCC 的 CD4+T 细胞和巨噬细胞呈负相关，同时进一步细化的免疫检查点相关性分析显示，C18orf54 主要与甲型肝炎病毒细胞受体 2 (HAVCR2)、具有 Ig 和 ITIM 结构域的 T 细胞免疫受体(TIGIT)和细胞毒性 T 淋巴细胞相关蛋白-4 (CTLA4) 相关。 还分析了表达 C18orf54 的 HCC 患者的预后和存活率，发现此类患者具有更高的邻近肝组织炎症发生率、更高的 child-Pugh 分级评分和更高的残余肿瘤复发率。 类似地，C18orf54 亚型患者的预后更差。 最后，我们进行了联合遗传分析，表明环孢霉素、槲皮素、睾酮和骨化三醇可能有效降低 C18orf54 mRNA 表达。结论:C18orf54 参与免疫浸润并促进 HCC 不良预后，可作为 HCC 的候选生物标志物。

关键字：肝细胞癌，C18orf54，免疫浸润，预后

4. How CLSPN could demystify its prognostic value and therapeutic targets for hepatocellular carcinoma: a crosstalk study

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Background

CLSPN, an essential molecule of the S-phase checkpoint in DNA replication stress, has been proven to be involved in the development of tumors. However, the roles of CLSPN in HCC have not been elucidated.

Methods

We systematically evaluated the expression of CLSPN, prognosis and immune infiltration in patients with HCC based on TCGA database. The Kaplan-Meier, multivariate cox regression analysis, nomogram and time-dependent ROC curve were applied to determine whether CLSPN is

an independent prognostic factor. The qRT-PCR and western blot was used to investigate CLSPN expression and knockdown efficacy, and the CCK8, transwell and flow cytometry assays were determined to its biological functions in HCC cell lines. Then, utilizing the TarBase database, we identified the competing endogenous RNA (ceRNA) regulator network. Moreover, the proteasome inhibition experiment and CO-IP assay were applied to explore the post-transcriptional modifications and potential molecular mechanisms of CLSPN in HCC. In addition, mass spectrometry was performed to detect proteins that may interact with CLSPN, which were enriched by COG/KOG, KEGG analysis, and PPI network.

Results

We firstly discovered and systematically verified the expression of CLSPN, and its high expression is an independent prognostic factor in HCC. CLSPN low-expression had higher infiltration levels of T cell CD4+ memory resting, monocyte, mast cell activated, while the level of T cell follicular helper, T cell regulatory, Macrophage M0, and B cell plasma were higher in patients with the high-expression. Then, CLSPN silencing inhibited the proliferation, migration, invasion and cell cycle progression of HCC cells. Furthermore, we established a key lncRNA PSMA3-AS1/hsa-miR-101-3p/CLSPN regulator axis in HCC. CLSPN was influenced by ubiquitination in HCC and was involved in the Wnt/β-catenin pathway to regulate HCC progression. In addition, we obtained CLSPN interaction protein profile, which involved in posttranscriptional modification, protein turnover, and biogenesis locating in cytoplasm, secreted, and mitochondrion.

Conclusions

It was the first time to discover and verify expression, prognosis, immunotherapy, RNAs regulator, posttranscriptional modification, and molecular mechanisms of CLSPN in HCC. These novel insights might accelerate the process of individualized diagnosis and precision therapeutics for patients with HCC.

Key Words： CLSPN, Hepatocellular carcinoma, Prognosis, Posttranscriptional modification, Immunotherapy, Wnt/β-catenin, Competing endogenous RNA

5. Spotlights on ubiquitin-specific protease 12 (USP12) in diseases: from multifaceted roles to pathophysiological mechanisms.

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Ubiquitination is one of the most signifcant post-translational modifcations that regulate almost all physiological processes like cell proliferation, autophagy, apoptosis, and cell cycle progression. Contrary to ubiquitination, deubiquitination removes ubiquitin from targeted protein to maintain its stability and thus regulate cellular homeostasis. Ubiquitin-Specifc Protease 12 (USP12) belongs to the biggest family of deubiquitinases named ubiquitin-specifc proteases and has been reported to be correlated with various pathophysiological processes. In this review, we initially introduce the structure and biological functions of USP12 briefy and summarize multiple substrates of USP12 as well as the underlying mechanisms. Moreover, we discuss the infuence of USP12 on tumorigenesis, tumor immune microenvironment (TME), disease, and related signaling pathways. This study also provides updated information on the roles and functions of USP12 in diferent types of cancers and other diseases, including prostate cancer, breast cancer, lung cancer, liver cancer, cardiac hypertrophy, multiple myeloma, and Huntington's disease. Generally, this review sums up the research advances of USP12 and discusses its potential clinical application value which deserves more exploration in the future.

Key Words：USP12, Deubiquitination, Tumorigenesis, Immune response, Cancer

6. 长链非编码 RNA CCL14-AS 通过调节 MEP1A 抑制结直肠癌细胞的侵袭和淋巴结转移

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背景：长链编码 RNA（lncRNAs）在结直肠癌（CRC）生物学中起着重要作用。结直肠癌中有几种与侵袭和转移相关的 lncRNA。然而，关注 lncRNA 在结直肠癌淋巴结（LN）转移中发挥作用的精准分子机制的研究仍然有限。

方法：在本研究中，通过分析 TCGA 数据集，我们发现 AC244100.2（称为 CCL14-AS），一种富含于细胞质中的新 lncRNA，与 LN 转移和 CRC 不良预后呈负相关。原位杂交用于检测临床结直肠癌组织中 CCL14-AS 的表达。使用各种功能实验，包括迁移试验和伤口愈合试验，以研究 CCL14-AS 对结直肠癌细胞迁移的影响。裸鼠腘淋巴结转移模型实验进一步证实了 CCL14-AS 在体内的作用。

结果：与邻近正常组织相比，结直肠癌组织中 CCL14-AS 的表达明显下调。此外，低 CCL14-AS 表达与结直肠癌患者的晚期 T 分类、LN 转移、远处转移和较短的无病生存期相关。在功能上，CCL14-AS 过表达抑制了体外结直肠癌细胞的侵袭性和裸鼠的 LN 转移。相反，CCL14-AS 的敲除促进了结直肠癌细胞的侵袭性和 LN 转移能力。机制上，CCL14-AS 通过与 MEP1A mRNA 相互作用下调 MEP1A 的表达，并降低其稳定性。MEP1A 的过表达挽救了 CCL14AS 过表达结直肠癌细胞的侵袭性和 LN 转移能力。此外，结直肠癌组织中 CCL14-AS 的表达水平与 MEP1A 的表达水平呈负相关。

结论：我们鉴定了一种新的 lncRNA，CCL14-AS，作为结直肠癌中潜在的肿瘤抑制因子。我们的发现证实了 CCL14-AS/MPE1A 轴作为结直肠癌进展中关键调节因子，这可以作为晚期结直肠癌的转移标志物和治疗靶点。

关键字：结直肠癌，转移，lncRNA，CCL14-AS，MEP1A

7. Deep learning-based pathology signature could reveal lymph node status and act as a novel prognostic marker across multiple cancer types

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Background: Identifying lymph node metastasis (LNM) relies mainly on indirect radiology. Current studies omitted the quantified associations with traits beyond cancer types, failing to provide generalization performance across various tumor types.

Methods: 4400 whole slide images across 11 cancer types were collected for training, cross-verification, and external validation of the pan-cancer lymph node metastasis (PC-LNM) model. We proposed an attention-based weakly supervised neural network based on self-supervised cancer-invariant features for the prediction task.

Results： PC-LNM achieved a test area under the curve (AUC) of 0.732 (95% confidence interval: 0.717-0.746, $p < 0.0001$) in five-fold cross-validation of multiple cancer types, which also demonstrated good generalization in the external validation cohort with AUC of 0.699 (95% confidence interval: 0.658-0.737, $p < 0.0001$). The interpretability results derived from PC-LNM revealed that the regions with the highest attention scores identified by the model generally correspond to tumors with poorly differentiated morphologies. PC-LNM achieved superior performance over previously reported methods and could also act as an independent prognostic factor for patients across multiple tumor types.

Disscuion: We presented an automated pan-cancer model for predicting the LNM status from primary tumor histology, which could act as a novel prognostic marker across multiple cancer types.

Key Words： deep learning, pan-cancer, pathology, lymphatic metastasis, prognosis

8. Deep learning-based pan-cancer approach to reveal tumor mutational burden status from whole slide images and act as a potential biomarker for tumor immunotherapy

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Background: Tumor mutational burden (TMB) is a potential genomic biomarker of immunotherapy. However, TMB detected through whole exome sequencing lacks clinical penetration in low-resource settings.

Methods: A multi-scale deep learning framework was proposed to addresses detection of TMB status from routinely used whole slide images to develop and verify a pan-cancer TMB prediction model (PC-TMB).

Results: The PC-TMB achieved a mean area under curve (AUC) of 0.818 (0.804-0.831) in the cross-validation cohort, which showed superior performance to each single-scale model. The improvements of PC-TMB over the single-tumor models were also confirmed by the ablation tests on ×10 magnification, and the highly concerned regions typically correspond to dense lymphocytic infiltration and heteromorphic tumor cells. PC-TMB algorithm also exhibited good generalization on external validation cohort with AUC of 0.732 (0.683-0.761).

Conclusion: We proposed a deep learning-based pan-cancer approach to reveal tumor mutational burden status from routinely used pathological slides.

Key Words： pan-cancer, deep learning, tumor mutational burden, deep learning, pathology, immunotherapy

9. Deep learning-based multi-model prediction for disease-free survival status in patients with clear cell renal cell carcinoma

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Background: Although separate analysis of individual factor can somewhat improve the prognostic performance, integration of multimodal information into a single signature is necessary to stratify patients with clear cell renal cell carcinoma (ccRCC) for adjuvant therapy after surgery.

Methods: A total of 414 patients with whole slide images, CT images, and clinical data from three patient cohorts were retrospectively analyzed. We performed deep learning and machine learning algorithm to construct three single-modality prediction models for disease-free survival of ccRCC based on whole slide images, cell segmentation, and computed tomography images, respectively. A multi-model prediction signature for disease-free survival were further developed by combining three single-modality prediction models and tumor stage/grade system. Prognostic performance of the prognostic model was also verified in two independent validation cohorts.

Results: Single-modality prediction models performed well in predicting the disease-free survival status of ccRCC. The multi-model prediction signature (MMPS) achieved higher area under the curve value of 0.742, 0.917, and 0.900 in three independent patient cohorts, respectively. MMPS could distinguish patients with worse disease-free survival, with HR of 12.90 (95% CI: 2.443-68.120, $p < 0.0001$), 11.10 (95% CI: 5.467-22.520, $p < 0.0001$), and 8.27 (95% CI: 1.482-46.130, $p < 0.0001$) in three different patient cohorts. In addition, MMPS outperformed single-modality prediction models and current clinical prognostic factors, which could also provide complements to current risk stratification for adjuvant therapy of ccRCC.

Conclusions: Our novel multi-model prediction for disease-free survival exhibited significant improvements in prognostic prediction for patients with ccRCC. After further validation in multiple centers and regions, the multimodal system could be a potential practical tool for clinicians in the treatment for ccRCC patients.

Key Words： deep learning, multi-model, disease-free survival, renal cancer, pathology

10. Histone lactylation-derived LINC01127 promotes the self-renewal of glioblastoma stem cells via the cis-regulating the MAP4K4 to activate JNK pathway

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Gliomas are the most prevalent and aggressive brain tumors, exhibiting high proliferation, abnormal glycolysis, and poor prognosis. LncRNAs act as regulatory molecules and play crucial roles in the malignant behaviors of GBM cells, including cell self-renewal. However, the regulatory mechanisms involved are largely unknown. In this study, we performed bioinformatics analysis to explore NF-κB pathway-related lncRNAs. ECAR and qRT-PCR were used to measure the relationship between glycolytic activity and lncRNA expression. Assays such as RIP-PCR and ChIP-PCR were employed to reveal the regulatory mechanisms of the lncRNA. Neurosphere formation and limiting dilution assays were performed to evaluate the self-renewal capacity of GBM cells. In our study, we identified an NF-κB pathway-related lncRNA named LINC01127 in GBM, which was found to be associated with poor progression of GBM. Functionally, the NF-κB pathway promoted warburg effect, which, in turn, induced the lactylation of H3 histone and increased the expression of LINC01127. Consequently, this enhancement of LINC01127 expression led to the promotion of self-renewal in GBM cells. Furthermore, LINC01127 regulated MAP4K4 expression in cis by directly guiding POLR2A to the MAP4K4 promoter regions, thereby leading to JNK pathway activation, and ultimately modulating the self-renewal of GBM cells. Moreover, the activated JNK pathway promoted the phosphorylation of IκBα. Overall, targeting LINC01127-mediated axis impeded orthotopic tumor growth in GBM xenografts. Taken together these results revealed that warburg effect induced histone lactylation drives NF-κB-related LINC01127 expression, thereby promoting the self-renewal of GBM cells through the MAP4K4/JNK/NF-κB axis, and providing substantial evidence that LINC01127 might provide a novel therapeutic strategy for GBM patients.

Key Words：Histone lactylation 、LINC01127 、MAP4K4 、Cis-regulation、GBM

11. CD161, a promising immune checkpoint and prognostic biomarker in NSCLC

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Objective: The use of immune checkpoint inhibitors (ICIs) has opened a new chapter in immunotherapy for non-small cell lung cancer (NSCLC), but only a few of patients benefited from it. Therefore, we still need to explore new available therapeutic targets to extend survival time of NSCLC. The purpose of this study was to evaluate the expression and predictive value of prognosis of CD161/KLRB1 in NSCLC.

Methods: The clinical data and RNA sequencing (RNA-Seq) data of 1016 patients with NSCLC in The Cancer Genome Atlas (TCGA) and 437 patients in the Gene Expression Omnibus (GEO) were analyzed retrospectively. In addition, single cell sequencing (scRNA-Seq) data from two NSCLC samples of the GEO database were used to analyze the location and function of CD161.

Results: CD161 was a potential biomarker of lung adenocarcinoma and an independent favourable prognostic factor for patients with non-small cell lung cancer. Meanwhile, CD161 showed a dynamic change with the gradual evolution of tumor. In addition, CD161, cooperating with other immune checkpoints, may affect anti-tumor immunity by mediating the release of inflammatory factors.

Conclusions: The expression of CD161 was closely related to the histopathology of patients and was an independent favourable prognostic index for patients with non-small cell lung cancer. CD161 may be a new and promising target in immunotherapy of NSCLC.

Key Words： non-small cell lung cancer, CD161, immune checkpoint, prognosis

12. CD155, a negative immune checkpoint in non-small cell lung cancer

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Objective: The purpose of this study was to evaluate the expression of poliovirus receptor (PVR/CD155) in non-small cell lung cancer (NSCLC) and its prognostic value, so as to provide a new target for the treatment of NSCLC.

Methods: The clinical data and RNA sequencing data of 1016 patients with NSCLC in public database The Cancer Genome Atlas (TCGA) and 437 patients with NSCLC in Gene Expression Omnibus (GEO) were analyzed retrospectively, in which NSCLC patients in TCGA database were served as training group and NSCLC patients in GEO database served as verification group. We analyzed the relationship among the expression of CD155 and clinicopathological features and anti-tumor immune response in two groups of patients, and discussed its value in predicting the prognosis of patients. In addition, single cell sequencing data from two NSCLC samples from the GEO database were used to analyze the localization and biological function of CD155.

Results:（1）CD155 was highly expressed in NSCLC. With the increase of the expression level of CD155, the age, gender, histopathology and clinical stage of the patients showed asymmetrical distribution. At the same time, the expression of CD155 was not related to clinical stage and pathological type. (2) CD155 was enriched on the surface of tumor cells and can participate in the migration, proliferation, differentiation, polarization, survival and adhesion of lung cancer cells. At the same time, it can negatively regulate anti-tumor immunity through immune-related signaling pathways. (3) CD155 was a poor prognostic factor in patients with lung cancer, which was independent of age and clinical stage.

Conclusions: The expression of CD155 in NSCLC was not related to gender, age, histopathological type and clinical stage. It was an independent poor prognostic factor and may become a new biomarker of NSCLC.

Key Words： Non-small cell lung cancer; CD155; prognosis; immune checkpoint

13. Ubiquitin Specific Peptidase 3: An Emerging Deubiquitinase that Regulates Physiology and Diseases.

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In normal physiological activities, ubiquitination is an extremely important post-transcriptional modification that links ubiquitin to substrates in a reversible process regulated by E3 ubiquitin ligases and deubiquitinases (DUBs). DUBs are a large family that can be divided into seven families based on structure and function: the ubiquitin-specific proteases (USPs), the otubain/ovarian tumor-domain containing proteins (OTUs), the ubiquitin carboxyl-terminal hydrolases (UCHs), the Machado-Joseph disease domain superfamily (MJDs), the monocyte chemotactic protein-induced proteins (MCPIPs), the JAB1/MPN/MOV34 proteases (JAMMs), the motif interacting with ubiquitin-containing DUB family (MINDY) and the novel ZUFSP (Zn-finger and UFSP domain protein). There is growing evidence that DUBs are closely associated with tumor development. The USP3 is coming into its own as a member of the USP family and is receiving more and more attention. In this review, we retrace all the current researches of USP3, describe the structure of USP3, elucidate its functions in DNA damage, immune and inflammatory responses and the cell cycle, and summarize the important role of USP3 in multiple cancers and diseases.

Key Words： DUBs, USP3, deubiquitination, regulation, cancer.

14. EZH2-H3K27me3-mediated Silencing of miR-139-5p Inhibits Cellular Senescence in Hepatocellular Carcinoma by Activating TOP2A

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Background: Epigenetic alterations play an important role in hepatocellular carcinoma (HCC) development. Enhancer of zeste homolog 2 (EZH2) is a well-known epigenetic modifier that functions as an oncogene in tumors by promoting the H3K27me3-mediated transcriptional repression of tumor suppressor genes. “Senescent cells” has been proposed as a possible core component of the hallmarks of cancer conceptualization. Induction of cell senescence and targeted elimination of these senescent tumor cells are new strategies for tumor therapy. However, the role of EZH2 in regulating cellular senescence remains poorly understood.

Methods: Bioinformatics analyses suggested that EZH2 and DNA topoisomerase II alpha (TOP2A) are coexpressed in tumors, including HCC. Kyoto Encyclopedia of Genes and Genome (KEGG) pathway enrichment analyses and gene set enrichment analyses (GSEA) suggests a correlation of EZH2 and TOP2A expression with cellular senescence in HCC. MicroRNA (miRNA) inhibitor and mimics, siRNA, PLKO-shRNA, and plenti6.3-miR-139 were used to upregulate or downregulate the expression of target genes. CCK8, EdU, clone formation, and senescence-associated β-galactosidase (SA-β-gal) staining assays were performed to assess cell proliferation and cellular senescence phenotypes. Dual-luciferase reporter and chromatin immunoprecipitation assays were performed to investigate the targeted binding and inhibition of TOP2A 3′ untranslated region (UTR) by miR-139-5p and the DNA enrichment of miR139-5p by EZH2 and H3K27me3. BALB/c nude mice were used to establish a xenograft tumor model and verify the phenotypes upon EZH2 and TOP2A silencing and miR-139 overexpression in vivo. In

addition, tissue microarrays were used to analyze the expression patterns and correlations among EZH2, TOP2A, and miR-139-5p expression in HCC.

Results: Bioinformatics analysis revealed that EZH2 and TOP2A are coexpressed in HCC. In vitro gain- and loss-of-function experiments showed that inhibition of EZH2 and TOP2A induces cellular senescence and inhibits proliferation of HCC cells. In vivo tumorigenesis assays indicated that EZH2 and TOP2A knockdown inhibits tumorigenesis by inducing cellular senescence. Mechanistically, EZH2 promotes TOP2A expression by regulating the H3K27me3-mediated epigenetic silencing of miR-139-5p. TOP2A is a direct target of miR-139-5p, and inhibition of miR-139-5p can reverse the promotion by EZH2 of TOP2A expression. The overexpression of miR-139-5p induces cellular senescence and inhibits proliferation of HCC cells both in vitro and in vivo. Clinically, expression of EZH2 and TOP2A are higher in HCC tissues than in normal tissues, and this high coexpression indicates a worse outcome of patients with HCC. Moreover, expression of EZH2 and TOP2A is significantly correlated with tumor differentiation grade, tumor invasion, and TNM stage in HCC. miR-139-5p expression is lower in HCC tumors than in normal tissues and is correlated with better prognosis of HCC patients.

Conclusions: Our study revealed the role of the EZH2/miR-139-5p/TOP2A axis in regulating cellular senescence and cell proliferation in HCC, enriching the molecular mechanisms of EZH2-mediated epigenetic regulation in HCC. Therefore, our results provide insight into the therapeutic potential of targeting EZH2 to induce cellular senescence and then destroy senescent cells for HCC.

Key Words： hepatocellular carcinoma; EZH2; H3K27me3; TOP2A; cellular senescence

15. An on-treatment decreased trend of serum IL-6, IL-8 as predictive markers quickly reflect short-term efficacy of PD-1 blockade combined with chemotherapy in advanced gastric cancer

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Purpose ：Immunotherapy has demonstrated efficacy in treating advanced gastric cancer (AGC), but only a subset of patients benefits. Our objective was to promptly identify prognostic biomarkers utilizing cytokines, in order to enhance the precision of clinical guidance and decision-making for PD-1 inhibitor-based cancer immunotherapy in AGC.

Materials and Methods ： In this retrospective study, we compared 36 AGC patients receiving PD-1 blockade immunotherapy combined with chemotherapy (termed as immunochemotherapy) with 20 AGC patients only receiving chemotherapy as the control group. We analyzed serum levels of IL-1β, IL-2R, IL-6, IL-8, IL-10, IL-17 and TNF-α using chemiluminescence immunoassay at three different time points after initiation of PD-1 blockade.

Results ： Compared to the controls patients treated with immunochemotherapy showed a global increase of all cytokines after treatment initiation. However, an on-treatment decreased trend in IL-6 or IL-8 level (with indefinite trends of IL-1β, IL-2R, IL-10, IL-17 and TNF-α) was found in the patients benefited from immunochemotherapy, but not in the not-benefited. Among these markers, the combination of IL-6, IL-8 and CEA showed the optimal evaluation performance in predictive short-term efficacy of immunochemotherapy for AGC patients.

Conclusion ： Reduction in IL-6/IL-8 levels during immunochemotherapy was associated with better sensitivity to the efficacy of immunochemotherapy. These blood-based biomarkers are convenient, predictive, quick, and could potentially play an important role in selecting patients who benefit from PD-1 blockade immunotherapy.

Key Words： Advanced gastric cancer, IL-6, IL-8, PD-1 blockade, predictive markers

16. 吸烟、代谢标志物和多级别胃黏膜病变及胃癌风险的关联：一项横断面研究

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[目的] 探讨上消化道高发现场人群吸烟状况、代谢标志物和多级别胃黏膜病变及胃癌风险的关联。

[方法] 选取河南林州上消化道肿瘤筛查队列中经病理诊断为肠上皮化生、高级别上皮内瘤变、胃癌及健康者共 139 人为研究对象，使用超高效液相色谱-高分辨率质谱法对基线血样的代谢物进行定量检测。采用线性回归分析吸烟状况与代谢标志物之间的关系，并进一步采用 logistics 回归分析代谢标志物与多级别胃黏膜病变及胃癌风险间的关系。筛选潜在代谢标志物，构建随机森林模型，评价其对多级别胃黏膜病变及胃癌风险诊断能力。

[结果] 在 1270 种代谢物中发现 57 种代谢物与吸烟状况相关，其中 4 个代谢物同时与多级别胃黏膜病变及胃癌风险相关，包括 4-甲基邻苯二酚-1-硫酸盐（效应值 2.82, 95% CI: 1.91~3.73, *P*<0.01, OR=1.41, 95% CI: 1.05~1.89, *P*<0.05）、4-乙酰基苯酚硫酸盐（效应值 3.08, 95% CI: 2.08~4.08, *P*<0.01, OR=1.35, 95% CI: 1.05~1.72, *P*<0.05）以及羟基可替宁（效应值 6.20, 95% CI: 5.19~7.21, *P*<0.01, OR=1.42, 95% CI: 1.07~1.88, *P*<0.05）与吸烟状况呈正相关的同时，增加胃黏膜病变及胃癌风险。乳糖神经酰胺（效应值-0.28, 95% CI: -0.51~-0.06, *P*<0.05, OR=0.21, 95% CI: 0.07~0.69, *P*<0.01）与吸烟状况呈现负相关的同时，降低胃黏膜病变及胃癌风险。整合这 4 种代谢物显著提升了预测多级别胃黏膜病变及胃癌进展的能力（AUC=0.714, 95%CI: 0.629~0.801）。

[结论] 在研究人群中发现 4 种代谢标志物同时与吸烟状况和多级别胃黏膜病变及胃癌风险存在关联，这可能部分解释了吸烟对胃癌的风险作用,同时可能作为识别高危人群和发现早期胃癌的生物标志物，具有潜在应用价值。

关键字： 胃癌；胃黏膜病变；吸烟；代谢组学

17. An inflammatory checkpoint generated by IL1RN splicing offers therapeutic opportunity for KRAS mutant intrahepatic cholangiocarcinoma

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KRAS mutations are causally linked to pro-tumor inflammation and identified as driving factors in tumorigenesis. Here, using multi-omics data gathered from a large set of patients, we showed that KRAS mutation was associated with a specific landscape of alternative mRNA splicing that connected to myeloid inflammation in intrahepatic cholangiocarcinoma (iCCA). Then, we identified a negative feedback mechanism in which the upregulation of interleukin 1 receptor antagonist (IL1RN)-201/203 due to alternative splicing confers vital anti-inflammatory effects in KRAS mutant iCCA. In KRAS mutant iCCA mice, both IL1RN-201/203 upregulation and anakinra treatment ignited a significant anti-tumor immune response by altering neutrophil recruitment and phenotypes. Furthermore, anakinra treatment synergistically enhanced anti-PD-1 therapy to activate intratumoral GZMB+ CD8+ T cells in KRAS mutant iCCA mice. Clinically, we found that high IL1RN-201/203 levels in KRAS mutant iCCA patients were significantly associated with superior response to anti-PD-1 immunotherapy.

Key Words： Tumor microenvironment, cholangiocarcinoma, IL1RN, alternative splicing, neutrophil.

18. PG I and PG II Appear Predictive of Post-operative Recurrence in Gastric Cancer Patients with Total Gastrectomy

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Objective: To investigate the potential of group I pepsinogen (PG I) and group II pepsinogen (PG II) as predictive markers for post-total gastrectomy recurrence in gastric cancer.

Methods: Ninety-six patients who underwent total gastrectomy for gastric cancer between June 2022 and June 2023 were included in this study. Clinical data, serum samples, and ascites samples were collected. Patients were categorized based on recurrence status at the time of sample collection and the primary tumor site. PG I and PG II levels in the samples were determined using chemiluminescent immunoassay, and the clinical utility of PG I and PG II following total gastrectomy for gastric cancer was evaluated through receiver operating characteristic (ROC) curve analysis.

Results: The study comprised 96 gastric cancer patients who underwent total gastrectomy, with 55 experiencing post-operative recurrence. The levels of serum PG I (27.86 vs. 26.05 ng/mL; $P < 0.0001$) and PG II (1.95 vs. 0.63 ng/mL; $P < 0.0001$) were significantly higher in the post-operative recurrence group compared to the non-recurrence group, with statistically significant differences. The secretion of PG I and PG II by metastatic cancer cells was correlated with the tissue site of the primary lesion. When the cut-off value for serum PG I was 26.93 ng/mL, the area under the curve (AUC) for PG I was 0.77; and the cut-off value for serum PG II was 0.96 ng/mL, it reached 0.90. When combined, their AUC reached 0.97.

Conclusions: These findings suggest that serum PG I and PG II serve as valuable biomarkers for predicting post-operative recurrence in gastric cancer patients with total gastrectomy.

Key Words： Gastric cancer, Post-operative recurrence, Total gastrectomy, Pepsinogen (PG), Group I pepsinogen (PG I), Group II pepsinogen (PG II)

19. Cancer Associated Fibroblast Derived SLIT2 Drives Gastric Cancer Cell Metastasis by activating NEK9

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The secretory properties of cancer-associated fibroblasts (CAFs) play predominant roles in shaping a pro-metastatic tumor microenvironment. The present study demonstrated that SLIT2, an axon guidance protein, produced by CAFs and promoted gastric cancer (GC) metastasis in two gastric cancer cell lines (AGS and MKN45) by binding to roundabout guidance receptor 1 (ROBO1). Mass-spectrometry analysis revealed that ROBO1 could interact with NEK9, a serine/threonine kinase. And their mutual binding activities were further enhanced by SLIT2. Domain analysis revealed the kinase domain of NEK9 was critical in its interaction with the intracellular domain (ICD) of ROBO1, and it also directly phosphorylated tripartite motif containing 28 (TRIM28) and cortactin (CTTN) in AGS and MKN45 cells. TRIM28 function as a transcriptional elongation factor, which directly facilitate CTTN activation. In addition, Bioinformatics analysis and experimental validation identified transcriptional regulation of STAT3 and NF-κB p100 by TRIM28, and a synergetic transcription of CTTN by STAT3 and NF-κB p100 was also observed in AGS and MKN45. Therefore, CAF-derived SLIT2 increased the expression and phosphorylation levels of CTTN, which induced cytoskeletal reorganization and GC cells metastasis. A simultaneous increase in the expression levels of NEK9, TRIM28 and CTTN was found in metastatic GC lesions compared with paired non-cancerous tissues and primary cancer lesions via IHC and Multiplex IHC. The analysis of the data from a cohort of patients with GC revealed that increased levels of NEK9, TRIM28 and CTTN were associated with a decreased overall survival rate. On the whole, these findings revealed the connections of CAFs and cancer cells through SLIT2/ROBO1 and inflammatory signaling, and the key molecules involved in this process may serve as potential biomarkers and therapeutic targets for GC.

Key Words： Gastric cancer metastasis, Cancer-associated fibroblasts, NEK9, Inflammation, Phosphorylation

20. Integrated analysis and validation of the TRIM28-H2AX-CDK4 diagnostic model assists to predict the progression of HCC

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Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality in the world. However, identifying key genes that can be exploited for the effective diagnosis and management of HCC remains difficult. The study aims to examine the prognostic and diagnostic value of TRIM28-H2AX-CDK4 axis in HCC. Analysis in TCGA, GSEA and Gene expression profiling interactive analysis online tools were performed to explore the expression profiles of TRIM28, H2AX and CDK4. Data demonstrating the correlation between TRIM28 expression levels and immune infiltration states or the expression of genes associated with immune checkpoints genes were exacted from TCGA and TIMER. Genetic alteration and enrichment analysis were performed using the cBioPortal and GEPIA2 tools. Finally, the expression of these proteins in HCC was then examined and validated in an independent cohort using immunohistochemistry. TRIM28 alteration exhibited co-occurrence instead of mutual exclusivity with a large number of immune checkpoint components and tumor-infiltrating immune cells, especially B cells, were found to serve roles in patients with HCC with different TRIM28 expression levels. Higher expression levels of TRIM28, H2AX and CDK4 were associated with a poorer prognosis and recurrence in patients with HCC according to TCGA, which was validated further in an independent cohort of patients with HCC. Area under curve revealed the superior predictive power of applying this three-gene signatures in this validation cohort. The diagnostic model based on this TRIM28-H2AX-CDK4 signature is efficient and provides a novel strategy for the clinical management of HCC.

Key Words： hepatocellular carcinoma, immune status, TRIM28, H2AX, CDK4

21. USP6 基因介导的肿瘤临床病理及分子病理学分析

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目的：探讨 USP6（ubiquitin-specific protease 6，泛素特异性蛋白酶）基因介导的肿瘤的临床病理、免疫表型及分子病理学特征。

方法：收集解放军总医院第四医学中心病理科 2021 年 6 月至 2023 年 7 月诊断为动脉瘤样骨囊肿、结节性筋膜炎 2 种 USP6 介导的肿瘤及单纯性骨囊肿、纤维瘤病、增生性肌炎等其它（肌）纤维母细胞增生性病变的病例共 87 例。回顾上述病例的临床及组织学特点，并进行免疫组织化学、荧光原位杂交（FISH）检测。

结果：USP6 介导的肿瘤共 45 例，男性 33 例，女性 12 例；中位年龄 23 岁（范围 17~51 岁）；肿瘤中位大小为 3.5cm（范围 1.0~11.0 cm）。获得随访的 45 例患者均无复发。组织学上，USP6 基因介导的肿瘤共同特征为病变主要由梭形细胞构成，呈旋涡状或束状排列，可见玻璃样变区域；瘤细胞以纤维母细胞/肌纤维母细胞为主，胞浆淡嗜伊红色、边界不清，细胞轻度异型性。结节性筋膜炎（nodular fasciitis，NF）18 例，可见黏液微囊，间质见渗出的红细胞、淋巴细胞、浆细胞、破骨细胞样小多核巨细胞以及杜顿巨细胞。动脉瘤样骨囊肿（aneurysmal bone cyst, ABC）27 例，可见充满血液的囊性区域，实性区域见多量破骨细胞样巨细胞，并见新生骨形成；其中 3 例为实体型 ABC，要注意和骨巨细胞瘤鉴别。87 例均进行了免疫组织化学染色，各类肿瘤梭形细胞成分均表现出典型的（肌）纤维母细胞表型，多表达 SMA 和 MSA，一般不表达结蛋白和 S-100 蛋白。对 87 例（肌）纤维母细胞增生或伴多核巨细胞浸润的病例进行 USP6 基因断裂重排的 FISH 检测，NF 中 66.7%（12/18）具有 USP6 基因断裂重排；ABC 中具有 USP6 基因断裂重排占比为 66.7% （18/27），并有 3.7%（1/27）具有 USP6 信号异常。单纯性骨囊肿、骨巨细胞瘤伴 ABC 样改变、骨母细胞瘤、骨旁骨肉瘤、骨巨细胞瘤、纤维瘤病、增生性肌炎中均未检测出 USP6 基因断裂重排（0/42）。

结论：不同疾病可具有相同或相似的 USP6 基因断裂重排，这一疾病可能是同一疾病谱的不同形态类型；USP6 基因介导的肿瘤需要与多种骨及软组织梭形细胞增生性病变进行鉴别，且易误诊为恶性肿瘤，应结合临床病史、影像特点、组织学特征及免疫组织化学等明确诊断，困难病例 FISH 检测 USP6 基因断裂重排具有重要的辅助诊断价值。

关键字：软组织肿瘤；骨肿瘤；USP6 基因；梭形细胞肿瘤

22. 胸部 SMARCA4 缺失性肿瘤的临床及分子病理学特征

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目的： 探讨胸部 SMARCA4 缺失性肿瘤的临床病理、免疫组织化学、分子遗传学、预后特征及鉴别诊断。

方法： 收集解放军总医院第四医学中心病理科 2022 年 10 月至 2023 年 8 月诊断为非小细胞肺癌（NSCLC）173 病例，对肿瘤组织进行 BRG-1 免疫组化标记，筛选出 Brg-1 表达缺失病例，确诊为胸部 SMARCA4 缺失性肿瘤，分析其临床、组织形态学、免疫组织化学及基因学检测结果，并对临床分期、治疗反应、预后进行评估及随访。

结果： 173 例 NSCLC 筛选出 6 例 SMARCA4 缺失性肿瘤，占比 3.47%，均为穿刺活检标本，其中 1 例确诊为胸部 SMARCA4 缺失性未分化肿瘤（SMARCA4-DUT），5 例确诊为 SMARCA4 缺失性肺癌（SMARCA4-DNSCLC）。患者均为男性，平均年龄 65 岁（57 岁~73 岁），均具有长期且重度吸烟史，人均吸烟 43 年（20 年~50 年）、32 支/日（20 支/日~50 支/日）。影像学肿瘤结节平均直径为 4.2cm（2.1cm~5.5 cm），均可见多发性转移灶，包括肺内转移、纵膈、锁骨上及腋窝淋巴结、胸壁、肝脏及骨转移。组织学上，SMARCA4-DUT 表现为差分化的失黏附性上皮样细胞，核偏位，胞浆红染横纹肌样，瘤细胞异型性明显，分裂像及坏死多见。SMARCA4-DNSCLC 表现为低分化实性腺癌、黏液腺癌、多形性肉瘤样癌等多种形态。免疫组化共同表现为 SMARCA4 编码 BRG1 蛋白表达缺失，SMARCA4-DUT 局灶性表达 CK，不表达 CK7、TTF1、P63、P40，过表达 CD34、SOX2、SALL4、Syn 及 p53；SMARCA4-DNSCLC 弥漫性表达 CK、CK7，不表达 CD34、S0X2、SALL4，可表达 TTF1、P63 及 P40。分子病理检测均表现为 SMARCA4 基因突变，未见 EGFR、RAS、BRAF、MET、ALK、ROS1、RET 等常见肺癌驱动基因突变。鉴别诊断包括具有横纹肌样分化的肉瘤、恶性黑色素瘤、淋巴瘤及经典型 NSCLC 等。6 例患者均因多发肿瘤病灶或转移未进行手术治疗而行常规化疗。随访 1 例 SMARCA4-DUT 患者 4 个月后死亡，其他 SMARCA4-DNSCLC 治疗后肿瘤处于进展状态。

结论： 胸部 SMARCA4 缺失性肿瘤是罕见的恶性肿瘤，以 SMARCA4 缺失表达为共同特征，包括 SMARCA4-DUT 和 SMARCA4-DNSCLC。临床确诊时往往出现肿瘤多发性转移，肿瘤恶性程度高、侵袭性强、缺乏靶向治疗基因突变，患者治疗效果差，生存期较短，预后不良。常规进行 BRG1 的免疫组化筛查，对识别及确诊该类型肿瘤具有重要的意义。

关键字 ：SMARCA4；BRG1；胸部 SMARCA4 缺失的未分化肿瘤；SMARCA4 缺失性肺癌

23. NGS 技术辅助骨与软组织肉瘤的诊断及治疗

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【摘要】骨与软组织肿瘤临床罕见，亚型众多，且肉瘤性病变恶性程度高、预后差，临床诊断及治疗面临巨大挑战。骨与软组织肿瘤的病理诊断目前仍基于传统的形态学观察，辅以免疫组织化学（IHC）标记。已广泛开展的荧光原位杂交（FISH）和基因突变检测（一代测序）为骨与软组织肿瘤的病理诊断提供了极大帮助，提高了诊断的准确率。近年来，随着分子检测技术的发展，二代基因测序（NGS）已广泛应用于肿瘤的分子诊断、靶向基因筛选以及表观遗传学分析等领域，其具有高通量同时检测多基因、多靶点、已知及未知基因变异，同时指导靶向治疗和免疫治疗等优势，使得 NGS 在骨与软组织肿瘤的诊治中发挥越来越重要的作用。本文通过以下几方面介绍 NGS 技术辅助骨与软组织肉瘤的诊断及治疗：（1）NGS 检测的技术优势；（2）NGS 检测可校正肉瘤诊断结果；（3）NGS 检测基因融合伴侣指导肉瘤的精准诊断；（4）NGS 检测助力发现新的肉瘤类型；（5）NGS 检测筛选潜在的靶向治疗药物；（6）NGS 检测指导靶向治疗；（7）NGS 应用于肉瘤诊断的临床及病理指南推荐情况介绍；（8）NGS 检测的技术环节要点。最后，通过 5 个病例举例进一步介绍 NGS 辅助骨与软组织肉瘤的诊断及治疗的应用场景和诊治经过，进一步阐明如何合理有效利用 NGS 技术辅助骨与软组织肉瘤的诊治，为更多的疑难少见骨与软组织肿瘤患者带来生存获益。推荐有条件的单位积极自主或借助可靠的技术平台开展 NGS 技术，不断提高骨与软组织肿瘤的诊治水平。

关键字：骨与软组织肿瘤；高通量测序；病理诊断；精准治疗

24. Novel hypoxia-induced HIF1α-circTDRD3-positive feedback loop promotes the growth and metastasis of colorectal cancer

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Tumor hypoxia and circular RNAs (circRNAs) are considered to play key roles in tumor progression and malignancy, respectively. Nevertheless, the biological functions and underlying mechanisms of specific circRNAs exposed to hypoxic microenvironments in colorectal cancer (CRC) remain largely elusive. Herein, a novel circRNA, circTDRD3, which is upregulated under hypoxic conditions, was identified. The expression of circTDRD3 was highly expressed in CRC tissues and positively correlated with overall survival, tumor size, lymph node invasion and clinical stage. CircTDRD3 facilitated CRC cell proliferation, migration and metastasis in vitro and in vivo. Mechanistically, circTDRD3 promoted HIF1α expression by sponging miR-1231, which facilitated CRC progression. Meanwhile, HIF1α directly combined with TDRD3 promoter to increase the expression of TDRD3 pre-mRNA. Then HIF1a-induced PTBP1 accelerated the formation of circTDRD3. Our findings reveal that circTDRD3 facilitates the proliferation and metastasis of CRC through a positive feedback loop mediated by the HIF1α/PTBP1/circTDRD3/miR-1231/HIF1α axis. Therefore, circTDRD3 may serve as a prognostic biomarker and therapeutic target for patients with CRC.

Key Words： Hypoxia,Colorectal cancer,circRNA,RBP

25. ZNF334 Increases the Sensitivity of Colorectal Cancer to 5-Fluorouracil Treatment by Inducing Cell Cycle Arrest and Apoptosis Cell Death

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5-Fluorouracil (5-FU) is known as a first-line chemotherapeutic agent against colorectal cancer (CRC), but drug resistance occurs frequently and significantly limits its clinical success. Our previous study showed that the Zinc finger protein 334 (ZNF334) gene was frequently methylated and functioned as a tumor suppressor in CRC. However, the relationship between ZNF334 and 5-FU resistance in CRC remains unclear. Here, we revealed that ZNF334 was more highly expressed in 5-FU-sensitive CRC tissues than in 5-FU-resistant CRC tissues, and this expression profile contributed to superior prognosis and increased survival in CRC patients. Restoring ZNF334 expression augmented the 5-FU sensitivity of CRC in vitro and in vivo by promoting cell cycle arrest and apoptosis cell death. Furthermore, apoptosis played a dominant role in ZNF334-induced cell death, as an autophagy inhibitor blocked cell death to a greater extent than the pancaspase inhibitor Z-VAD-FMK. ZNF334 inhibition by siRNA decreased the apoptosis response and 5-FU sensitivity. Mechanistically, we showed that CDK1-cyclinB1 inactivation was a key determinant in ZNF334-induced apoptosis. Ectopic expression cyclinB1, an activator of cell cycle, suppressed apoptosis and 5-FU-induced cell death in ZNF334-reexpressing CRC cells. Taken together, our findings suggest for the first time that ZNF334 increases the sensitivity of CRC to 5-FU treatment by inducing cell cycle arrest and cell cycle-dependent apoptosis cell death. ZNF334 may be a potential prognostic marker for predicting 5-FU sensitivity in CRC patients.

Key Words： Colorectal cancer, 3D organiod, ZNF334, Chemotheraphy sensitivity

26. NTF4 plays a dual role in breast cancer in mammary tumorigenesis and metastatic progression

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Breast cancer metastasis can happen even when the primary tumor is relatively small. But the mechanism for such early metastasis is poorly understood. Herein, we report that neurotrophin 4 (NTF4) plays a dual role in breast cancer proliferation and metastasis. Clinical data showed high levels of NTF4, especially in the early stage, to be associated with poor clinical outcomes, supporting the notion that metastasis, rather than primary cancer, was the major determinant of breast cancer mortality for patients. NTF4 promoted epithelial-mesenchymal transition (EMT), cell motility, and invasiveness of breast cancer cells in vitro and in vivo. Interestingly, NTF4 inhibited cell proliferation while promoting cellular apoptosis in vitro and inhibited xenograft tumorigenicity in vivo. Mechanistically, NTF4 elicited its pro-metastatic effects by activating PRKDC/AKT and ANXA1/NF-κB pathways to stabilize SNAIL protein, therefore decreasing the level of E-cadherin. Conversely, NTF4 increased ANXA1 phosphorylation and sumoylation and the interaction with importin β, leading to nuclear import and retention of ANXA1, which in turn activates the caspase-3 apoptosis cascade. Our findings identified an unexpected dual role for NTF4 in breast cancer which contributes to early metastasis of the disease. Therefore, NTF4 may serve as a prognostic marker and a potential therapeutic target for breast cancer.

Key Words： Breast cancer, NTF4, epithelial-mesenchymal transition, metastasis, apoptosis

27. A novel miR-490-3p/hnRNPA1-b/PKM2 axis intermediates the Warburg effect and proliferation of colon cancer via PI3K/AKT pathway

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Heterogeneous ribonucleoprotein A1 (hnRNPA1) has been reported to enhance Warburg effect and promote colon cancer (CC) proliferation, but the role and mechanism of miR-490-3p/hnRNPA1-b/PKM2 axis in CC are not yet elucidated. Paraffin-embedded pathological sections from 220 colon cancer patients were collected and subjected to immunohistochemical analysis to determine the expression of hnRNPA1-b. The relationship between the expression values and the clinicopathological features of the patients was investigated. Differences in mRNA expression were analyzed using qPCR, while differences in protein expression were analyzed using Western blot. Cell proliferation was evaluated using CCK8 and EdU assays, and cell cycle and apoptosis were assessed using flow cytometric assays. The targeted binding of miR-490-3p to hnRNPA1-b was validated using a dual luciferase reporter assay. Warburg effect was evaluated through glucose uptake and lactic acid production assays. The expression of hnRNPA1-b was significantly increased in CC tissues and cells compared to normal controls ($P<0.05$). Immunohistochemical results demonstrated significant variations in the expression of the hnRNPA1-b antigen among different stages of CC, including stage I, II-III, and IV. Furthermore, the clinicopathologic characterization revealed a significant correlation between hnRNPA1-b expression and clinical stage as well as T classification. HnRNPA1-b was found to enhance the Warburg effect through the PI3K/AKT pathway, thereby promoting proliferation of HCT116 and SW620 cells. However, the proliferation of HCT116 and SW620 cells was inhibited when miR-140-3p targeted and bound to hnRNPA1-b, effectively blocking the Warburg effect.

These findings suggest that the novel miR-490-3p/hnRNPA1-b/PKM2 axis could provide a new strategy for the diagnosis and treatment of CC.

Key Words： hnRNPA1-b miR-490-3p Colon cancer Alternative splicing Warburg effect

28. E2 + norethisterone promotes the PI3K–AKT pathway via PGRMC1 to induce breast cancer cell proliferation

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Objective: This study aimed to find evidence that progesterone receptor membrane component 1 (PGRMC1) promotes estradiol (E2) þ norethisterone (NET)-induced breast cancer proliferation through activation of the phosphatidylinositol-3-kinase (PI3K)–AKT pathway.

Methods: PGRMC1-mediated breast cancer cellular proliferation and phosphorylation of PGRMC1 were studied using wild-type (hemagglutinin [HA]-tagged) MCF-7 cells, which were stably transfected with expression vector containing HA (MCF-7-HA cells), PGRMC1 (MCF-7-PGRMC1 cells) and Ser181 point mutated PGRMC1 (MCF-7-PGRMC1-S181A cells). Bioinformatics, cell proliferation, western blot, isobaric tags for relative and absolute quantitation (iTRAQ)-based RNA sequencing, real-time quantitative poly_x0002_merase chain reaction (RT-qPCR) and cell cycle in vitro assays were performed to indicate the function of PGRMC1 and its possible mechanisms in breast cancer.

Results: NET þ E2 elicited a significant proliferation in MCF-7-Vec at 10_x0002_ 6 M and 10_x0002_ 10 M, respectively. MCF-7-PGRMC1 did increase the phosphorylation of AKT or ERK, which can be blocked by treatment with casein kinase 2 (CK2) inhibitor quinalizarin or in MCF-7-PGRMC1-S181A cells. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealed that the PI3K–AKT pathway is upregulated in MCF-7- PGRMC1 cells. Importantly, upregulation of the PI3K–AKT pathway mainly through promotion of cell cycle regulation strongly promoted cell proliferation in MCF-7-PGRMC1 cells.

Conclusions: CK2 is involved in phosphorylation of PGRMC1 at S181. The mechanism for the action of PGRMC1 for mediating proliferative progestogen effects obviously starts with promotion cell cycle regulation, and then activation of the PI3K–AKT pathway

Key Words： Breast cancer; PGRMC1; phosphorylation; PI3K–AKT

29. Testosterone promotes the migration, invasion and EMT process of papillary thyroid carcinoma by up-regulating Tnnt1

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Purpose ： To explore the key genes and molecular pathways in the progression of thyroid papillary carcinoma (PTC) promoted by testosterone using RNA-sequencing technology, and to provide new drug targets for improving the therapeutic effect of PTC.

Methods： Orchiectomy (ORX) was carried out to construct ORX mouse models. TPC-1 cells were subcutaneously injected for PTC formation in mice, and the tumor tissues were collected for RNA-seq. The key genes were screened by bioinformatics technology. Tnnt1 expression in PTC cells was knocked down or overexpressed by transfection. Cell counting kit-8 (CCK-8), colony formation assay, scratch assay and transwell assay were adopted, respectively, for the detection of cell proliferation, colony formation, migration and invasion. Besides, quantification real-time polymerase chain reaction (qRT-PCR) and western blot were utilized to determine the mRNA and protein expression levels of genes in tissues or cells.

Results ： Both estradiol and testosterone promoted the growth of PTC xenografts. The key gene Tnnt1 was screened and obtained by bioinformatics technology. Functional analysis revealed that overexpression of Tnnt1 could markedly promote the proliferation, colony formation, migration, invasion, and epithelial-to-mesenchymal transition (EMT) process of PTC cells, as well as could activate p38/JNK pathway. In addition, si-Tnt1 was able to inhibit the cancer-promoting effect of testosterone.

Conclusion ： Based on the outcomes of bioinformatics and basic experiments, it is found that testosterone can promote malignant behaviors such as growth, migration, invasion and EMT process of PTC by up-regulating Tnnt1 expression. In addition, the function of testosterone may be achieved by activating p38/JNK signaling pathway.

Key Words： Papillary thyroid carcinoma · RNA sequencing · Testosterone · Tnnt1 · p38/JNK signaling pathway

30. Gastric cancer patient-derived organoids model for the therapeutic drug screening

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Background: Gastric cancer (GC) is a highly heterogeneous disease featuring many various histological and molecular subtypes. Therefore, it is imperative to have well-characterized in vitro models for personalized treatment development. Gastric cancer patient-derived organoids (PDOs), re-capitulating in vivo conditions, exhibit high clinical efficacy in predicting drug sensitivity to facilitate the development of cancer precision medicine.

Methods: PDOs were established from surgically resected GC tumor tissues. Histological and molecular characterization of PDOs and primary tissues were performed via IHC and sequencing analysis. We also conducted drug sensitivity tests using PDO cultures with five chemotherapeutic drugs and twenty-two targeted drugs.

Results: We have successfully constructed a PDOs biobank that included EBV+, intestinal/CIN, diffuse/GS, mixed and Her2+ GC subtypes, and these PDOs captured the pathological and genetic characteristics of corresponding tumors and exhibited different sensitivities to the tested agents. In a clinical case study, we performed an additional drug sensitivity test for a patient who reached an advanced progressive stage after surgery. We discovered that the combination of napabucasin and COTI-2 exhibited a stronger synergistic effect than either drug alone.

Conclusion: PDOs maintained the histological and genetic characteristics of original cancer tissues. PDOs biobank opens up new perspectives for studying cancer cell biology and personalized medicine as a preclinical study platform.

Key Words： gastric cancer, organoids biobank, napabucasin, COTI-2, personalized medicine

31. A preliminary exploration of the application of gene methylation in the detection of cervical adenocarcinoma

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Background: Cervical cancer (CC) is a serious health risk to women and is one of the four most common female malignancies worldwide. The main histologic types of CC include Squamous Cell Carcinoma (SCC) and Endocervical Adenocarcinoma (ECA), with SCC accounting for about 70% of cervical cancers, and ECA accounting for 20-30%. With the continuous improvement of cervical cancer screening strategies and the availability of prophylactic HPV vaccines, the incidence of cervical cancer has shown a substantial decline over the past 30 years, but this decline varies by histologic type. Overall, the incidence of SCC has been declining in some developed countries. However, ECA is a group of heterogeneous tumors, with different histological types possessing different pathogenic mechanisms and molecular features, and its onset is deep and difficult to identify, so the existing detection techniques have difficulties in screening for ECA. Methylation of host genes in cervical cancer patients is a key factor promoting progression to CC in patients with precancerous lesions. Currently, several genes have been found to be methylated in cervical tissue, and gene methylation has been shown to be useful for cervical cancer screening and diagnosis. In recent years, some scholars have begun to study the gene methylation status in different cervical cancer histologic types. They often compared it with the gold standard for pathological classification and grading, and are committed to the discovery of novel auxiliary diagnostic markers for cervical cancer. Therefore, this study aims to identify potential molecular markers of gene co-methylation regions for ECA screening and diagnosis.

Methods: The study utilized a machine learning approach to develop diagnostic models for differentiating between normal and cervical cancer patients, as well as between ECA and squamous cell carcinoma (SCC). 42 patients with cervical cancer (18 ECA, 16 SCC, and 8 paraneoplastic normal tissue) who underwent surgical treatment at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Science and Peking Union Medical College from 2020 to 2023 were selected for the study. Next, We screened the 45 most common human methylated genes incervical cancer and its precancerous lesions through the preliminary literature search. The high_x0002_association regions were filtered by dividing the high-density CpG regions. The methylation scores were calculated using Methylation haplotype Load (MHL). The MHL values were filtered to obtain the high-association regions of highly methylated loci. These locis were used to evaluate the differences in methylation patterns between normal tissues, SCC and ECA, and to construct the diagnostic model for distinguishing normal and cervical cancer tissues, ECA and SCC through three kinds of machine learning (random forest model、naive bayes model and support vector machine model).

Results: A total of 47 site regions of 25 genes were classified as highly associated methylation regions. The optimal model variables were determined by ten-fold cross-validation, which revealed that 10 hypermethylated sites in 8 genes were most suitable for differentiating cervical cancer tissues (SCC and ECA) from normal tissues and taht 20 hypermethylated sites in 15 genes were most suitable for differentiating SCC and ECA. Then, the study evaluated the effectiveness of different machine learning models in differentiating between normal and cervical cancer tissues. The random forest (rf) model had an area under receiver operating characteristic curve (AUC) of 0.8333 (95% CI: 0.5909-1.0000), with a sensitivity of 100.00%, a specificity of 83.30%, and a detection rate of 100.00% for cancerous tissues and 93.75% for normal ones. The naive bayes (nb) model had an AUC of 0.8333 (95% CI: 0.5909-1.0000) with a sensitivity of 100.00% and specificity of 66.67%, and the detection rate was 85.29% for cancerous tissues and 100.00% for normal tissues. The support vector machine (svm) model had an AUC of 1.000, a sensitivity of 100.00%, a specificity of 83.30%, a detection rate of 91.18% for cancerous tissue, and a detection rate of 50.00% for normal tissue. DeLong test was used to measure whether there was a difference in ROC between each model. The delong test showed that rf had better diagnostic efficacy relative

to nb (z=2.098, P=0.0359) and svm (z=2.823, P=0.0048), while nb had better diagnostic efficacy than svm (z=2.282, P=0.0225). To differentiate between ECA and SCC, the diagnostic performance of three classification models were evaluated. Random Forest (RF) achieved an AUC of 0.8889 (95% CI: 0.5809-1.0000), with a sensitivity of 100.00%, a specificity of 66.67%, a detection rate of 100.00% for SCC and 93.75% for ECA. Naive Bayes (NB) achieved an AUC of 0.6667 (95% CI: 0.0134-1.0000), with a sensitivity of 66.67%, specificity of 33.33%, and detection rate of 83.33% for SCC and 87.50% for ECA. Support Vector Machine (SVM) achieved an AUC of 0.7778 (95% CI: 0.2908-1.0000), with a sensitivity of 100.00%, specificity of 33.33%, and detection rate of 44.44% for SCC and 87.50% and 81.25% for ECA, respectively. Delong test showed that RF had better diagnostic efficacy relative to NB (z=4.608, P<0.001), while NB had better diagnostic efficacy than SVM (z=2.788, P=0.0053). Conclusions: Through co-methylation assays, we determined the patterns of host gene methylation in ECA and SCC, and constructed models for the preliminary differentiation between normal and CC, ECA and SCC. A random forest model based on highly correlated co-methylation genes can accurately assess the risk of cervical cancer in women and effectively distinguish between patients with ECA and SCC. This model can serve as a valuable complementary diagnostic technique for cervical cancer.

Key Words： Endocervical adenocarcinoma; Methylation; Machine learning; Diagnostic model

32. Expression of Snai2 and FSCN1 proteins in nasopharyngeal squamous cell carcinoma and their prognostic significance

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Objective ： To investigate the expression of Snail superfamily Zinc Finger Transcription Factor 2(Snai2) and Snail Actin-binding protein 1(FSCN1) in nasopharyngeal carcinoma (NPC) and their prognostic significance.

Methods ： A total of 121 patients with nasopharyngeal squamous-cell carcinoma admitted to our hospital from January 2019 to January 2019-2023,The expression of Snai2 and FSCN1 protein

was detected by immunohistochemistry, and the clinicopathological features were analyzed. Kaplan-meier curves were used to analyze the relationship between Snai2, FSCN1 and the prognosis of NPC, and COX regression model was used to evaluate the prognostic factors of NPC.

Results：The positive rates of Snai2 and FSCN1 proteins in NPC tissues were significantly higher than those in adjacent tissues（P＜0.05）,The expression of Snai2 and FSCN1 protein was related to tumor differentiation, lymph node metastasis and TNM stage(P<0.05); The overall 5-year survival rate of NPC patients was 76.03% . The 5-year survival rate of Snai2 positive expression group was 67.61% (48/71), which was significantly lower than that of Snai2 negative expression group (88.00%,44/50)（=9.049，P＜0.05），The 5-year survival rate of FSCN1 positive expression group was 70.59% (60/85) , significantly lower than that of FSCN1 negative expression group (88.89% (32/36)（=6.928，P＜0.05），Multivariate regression analysis showed that SNAI2 and FSCN1 were independent prognostic factors except TNM stage(P<0.05).

Conclusion ： The increased expression of SNAI2 and FSCN1 proteins in nasopharyngeal squamous-cell carcinoma is an independent risk factor for the prognosis of NPC.

Key Words：Nasopharyngeal squamous-cell carcinoma；Snail Zinc Finger Transcription Factor；Actin-binding protein；clinicopathological features； prognosis

33. Identification of antioxidant enzyme B166 as a novel biomarker for glioma patients

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Antioxidant enzyme B166 (B166) - mediated detoxification of H2O2 into water and oxygen is a pivotal process to sustain a favorable redox homeostasis in mitochondria and suppress cell death. Here, we identify that B166 is highly expressed in GBM tumor tissues and a potential novel biomarker to predict unfavorable prognosis of GBM patients. GBM cells upregulate the expression of B166 via SREBP1-a-mediated transcription and reduce the endogenous ROS levels, maintaining the cellular redox homeostasis and normal morpho-function of mitochondria.

SREBP1 knock down decreases B166 expression on both RNA and protein levels. We reveal that overexpression of SREBP1-aN, the active form of SREBP1-a, increases B166 isoform 1 (V1) and 5 (V5) levels in the mitochondria and nucleus, respectively. Pharmacological suppression of SREBP1 or genetic inhibition of B166 disrupts the redox homeostasis, leading to the generation of high levels of oxidative stress, which in turn causes dramatic damages to the mitochondria and kills GBM cells ultimately. We show that SREBF1 level is strongly associated with B166, FASN and SCD expression in patients' tumor tissues of GBM cohort from TCGA and protein levels of SREBP1 and B166 are significantly correlated in our PHGBM cohort. Thus, targeting B166 could be a promising therapeutic approach for GBM.

Key Words： glioblastoma, biomarker, redox homeostasis, mitochondria

34. 基于 6 种氧化应激相关 lncRNA 的子宫内膜癌预后预测模型的建立

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目的：长非编码 RNA（lncRNA）通过多种机制在癌症进展中发挥癌基因或抑癌基因的作用，有可能成为可靠的生物标志物和癌症治疗的新靶点。然而，lncRNA 在肿瘤氧化应激调节中的作用尚未得到明确证明。本研究旨在筛选与子宫内膜癌症（EC）患者预后相关的氧化应激相关 lncRNA（oslncRNA），并评估其与免疫检查点抑制剂（ICIs）、肿瘤免疫微环境（TIME）以及放疗反应的相关性，为 EC 的个性化治疗提供新思路。

方法：从 TCGA 子宫内膜癌项目（TCGA-UCEC）获得 RNA-seq 数据，并通过 EdgeR 和共表达分析筛选 oslncRNA。使用单变量 Cox 回归、LASSO 算法和多元 Cox 回归获得预后相关 oslncRNA，并用于构建风险预测模型。使用 ROC 曲线优化预后模型的阈值，并将 EC 患者相应地分为高危组和低危组。分析了风险得分与 10 种免疫细胞浸润丰度、ICIs 和 T 细胞增殖合成驱动基因表达的相关性。为模型中的 6 个 oslncRNA 建立了 ceRNA 网络。根据放疗反应将 EC 患者分为放疗耐受组（R）和放疗敏感组（S），并用 Fisher 精确检验分析模型分组与放疗分组的相关性。

结果：2280 个 oslncRNA 与氧化应激相关基因共表达（|R|>0.4，p＜0.005）。基于 6 个 oslncRNA（AP001885.2、LINC0757、AL157400.2、AC092112.1、AP003174.1、MIR7-3HG）建立了最终模型（p=0.0022）。20 个 ICI 基因，包括 PDCD1LG2、PDCD10、PDCD4-AS1、PDCD5P1 等，以及 10 个 T 细胞增殖驱动基因，包括 AHCY、CXCL12、GPN3、LT8R 等，与模型风险评分显著相关（p<0.05）。AL157400.2、AC092112.1 和 AP003174.1 的表达与 T 细胞丰度显著正相关，AP001885.2 和 AL157400.2 与成纤维细胞丰度显著负相关（p<0.05）。ceRNA 网络表明，通过 31 个 miRNA，MIR7-3HG 调节 121 个蛋白质编码基因，包括 HMGA2、CCND2、PTEN、HMGA1、CDK6、MYCN、MCL1、CCND1、MYC、TP53、BCL9、BCL2、DNMT1、E2F2、IGF1 和其他与癌症产生、发展和转移密切相关的基因。

结论：基于 6 个 oslncRNA 的预后风险评分预测模型与 EC 患者的 OS 密切相关，可作为预测 EC 预后的独立生物标志物。风险评分与多个 ICI 基因的表达以及多种类型免疫细胞的浸润丰度显著相关，表明我们的模型在为 EC 提供个性化治疗方面具有一定的参考价值。

关键字：子宫内膜癌，氧化应激 lncRNA，Cox 回归，生存分析，预后，免疫检查点抑制剂

35. Association between psychological distress and gastric cancer: a Mendelian randomization study

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Background: Gastric cancer is a significant global health issue. Psychological distress is a negative emotional state characterized by symptoms of depression and anxiety. In recent years, numerous domestic and international epidemiological studies have shown that there is a close relationship between psychological distress and gastric cancer. Psychological distress is highly prevalent in patients with gastric cancer. Observational studies have reported the association between psychological distress and the risk of gastric cancer. However, traditional observational

studies are susceptible to potential unmeasured confounders or reverse causality, which are unable to determine a causal association between psychological distress and gastric cancer, as well as to fully distinguish whether psychological distress causes gastric cancer or gastric cancer causes psychological distress. Mendelian Randomization (MR) is considered the best alternative to the Randomized Controlled Trial (RCT), with an evidence-based level only slightly inferior to that of RCT. MR randomly assigns alleles during gamete formation, effectively avoiding potential biases, confounders and reverse causal relationships in traditional epidemiological methods, and further analyzing the causal relationship between psychological distress and gastric cancer in this study. East Asia has one of the highest gastric cancer burdens in the world. The prevalence of psychological distress is high in the Japanese population, too. Therefore, this study investigated the causal association between psychological distress and gastric cancer in the Japanese population using MR.

Method: Genetic risk variants / Single-nucleotide polymorphisms (SNPs) were used as instrumental variables to investigate the causal association between psychological distress and gastric cancer using a Two-Sample Mendelian Randomization (TSMR) approach based on the large Japanese population Genome-Wide Association Studies (GWAS) data. Summary GWAS data for psychological distress were obtained from the Direct To Consumer (DTC) genetic testing program of the Japan Health Data Laboratory (N=10330, 3981 cases and 6349 controls), and summary GWAS data for gastric cancer were obtained from Japanese Encyclopedia of Genetic association by Riken (JENGER) (N=202308, 6563 cases and 195745 controls). Subjects'psychological distress status was evaluated online using the The Kessler Psychological Distress Scale (K6). The K6 scale consists of six dimensions: sadness, despair, restlessness or irritability, nervousness, effort to do anything, and worthlessness. The scale assesses the frequency of the above six dimensions' occurrence in the past month and scores them: Never (0), Not very often (1), Some of the time (2), Most of the time (3), All the time (4). The final K6 scale score is the sum of the scores of the above six dimensions. Subjects with K6 scale scores in the range of 5-24 were determined to be in the psychologically distressed group, and subjects with K6 scale scores in the range of 0-4 were determined to be in the non-psychologically distressed group, while subjects with a history of major depressive disorder were included in the psychologically distressed group. Screening of instrumental variables was performed according to the instrumental

variable hypotheses: (i) SNPs are strongly associated with psychological distress; (ii) SNPs are independent of confounders of gastric cancer and psychological distress; and (iii) SNPs can only influence gastric cancer through psychological distress. Inverse-Variance Weighted (IVW) was used as the main causal effect analysis, and MR-Egger regression, Weighted Median Estimator (WME), Penalized Weighted Median (PWM), and Weighted Mode (WM) as the reference causal effect analysis. Strict quality control was performed on the GWAS data: (i) SNPs with low Minor Allele Frequency (MAF) (MAF < 0.01) were excluded; (ii) SNPs that did not qualify for Hardy_x0002_Weinberg equilibrium thresholds were excluded ($P < 1.0\times10^{-6}$); (iii) SNPs with low call rates were excluded (call rate < 0.95). Sensitivity analysis was performed using leave-one-out analysis; horizontal pleiotropy test was performed using MR-Egger intercept and MR-PRESSO; and heterogeneity test was performed using Cochran's Q test.

Results： According to the instrumental variable hypotheses, five SNPs associated with psychological distress were selected as instrumental variables (rs10145269 、 rs11752111 、 rs6073833 、 rs7634143 、 rs9384356). The result of the IVW (fixed-effects) was OR=1.331 (95%CI:1.035-1.713; β=0.286; P=0.026), indicating a causal association between psychological distress and gastric cancer, with psychological distress increasing the risk of gastric cancer. The result of the IVW (random-effects) was OR=1.331 (95%CI:1.011-1.754; β=0.286; P=0.042). The result of the MR-Egger regression was OR=1.558 (95%CI:0.283-8.565; β=0.443; P=0.646). The result of the WME was OR=1.363 (95%CI:0.879-2.114; β=0.309; P=0.167).The result of the PWM was OR=1.363 (95%CI:0.737-2.519; β=0.309; P=0.324). The result of the MW was OR=1.613 (95%CI:0.867-3.000; β=0.478; P=0.206). Except for IVW, the results of the other MR methods were not significant, but their directions of effects were consistent with the IVW methods. Sensitivity analysis indicated stable results; the MR-Egger intercept (P=0.866) and MR-PRESSO (P=0.462) indicated no horizontal pleiotropy; the Cochran's Q test indicated no heterogeneity(MR-Egger: P=0.193; IVW: P=0.331).

Conclusion: In the Japanese population, causal association was found between psychological distress and gastric cancer, and psychological distress increased the risk of gastric cancer. Early screening and intervention for psychological distress in the population should be strengthened in the future to reduce the incidence of gastric cancer and alleviate the heavy gastric cancer burden.

Key Words： Psychological distress; Gastric cancer; Mendelian randomization; Causal inference

36. Association of HPV16/18 genotype infection with the Silva Pattern classification system in HPV_x0002_associated Endocervical adenocarcinomas

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Background: Cervical cancer (CC) poses a heavy cancer burden for women worldwide. The two predominant histological categories of CC are Squamous cell carcinoma (SCC) and Endocervical adenocarcinoma (ECA) while the morbidity of SCC has been declining and the morbidity of ECA has been increasing in some developed countries. Treatment and management of ECA are primarily dependent on the size of the tumor, depth of invasion, and FIGO (The International Federation of Gynecology and Obstetrics) stage. However, the FIGO stage has limitations in the clinical management of patients with ECA. A new 3-tier pattern system (Silva pattern) for ECA was recently presented, which was associated with tumor metastasis and recurrence. This system classifies ECA into pattern A, pattern B, and pattern C based on the degree of destructive stromal invasion, which is a more reliable tool for clinicians in assessing the prognosis of patients with ECA. HPV-associated adenocarcinoma (HPVA) is the most common histological category of ECA and persistent High-Risk Human papillomavirus (HR-HPV) infection is an essential risk factor for HPVA. Among HR-HPV, HPV16 and 18 are the most prevalent genotypes responsible for CC. However, there have been no studies on the association between HPV16/18 genotype and Silva patterns, and whether different HPV genotypes have an impact on the Silva pattern remains unreported.

Method: A total of 240 surgical specimens with HPVA from nine tertiary central hospitals across China between 2005 and 2011 were diagnosed and performed the Silva pattern classification according to the WHO classification of female genital tract cancers in 2020. The hospitals were located in seven different geographical regions of China, including the North, Northeast, Northwest, Central, East, Southwest, and West. The pathology technicians at the Cancer Institute/Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College

(CHCAMS) have sectioned all paraffin-embedded tissue blocks. The first and last 4-μm paraffin sections were utilized for H&E staining, while two middle 4-μm sections were used for immunohistochemical PR and p16 staining. An additional two middle 4-μm sections were used forimmunohistochemical backup. For HPV DNA genotyping detection, three 8-μm sections were used. HPV DNA was detected using the SPF10-DEIA-LiPA25 assay in all specimens. 15 HPV genotypes in 226 HPV DNA-positive specimens were detected using the WTS-PCR assay, including 12 HR-HPV types (HPV16, 18, 31, 35, 39, 45, 51, 52, 56, 58, 59, and 66) and 3 low-risk HPV types (HPV11, 34, and 44). An attribution algorithm was used to calculate the attribution rate of HPV16/18. Pathologists from CHCAMS re-evaluated all hematoxylin and eosin (H&E), as well as p16 and PR immunostaining sections of the cases.

Results: The mean age of all patients with HPVA was 44.4 years, ranging from 26-76 years. A total of 226 (94.2%) patients were positive for HPV DNA, and 14 (5.8%) were negative. There were 179 patients (77.8%) who were in FIGO stage I, and 51 patients (22.2%) were in stage II or above. Out of all HPVA cases, 29 patients (12.1%, 29/240) were found to have tumors with Silva pattern A, 122 (50.8%, 122/240) had pattern B tumors, and 89 (37.1%, 89/240) had pattern C (representing the worst tumors), which showed that Silva pattern B was the most prevalent. The attribution of HPV16 in Silva pattern A, B, and C was 58.0%, 51.7%, and 33.8%, respectively (β = -0.271, P=0.123). Similarly, the attribution of HPV18 was found to be 29.8%, 39.7%, and 49.5% in pattern A, B, and C, respectively. Notably, there was a statistically significant linear relationship between the prevalence of HPV18 and the Silva pattern (β = 0.099, P=0.002). The co-positive rates of HPV and p16 in all HPVA patients were 80.4%, with the highest positivity in pattern A (89.7%), followed by pattern B (81.1%), and the lowest HPV/p16 positivity was observed in pattern C (76.4%). The co_x0002_positive rate of HPV and p16 decreased with increasing destructive stromal invasion (from pattern A to C). Only two out of 240 cases of HPVA showed positive expression of PR. A total of 183 cases of usual-type adenocarcinoma were identified, with 95 patients (51.9%) having pattern B tumors, 59 patients (32.2%) having pattern C tumors, and only 29 cases (15.8%) having pattern A tumors. Among cases of ISMC (invasive stratified mucin-producing carcinoma), 57.1% (16/28) were pattern C, and 42.9% (12/28) were pattern B. Of the 13 cases of mucinous NOS (not otherwise specified), 50% were pattern C, and all others were pattern B. The distribution of the Silva pattern in categories of HPVA was statistically

significant (P=0.002). The multivariable analysis revealed that the tumor embolus, FIGO stage, and invasive depth were associated with Silva patterns (P < 0.05) .

Conclusion: 1. HPV18 infection in patients with endocervical adenocarcinoma is associated with more invasive morphological characteristics compared to HPV16 infection; 2. Patients with HPV and p16-negative adenocarcinomas exhibit worse morphological behavior; 3. The distribution of Silva pattern varies among different pathological categories of HPVA.

Key Words： Endocervical adenocarcinoma, Silva pattern, Human papillomavirus, Attribution

37. 基于 DIA 的蛋白组学技术探究肺腺癌骨转移的发病机制

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目的：从分子水平探究肺腺癌骨转移血清蛋白组学的变化，为肺腺癌骨转移的发生,发展机制研究及分子靶向药物的研发提供理论依据。

方法：基于高分辨质谱的全扫描数据非依赖采集（Data Independent Acquisition，DIA）定量蛋白质组学技术，比较肺腺癌骨转移患者与肺腺癌非骨转移患者蛋白种类和浓度的差异。而后根据这些差异蛋白进行生物信息学分析：GO 功能及富集分析,Pathway 代谢通路富集和蛋白-蛋白相互作用网络（PPI） 分析。

结果：在待测血清样品中共检测到 2585 个蛋白。通过对比 6 个肺腺癌骨转移患者与 6 个肺腺癌非骨转移患者血清样品的蛋白图谱特征，发现共有 18 个蛋白具有显著性差异。GO 富集分析结果表明 biological process (BP),cellular component (CC) 和 molecular function (MF) 三个本体中分别有 157 个,130 个和 30 个显著性差异的条目（GO terms）。KEGG pathway 分析提示这些差异蛋白显著地富集在 Proteoglycans in cancer、TGF-beta signaling pathway、NOD-like receptor signaling pathway 、Transcriptional misregulation in cancer 等代谢通路上。进一步的 PPI 分析表明 20 条代谢通路和 7 个蛋白相互关联,具体包括癌症相关的代谢途径 MAPK signaling pathway 、cGMP-PKG signaling pathway 、Thyroid hormone signaling pathway 等，以及与癌症发生密切关联的的蛋白 VCAN、DCN1、PSMA2 等。

结论：一些潜在的生物标志物可能用于早期诊断肺腺癌骨转移，同时 TGF-β信号通路、NOD 样受体信号通路在肺腺癌骨转移的发生起到了重要作用。

关键字：DIA；蛋白组学；肺腺癌；MAPK；骨转移

38. ATP1A1、TINK 及 SPTBN1 作为肺腺癌骨转移的生物标志物

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肺癌是我国乃至全球癌症相关死亡的主要原因，发病率逐年上升。非小细胞肺癌(NSCLC) 占所有肺癌的 80% 以上。NSCLC 可进一步细分为腺癌（AD），鳞状细胞癌（SQCC）和大细胞癌（LCC），分别约占所有肺癌病例的 40%、25%-30%和 5-10% 。肺癌（LC）相关死亡的主要因素是远处转移，这是一种不可避免的肺癌生长结果。大多数肺癌在脑（15-43%）和肝（33-40%）内转移，并且各种临床肺癌亚型具有特定的有利转移部位。特别是，脑转移和肝转移在 SCLC 患者中更为常见，而骨转移在 NSCLC 患者中更为常见。研究表明，50%的肺癌患者在尸检中也发现了骨转移。肺癌骨转移患者的中位生存时间仅为 6 个月至 10 个月，治疗后 1 年的生存率仅为 40%-50%。虽然在转移性 NSCLC 的整体管理方面取得了相当大的进展，但骨转移仍然是发病率、死亡率和生活质量下降的常见原因。血清蛋白标志物检测是液体活检，具有创伤小，易采集、便于动态监测，可以早期提示肿瘤微环境的变化等优点。本研究运用深度血液 DIA 蛋白质组学技术探寻在肺腺癌组与肺腺癌骨转移组之间的差异表达的血清蛋白，旨在发现新型蛋白标志物，为肺腺癌骨转移的早期筛查诊断及治疗提供新的思路。

方法:采用 4D-DIA 蛋白质组学技术，纳入 6 例肺腺癌（lung adenocarcinoma，LUAD）及 6 例肺腺癌骨转移（lung adenocarcinoma bone metastasis，LUADBM)患者进行血清蛋白质组学分析，筛选出上调差异蛋白 ATP1A1、TINK 及下调差异蛋白 SPTBN1; 收集我院肺腺癌患者 181 名（非骨转移 100 名，骨转移 81 名）空腹血，通过酶联免疫吸附测定（ELISA）检测 ATP1A1、TINK 及 SPTBN1 的表达。

结果：ATP1A1、TINK 及 SPTBN1 表达在两组中有显著差异；ATP1A1、TINK 在肺腺癌骨转移患者中表达上调（$P<0.05$），SPTBN1 在肺腺癌骨转移患者中表达下调（$P<0.05$）。

结论：ATP1A1、TINK 及 SPTBN1 可以作为肺腺癌骨转移非侵入性诊断和早期诊断的生物标志物，具有良好的诊断效能，为肺腺癌骨转移的早期诊断及治疗提供新线索。

关键字：肺腺癌；骨转移；ATP1A1；TINK；SPTBN1；早期诊断

39. 血清外泌体 NSD1 作为肺腺癌骨转移的新型生物标志物

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目的：肺癌是一种严重的恶性疾病，85%的肺癌病例被归类为非小细胞肺癌（Non-small cell lung cancer，NSCLC），其中肺腺癌约占肺癌的 40%，是转移能力最强、病死率最高的亚型。骨组织是除肺、肝外转移最多的部位，是人体内血行转移最重要的部位之一。在 NSCLC 的发展过程中约有 30%~40%的患者被诊断骨转移，转移部位包括中轴骨及其他部位，而骨骼受累可能是严重并发症的来源，也称为骨骼相关事件，包括病理性骨折、恶性高钙血症和脊髓压迫等。这些不良症状在增加患者家庭经济负担的同时，也严重影响患者身心健康，一旦患者在伴癌生存的期间发现骨转移，将大大降低患者生存时间。研究表明，即使发现及时，给予相应的抑制骨转移的药物，患者的 1 年生存率也仅有 40%~50%。骨转移在肺癌中具有重要的临床意义，但其病理机制尚不清楚。因此，将肺腺癌骨转移患者作为核心研究对象，深入研究骨转移的发病机制，系统筛选早期诊断和潜在治疗靶点，必将为临床研究骨转移提供重要依据，为促进临床生存和预后提供新的认识。

方法：选取经电子支气管镜或经 CT 引导下肺穿刺活检取得病理标本，后由我院病理科明确诊断肺腺癌的患者（未进行任何抗肿瘤治疗）8 例，均已行全身骨显像检查，其中有骨转移患者作为实验组（A 组，5 例），无骨转移患者作为对照组（B 组，3 例）。首先对收集的血清进行统一预处理，采用试剂盒法提取外泌体，透射电子显微镜（Transmission Electron Microscope，TEM）及纳米粒子跟踪分析（Nanoparticles Tracking Analysis，NTA）鉴定外泌体。采用基于离子淌度质谱的 4D Label-free 对提取鉴定后的外泌体蛋白质进行质谱分析，并对数据进行分析。根据测序结果，将 Fold change≥2.0 作为判断标准且依据 $p<0.05$）将筛选出差异明显的基因进行验证，采用实时荧光定量 PCR 的方法对 基因的表达量进行检测；

结果：对 100 名肺腺癌患者及 81 名肺腺癌骨转移患者血清外泌体 NSD1 表达量 检测后发现，肺腺癌骨转移患者血清外泌体中的 NSD1 表达量明显升高 （$p<0.05$）；通过 ROC

曲线评估该分子的诊断效能发现：AUC 曲线下面积为 0.7133，敏感度为 70.9%，特异度为 62.7%(95% CI: 0.655-0.721)。统计结果显示 NSD1 表达水平与肺腺癌骨转移密切相关。

结论：血清外泌体 NSD1 可作为肺癌骨转移早期诊断的生物标志物，为肺腺癌骨转移的早期筛查、诊断提供了新的思路，具有较好的应用前景。

关键字：肺腺癌；外泌体；骨转移；NSD1；早期筛查

40. A novel CSN5/CRT O-GlcNAc/ER stress regulatory axis in platinum resistance of epithelial ovarian cancer

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Background ： High levels of COP9 signalosome subunit 5 (CSN5) in epithelial ovarian cancer (EOC) are associated with poor prognosis and are implicated in mediating platinum resistance in EOC cells. The underlying mechanisms, however, remained undefined. This study aimed to elucidate the molecular process and identify potential therapeutic targets.

Methods ： RNA-sequencing was used to investigate differentially expressed genes between platinum-resistant EOC cells with CSN5 knockdown and controls. O-GlcNAc proteomics were employed to identify critical modulators downstream of CSN5. The omics findings were confirmed through qRT-PCR and immunoblotting. In vitro and in vivo experiments assessed the sensitivity of resistant EOCs to platinum.

Results ： We demonstrated a correlation between aberrant O-GlcNAc and endoplasmic reticulum (ER) stress disequilibrium in CSN5-mediated platinum resistance of EOC. Genetic or pharmacologic inhibition of CSN5 led to tumor regression and surmounted the intrinsic EOC resistance to platinum both in vitro and in vivo. Integration of RNA-sequencing and O-GlcNAc proteomics pinpointed calreticulin (CRT) as a potential target of aberrant O-GlcNAc modification. CSN5 upregulated O-GlcNAc-CRT at T346 to inhibit ER stress-induced cell death. Blocking T346 O-GlcNAc-CRT through CSN5 deficiency or T346A mutation resulted in Ca2+ disturbances, followed by ER stress overactivation, mitochondrial dysfunction, and ultimately cell apoptosis.

Conclusion ： This study reveals that CSN5-mediated aberrant O-GlcNAc-CRT acts as a crucial ER stress checkpoint, governing cell fate response to stress, and emphasizes an unrecognized role for the CSN5/CRT O-GlcNAc/ER stress axis in platinum resistance of EOC.

Key Words：COP9 signalosome subunit 5; Calreticulin O-GlcNAcylation; Endoplasmic reticulum stress; Ovarian cancer; Platinum resistance

41. Bioinformatics Analysis and Experimental Validation of m3C RNA Methylation Regulators in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common malignant tumors of the digestive system; however, its etiology remains unclear. Clarifying its pathogenesis is essential to improve the prognosis of patients with HCC. Studies have shown that the 3-methylcytidine (m3C) methylation regulator is closely related to the occurrence and development of tumors and has an excellent potential prognostic value. In the present study, 486 patients with HCC were collected from TCGA and GEO databases, and 16 patients with HCC and adjacent tissues in our hospital were collected. The expression level, mutation of six m3C regulators, and their relationship with the prognosis of patients were comprehensively analyzed, and an m3C scoring system was simultaneously constructed for quantifying m3C modifications. The expression of m3C regulators in HCC was generally different, and most were related to patient prognosis. We further determined two different m3C modification modes in HCC samples. We found differences in clinical characteristics and total survival times between different modification classifications, which further proved that patients with higher m3C scores had longer survival times and better clinical characteristics. This study explored the genetic variation and prognostic value of m3C methylation regulators in HCC and designed a scoring system to predict the prognosis of HCC, providing help for the treatment and prognosis of HCC patients.

Key Words：bioinformatics; m3C methylation; hepatocellular carcinoma; clinical prognosis

42. miR-30e-5p 在心肌梗死发病中的作用机制研究

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随着研究技术的进步以及设备的逐渐完善，越来越多的研究表明，microRNA 作为心肌梗死发病影响因素的一个关键标志物和靶点的结论逐步得到验证，不仅仅是在微观分子方面得到验证，在宏观实验对象方也得到验证。大量的生物学信息分析表明，不发生心肌梗死的实验对象中 miR-30e-5p 表达明显低于发生心肌梗死的对象，因此可以在很大程度上认为 miR-30e-5p 参与了心肌梗死的发生发展。心肌梗死的发病病因主要与脂质沉积有关，随着社会生活水平的逐步提高，其高致病性和高发病率对于人群的威胁逐渐增加，尽管医疗技术的提高已经在发病前和发病后做到了预防和治疗，但是由于多种 miR 在发病中的作用，这使得心肌梗死的发生逐步出现“瀑布效应”，两者相互影响，相互作用。心肌梗死的形成是经过一个动态变化而逐渐形成的，它的主要病理变化是心脏的供血血管高度狭窄和血管急性闭塞所形成的，主要病因是冠状动脉粥样硬化和外围冠脉栓塞炎症，而 microRNA 作为一种小的非编码 RNA，在转录后抑制基因表达，在调节疾病进展的关键机制中，参与其中。因此，通过新的 miRNA 靶向治疗手段以及方式不仅抑制为 AMI 的发病，也可以诊断和治疗 AMI。miR-30e-5p 作为 microRNA 的一种，在 AMI 中发挥着重要作用。本综述在综合国内外多篇文献的基础之上，通过对比以及归纳分析，将 miR-30e-5p 在心肌梗死发病中的作用进行阐述，以期为 AMI 的诊断、治疗以及预防开辟新的手段。

关键字：miR-30e-5p，心肌梗死，发病机制，影响因素

43. c-Kit 在临床常见癌症中的研究进展

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目的：肿瘤进展与受体酪氨酸激酶（RTKs）的活性及其细胞内信号转导途径密切相关。c-kit 是其中一种 RTKs，它的几种突变异构体已被证实与胃肠道间质瘤、急性髓系白血病和黑色素瘤等人类恶性肿瘤密切相关。

方法：通过查阅大量文献，综述 c-Kit 在癌症中的研究进展，着重描述 c-Kit 的结构、功能、参与细胞内不同的信号转导，c-Kit 在癌症中的病理生理学作用及 c-Kit 阳性肿瘤的靶向治疗。

结果：原癌基因 c-Kit 定位于人类染色体 4q11-12，由于其与配体干细胞因子（SCF）结合，因此也称为 SCF 受体。c-Kit 是由疏水性跨膜、细胞外配体结合结构域和细胞质结构域三部分组成。在生理条件下，c-Kit 与 SCF 结合后激活下游的信号通路，继而可调节细胞增殖、存活和迁移等过程，对于维持机体多个器官及系统的功能具有重要意义。c-Kit 可通过不同的细胞内通路参与信号转导。例如，在成纤维细胞和造血细胞中，c-Kit 通过 PI3K 通路促进细胞存活与增殖；在造血细胞中，通过 JAK/STAT 通路激活各个基因转录；在造血祖细胞中，通过 Src 家族激酶通路诱导细胞的趋化与增殖；在造血祖细胞中，通过 MAPK 通路加强基因转录和分化。目前，多项研究已建立起 c-Kit 功能失调与不同类型癌症的关系，在所研究的 59 种主要癌症类型中，有 2.86%存在 c-Kit 突变。功能获得性 c- kit 突变已被发现代表多种癌症发展中的致癌驱动事件，包括胃肠道间质瘤、黑色素瘤某些亚型、急性髓系白血病、精原细胞瘤、甲状腺癌和乳腺癌等。此外，c-Kit 在癌症形成和癌症进展的许多机制调节中发挥着重要作用。为了靶向和抑制失调的 c-Kit，各类小分子抑制剂被广泛研发，其中包括甲磺酸伊马替尼、舒尼替尼、瑞格非尼、利培替尼和阿瓦普利替尼等。为了克服小分子抑制剂治疗某些野生型或突变型 c-Kit 阳性癌症中产生的耐药性，单克隆抗体（mAb）继而被研发，如抗 D4 mAb，还有 LOP628 和 NN2101-DM1 两种人源化抗 c-Kit 抗体。结论 c-kit 的激活突变、扩增或过度表达诱导了许多人类恶性肿瘤的发生和进展，其中参与的信号传导各有不同。目前已研制出的各类小分子抑制剂和 mAb 正被逐步投入临床使用，用于治疗各种 c-Kit 阳性的肿瘤。未来期待更多靶向 c-Kit 阳性肿瘤的治疗药物被研发出。

关键字：c-Kit，干细胞因子受体，癌症，信号转导，病理机制，靶向治疗

44. Targeting gut microbial nitrogen recycling and cellular uptake of ammonium to improve bortezomib resistance in multiple myeloma

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Background: Gut microbe alterations are closely related to the tumorigenesis and development of cancers. However, the relationship between gut microbe and drug resistance of multiple myeloma (MM) has not been reported.

Methods： The feces and serum samples of healthy donors (HD), newly diagnosed MM patients (ND) and relapsed MM patients (RM) come from multiple clinical institutions (License number:

202305359). The 5TGM1 MM mouse models were prepared to examine the effect of nitrogen-recycling bacteria on MM in vivo (License number: D2022058).

Results： To probe the difference in gut microbiome between HD and MM patients, we performed shotgun metagenomic sequencing of fecal samples from a cohort of HD, ND and RM, and found that ND and RM show a significantly higher alpha diversity and *Citrobacter freundii* (CFr) was significantly enriched in RM. Owing to CFr is a nitrogen-recycling bacteria, we detected the concentration of NH_4^+ and urea in MM patient's feces and serum, and found that NH_4^+ increased significantly in RM, and the relative abundance of CFr was positively correlated with NH_4^+ in feces and serum of RM. Subsequently, we confirmed that NH_4^+ can promote the drug resistance of MM cells to bortezomib (BTZ) through in vitro and in vivo experiments. Meanwhile, we constructed a CFr deaminase gene deletion (CFr-KO) strain, and found that CFr produces a large fraction of NH_4^+ by expressing deaminases, and NH_4^+ molecules produced in the intestinal tract subsequently enter the circulation and eventually travel to the bone marrow, causing MM cells to become resistant to BTZ. Finally, we treated MM cells with NH_4^+ and detected the expression of resistance related protein. It was found that NH_4^+ can upregulate the expression of NEK2, and NH_4^+ can increase the acetylation of NEK2 and reduce its ubiquitin degradation, thus maintaining its protein stability.

SLC12A2 as the key transmembrane transporter that mediates the uptake of NH_4^+ by MM cells, we discovered that furosemide sodium (Fus) can downregulate the expression of SLC12A2 in MM cells. Fus inhibits NH_4^+ uptake in MM cells and reduces the BTZ resistance-promoting effects of NH_4^+ supplementation in vitro and in vivo. Next, we analyzed the effect of Fus treatment in MM patients, finding that the MM patients treated with Fus achieved longer progression-free survival and higher curative effect scores. Finally, to explore additional strategies for tackling drug resistance in MM, we performed single *Clostridium butyricum* (CBu) and triple probiotic (TPro) transplantation by gavage, and we found that in keeping with the effect of CBu transplantation, TPro, an CFDA-approved clinical drug, exhibited consistent efficacy in alleviating BTZ resistance.

Conclusions： In summary, we identify, for the first time, CFr and NH_4^+ as key modulators of MM relapse, unveil novel molecular mechanisms for drug resistance in MM patients, and provide new therapeutic strategies for the intervention of MM progression and drug resistance.

Key Words：Multiple myeloma; Intestinal nitrogen-recycling bacteria; Ammonium; NEK2；Drug resistance

45. 不同年龄下 CA125 筛查卵巢癌最佳切点值探讨及验证

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目的：虽然 CA125 广泛用于筛查卵巢癌，但多数研究针对所有人群采用相同的 CA125 诊断切点值进行筛查。相对有限的研究探索并验证不同年龄下 CA125 筛查卵巢癌的最佳切点值。

方法：基于天津市常见恶性肿瘤联合筛查项目人群及同期天津市常见恶性肿瘤病例队列人群，选取 2017 年以来基线未患癌且接受 CA125 检测的女性，通过多渠道随访匹配获得卵巢癌结局。采用 Logistic 回归下的 ROC 曲线和曲线下面积（AUC）评价 CA125 筛查卵巢癌的总体准确性及最佳切点值。同时分别探讨<60 岁，60-69 岁及≥70 岁不同年龄亚组的 CA125 筛查准确性及最佳切点值，以及相应年龄别特异性 CA125 筛查切点值下，卵巢癌筛查的灵敏度和特异度。采用 Bootstrap 重抽样方法进行内部验证，并采用 PLCO 试验人群进行外部验证。

结果：共计 41620 名女性最终纳入研究，中位随访 1.22 年后，共计发现 413 例卵巢癌病例。CA125 筛查卵巢癌的总体 AUC 为 83.0%，最佳切点值为 26.8U/mL。根据年龄分组后，<60 岁，60-69 岁及≥70 岁女性 CA125 筛查卵巢癌的 AUC 分别为 78.8%，88.6%，89.1%，最佳切点值分别为 26.8U/mL，20.3U/mL 和 28.0U/mL。基于年龄别特异性的 CA125 筛查切点值，阳性人群相较于阴性人群，卵巢癌风险的 OR(95%CI)分别为 11.18(8.54-14.63)，39.26(23.85-64.62)，25.00(12.85-48.61)，相应灵敏度分别为 67.1%，82.9%，81.4%，特异度分别为 84.6%，89.0%，85.1%。内部及外部验证均得到类似的结果及趋势。

结论：为提高筛查效果，减少卵巢癌漏诊，推荐采用年龄别特异性的 CA125 筛查切点值在一般风险人群进行卵巢癌筛查。

关键字：卵巢癌；糖类抗原 125；筛查；年龄别筛查切点值

46. DMGDH 与 CUL4A 相互作用调控 P53 稳定性在前列腺癌发展中的作用研究

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研究目的：本研究旨在探究 DMGDH 在前列腺癌发生和发展中的作用机制，尤其是其与 CUL4A 之间的相互作用及其对 P53 蛋白稳定性的影响。

材料与方法：通过 qRT-PCR 方法分析了前列腺癌患者组织和 PC3 前列腺癌细胞中 DMGDH 的表达。利用慢病毒转染法在 PC3 细胞中过表达 DMGDH，并通过 qRT-PCR 和 Western blot 进行验证。采用 CCK8 和 Transwell 实验评估 DMGDH 对 PC3 细胞增殖和侵袭能力的影响，同时应用流式细胞术检测了细胞凋亡率。在探究 DMGDH 的分子机制时，首先通过 Western blot 分析确认了 DMGDH 对 P53 蛋白表达量的影响，并进行了 CHX（放线菌酮）实验以评估 P53 蛋白的稳定性。采用泛素化实验，包括转染 HA-Ub 质粒和使用蛋白酶体抑制剂 MG132，来检测 P53 蛋白的泛素化程度。最终，通过共沉淀实验来探讨 DMGDH 与 CUL4A 之间的相互作用。

结果：DMGDH 在前列腺癌组织及 PC3 细胞中的表达显著高于正常对照组。在过表达 DMGDH 的 PC3 细胞中，观察到细胞增殖和侵袭能力的显著提升以及细胞凋亡率的降低，暗示 DMGDH 在前列腺癌的发展中可能起到促进作用。在分子层面上，过表达 DMGDH 显著降低了 PC3 细胞中 P53 蛋白表达水平。CHX 实验结果表明，DMGDH 过表达显著缩短了 P53 蛋白的半衰期。泛素化实验揭示了在过表达 DMGDH 的细胞中 P53 的泛素化水平增加，表明 DMGDH 可能影响 P53 的稳定性和降解。免疫共沉淀实验结果进一步证实了 DMGDH 与 CUL4A 存在相互作用，后者可直接介导 P53 的泛素化水平。

结论：本研究确认了 DMGDH 在前列腺癌的发展中扮演促癌的角色，并揭示了其通过与 CUL4A 相互作用，加速 p53 泛素化进程，影响 P53 蛋白的稳定性的潜在机制。这些发现强调了 DMGDH 在前列腺癌病理学中的重要性，可能使其成为潜在的预测标志。这为前列腺癌的分子病理学研究和潜在治疗策略提供了新的视角，为进一步探索针对 DMGDH 的治疗方法提供了基础。

关键字：DMGDH；CUL4A；前列腺癌；泛素化

47. 芦荟大黄素通过抑制中性粒细胞胞外诱捕网的形成抑制结肠癌的发展

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研究目的：本研究旨在探究芦荟大黄素（AE）对结肠癌发生发展的作用及相关分子机制，评估 AE 在结肠癌治疗中的潜在应用。

材料与方法：本研究使用了 50 只 C57/B6 小鼠，将其随机分为 5 组：对照组、模型组、低剂量治疗组（1.5mg/kg）、中剂量治疗组（3mg/kg）和高剂量治疗组（4.5mg/kg）。为了建立结肠癌模型，除对照组外，其他小鼠均通过葡聚糖硫酸钠（DSS）联合偶氮甲烷（AOM）处理。随后，对模型小鼠实施 AE 的药物干预。实验结束后，记录并分析小鼠的结肠肿瘤数量和结肠长度。同时，通过 HE 染色进行结肠组织的病理学评估，利用免疫组化、Western blot 和 ELISA 实验方法检测中性粒细胞胞外诱捕网（NETs）相关标志物蛋白（如 PAD4 和 H3cit）的表达变化。此外，在体外实验中，从小鼠脾脏分离中性粒细胞，并在 AE 的共孵育下评估其对 NETs 形成的影响，以及对结肠癌细胞系 CT26 增殖和迁移的作用。

结果：在模型组中，小鼠结肠肿瘤数量明显增加，结肠长度缩短，并且结肠组织出现了显著的病理损伤。此外，模型组小鼠的结肠和外周血中 PAD4 和 H3cit 蛋白的表达水平显著升高，暗示 NETs 的形成增加。相比之下，在接受 AE 治疗的各剂量组中，小鼠的结肠肿瘤数量随着药物剂量的增加而减少，结肠长度相应增加，结肠病理损伤程度逐渐减轻。同时，结肠和外周血中 PAD4 和 H3cit 蛋白的表达水平随着 AE 剂量的增加而降低，表明 NETs 的形成受到抑制。在体外实验中，NETs 被证实可以促进 CT26 细胞的增殖和迁移，而 AE 能够显著抑制 NETs 的形成，并进一步抑制 NETs 对 CT26 细胞增殖和迁移能力的促进作用。

结论：AE 通过抑制 NETs 的形成有效地抑制了结肠癌的发展，该发现不仅证明了 AE 在结肠癌治疗中的潜在应用价值，也为基于 NETs 抑制的新型结肠癌治疗策略的开发提供了重要的科学依据。

关键字：芦荟大黄素、结肠癌、中性粒细胞胞外诱捕网、增殖和迁移

48. 去氢松香酸通过抑制 IMPDH2 促进 PPARγ表达抑制肝癌细胞增殖迁移和侵袭

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研究目的：本研究旨在探究去氢松香酸在肝癌细胞增殖、迁移和侵袭中的作用及其机制，特别是其对肝癌细胞中 IMPDH2 和 PPARγ信号通路的影响。

材料与方法：本研究采用 CCK8 法来评估去氢松香酸对 HepG2 和 HCCLM3 两种肝癌细胞增殖的抑制效果，通过 Transwell 实验评估其对肝癌细胞迁移和侵袭的影响，利用流式细胞术检测其诱导的肝癌细胞凋亡情况。通过 qRT-PCR 和 Western blot 技术检测了去氢松香酸对 IMPDH2 和 PPARγ的表达水平的影响。为进一步明确 IMPDH2 和 PPARγ在去氢松香酸作用机制中的作用，本研究在肝癌细胞中进行了 IMPDH2 的过表达实验，并与 PPARγ激动剂共孵育，随后观察和分析了这种条件下肝癌细胞增殖、迁移、侵袭及凋亡情况的变化。

结果：去氢松香酸呈剂量依赖性地抑制 HepG2 和 HCCLM3 肝癌细胞的增殖、迁移和侵袭，并能够诱导细胞凋亡。此外，去氢松香酸降低了 IMPDH2 的表达，并提高了 PPARγ的表达水平。过表达 IMPDH2 的实验结果显示，IMPDH2 的增加部分抵消了去氢松香酸的抑制效果，而 PPARγ的激活则恢复并增强了去氢松香酸的抗肝癌效果。

结论：去氢松香酸能通过抑制 IMPDH2 并激活 PPARγ来抑制肝癌细胞的增殖、迁移和侵袭，以及诱导细胞凋亡。这一发现不仅展示了去氢松香酸作为肝癌治疗药物的潜力，而且为 IMPDH2 和 PPARγ作为肝癌治疗的潜在靶点提供了有力的实验依据。

关键字：去氢松香酸、肝癌、凋亡、肌苷一磷酸脱氢酶、过氧化物酶体增殖物激活受体

49. 组蛋白甲基化及乙酰化修饰在肺癌发病机制的研究进展

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原发性肺癌是我国最常见的恶性肿瘤之一。2015 年约有 787,000 例新发病例，占所有恶性肿瘤发病率的 20.0%。而组蛋白修饰，尤其是甲基化和乙酰化在肺癌的发生和发展中起着至关重要的作用。这些修饰通过改变组蛋白与 DNA 的结合，影响染色质和基因表达的

状态来参与肺癌的发生发展，包括参与调控肺癌发生，促进癌细胞转移，促进肿瘤细胞增殖，促进上皮-间充质的转化等具有重要意义，明确组蛋白甲基化修饰及乙酰化修饰的作用机制和靶点，能有针对地选取组蛋白甲基化修饰以及组蛋白乙酰化修饰的抑制剂，有望为肺癌的诊断与治疗提供新突破。

关键字：肺癌；组蛋白甲基化修饰；组蛋白去甲基化修饰；组蛋白乙酰化修 饰；组蛋白去乙酰化修饰；

50. 化疗后血清 CA125 下降速率与晚期卵巢癌铂耐药的相关性分析

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目的：探讨化疗后血清 CA125 的下降速率在预测晚期卵巢癌患者铂耐药发生中的临床价值。

方法：选取 2018 年 1 月至 2022 年 12 月于我院妇科收治的 150 例初治晚期卵巢癌患者按照复发情况分为铂敏感复发组、铂耐药复发组及缓解组，监测术前及各疗程化疗血清 CA125 水平，计算血清 CA125 的半衰期、转阴时间及下降比率，分析与铂耐药发生的相关性。

结果：铂耐药复发组患者术后化疗后 CA125 半衰期显著长于铂敏感复发组及缓解组（P<0.05）。铂耐药复发组患者术后化疗的总疗程数、至 CA125 转阴的化疗疗程数显著多于铂敏感复发组及缓解组（P<0.05），而三组在 CA125 转阴后追加的化疗疗程数无显著差异（P>0.05）。术后各疗程化疗 CA125 的水平在铂耐药复发组显著高于铂敏感复发组及缓解组（P<0.05）。三组化疗后 CA125 下降比率均有差异，铂耐药复发组患者在化疗 1 疗程后 CA125 下降比率显著低于铂敏感复发组及缓解组。

结论：化疗后血清 CA125 的下降速率慢，发生铂耐药的风险高。监测各疗程化疗后 CA125 的下降情况可对预测铂耐药的发生有一定的指导意义。

关键字：CA125 下降速率；卵巢癌；铂耐药

51. High copy number of mitochondrial DNA (mtDNA) predicts good prognosis in ovarian cancer patients

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Background ： Mitochondrial DNA copy number (mtDNA-CN) were associated with the prognosis of many types of cancer patients. However, whether mtDNA-CN in formalin-fixed paraffin-embedded (FFPE) contribute to clinical outcomes of ovarian cancer (OV) remains to be determined.

Methods： First, the mtDNA-CN of FFPE from 150 OV patients was measured using next-generation sequencing (NGS). Then, we evaluated the association between mtDNA-CN and clinical characteristics. Next, the OV patients were categorized into two groups based on optimal cut-off value of mtDNA-CN that was calculated by the “survival” R package. Last, Kaplan–Meier curves and Cox proportional hazards regression model were applied to investigate the association of mtDNA-CN with overall survival (OS) of patients.

Results： We found mtDNA-CN in FFPE sample of OV were found significantly higher than that in non-OV FFPE sample($P<0.001$). Furthermore, increased mtDNA-CN was significantly negatively associated with FIGO stage($P<0.01$) and survival status ($P<0.05$). Multivariate Cox regression analysis demonstrated that mtDNA-CN was an independent prognostic factor for OS in OV patients (HR:0.30,95% CI:0.09-0.99, $P<0.05$). More importantly, high mtDNA-CN were closely relevant to longer survival in OV patients, so further analysis was mainly in the advanced stage subgroup.

Conclusions： In conclusion, the present study provide the strong evidences that high mtDNA-CN may be a useful good prognostic factor in OV patients.

Key Words： ovarian cancer, mitochondrial DNA copy number, FFPE, prognosis

52. SRT1720 inhibits bladder cancer cell progression by impairing autophagic flux

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Bladder cancer (BC) is the most common cancer of the urinary tract, with poor survival, high recurrence rates, and lacking of targeted drugs. In this study, we constructed a library to screen compounds inhibiting bladder cancer cells growth. Among them, SRT1720 was identified to inhibit bladder cancer cell proliferation in vitro and in vivo. SRT1720 treatment also suppressed bladder cancer cells migration, invasion and induced apoptosis. Mechanism studies shown that SRT1720 promotes autophagosomes accumulation by inducing early-stage autophagy but disturbs the late-stage of autophagy by blocking fusion of autophagosomes and lysosomes. SRT1720 appears to induce autophagy related proteins expression and alter autophagy-related proteins acetlyation to impede the autophagic flux. LAMP2, an important lysosomal associated membrane protein, may mediate SRT1720-inhibited autophagic flux as SRT1720 treatment significantly deacetylated LAMP2 which may influence its activity. Taken together, our results demonstrated that SRT1720 mediated apoptosis and autophagic flux inhibiton may be a novel therapeutic strategy for bladder cancer treatment.

Key Words： Bladder cancer, SRT1720, autophagy, acetylation, lysosome

53. Raltitrexed induces apoptosis through activating ROS-mediated ER stress by impeding HSPA8 expression in prostate cancer cells

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Prostate cancer is the most common malignant tumor in males, which frequently develops into castration-resistant prostate cancer (CRPC). CRPC metastasis is the main reason for its high mortality rate. At present, it lacks effective treatment for patients with CRPC. Raltitrexed (RTX) has been shown to be effective in the treatment of colorectal cancer. However, the effect of RTX on prostate cancer and the underlying mechanism remain unknown. In the current study, we found that RTX could dose-dependently inhibit proliferation, migration, colony formation and induce apoptosis in DU145 and PC-3 cells. RTX also increased ROS generation in prostate cancer cells. Pretreatment with N-acetyl-L-cysteine (NAC) significantly prevented RTX-induced cell apoptosis and endoplasmic reticulum (ER) stress signaling activation in prostate cancer cells. Additionally, we found RTX-induced ROS generation and ER stress activation depended on the expression of heat shock protein family A member 8 (HSPA8). Over-expression of HSPA8 could alleviate RTX-induced cell apoptosis, ROS generation and ER stress signaling activation. Finally, our study also showed that RTX attenuated the tumor growth of prostate cancer in the DU145 xenograft model and significantly downregulated HSPA8 expression and activated ER stress signaling pathway in tumor tissues. Our study is the first to reveal that RTX induces prostate cancer cells apoptosis through inhibiting the expression of HSPA8 and further inducing ROS-mediated ER stress pathway action. This study suggests that RTX may be a novel promising candidate drug for prostate cancer therapy.

Key Words： Prostate cancer; Raltitrexed; Reactive oxygen species; ER stress; HSPA8; Apoptosis

54. Multi-omics analysis reveals NNMT as a master metabolic regulator of metastasis in esophageal squamous cell carcinoma

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Metabolic reprogramming has been observed in cancer metastasis, whereas metabolic changes required for malignant cells during lymph node metastasis of esophageal squamous cell carcinoma (ESCC) are still poorly understood. Here, we performed single-cell RNA sequencing (scRNA-seq) of paired ESCC tumor tissues and lymph nodes to uncover the reprogramming of tumor microenvironment (TME) and metabolic pathways. By integrating analyses of scRNA-seq data with metabolomics of ESCC tumor tissues and plasma samples, we found nicotinate and nicotinamide metabolism pathway was dysregulated in ESCC patients with lymph node metastasis (LN+), exhibiting as significantly increased 1-methylnicotinamide (MNA) in both tumors and plasma. Further data indicated high expression of N-methyltransferase (NNMT), which converts active methyl groups from the universal methyl donor, S-adenosylmethionine (SAM), to stable MNA, contributed to the increased MNA in LN+ ESCC. NNMT promotes epithelial–mesenchymal transition (EMT) and metastasis of ESCC in vitro and in vivo by inhibiting E-cadherin expression. Mechanically, high NNMT expression consumed too much active methyl group and decreased H3K4me3 modification at E-cadherin promoter and inhibited m6A modification of E-cadherin mRNA, therefore inhibiting E-cadherin expression at both transcriptional and post-transcriptional level. Finally, a detection method of lymph node metastasis was build based on the dysregulated metabolites, which showed good performance among ESCC patients. For lymph node metastasis of ESCC, this work supports NNMT is a master regulator of the cross-talk between cellular metabolism and epigenetic modifications, which may be a therapeutic target.

Key Words： esophageal squamous cell carcinoma, metabolism reprogramming, N-methyltransferase, E-cadherin, metastasis

55. Sanguinarine chloride induces ferroptosis by regulating ROS/BACH1/HMOX1 signaling pathway in prostate cancer

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Background ： Sanguinarine chloride (S.C) is a benzophenanthrine alkaloid derived from the root of sanguinaria canadensis and other poppy-fumaria species. Studies have reported that S.C exhibits antioxidant, anti-inflammatory, proapoptotic, and growth inhibitory effects, which contribute to its anti-cancer properties. Recent studies suggested that the antitumor effect of S.C through inducing ferroptosis in some cancers. Nevertheless, the precise mechanism underlying the regulation of ferroptosis by S.C remains poorly understood.

Methods ： A small molecule library was constructed based on FDA and CFDA approved small molecular drugs. CCK-8 assay was applied to evaluate the effects of the small molecule compound on tumor cell viability. Prostate cancer cells were treated with S.C and then the cell viability and migration ability were assessed using CCK8, colony formation and wound healing assay. Reactive oxygen species (ROS) and iron accumulation were quantified through flow cytometry analysis. The levels of malondialdehyde (MDA) and total glutathione (GSH) were measured using commercially available kits. RNA-seq analysis was performed to identify differentially expressed genes (DEGs) among the treatment groups. Western blotting and qPCR were utilized to investigate the expression of relevant proteins and genes. In vivo experiments employed a xenograft mice model to evaluate the anti-cancer efficacy of S.C.

Results ： Our study demonstrated that S.C effectively inhibited the viability of various prostate cancer cells. Notably, S.C exhibited the ability to enhance the cytotoxicity of docetaxel in DU145 cells. We found that S.C-induced cell death partially relied on the induction of ferroptosis, which was mediated through up-regulation of HMOX1 protein. Additionally, our investigation revealed that S.C treatment decreased the stability of BACH1 protein, which contributed to HMOX1expression. We further identified that S.C-induced ROS caused BACH1 instability by suppressing USP47expression. Moreover, In DU145 xenograft model, we found S.C significantly inhibited prostate cancer growth, highlighting its potential as a therapeutic strategy. Collectively,

these findings provide evidence that S.C could induce regulated cell death (RCD) in prostate cancer cells and effectively inhibit tumor growth via triggering ferroptosis. This study provides evidence that S.C effectively suppresses tumor progression and induces ferroptosis in prostate cancer cells by targeting ROS/USP47/BACH1/HMOX1 axis.

Conclusion ：This study provides evidence that S.C effectively suppresses tumor progression and induces ferroptosis in prostate cancer cells by targeting the ROS/USP47/BACH1/HMOX1 axis. These findings offer novel insights into the underlying mechanism by which S.C inhibits the progression of prostate cancer. Furthermore, leveraging the potential of S.C in targeting ferroptosis may present a new therapeutic opportunity for prostate cancer.

Key Words：Ferroptosis, Sanguinarine chloride, prostate cancer, HMOX1, BACH1.

56. ABHD12 是乳腺癌可靠的诊断标志物且与肿瘤演进相关

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目的：初步探索 ABHD12 分子在乳腺癌中的诊断及预后价值，并明确其对肿瘤演进的影响。

方法：从公共数据库中获取乳腺癌样本及正常乳腺组织的高通量测序数据及随访信息，基于 R 语言进行泛癌分析、生存分析、Cox 回归分析、功能富集分析、免疫浸润分析及相关性分析等。用 siRNA 转染乳腺癌 MCF-7 细胞，Western Blot 实验检测 ABHD12 蛋白表达水平。利用集落形成实验、CCK8 实验、划痕实验及 Transwell 实验检测下调 ABHD12 表达水平对 MCF-7 细胞增殖、侵袭与迁移能力的影响。

结果：ABHD12 在多种癌症中呈现显著高表达，且在乳腺癌中能极佳地区分肿瘤样本与正常样本（曲线下面积为 0.917）。ABHD12 高表达患者具有更短的总生存期（P = 0.002）、疾病特异生存期（P = 0.009）和无进展生存期（P = 0.009）。功能富集分析表明 ABHD12 可能与过氧化物酶体脂质代谢、DNA 链延长、线粒体嵴形成、胰岛素加工及 CYP2E1 响应等功能通路有关。免疫浸润分析表明 ABHD12 低表达患者的肿瘤微环境中具有更丰富的免

疫细胞浸润。相关性分析表明 ABHD12 与多种免疫检查点呈显著负相关。集落形成实验、CCK8 实验、划痕实验及 Transwell 实验结果一致提示，敲低 ABHD12 表达可显著削弱 MCF-7 细胞的恶性生物学行为（$P < 0.05$）。

结论：初步分析表明，ABHD12 在乳腺癌中高表达，且与肿瘤演进相关，有望成为乳腺癌的新型诊断标志物和潜在治疗靶点。

关键字：ABHD12，乳腺癌，生物信息学，诊断，预后，肿瘤演进

57. 肺癌预后与 METTL3 表达的相关性 Meta 分析

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目的：采用系统评价方法，探讨 METTL3 的异常表达与肺癌的不良预后的相关性，为临床预防肺癌不良预后提供理论参考。

方法：计算机检索 中国知网、中国生物医学文献数据库、PubMed、Embase、Web of Science、ScienceDirect 等数据库，收集 METTL3 与肺癌不良预后的相关研究。检索时限为建库起至 2023 年 6 月 10 日。由 2 名研究人员独自筛选文献并提取数据，交叉核对并达成一致。2 名研究人员独立采用纽卡斯尔-渥太华量表（NewcastleOttawa Scale,NOS）进行文献质量评价，交叉核对并达成一致。使用漏斗图评估文献的发表偏移。采用比值比（odds ratio, OR）及 95%可信区间（confidence interval, CI）评价关联强度，采用 RevMan5.3 统计软件进行 Meta 分析。

结果：本分析共纳入了 10 项研究，共包括 2697 例患者。10 项病例对照研究的 NOS 评分均≥6 分。Meta 分析结果显示，METTL3 异常表达与肺癌不良预后显著相关（OR=1.26, 95% CI 1.11~ 1.43, P=0.0005）。此外，METTL3 的异常表达与分化程度(OR=1.76, 95%CI 1.32 ~2.35, P=0.0001)、TNM 分期(OR=1.69, 95% CI 1.35~ 1.76, P=0.016)和性别(OR=0.73, 95% CI 0.55~ 0.97, P=0.029)相关。

结论：当前研究证据显示，METTL3 异常表达是肺癌潜在的预后标志物。但考虑到纳入文献质量及文献数量等的影响，本研究结果亟待更多高质量的临床研究进一步验证。

关键字：肺癌；METTL3；m6A；预后；Meta 分析

58. Risk-stratified multi-round PSA screening for prostate cancer integrating the screening reference level and subgroup-specific progression indicators

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Background: Although prostate-specific antigen (PSA) is widely used in prostate cancer (PCa) screening, nearly half of PCa cases are missed and less than one-third of cases are non-lethal. Adopting diagnostic criteria in population-based screening and ignoring PSA progression are presumed leading causes.

Methods:A total of 31,942 participants with multi-round PSA tests from the PLCO trial were included. Time-dependent receiver-operating-characteristic curves and area-under-curves (tdAUCs) were performed to determine the screening reference level and the optimal subgroup-specific progression indicator from eight indicators. Effects of risk-stratified multi-round PSA screening were evaluated with multivariable Cox regression and measured with hazard ratio and 95% confidence intervals [HR(95%CIs)].

Results: After a median follow-up of 11.6 years, a total of 3,484 PCa cases and 216 PCa deaths were documented. The tdAUC of 10-year incidence PCa with PSA was 0.816, and the cut-off value was 1.61 ng/ml. Compared to subgroup with stable negative PSA[FR(-)/LR(-)], HRs(95%CI) of PCa incidence were 1.66(1.20-2.29), 8.29(7.25-9.48), and 14.52(12.95-16.28) for subgroups with loss of positive PSA[FR(+)/LR(-)], gain of positive PSA[FR(-)/LR(+)], and stable positive PSA[FR(+)/LR(+)]; while HRs(95%CI) of PCa mortality were 1.47(0.52-4.15), 5.71(3.68-8.86), and 5.01(3.41-7.37). After excluding regressive PSA(namely FR(+)/LR(-), absolute velocity was the shared optimal progression indicator for subgroups with FR(-)/LR(-), FR(-)/LR(+), and FR(+)/LR(+), with tdAUCs of 0.665, 0.681 and 0.741, and cut-off values of 0.07, 0.21, and 0.33 ng/ml/year. After reclassifying participants into groups with positive and negative progression

based on subgroup-specific progression indicators, incidence HR(95%CI) were 2.41(1.87-3.10), 2.91(2.43-3.48), and 3.16(2.88-3.46) for positive progression compared to negative progression within subgroups of FR(-)/LR(-), FR(-)/LR(+), and FR(+)/LR(+), while mortality HR(95%CI) were 2.22(0.91-5.38), 2.37(1.28-4.38), and 2.98(1.94-4.59). Overall, to improve screening performances by excluding FR(+)/LR(-), FR(-)/LR(-) and any subgroup-specific negative progressions, optimized screening strategy not only significantly reduce 32.4% of missed PCa (54.0%[1881/3484] vs. 21.6%[754/3484], P <0.001), but also detected additional 8.0% of high-grade PCa (Gleason score 7-10: 36.0%[665/1849] vs. 28.0%[206/736], P <0.001) than traditional screening strategy.

Conclusions: Risk-stratified multi-round PSA screening strategy integrating the screening reference level and the optimal subgroup-specific progression indicator of PSA could be recommended as a fundamental strategy to reduce missed diagnosis and improve the detection of high-grade PCa cases.

Key Words： Prostate cancer; PSA; screening; progress; velocity

59. 去氢松香酸通过调控 TFRC-mTOR 通路对肝癌 HepG2 细胞自噬及增殖的作用研究

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研究目的：探究去氢松香酸对肝癌 HepG2 细胞的抑制作用，及其通过调控转铁蛋白受体（TFRC）和 mTOR 信号通路促进细胞自噬的潜在机制。

材料与方法：本研究采用 CCK8 法评估去氢松香酸对 HepG2 细胞增殖的影响，并通过 RNA-seq 及 KEGG 通路分析探究影响的分子机制。Western blot 技术用于检测去氢松香酸处理前后 TFRC、自噬相关蛋白（LC3B 和 beclin1）及磷酸化 mTOR（p-mTOR）的表达变化。自噬双标记腺病毒 mCherry-EGFR-LC3 感染实验评估去氢松香酸对自噬活性的影响。此外，通过慢病毒转染技术在 HepG2 细胞中过表达 TFRC（oe-TFRC）和对照（oe-NC），以进一步验证 TFRC 在去氢松香酸作用中的角色。

结果：去氢松香酸以剂量依赖性方式显著抑制 HepG2 细胞的增殖，IC50 为 22μM。RNA-seq 的结果表明，去氢松香酸处理后，影响自噬信号通路的基因表达上调，mTOR 信号通路的基因表达下调。去氢松香酸处理后 TFRC 和 p-mTOR 蛋白表达降低，而 LC3B 和 beclin1 表达升高，且自噬小体数量显著增加（P<0.05）。相比于 oe-NC 组，oe-TFRC 组中 TFRC 蛋白表达增加，去氢松香酸对 HepG2 细胞的抑制作用减弱，IC50 值提高，p-mTOR 蛋白表达增加，而 LC3B 和 beclin1 表达降低，自噬小体数量减少（P<0.05）。

结论：去氢松香酸通过抑制 TFRC 介导的 mTOR 信号通路，促进自噬，从而抑制肝癌 HepG2 细胞的增殖。

关键字：去氢松香酸、转铁蛋白受体、mTOR 信号通路、自噬、肝癌

60. 免疫组化双染在病理诊断中的应用

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目的：对于免疫组化双重染色的效果进行评估，验证双重染色在肿瘤病理诊断中的价值。

方法：本文采用 P63/34βE12/p504S，CK5/6+TTF-1 两种不同鸡尾酒抗体组合分别对前列腺组织，以及肺癌组织进行染色，并对结果进行分析。

结果：在 P63/34βE12/p504S 鸡尾酒抗体染色中，P63 和 34βE12 表达于基底细胞，染色呈棕色，p504S 表达于腺癌细胞，呈红色。该技术有助于良性前列腺增生，前列腺上皮内瘤变，前列腺癌的鉴别。CK5/6+TTF-1 鸡尾酒抗体染色中 CK5/6 表达于肺鳞癌细胞中，呈红色，TTF-1 表达于肺腺癌细胞中，呈棕色。通过 CK5/6+TTF-1 免疫组化双重染色可对肺癌类型进行精准区分。

结论：免疫组化双染在同一切片上检测两种不同的抗原表达，同时观察两种不同的染色结果，使得阅片更加直观，判读更加快捷，可以减少工作量，对于活检珍贵小样本具有重要意义。

关键字：免疫组化；双重染色；病理诊断应用

61. 转录组和差异甲基化整合分析鉴定三阴性乳腺癌诊断和预后的关键基因

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背景：三阴性乳腺癌（triple-negative breast cancer，TNBC）是一种侵袭性亚型，其特征是雌激素受体、孕激素受体和人表皮生长因子受体 2 表达缺失。它以其高侵袭性和恶性性而闻名，使其成为预后最差和治疗选择有限的乳腺癌亚型。鉴于管理 TNBC 的挑战，迫切需要确定新的生物标志物，以帮助该疾病的早期诊断和治疗。

方法：在本研究中，我们整合转录组和甲基化数据来鉴定 TNBC 中甲基化的差异表达基因（methylated differentially expressed genes，MDEGs）。随后，我们进行了 GO 分析、KEGG 通路分析和 PPI 网络分析，以全面了解与这些 MDEGs 相关的生物学功能和通路，以确定枢纽基因。此外，采用 ROC 曲线分析和 Kaplan-Meier 法估计 hub 基因对 TNBC 诊断和预后的影响。

结果：转录谱整合综合分析显示，98 个基因表达上调，87 个基因表达下调。此外，通过结合甲基化数据，我们鉴定了 22 个因低甲基化而高表达的基因（high expression due to hypomethylation，hypo-MDEGs）和 32 个因高甲基化而低表达的基因（low expression due to hypermethylation，hyper-MDEGs）。这些 hypo-MDEGs 主要在细胞核分裂、细胞器分裂、纺锤体形成、染色体和着丝粒发育以及蛋白结合方面发挥作用。KEGG 结果显示，这些 hypo-MDEGs 富集在孕酮介导的卵母细胞成熟、细胞周期调控和卵母细胞减数分裂等方面。另一方面，hyper-MDEGs 与细胞增殖、激素反应途径、疼痛感知机制、细胞外基质成分改变以及涉及硫化合物（如肝素和糖胺聚糖）的相互作用相关。PPI 网络分析发现 7 个枢纽基因 CCNB1、KIF11、MKI67、KIF23、FOXM1、PLK1 和 EXO1 在 TNBC 癌组织中高表达，

且它们之间呈正相关（P 均<0.05）。ROC 曲线分析显示，7 个基因的 AUC 值均大于 0.7（P 均<0.05）。KM 分析显示 CCNB1、KIF11、MKI67 和 PLK1 的风险比均大于 1（P 均<0.05）。

结论：本研究确定了一组 7 个 hypo-MDEGs，具体为 CCNB1、KIF11、MKI67、KIF23、FOXM1、PLK1 和 EXO1。这些基因与细胞周期和有丝分裂过程有关，对 TNBC 的诊断和预后有影响。此外，它们为 TNBC 的分子机制提供了潜在的见解，同时也提出了新的生物标志物，可以帮助准确诊断和治疗 TNBC。

关键字：三阴性乳腺癌，转录组，DNA 甲基化，诊断，预后

62. Multi-Omics Study on the Molecular Mechanism of Anlotinib in Regulating Tumor Metabolism

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Background: Anlotinib, an orally administered small molecule inhibitor of receptor tyrosine kinases (RTKs), exerts significant anti-angiogenic and vascular normalization effects. However, the mechanisms underlying its involvement in tumor metabolic reprogramming are still unclear. This study aims to investigate the distribution and expression levels of metabolites within tumors after anlotinib treatment using spatial metabolomics analysis.

Methods: This study involves spatially analyzing the distribution differences of metabolites post-anlotinib administration and integrating transcriptomics and proteomics to explore the internal mechanisms of anlotinib action at a molecular level.

Results: By integrating the transcriptomics and proteomics analyses, we identified that anlotinib treatment primarily modulated four metabolic pathways, including taurine and hypotaurine metabolism, steroid synthesis, pentose phosphate pathway, and lipid biosynthesis.This regulation significantly influenced the metabolic levels of compounds such as sulfonic acids, cholesterol, inositol phosphate pyrophosphate, and palmitoyl-CoA in the tumor, thereby impacting tumor initiation and progression.

Conclusions: This study provides potential metabolic biomarkers for anlotinib treatment in tumors, and may identify potential biomarkers and pathways associated with the therapeutic efficacy of anlotinib treatment.

Key Words ： Anlotinib; Spatial metabolomics; Crotonyl Coenzyme A; Taurine; Tumor Microenvironment

63. Silencing CD38 enhances anti-CD38 CAR-T anti-lymphoma activity

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Objective ： Construct shRNA targeting CD38 anti-CD38 CAR-T cells, and observe their proliferation and anti-lymphoma ability.

Methods：Construct shRNA targeting CD38 CAR-T CAR molecules, transduce human primary T cells to prepare CAR-T cells with retroviral vectors. Two groups of shRNA CD38 CAR-T cells were used as the experimental group, and CD38 CAR-T cells were used as the control group. QPCR method was used to detect the CD38 mRNA expression level of CAR-T cells;CFSE method was used to detect the proliferation of CAR-T cells co-cultured with Raji-luc (human Burkitt lymphoma); Using luciferase chemiluminescence to detect the killing efficiency of CAR-T cells on Raji-luc cells at different target ratios (1:1, 1:2, 1:4, 1:8); ELISA method was used to detect the level of interferon gamma (IFN- gamma) in the supernatant after CAR-T cells killed Raji-luc; Flow cytometry was used to detect the expression level of PD-1, a biomarker of exhaustive T cells on the surface of CAR-T cells.

Results：CAR positive rate of CD38 CAR-T, shRNA1-CD38 CAR-T and shRNA2-CD38 CAR-T cellwas 65.3%, 63% and 60.4%, respectively, and CAR-T cells were successfully constructed. Compared with the CD38 CAR-T group, the expression of CD38 mRNA in the shRNA2-CD38 CAR-T group was significantly reduced ($P<0.01$); Stronger ability to culture in vitro proliferation ($P<0.05$); When killing Raji-luc tumor cells, the killing efficiency is higher ($P<0.05$); The release level of interferon gamma is higher (all $P<0.05$); The expression level of PD-1 on the surface was

lower (P<0.05). Compared between the shRNA1-CD38 CAR-T group and the CD38 CAR-T group, there were no significant differences in the experimental results (all P>0.05).

Conclusion： Successfully constructed an anti-CD38 CAR-T cell that targets CD38 by shRNA, which can effectively kill Raji-luc. Compared with anti-CD38 CAR-T cells, it has stronger proliferation ability and anti-lymphoma ability, and reduces the exhaustion of CAR-T cells.

Key Words： lymphoma; CD38; CAR-T; shRNA

64. Lysine butyrylation of HSP90 regulated by KAT8 and HDAC11 confers chemoresistance

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Posttranslational modification dramatically enhances protein complexity, but the function and precise mechanism of novel lysine acylation modifications remain unknown. Chemoresistance remains a daunting challenge to successful treatment. We found that lysine butyrylation (Kbu) is specifically upregulated in chemoresistant tumor cells and tissues. By integrating butyrylome profiling and gain/loss-of-function experiments, lysine 754 in HSP90 (HSP90 K754) was identified as a substrate for Kbu. Kbu modification leads to overexpression of HSP90 in esophageal squamous cell carcinoma (ESCC) and its further increase in relapse samples. Upregulation of HSP90 contributes to 5-FU resistance and can predict poor prognosis in cancer patients. Mechanistically, HSP90 K754 is regulated by the cooperation of KAT8 and HDAC11 as the writer and eraser, respectively; SDCBP increases the Kbu level and stability of HSP90 by binding competitively to HDAC11. Furthermore, SDCBP blockade with the lead compound V020-9974 can target HSP90 K754 to overcome 5-FU resistance, constituting a potential therapeutic strategy.

Key Words： Cancer therapeutic resistance, Post-translational modifications, Proteomic analysis, Drug development

65. lncRNA KCNQ1OT1 靶向调控 miR-3194-3p/PLK1 信号轴在 NSCLC 细胞的增殖侵袭和迁移中的作用研究

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研究目的：探究长链非编码 RNA（lncRNA KCNQ1OT1）在非小细胞肺癌（NSCLC）细胞增殖、侵袭和迁移中的作用及其机制。

材料与方法：利用 StarBase 数据库分析 NSCLC 中 lncRNA KCNQ1OT1 的表达模式，预测其靶向的 miRNA 及其靶基因。收集 30 例 NSCLC 临床患者肿瘤及相邻非肿瘤组织样本，通过 qRT-PCR 技术检测 lncRNA KCNQ1OT1、miR-3194-3p 和 PLK1 的表达，并分析它们之间的相关性。使用免疫组化技术评估 PLK1 在肿瘤及相邻组织中的表达。在 A549 细胞中进行双荧光素酶报告基因实验，以验证 lncRNA KCNQ1OT1 与 miR-3194-3p 以及 miR-3194-3p 与 PLK1 之间的靶向关系。使用慢病毒的转染法，将敲低 lncRNA KCNQ1OT1 和敲低 miR-3194-3p 的 shRNA 转染入 A549 细胞。采用 qRT-PCR 技术测定细胞中 lncRNA KCNQ1OT1、miR-3194-3p 和 PLK1 的表达，CCK-8 实验评估细胞增殖，Transwell 实验检测细胞侵袭和迁移能力。

结果：NSCLC 中 lncRNA KCNQ1OT1 的表达上调，与 miR-3194-3p 呈现碱基互补性，而 miR-3194-3p 与 PLK1 之间存在碱基互补性。与相邻非肿瘤组织相比，NSCLC 肿瘤组织中 lncRNA KCNQ1OT1 和 PLK1 表达增加，miR-3194-3p 表达降低。lncRNA KCNQ1OT1 与 miR-3194-3p 的表达呈负相关，miR-3194-3p 与 PLK1 表达呈负相关。在 A549 细胞中，lncRNA KCNQ1OT1 靶向抑制 miR-3194-3p 表达，而 miR-3194-3p 靶向抑制 PLK1 表达。敲低 lncRNA KCNQ1OT1 可抑制 A549 细胞的增殖、侵袭和迁移，而敲低 miR-3194-3p 可逆转敲低 lncRNA KCNQ1OT1 对 A549 细胞增殖、侵袭和迁移的抑制效果。

结论：lncRNA KCNQ1OT1 通过靶向调控 miR-3194-3p/PLK1 信号轴，促进 NSCLC 细胞的增殖、侵袭和迁移。

关键字：非小细胞肺癌、长链非编码 RNA、微小 RNA、侵袭和迁移

66. Circ_MACF1 靶向调控 PLK1 在 NSCLC 细胞的增殖侵袭和迁移中的作用研究

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研究目的：探究环状 RNA（circ_MACF1）在非小细胞肺癌（NSCLC）细胞增殖、侵袭和迁移中的作用及其机制。

材料与方法：利用 StarBase 数据库分析 NSCLC 中 circ_MACF1 的表达模式，预测其靶基因。收集 30 例 NSCLC 临床患者肿瘤及相邻非肿瘤组织样本，通过 qRT-PCR 技术检测 circ_MACF1 和 PLK1 的表达，并分析它们之间的相关性。使用免疫组化技术评估 PLK1 在肿瘤及相邻组织中的表达。在 A549 细胞中进行双荧光素酶报告基因实验，以验证 circ_MACF1 与 PLK1 之间的靶向关系。使用慢病毒的转染法，将敲低 circ_MACF1 和敲低 PLK1 的 shRNA 转染入 A549 细胞。采用 qRT-PCR 技术测定细胞中 circ_MACF1 和 PLK1 的表达，CCK-8 实验评估细胞增殖，Transwell 实验检测细胞侵袭和迁移能力。

结果：NSCLC 中 circ_MACF1 的表达下调，与 PLK1 呈现碱基互补性。与相邻非肿瘤组织相比，NSCLC 肿瘤组织中 circ_MACF1 表达降低，PLK1 表达升高。circ_MACF1 与 PLK1 的表达呈负相关。在 A549 细胞中，circ_MACF1 靶向抑制 PLK1 表达。敲低 circ_MACF1 可促进 A549 细胞的增殖、侵袭和迁移，而敲低 PLK1 可逆转敲低 circ_MACF1 对 A549 细胞增殖、侵袭和迁移的促进效果。

结论：Circ_MACF1 通过靶向干扰 PLK1 表达，从而抑制 NSCLC 细胞的增殖、侵袭和迁移。

关键字：非小细胞肺癌、环状 RNA、侵袭和迁移

67. N4-acetylcytidine modification of lncRNA CTC-490G23.2 promotes cancer metastasis through interacting with PTBP1 to increase CD44 alternative splicing

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Although N4-acetylcytidine (ac4C) modification affects the stability and translation of mRNA, it is unknown whether it exists in noncoding RNAs, and its biological function is unclear. Here, nucleotide-resolution method for profiling CTC-490G23.2 ac4C sites and gain- and loss-of-function experiments revealed that N-acetyltransferase 10 (NAT10) is responsible for ac4C modification of long noncoding RNAs (lncRNAs). NAT10-mediated ac4C modification leads to the stabilization and overexpression of lncRNA CTC-490G23.2 in primary esophageal squamous cell carcinoma (ESCC) and its further upregulation in metastatic tissues. CTC-490G23.2 significantly promotes cancer invasion and metastasis in vitro and in vivo. Mechanistically, CTC-490G23.2 acts as a scaffold to increase the binding of CD44 pre-mRNA to polypyrimidine tract-binding protein 1 (PTBP1), resulting in a oncogenic splicing switch from the standard isoform CD44s to the variant isoform CD44v(8-10). CD44v(8-10), but not CD44s, binds to and increases the protein stability of vimentin. Expression levels of CTC-490G23.2 and CD44v(8-10) can predict poor prognosis in cancer patients. Furthermore, the antisense oligonucleotide (ASO)/SV40-LAH4-L1 peptide self-assembled nanocomplexes targeting CTC490G23.2 exerts a significantly suppressive effect on cancer metastasis. The outcome of this study will provide new mechanistic insight into the ac4C modification of lncRNAs and useful clues for the development of novel systemic therapies and prognostic biomarkers.

Key Words： N4-acetylcytidine modification of lncRNA, cancer metastasis, RNA binding protein PTBP1, CD44 alternative splicing, nanoparticle therapy

68. 病理技师应熟练掌握肿瘤标志物的应用

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【摘要】 病理技师在日常的病理技术工作中，不但要掌握各项免疫组化技术，还要熟悉肿瘤标志物在日常病理诊断中的应用，这对于病理技师在观察免疫组化结果和质控方面有很大的帮助。一位优秀的病理技师应该具备较强的动手能力和初步病理诊断的技能，要熟悉各个病理诊断，每个病例需开出哪些肿瘤标志物的医嘱，用何种标志物对此肿瘤的表达更好。病理技师应不断地学习和更新知识，不断地总结经验和创新，当今的病理技术工作已不再局限于动手操作的过程，而是需要大量的病理基础知识与其相适应，如今的病理诊断也越来越依赖于新的病理技术，这就需要我们不断地提高病理技术专业水平来适应当今生物医学与病理医学技术的发展。

关键字：病理技师：肿瘤标志物；应用

69. 血清外泌体蛋白组反映神经母细胞瘤组织的分子特征

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神经母细胞瘤（NB）缺乏准确、方便的早期诊断方法。外泌体因可以携带肿瘤特异性分子，有望成为肿瘤生物标志物的潜在来源。我们对血清外泌体进行了蛋白质组学分析并鉴定了诊断 NB 的潜在生物标志物。发现阶段通过 label free 蛋白质组学分析 NB 患者 (n = 10) 和健康对照 (HC) (n = 10) 的血清外泌体。验证阶段通过多重反应监测(MRM) 在一个包含在 NB 患者 (n = 20)、HC (n = 20) 和其他非 NB 癌症患者 (n = 10) 的独立队列中鉴定和验证了潜在的诊断生物标志物。另外我们还联合分析了外泌体蛋白组、NB 组织转录组和单细胞 RNA 测序 (scRNA-seq) 数据。

Label free 蛋白组总共鉴定了 948 个外泌体蛋白，其中有 104 个在 NB 患者和健康者间表达显著差异的蛋白。功能富集分析表明了 NB 患者高表达的外泌体蛋白主要与在肿瘤中发挥重要作用的生物途径相关。MRM 成功验证了 26 个潜在的蛋白生物标志物。基于七种

蛋白生物标志物表达水平的逻辑回归模型可以高效的区分 NB 患者与 HC 或其他非 NB 癌症患者。外泌体蛋白组和组织转录组分析表明了几种外泌体生物标志物的转录表达水平与 NB 患者的预后显著相关。根据已发表的 scRNA-seq 数据，恶性肿瘤细胞高表达的基因也在 NB 患者血清 外泌体中显著富集。我们通过分析 scRNA-seq 数据，还发现几种候选的外泌体生物标志物在肿瘤组织中不同细胞亚群中表达。

总之，分析血清外泌体的蛋白谱可以深入了解 NB 的潜在机制，外泌体蛋白组部分反映了 NB 组织的分子特征。血清外泌体含有用于诊断或预测 NB 的潜在蛋白质生物标志物，代表了肿瘤组织来源的液体活检方案。

关键字：外泌体、神经母细胞瘤、蛋白组、液体活检、MRM、生物标志物

70. 一种国产前列腺特异性抗原检测试剂盒（荧光免疫层析法）的临床性能评价应用

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目的：根据美国临床和实验室标准化协会（Clinical and Laboratory Standards Institute，CLSI）EP9-A3 指南对国产 VivaDiagTM 前列腺特异性抗原检测试剂盒（荧光免疫层析法）进行临床性能研究，评价该试剂盒在临床上使用的安全性与有效性。

方法：使用杭州微策生物技术股份有限公司生产的 VivaDiag™ 前列腺特异性抗原检测试剂盒（荧光免疫层析法）（简称“考核试剂”）与市场上已获 CE 认证的同类产品 ichroma™ PSA 试剂盒（简称“对比试剂”）进行平行比对试验。两者同时检测前列腺相关疾病人群的血清、EDTA 血浆及全血样本共 425 例。根据 EP9-A3 指南，对考核试剂与对比试剂的检测结果进行符合率分析、Kappa 分析、Passing-Bablock 回归分析、相关性分析、Bland-Altman 分析和医学决定水平处偏倚评估，证明考核试剂在临床应用上与对比试剂具有可比性。

结果：经过符合率分析、Kappa 分析、Bland-Altman 分析和医学决定水平处偏倚评估，证明考核试剂和对比试剂对于血清、血浆和全血样本的检测结果具有较好的一致性，经过 Passing-Bablok 回归分析和 Pearson 相关性分析，证明考核试剂和对比试剂对于血清、血浆和全血样本的检测结果具有较好的相关性。

结论：由杭州微策生物技术有限公司生产的 VivaDiag™ 前列腺特异性抗原检测试剂盒（荧光免疫层析法）在临床性能上与进口试剂具有较好的可比性，各项性能及检测指标均能达到临床检验的要求，能满足临床检测的需要。

关键字：EF9-A3；前列腺特异性抗原；前列腺癌；荧光免疫层析法；抗原检测试剂盒

71. 病理技师应是全自动免疫组化仪的主导者

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【摘要】 随着免疫组化标准化的逐步实行和病理科设备的不断更新，全自动免疫组化染色仪已全面进入病理科，病理技师从烦琐的手工操作中解脱出来，极大地提高了免疫组化的工作效率，同时也将免疫组化标准化工作推上了一个新台阶。为了不断提高病理科免疫组化结果的可靠性，还应具备以下条件：（1）合格的免疫组化实验室，（2）标准化的免疫组化染色程序，（3）配备高质量合格的免疫组化染色仪，（4）全自动免疫组化染色仪的应用并不是让病理技师彻底休息，病理技师仍然是免疫组化仪的主导者，技师应与免疫组化仪器工程师定期沟通与交流，来持续改进和优化免疫组化染色仪的程序或指导更新设备，更好的为免疫组化工作服务，（5）科室免疫组化质控体系的建设，（6）合格稳定的免疫组化试剂，（7）科学的设立对照实验，（8）阳性和阴性结果的正确判读，（9）病理诊断中抗体的联合应用，（10）有丰富经验的病理医生和病理技师的相互配合。同时，病理技师必须树立高度的责任心，技师的工作质量是免疫组化染色结果成功的关键，它不仅提高了病理诊断的可靠性，也将进一步促进病理科免疫组化工作持续健康的发展。

关键字：病理技师；免疫组化仪；主导者

72. （AI）人工智能将成为病理诊断领域的强力助推剂

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摘要：当今的（AI）人工智能已进入医学诊断的众多领域，应用包括疾病诊疗、医疗辅助、药物开发等。而病理诊断是一种基于图像信息的诊断方式，被誉为疾病诊断的“金标

准”，但由于自动化程度较低，病理医生缺乏等诸多因素，在目前病理诊断领域中，还处于起步发展阶段。本文通过分析医疗大数据与病理技术开发及病理 AI 图像识别技术开发的现状，进而分析了（AI）人工智能助推病理转向数字化诊断技术的发展前景，可以有效提升病理诊断的效率，由此可见（AI）人工智能将成为病理诊断领域的强力助推剂。

关键字：AI；人工智能；病理诊断

73. 不断提高急危重病人抢救质量，开展人性化抢救措施--

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目的：为了解决在抢救室铁大门隔离门外一众急危重病人家属免遭精神打击及迫切需要知道病人家属抢救过程及第一时间知道抢救效果，减轻或避免由此产生的继发性病人家属精神打击和精神压力，避免诱发家属也相继发生急危重病的严重后果，特研究解决上述不足的有效防治方法，供大家参考应用。

方法：总结本人抢救急危重病人的经历、经验，及所见所闻的相关常识、经验、人文和其表现的不足，提出改革措施和防治方法。

结果：本人长期工作在县级及县以下医院一线急诊科（120 急救）及内科医师，经常抢救急危重病人，亲身经历、主持及耳闻目睹了无数次抢救急危重病人的全过程，现总结如下现实：

1、县级及以下医院抢救室一般是不设紧闭大门的，抢救时病人家属可以随意进出抢救室。

2、城市大医院一般均设立抢救室隔离家属的大铁门，常常叫做门禁，隔离家属抢救病人，使病人家属不知道抢救病人的全过程，完全不透明，这种措施，明显违背了病人抢救措施的家属及病人知情权，可能造成严重后果，等 10 种现实结果。

结论：医院抢救急危重病人，是经常性的、随时都在发生和开展的医疗过程，特别是在市级以上大医院，各科抢救室均是重点科室或单位，为了解决在抢救室铁大门隔离门外一众急危重病人家属免遭精神打击及迫切需要知道病人家属抢救过程及第一时间知道抢救效果，减轻或避免由此产生的继发性病人家属精神打击和精神压力，避免诱发家属也相继发生急危重病等相关的严重后果，特研究解决上述不足的有效防治方法如下：

1、全国各级医院抢救室的大门均需要有序敞开，在允许病人家属进入抢救室观看病人抢救全过程的情况下，开展及时、合理、正确地全方位的抢救。

2、若不能立即打开抢救室大门，应该逐渐开展并在短期内打开抢救室大门。

3、在抢救室环境安全的情况下，允许病人家属进入抢救室观看病人抢救全过程，并在力所能及的情况下，指导病人家属帮助、协助医护人员抢救。

4、医护人员随时对进入抢救室的家属进行沟通，内容包括病人所患疾病、病情轻重、抢救措施，主要抢救措施应告知病人家属。

5、由医护专人与病人家属沟通，签署相关知情同意书，或由科主任、医务科领导、院主管领导等与病人主管家属沟通。

6、不断学习业务知识，提高业务水平，掌握真正的抢救技术，做到在急救状态下快速、正确、及时、合理、科学地抢救病人，在透明的情况下，病人家属即使是医疗专业人士，也不能找出抢救错误。使病人家属明白病人死因完全是病重所致，而不存在任何医源性致死的可能性。

7、国家卫生健康委员会应该明文发布相关规定，各级医院遵照执行。

8、各级医院应建立保安制度，保证医护人员正常抢救病人。

9、各级医院应建立告知制度，明确在医院内，特别是在抢救病人时，不听医护人员的指导，无理取闹要负法律责任的，同时告知，若有异议可当场同医护人员沟通，使医患密切配合，共同以最好水平来救治病人，必要时可通过各种正规渠道向医院反映问题。

10、明确说明，只有在急病人及其家人所急，痛病人及其家人所痛的情况下，不断学习和精通专业技术知识，才能顺利、更好地抢救病人，才能达到人性化抢救措施，才能很自然地打开抢救室的大铁门，让病人家属自由地观看抢救过程和安抚急危重病人，更有助于医护人员正常地完成救死扶伤的基本职责。

11、抢救病人时，打开抢救室的大铁门，让病人家属自由地观看抢救过程和安抚急危重病人，是更好和最好的杜绝医疗纠纷、杜绝病人家属的过激行为、有利于提高抢救效果和防治继发性病人家属患病的很有效、很方便的方法。

12、国家卫生健康委员会等相关部门，应该引起重视，应该尽快回顾性总结相关关闭抢救室大铁门医疗救治的真正弊端，研究证实本研究和建言献策的真实性，尽快顺利实施本建言献策。

Key words:Law and regulations in health and medicine; Administration of health and medicine; Emergency treatment for critical diseases; Proposals; Diseases prevention and cure.

关键字：医疗卫生法规；医疗行政管理；危重病急救；建言献策；防病治病。

74. The Carbon Capture, Utilization and Storage has been being no effective to prevent climate change impacts and living environment, the proposals suggested

Hanyou Xu

Objective: In order to prevent and cure the more and more worse greenhouse effects, climate change impacts and living environment for man kinds, new administration strategies must be created. So the research has been done.

Methods: Summarized and research the present situations and facts of preventing and curing the worse green house effects, climate change impacts and living environment. And create the new administration strategies.

Results: The present situations and facts of preventing and curing the worse green house effects, climate change impacts and living environment are critical and in emergency. And the solutions have not been being effective. There are 8 facts for less effective doing have been summarized. They include the world now, mainly pay attention to CO2 emission reducing, but not all greenhouse gases, etc.. And the 9 new administration strategies have been proposed. The first one is that China, other countries and international professional agencies must change their administration thinking immediately. And pay broad and whole attention to reduce whole greenhouse gases to the aims of zero emission. Not just only play technology of Carbon Capture, Utilization and Storage. The second one is that China, other countries and international professional agencies must put the recovering the worse greenhouse effects and climate change impacts as first duty and responsibility. And the other 7 strategies are in the text.

Conclusion: It is imperative to prevent and cure the worse green house effects, climate change impacts and living environment for man kinds as soon as possible. As the man kinds have been

suffering from the worse living environment day and night in more and more intensive speed and damage. The research have summarized the 8 principles facts about the shortcomings in controlling the worse green house effects and climate change impacts. Which should be paid attention by the related professionals and administrators. And the 9 proposed new administration strategies should also be referenced by the related professionals and administrators. As this kind of research has not been reported by other professionals

Key Words： Greenhouse gases; Greenhouse effects; Climate changes severe impacts; Man kinds living; Healthy environment; Public health; Carbon capture, Utilization and Storage; Proposals.

75. Everywhere in China all air conditioners, ice chestn and refrigerators have been consuming and emitting the Freon and alike chemicals. It is imperative to cure

Hanyou Xu

Beijing Cerebrovascular disease Hospital, China.

Objective: In order to prevent and cure the more and more worse greenhouse effects, climate change impacts and living environment for man kinds, new dangerious factors must be found, identified and prevented.

Method: Summarized and research the facts of China as the top consumer of refrigerant. So China is the top consumer and elininater of the Freon and alike chemicals. So call for preventing and curing the worse green house effects, climate change impacts caused by the Freon and alike chemicals.

Results: As China is the biggest country in the world with 1.4billions people and top economic power. China should be the leader to control the Freon and alike chemicals, and the green house effect and the global warming. But now, China has been still being the top consumer of the Freon and alike chemicals or the top consumer of refrigerant. We must face squarely what shortcomings we have had. And correct it at once.As the facts tell us the Freon and alike chemicals have been the dangerious factors of the green house effect and the

global warming. So we can create new policy and science to reduce and control the Freon and alike chemicals at once. And so on the green house effect and the global warming.

Everywhere in China there has been being all air conditioners, ice chestn and refrigerators have been consuming and emitting the Freon and alike chemicals.

After China had been producing main part of CFC of Freon in the world. And the CFC of Freon have been banned. China has been changing to HCFC of Freon and HFC of Freon as substitutes.

It has been being known to all that every place in China, where people live and work. There must have air conditioners, ice chestn and refrigerators. From family households, factories, government offices, hospitals, tools of transportation, even the spacecrafts have been being equipped with air conditioners, ice chestn and refrigerators. All the air conditioners, ice chestn and refrigerators have been consuming and emitting the HCFC of Freon and HFC of Freon after CFC of Freon.

Because the China is the biggest country in the world. The population of China is the much too more than any other country in the world. So the family households, factories, government offices, hospitals, tools of transportation must be much too more than any other country in the world. Therefore, the air conditioners, ice chestn and refrigerators also must be much too more than any other country in the world. At present, China must have been consuming and emitting the HCFC of Freon and HFC of Freon more than other countries.

HCFC and HFC of Freon are not green products and environmental protection products

Though HCFC of Freon has less effect to deplete the Ozone Layer. But it is not the perfect substances. Some HCFC of Freon have been being banned from usage. Which indicate that the HCFC of Freon are not green products and environmental protection products.

While theoretically, the ODP (The Ozone Depletion Potential) of HFC of Freon is 0. But the Global warming potential(GWP) is very high. Therefore, the HFC of Freon are also not green products and environmental protection products. While China has been being the biggest and main producer and consumer of the banned CFC of Freon and the biggest and main producer and consumer of the HCFC and HFC of Freon. So Chinese air conditioners, ice chestn and refrigerators must make more Ozone Depletion and Global warming substances.

Conclusion: The concrete policies must be created as soon as possible. Reducing the top consumer and elininater of the Freon and alike chemicals or create new chemicals without the worse green house effects, climate change impacts were China's and world's imperative policy.

Key Words： Climate change; Environmental protection; Freon; Ozone depletion; Health promotion.

76. Near all food seeds have been being man-made，are they healthful to mankind？---

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Introduction and Objective: As the public facts living by every people and every day that, by the modern agriculture science developing, more and more food stuffs, vegetables, melon, fruit,eggs, poultry and meats have been produced. The methods are near all their seeds or animal reproduction have been being man made by modern genetic engineering. And further more, the food stuffs, vegetables, melon, fruit have been being off-season planted. All the unnatural productions of food really have been eaten into the man kinds day and day, years and years.

I have the first experiences and the first hands information that China have been being something of more advantage, modern and the most amount of productions in these unnatural productions of food. It is the facts that other countries in the world also have been producing these unnatural food stuffs, vegetables, melon, fruit, eggs, poultry and meats.

While the genetically modified soybeans and the alike food stuffs have been being the hot topics in science and health influences. These genetically modified food stuffs have been very cautiously accepted by peoples and by every country government. But the present situation in the world is that near all the food seeds or animal reproduction have been being man made by modern genetic engineering, maybe in less tension compared to the genetically modified soybeans. We may call them as sub genetically modified seeds and their food productions. However, they have been being all genetically modified and different from the former natural food seeds or animal reproduction in different grades.

So as the off-season planting and their food productions have been all far from the natural food which also have been being hot argument topic of health influences by people.

Methods: Summarized the present situation in food securities. Proposed the emergency treatment methods and proposals.

Results: While the Earth and the space or the universe must like a human being which her normal lives must be supported by her normal physiology of every organ and every cell. And the human organs and cells have been united and interacted harmoniously to pay the way for normal life. Any abnormal cells and organs activities must cause pathology, sick,even death.

But at present, in our Earth and the space or the universe, the former harmonious and natural organs and cells in the Earth and the space or the universe have been being invaded. The organs and cells in the Earth and the space or the universe are the plants of food stuffs, vegetables, melon, fruit,eggs, poultry, animals, mankind and its other biology, ecology and environment, etc.. While in our Earth and the space or the universe, the formal natural plants of all food,the animals have been changing a lots. The off-season planting also has been contributing a lots changes to our Earth and the space or the universe. The former harmonious biology, ecology and environment should be sure to be changed in our Earth and the space or the universe. Adding the speeding advantage of our space and universe by the orbiting satellites, spacecrafts, space stations and their spaceships and other invading factors to the Earth and the space, the former harmonious biology, ecology and environment should be sure to be changed speedily in our Earth and the space or the universe.

Therefore, at these critical situation, the former harmonious biology, ecology and environment can change their units, organs, cells or molecules. So the new emerging infection and communicable diseases have been being developed. And the climate changes impacts have been being more and more heavily. The most imprinted the bones and inscribed on the memory has been being the COVID-19 pandemic around the world more than three years.

Conclusion: As this paper is to summarize facts and syndromes harmful to the man kind by the unnatural science and create the new strategies to cure them. So my proposals are as follows:

1. Stop the productions of the unnatural seeds and their food as soon as possible.

2. Productions of the food seeds and their food must go back to the nature ones as soon as possible.

3. Researching and accessing or evaluating side effects of the unnatural seeds and their food and unnatural eggs, poultry and meats to the health of mankind, plant, biology, ecology and environment in short and long research effect periods. If proving the bad effects, all the productions of the unnatural seeds and all the unnatural food must be stopped at once.

4. Developing the true and good science to produce health foods to feed the mankind.

5. The immediate decision must be made to publish the knowledge to the politicians all over the world and the United Nations and its organizations to pay attention to the problems imperatively.

6. China, as the big country in population, economic, food production should go ahead to security the food healthy, public health promotion, climate change recovering and biology, ecology, environment well up.

7. My opinion should be referenced by the officials and politicians.

Key Words: Food security; Public health; Man made food seeds; ecology and environment disturb; unnatural genetic modified food.

77. 中国医保难以保障健康中国，改革势在必行---

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目的：为了真正实现健康中国人民大众的基本目标和诉求，使人民大众平平安安地生活，使中国医保真正发挥保障健康中国的的基本目的，特研究总结中国医保的现状及提出有效改革措施，以供参考。

方法：作为高年资医生，长期经历医院医保管理策略，结合当今社会现实，总结当今中国医保存在的不足和事实，提出改革措施，并建言献策，交流促进中国医保良性发展。

结果：当今中国医保存在下列不足和事实：

1、虽然医保在大众中广泛实施，但大众看病、治疗、康复、预防、保健，所需要的花费经济支出，不见减少，反倒逐渐增加。包括无症状、无病时的打预防针、健身运动费用、健康体检，等健康支出费用不断增加；新农合、居民医保每年缴纳费用逐年增加，患病时，使用医保结算，个人所花费，与实施医保前的个人经济支出相差无几，甚至远远高于实施医

保前所花的金钱，更不用说，国内外不断发生的流行范围大小不等的新发传染病所造成的经济、心理、生理巨大付出，难以用金钱衡量。

2、中国医保把维护大众健康的中心主力军，全国各级预防保健、医疗机构的医务工作者、特别是医生强加上了“紧箍咒”,可以说是完全限制了医务工作者、医生的科学行医自由，“用医保基金设立的各种限制使用范围，来倒逼、限制医务工作者、医生的医疗行为”，这是中国医保管理的基本方法和原则。

无数个新闻报道和医生吐槽，并没有改变医保管理局作为医生的财神爷的现状。

3、大家都知道，医学科技是一个发展中的科学，是在临床实践中不断发现新病情、新疾病、创新新诊断和治疗新方法的过程，中国医保的管理基本方法、规定和原则，以固定的、僵死的、落后的、不能创新的管理死规定，来管理如此变化多端、现有治疗方法急需不断革新的广大医生大脑和科学行医医生，就是外行以经济手段，来管理内行的非科学、非常错误的管理政策。

4、中国医保管理系统不断壮大和加强，其工作内容完全是徒劳、劳民伤才，其实质是以有限的经济支出，想来达到健康中国的目的，是严重地违背了社会科学规律，严重地违背了医学自然科学规律，严重地违背了马克思主义、唯物辩证法及科学发展观的基本原理，完全没有把马克思主义、唯物辩证法的基本原理，同中国具体实际相结合，没有把中国特色的社会主义的现实特点，也即没有把中国大众健康和医学科学的具体科学特点，做科学的分析，以严重地限制医学、社会科学发展的中国医保管理措施和政策，来梦想达到健康中国的基本目的，是注定要失败的。

5、中国特色的社会主义的特点，应该以大众健康、健康中国为基本目的公益性管理措施为目的，以能达到公益性健康中国的方法为管理政策，不能以市场经济和以当今医保经济限制手段来实施和梦想达到健康中国的目的。

而当今现实是，不论是公立医院，或民营私立医院，虽然假冒称为非营利性医院，但实质是企业管理为手段，来达到最大盈利为目的，来赚取病人和老百姓的钱，从而为公立医院职工发工资、发生活费，从而为民营医院不倒闭而不断努力，很明显，这样的管理政策，是永远不能实现健康中国的基本目的的，实质上目前的社会现象是，各种医院是打着为人民服务的旗号，来挣取生存生活费，有的甚至连为人民服务的牌子也不打，直接在医院大门等医疗机构大门上贴出“生意兴隆”的对联。

6、由于违背了社会科学和自然科学发展规律，没有把马克思主义、唯物辩证法的基本理论，与中国具体实际相结合，没有认清中国特色的社会主义的基本特性和基本需求，制定

出了错误的中国医保管理政策，导致与医保及其基金相关方面，大量的犯罪案例出现，众所周知，有关骗保、套取医保基金的犯罪案例屡见报端，案例很多，这些事实就是最好的佐证，说明中国医保的管理政策是错误的，是不能满足健康中国的中国人民的基本需求的。

结论：针对上述现实和不足，现建言献策，提出如下改革措施：

1、中国应尽快建立为大众免费医疗的医保政策，国外也有很多国家早已实施为大众免费医疗的医保政策。

2、中国医保筹集基金的政策，可保持现有的政策，但医保基金只是为大众免费医疗提供资金支持。

3、取消医保对全国各地各级合法正规的医疗卫生机构医务人员的任何执业限制，使广大医卫工作者，发挥最大的自由和发挥其最大的聪明才智，全心全意为人民服务，全心全意、自由地科学地救治病人。不存在医保能罚医务人员钱的政策。

4、公立医院的所有医务人员和其他职工，像公务员或教师一样的待遇，和类似的管理。

5、民营医院仍按企业自主管理，收费服务，自负盈亏，为大众提供补充性收费医疗保健服务，不能使用医保基金，医保基金只应用于免费医疗。

6、建立国际合作机制，根据国家之间的友好关系级别，对外国公民也可实施免费医疗的政策

关键字：健康中国；中国医保；管理政策；医学科技；医疗服务；建言献策。

78. ---为了确保大众食品安全，所有经过基因改造育种所收获的食品原料均应科学地认定为新食品原料

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前言和目的：随着科技的发展，生物技术在医学和农业等方面，已被广泛应用，目前普遍使用的非大幅度改变基因但食品原料作物基因也有改变的育种方法，即所谓的“人工基因改良”育种，所生产的食品原料，已广泛应用于粮食生产中，比如当今小麦生产、大豆生产、玉米生产、稻谷生产及瓜果蔬菜，等食品材料的生产，均经过当今“人工基因改良”育种所生产，已经过多年的“人工基因改良”的种子种植-食品原料生产-收获-食品-大众食用-代谢-进入土壤等大自然-“人工基因改良”的种子种植-食品原料生产，这样循环往复周而复始，很多年

过去了，至今，这些经过“人工基因改良”育种，所生产的食品原料，一直被国家随意地认定为是传统食品或原料，不加任何食品安全性审查，更谈不上做无毒、无害，对人体健康不造成任何急性、亚急性、慢性或者其他潜在性危害的鉴定，就直接让广大人民群众食用。

为了保护大众的健康，特做研究，以科学的态度，来看待农业分子生物学高科技，创造产生的新粮食、食品种子及其产品，特提出，所有经过基因改造育种所收获的食品原料均应科学地认定为新食品原料，必须经过食品安全严格审查，确认对大众无害后，才能食用。

方法：总结当前中国“人工基因改良”的种子种植所产生的食品原材料，直接进入大众餐桌被大众食入并存在严重安全隐患的现状，特提出所有经过基因改造育种所收获的食品原料均应科学地认定为新食品原料的观点。

结果：根据目前“人工基因改良”育种的方法，主要分为，人工化学致突变法、基因编辑法、物理促突变法（包括太空非人类环境状态下致突变，等），等等多种方法，获得粮食“人工基因改良”育种，这些方法均是在非自然状态下育种产生，以前人类从来未食用过的新生食品原料。

根据《新食品原料安全性审查管理办法》，第二条　新食品原料是指在我国无传统食用习惯的以下物品:

（一）动物、植物和微生物；

（二）从动物、植物和微生物中分离的成分；

（三）原有结构发生改变的食品成分；

（四）其他新研制的食品原料。

第三条　新食品原料应当具有食品原料的特性，符合应当有的营养要求，且无毒、无害，对人体健康不造成任何急性、亚急性、慢性或者其他潜在性危害。

第四条　新食品原料应当经过国家卫生计生委安全性审查后，方可用于食品生产经营。

很显然，现代食用的大多数食品，包括小麦、大米、大豆、玉米，等作物，均是经过上述“人工基因改良”育种所产生的，若按照严格的科学定义和分类，这些食品原料，肯定属于“在我国无传统食用习惯的物品”，之前肯定未吃过这些经过上述“人工基因改良”育种所产生的粮食等食品原料，因此，这些经过上述“人工基因改良”育种所产生的粮食等食品原料，按照严谨科学地划分，应属于新食品原料，有一些生物医学知识的人，都知道，这些经过上述“人工基因改良”育种所产生的粮食等食品原料，经过基因分子水平的人工变异，肯定要发生复杂的生物生化变化，其所产生的新食品原材料中所含的化学成分以及经过原材料，再加工成

生食品及再加工成上餐桌的食用品，其化学变化，肯定和自然产生的、我国传统食用习惯的物品不相同，因此，所有经过基因改造育种所收获的食品原料均应科学地认定为新食品原料。

结论：综上所述，为了确保大众食品安全，我不得不在此建议，所有经过基因改造育种所收获的食品原料均应科学地认定为新食品原料，并且应严格按照《新食品原料安全性审查管理办法》，严格审查这些经过基因改造育种所收获的食品原料，是否“符合应当有的营养要求，且无毒、无害，对人体健康不造成任何急性、亚急性、慢性或者其他潜在性危害”。同时在此建议，为了确保大众食品安全，中国的《新食品原料安全性审查管理办法》，不能依靠欧洲、美国、日本、韩国，等国家，通过的新食品原料作为标准参考依据，当前中国必须要跟在其屁沟后跑，也必定要通过，应该以严格的科学作为标准，来评判。欧洲、美国、日本、韩国，等国家，通过的经过基因改造育种所收获的食品原料，中国也必定要通过，这样就不讲科学了。

本研究可作为全世界通过“人工基因改良”育种所产生的食品原料，直接让大众食入的国家参考应用，中国若立即实施本建议，将可能是食品安全和大众健康一项划时代的优良改革和斧正。

本研究对各种疾病的病因、预防、治疗、预后等方面至少可能有一定的联系，应该同时引起医学学术界高度重视，我的研究对于疾病的社会-生理-病理-心理等方面的病因、预防、治疗、预后等方面，有着重要的意义。

关键字：食品安全；大众健康；基因工程育种；基因编辑育种；基因化学突变育种；建言献策。

79. 为了确保大众健康、粮食、生物安全性，建议立法保证粮食新品种改良拒绝种子基因无保障地变异---

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概述和目的：随着科技的发展，生物技术在医学和农业等方面，已被广泛应用，特别是基因工程在农业科技方面应用非常广泛，其中包括基因技术育种，应用非常广泛，包括转基因大豆及其它粮食，已走上群众的餐桌，转基因粮食对大众健康及生物、生态安全性，至今已引起持续不断的关注和争论，对于目前普遍使用的非大幅度改变基因但粮食作物基因也有

改变的育种方法，所生产的粮食，是否也会对大众健康及生物、生态安全性，特别是大众健康也产生不可忽视的影响？这方面的流行病学调查和病理生理变化及是否致病，很少有研究，可以说是一片空白，为了保障大众健康和生物、生态安全性，很有必要引起重视并研究清楚，当前在中国等国家普遍使用的非大幅度改变基因但粮食作物基因也有改变的育种方法，所生产的粮食，是否也会对大众健康及生物、生态安全性，特别是大众健康是否也产生不可忽视的影响，在此，特建议，国家应立即建立相关法规，保证粮食新品种改良拒绝种子基因无保障地变异，也就是立法规在保障大众健康和生物、生态安全的情况下，开展改良育种。

方法：总结当代粮食育种的特点和人民生活中对中国常用食物的品味差异，提出该粮食育种生产的粮食食用后，可能存在的安全隐患，提出立法规保障大众健康和生物、生态安全。

结果：

1、现在中国常用的粮食，如小麦、大米、黄豆、玉米，等粮食育种，均采用了在实验室、施加化学因素、物理因素等人工干预下，从而在改变种子基因的状态下，不断筛选出高产的“优良品种”，继而推广应用种植，产生的粮食直接进入大众的餐桌，在大众体内广泛、长期代谢，并进入生态循环。

2、当今，上述粮食作物的传统、早期、自然环境下授粉育种、选择优良品种的操作方法，逐渐停止。

3、很早年以前，有很多老年人，就不由自主地、发自内心地、无任何目的地随意说出，现在的小麦白面馒头的味道，远远不如自然育种所做的白面馒头的味道，用他们的原话是这样说的：“现在的白馍，没有以前的馍味！”，没有以前好吃，这些至少可以说明了，当今新方法育种所产生的粮食，所做的馒头等食品的质量，有明显下降，其原因至少有可能与当今新方法育种有一定的关系。

4、中国目前还没有研究和检测当今新方法育种所制作的食品，对大众健康和生物、生态安全性的影响，也就是说，大众食用人工培育的新品种粮食后，没有作进一步的监测、研究和追踪，是否对大众健康和生物、生态安全性有害，或无害。

5、更没有发现，其与自然育种选种的粮食对大众健康和生物、生态安全性的比较，更谈不上，象新药、保健食品审批那样，提供是否有致癌、致畸、毒副作用的研究报告。但，当今新方法育种所制作的粮食、食品，严格来说，应该看作保健品来监管、审批，审批通过，才能大批量生产。

6、中国目前还没有出台相关法规，保证粮食新品种改良拒绝种子基因无保障地变异，也就是中国还没有立法规在保障大众健康和生物、生态安全的情况下，开展改良育种。

结论：大众健康是头等大事，粮食、食品安全是大众健康最重要、最直接的保障，面对生物、生态环境的的不断恶化，新发传染病的不断产生，必须要有严禁、科学的态度对待粮食等安全问题，在科技不断发展、发达的情况下，粮食育种安全这样一个最基本、最重要的问题没有保证，是不应该的。

本研究，总结中国粮食育种的一些事实，及其可能造成的不良影响，在此提请和建言献策如下：

1，建议立法保证粮食新品种改良拒绝种子基因无保障地变异，保障大众健康和生物、生态安全；

2，提出，人工培育粮食新品种在全面播种、进入大众餐桌前，必须要进行安全性检测，合格后方可进行种植、生产和食用；

3，同时建议，之前人工培育的新粮食品种，也应该做相关安全性检测，做相关流行病学调查，发现问题，及时终止该粮食种植和食用，确保安全；

4，中国作为大国，应该为世界粮食安全做贡献，提出中国标准和中国方案，作为世界标准参考利用或定为世界标准；

5，本研究可作为联合国相关组织、及相关政府、非政府组织及其他国家参考应用，共同为人类粮食安全做贡献。

6，只有粮食育种安全，才能保障粮食安全，从而才能保障生物、生态环境安全及大众健康；

7，建议尽可能在自然状态下，粮食自然授粉、自然选种。

鉴于大众带病状态及多种疾病患病率、死亡率居高不下，本研究对各种疾病的病因、预防、治疗、预后等方面至少可能有一定的联系，应该同时引起医学学术界高度重视，我的研究对于疾病的社会-生理-病理-心理等方面的病因、预防、治疗、预后等方面，有着重要的意义。

关键字：粮食育种；粮食安全；生态安全；大众健康；建言献策。

80. 居民环卫及环卫工人健康提高的几点建议建言献策--

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目的：为了防治在搞好环境卫生的过程中所造成的环境污染，及防治、提高广大清洁、环卫工的人身健康，促进健康中国、健康社会的基本目的和大众需求，特作本研究和建言献策。

方法：总结本人社会经历有关清洁、环卫工人的基本工作过程现实，和查阅相关科学研究文献，找出不足，创新改革、防治的新点子和新策略，为人类社会的进步做一些贡献。

结果：

1、搞好环境卫生的过程中所造成的环境污染情况

1.1.当今清洁工作的工作，最常见的是清扫环境，有的是人工清扫，有的是机器清扫，这样均会给环境造成灰尘沸腾和飘扬，这样，不仅会给清洁工造成健康损害，还会给过路人及常住居民造成污染和健康损伤，这也是城市肺癌发病率很高的原因之一吧【1】。

1.2.大家或有点知识的公民都知道，冬季到来，大雪致道路不通、行走困难，为了快速疏通道路，常应用融雪化学物品洒向路面，这样一来，使用融雪化学物品的量会很大，肯定会给环境和大气造成持久地污染，损害道路、桥梁、田地、粮食、空气，等，严重污染环境。之前下雪向道路撒食盐的做法已经不用啦，单纯撒食盐环境污染会很小。

1.3.春夏秋季或冬季到来，高温、干旱不断发生，为了解决缺水、高温、干旱问题，解决办法就是人工降雨或人工降雪，大家知道，人工降雨或人工降雪必须要发射炮弹或火箭，发射一牧炮弹或火箭，所释放或造成的环境污染物质是巨大的，从制造到发射的过程，所产生的污染物难以估量，每次人工降雨或人工降雪必须发射很多炮弹或火箭，这样所造成的环境污染是巨大的。

1.4.当然，环卫工人所做的工作内容很多，肯定不限于打扫卫生，工作量也很大，包括垃圾的收集和清理，等众多内容，科技发展到当今，人类的垃圾合理化处理，解决了很多环境污染问题，但离达到无污染的理想标准，肯定是还有很远的距离，还需要不断努力和发展。

2.搞好环境卫生的过程中所造成环卫工人健康损伤和危害

2010 年华中科技大学同济医学院公共卫生学院的研究者对武汉市中心城区环卫工人健康与保障调查，得出结论，武汉市中心城区环卫工人两周患病率和慢性病患病率均高于一般

人群，卫生服务利用水平低于一般人群，社会保障水平也较低；城管、医保和劳保部门应采取协调措施，完善环卫工人特别是其中的临时工和工龄较短者的医疗保障及社会保障【2】。清洁工人面临着健康问题的同时，当前还存在如下问题：

2.1.中国清洁工人现在的处境，可以说仍然是被遗忘的角落，虽然不遗余力地做着美化环境的辛苦工作，但对其生活和健康问题的关心程度，还很不到位。

2.2.中国清洁工人普遍年龄较大，年轻人不干，常常是农民工或临时工，常没有社会保险。

2.3.近 20 多年来，没有发现有关中国清洁工人健康防治现状流行病学、公共卫生学研究，就是说，对其健康危害问题，没有重视，置之不理，听之任之。

2.4.随着中国经济的发展，人民大众的生活水平在提高，但中国清洁工人的心理健康问题未得到相应防治，未得到提高。

结论：为了解决上述问题，特提出如下改革建议和建言献策：

1、切实建立雇佣中国清洁工人依靠劳动法和劳动合同法为基本劳动保障准绳的制度，雇佣的清洁工人必须签订劳动合同，缴纳社会保险；

2、被依法雇佣的清洁工人必须有社会保险，若是农民工、无业人员或下岗工人，即使达到或超出退休年龄，也必须缴纳社会保险；

3、建立合法雇佣的清洁工人，实施特殊的医疗保险制度，像中国石油系统或五保人员那样的医疗保障优惠制度，对清洁工人实施医疗保障；

4、建立清洁工人免费每年至少体检一次的健康保障制度；

5、建立清洁工人工作时佩戴防污染口罩或面具的劳动保护制度，加强清洁工人劳动保护所用防污染口罩、防污染面具、防污染手套、鞋子、工作服的研制和生产使用；

6、建立清洁工人打扫卫生工作时，需喷施水雾的方法，来防治粉尘、灰尘飘飞弥漫、污染空气的方法制度；

7、建立制度，以经济和制度作保障，定期积极开张中国环卫清洁工人卫生健康现状调查，为正确制定防治制度打下基础；

8、建立中国清洁工与清洁工种有关的教育、研究机构或中、高等教育专业，开展防治垃圾、清洁等相关的科学防治研究，为更好地防治垃圾、清洁等相关工种的危害和高水平的治理，打下坚实的人才梯队和技术支撑。

9、开展国际间垃圾、清洁等相关工种的科研、工作交流，提高大众清洁环境的获得美感和健康收益。

10、大雪使道路结冰时，建议禁用有任何危害作用的融雪剂化学物质铺撒向道路等环境，以防止添加环境污染因素。

11、尽可能杜绝使用人工降雨、人工降雪炮弹、导弹。

12、本研究和建言献策值得尽快实施利用。

关键字：环境卫生；环境清洁工种；清洁工人；健康保障：健康中国；健康世界；建言献策

81. 雷公藤甲素通过 PLK1 的 O-GlcNAc 修饰抑制子宫内膜癌细胞增殖、迁移和细胞周期进展

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研究目的：探究雷公藤甲素对子宫内膜癌细胞的影响及其潜在的分子机制。

材料与方法：使用不同浓度的雷公藤甲素（5、10、25、100 和 500 nmol/L）处理子宫内膜癌 ISHIKAWA 细胞株。细胞增殖水平通过 CCK-8 法进行评估，细胞迁移能力通过 Transwell 实验测定，细胞周期进展通过流式细胞术分析。通过 Western blot 技术检测极性蛋白激酶 1（PLK1）和 O-连接β-N-乙酰葡糖胺（O-GlcNAc）转移酶（OGT）的蛋白表达水平，同时采用免疫共沉淀（co-IP）方法探究 PLK1 与 OGT 之间的相互作用。对 ISHIKAWA 细胞进行 flag-NC 和 flag-PLK1 的转染，采用 25 nmol/L 雷公藤甲素进行处理，以评估过表达 PLK1 对细胞增殖、迁移和细胞周期进展的影响，并检测 PLK1 与 OGT 的蛋白表达水平和相互作用。此外，通过质谱（MS）分析纯化的 PLK1 蛋白以确定 O-GlcNAc 修饰水平。在 ISHIKAWA 细胞中分别加入 OGA 抑制剂（Thiamet G，200 μmol/L）和 OGT 抑制剂（OSMI，100 μmol/L），以评估 O-GlcNAc 修饰水平对细胞增殖、迁移和细胞周期进展的影响，并检测 PLK1 与 OGT 的相互作用。

结果：雷公藤甲素呈现剂量依赖性地抑制 ISHIKAWA 细胞的增殖、迁移和细胞周期进展，并显著促进 PLK1 和 OGT 蛋白的表达（$P<0.05$）。在 ISHIKAWA 细胞中，PLK1 与 OGT 存在明显的相互作用，该相互作用在雷公藤甲素的作用下显著增强（$P<0.05$）。相比于 flag-NC 组，flag-PLK1 组细胞的增殖、迁移和细胞周期进展受到更显著的抑制，且 PLK1 与 OGT 之间的相互作用增强（$P<0.05$）。在 PLK1 蛋白中检测到了 O-GlcNAc 修饰的存在。与对照组

相比，Thiamet G 处理组的细胞增殖、迁移和细胞周期受到抑制，同时 PLK1 与 OGT 的相互作用增强（P<0.05）；而 OSMI 处理组显示出细胞增殖、迁移和细胞周期的增强，PLK1 与 OGT 的相互作用减弱（P<0.05）。

结论：本研究表明，雷公藤甲素通过促进 PLK1 的 O-GlcNAc 修饰，从而有效抑制了子宫内膜癌细胞的增殖、迁移和细胞周期进展，揭示了其潜在的抗肿瘤机制。

关键字：雷公藤甲素、子宫内膜癌、极性蛋白激酶 1、O-连接β-N-乙酰葡糖胺转移酶、免疫共沉淀

82. 迫切需要切实建立相关制度，杜绝野外溺水反复发生

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目的：生活实践告诉我们，每年耳闻、看新闻报道，均听说有少年学生野外溺水身亡，为了防治溺水悲剧不再发生，在此特研究总结出几项管理制度，来防治或杜绝野外溺水，希望能被参考应用，从而达到预期目的。

方法：总结溺水不幸事故的反复发生但防治效果不佳事实，结合现实生活实际，总结防治溺水的有效救治管理方法，从而达到防治悲剧再次发生的目的。

结果：全国各地每年均有野外溺水的不幸事故发生，但从事实来看，防治效果始终不能令大众满意，因此，迫切需要研究总结有效防治溺水事件再次发生的方法势在必行。

本研究总结出如下有效防治野外溺水的管理规定：

1、建立全国统一、准确、全面的溺水身亡、伤害、致病、致残及相关经济等方面损失的大数据库；

2、收集全国各地溺水身亡、伤害、致病、致残及相关经济等方面损失的每一个案例；

3、积极组织相关医学专家、水利专家、救灾专业人士及相关行政管理部门，研讨上述相关数据库、伤亡病例及社会影响，从而做出正确的防治策略；

4、积极开展溺水身亡、伤害、致病、致残的危急时刻，患者的病理生理、心理、行为规律研究；

5、开展国际性交流和合作；

6、各地各级中小学校，均要开展防野外溺水课程；

7、建立各地各级中小学校，班级、学校防野外溺水责任制，规定，若那个学校、班级学生发生野外溺水事故，班级各科教师及校领导在晋升、加薪、晋级等方面一票否决。

8、建立防野外溺水河长制度。

9、联合相关专业部门，探查各水域水情实况，并做相应明示，以利公众对相关水情的切实了解，从而有利于野外溺水的发生。

10、建立制度，勒令家长认真做好监护人的职责，并由家长签订保证书，密切配合学校、防野外溺水河长及有关部门，做好防野外溺水措施。

11、建立制度，若发生暴雨、山洪、泥石流等自然灾害时，或预警时，学校、家长、防野外溺水河长及有关部门，要提前做好防范措施，如：提前转移到安全地带、防治青少年等无自主行为能力的人外出等措施。

结论：本研究所创新的有效防治野外溺水的管理规定，值得参考应用。

关键字：溺水防治；意外死亡；溺水身亡；管理策略；大众健康提高；建言献策。

83. 一种新的放射性损伤敏感性监测方法的探讨--

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目的：为了减轻放射性损伤，特别是放射性医疗损伤，探讨一种监测人体对放射性损伤敏感性的方法。

方法：通过一例临床放射性损伤敏感性的特点，明显表现在皮肤在 CT 照射后，发生明显损伤的病情，得到启发，研究发现一种监测放射性损伤敏感性的方法。

结果：鉴于放射性诊疗的必要性，及其放射性损伤副作用的严重性，探索一种新的放射性损伤敏感性监测方法势在必行，要达到有效放射性损伤敏感性监测，从而达到精准、个性化治疗的目的，应该在放射性损伤敏感性监测时，不能再做全身性放射性照射，或不做放射性照射。

结合上述病例，病人对放射性损伤敏感，对于放射性损伤敏感性监测，我们可以监测病人的皮肤，对病人做相关刺激，观察病人的敏感性，若观察到病人高敏性，说明病人对外界刺激高度敏感，从而指导病人尽可能不做放射性诊疗，或做低剂量的放射性诊疗操作。

对于病人皮肤敏感性试验的刺激因子的选择，最好的刺激因子应该是，皮肤放射性照射，利用特制的非常局限的放射性照射仪器，局限性、不同剂量的单纯小片状照射皮肤，然后检测皮肤的损伤程度，得出皮肤对放射性是否敏感及相关照射剂量，从而判断病人是否对放射性诊疗是否敏感，及敏感病人对所需要的健康低剂量照射的剂量，从而达到精准、个性化有效治疗的目的。

该检测方法适用于对病人的监测，和对医务人员的监测，还可以应用到其他与放射性损伤有关的职业人员的监测。

结论：本研究总结一个敏感病人皮肤放射性损伤的临床特点和表现，结合当今放射性损伤防治现状和迫切需要精准、个性化有效放射性诊断和治疗的现状，创新一种新的放射性损伤敏感性监测方法，该方法简单易行，对病人损伤小或几乎无损伤，值得进一步研究和实施，以减少放射性诊疗操作时的放射性损伤到最低程度，达到理想的放射性诊疗效果。

当然，本研究仅仅是研究设想和方案，需要进一步研究实施，及临床实验性应用，最终广泛应用于临床。

本研究应该有巨大的经济效益和社会效益，值得国内外参考应用。

关键字：放射性损伤；放射损伤敏感性；检测方法；精准放射性诊疗；临床病例。

84. 医用放射性损伤的防治进展和防治建议--

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目的：为了更好地做好放射性诊疗和防治医用放射性损伤，特作此研究。

方法:总结当前医用放射性诊疗现状，及医用放射性损伤的防治进展，提出防治建议。

结果：研究提出了 10 项医用放射性损伤的防治方法如下：

1.重视医用放射性诊疗器械诊疗操作时的防护，不仅操作者要做好防护，病人也要做好严格防护。

2.健康体检应规定不做 CT 检查，可做磁共振检查，或低微放射剂量的拍片检查。

3.作为放射性损伤的敏感部位眼睛的防护，应该引起高度重视，务必使放射性诊疗操作者和受检查治疗者，防护其眼睛等其他器官。

4.大力开展精准放射性诊疗操作的研究。

5.大力开展精准放射性诊疗操作的防治方法。

6.大力研究放射性损伤的临床治疗。

7.在全国范围内大力开展放射性损伤有关知识的健康宣教。

8.医学科技需要进一步发展，开发研究替代放射性诊疗操作的新的医疗器械，或开发研究更低辐射剂量的医疗器械。

9.建议建立新法规，实施放射性诊疗操作限制制度，像抗菌素使用那样，建立放射性诊疗操作处方权制度。

10.建立法规，优化医院开展放射性诊疗器械准入制度。

结论：在当今滥用 CT 作为一般常规体检检查方法的情况下，医用放射性损伤的防治迫切和势在必行，本研究提出的 10 项医用放射性损伤的防治方法，弥补了医用放射性损伤防治的不足，非常值得参考应用。

关键字：医用放射性损伤；医用放射性诊疗；放射性损伤防护；放射性损伤防护策略；精准放射性诊疗。

85. Novel gene signature for predicting biochemical recurrence-free survival of prostate cancer and PRAME modulates prostate cancer progression

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Biochemical recurrence (BCR) is considered as an early sign of prostate cancer (PCa) progression after initial treatment, such as radical prostatectomy and radiotherapy; hence, it is important to stratify patients at risk of BCR. In this study, we established a robust 8-gene signature (APOF, Clorf64, RPE65, SEMG1, ARHGDIG, COMP, MKI67 and PRAME) based on the PCa transcriptome profiles in the Cancer Genome Atlas (TCGA) for predicting BCR-free survival of PCa, which was further validated in the MSK-IMPACT Clinical Sequencing Cohort (MSKCC) PCa cohort. Moreover, we found that one risk-related gene (PRAME) was upregulated in tumor

samples, particularly in high-risk group was well as in patients metastatic tumor and was correlated with chemotherapeutic drug response. In vitro experiments showed that knocking down PRAME reduced the proliferation, migration, and invasion of PCa cells. Therefore, our study established a new 8-gene signature that could accurately predict the BCR risk of PCa. Inhibition of PRAME attenuated the proliferation, invasion, and migration of PCa cells. These findings provide a novel tool for stratifying high-risk PCa patient and shed light on the mechanism of PCa progression.

Key Words：Prostate cancer, biochemical recurrence, prognostic signature, PRAME

86. 黄芪甲苷调控免疫细胞抗肿瘤作用机制研究进展

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黄芪是我国传统的补虚药物之一，现代临床中常应用黄芪与多味中药配伍用于抗肿瘤治疗，疗效确切。现代药理学显示，黄芪的活性成分主要有多糖类、皂苷类以及黄酮类三大类，而作为皂苷类的黄芪甲苷是评价黄芪质量的主要指标和发挥药效的重要物质基础，其被证实具有调节免疫和抗肿瘤等药理作用。大量研究证实，黄芪甲苷通过调节肿瘤免疫微环境中巨噬细胞、T 淋巴细胞、调节性 T 细胞、树突状细胞以及自然杀伤细胞等免疫细胞，提高免疫细胞的功能、活性以及相关细胞因子的分泌和表达，增强免疫应答能力，扭转免疫抑制状态，从而提高免疫细胞对肿瘤细胞的杀伤和消灭能力，更好地发挥抗肿瘤作用。本文通过收集近年来黄芪甲苷抗肿瘤治疗的相关研究，从黄芪甲苷调节免疫细胞以发挥抗肿瘤作用的具体机制方面进行论述，以期为研究黄芪及黄芪甲苷相关的新型临床抗肿瘤药物提供新的理论依据，提高中医药在抗肿瘤综合治疗方面的应用度和有效性。

关键字：黄芪甲苷；免疫细胞；抗肿瘤；研究进展

87. 中药单体调控免疫细胞治疗肺癌的作用机制研究进展

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肺癌是世界范围内最常见的呼吸道恶性肿瘤，也是我国发病率和死亡率最高的肿瘤疾病之一，肺癌的防治工作已经成为急需解决的重大科学问题。近年来，中医药在抗肺癌综合治疗中应用广泛，疗效确切。大量研究发现，中药单体如多糖类、黄酮类、皂苷类、二萜醌类、酚类、五环三萜类以及香豆素类等可以通过调节肺癌肿瘤免疫微环境中巨噬细胞、自然杀伤细胞、髓系抑制细胞、T 细胞、调节性 T 细胞、B 细胞以及树突状细胞等免疫细胞以及相关免疫细胞因子如 IL-2、IL-10、TNF-α、IFN-γ等，增加免疫细胞的数量、活性以及相关细胞因子的分泌和表达，提高免疫细胞的功能，改善肺癌肿瘤免疫微环境，扭转免疫抑制状态，从而增强免疫细胞对肺癌肿瘤细胞的杀伤作用，更好地发挥抗肺癌治疗的作用。本文通过收集近年来国内外中药单体在抗肺癌治疗中的相关文献，从中药单体调节免疫细胞及其抗肺癌作用具体机制方面进行论述，以期为中药单体相关的新型临床抗肺癌药物研发提供新的理论依据，促进中西医结合治疗肺癌在临床中的广泛应用。

关键字：中药单体；免疫细胞；肺癌；机制研究

88. Prevalence, Patterns, Risk factors and Outcomes of Peritoneal Metastases after Laparoscopic Hepatectomy for Hepatocellular Carcinoma: a Multicenter Study from China

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Background: We aim to investigate the prevalence, patterns, risk factors, and outcomes of peritoneal metastases (PM) after curative laparoscopic hepatectomy (LH) for hepatocellular carcinoma (HCC).

Methods: A multicenter cohort of 2138 HCC patients who underwent curative LH from August 2010 to December 2016 from seven hospitals in China was retrospectively analyzed. The incidence of PM following LH was evaluated and compared with that in open hepatectomy (OH) after 1:1 propensity score matching (PSM).

Results: PM prevalence was 5.1% (15/295) in the early period [2010–2013], 2.6% (47/1,843) in the later period [2014–2016], and 2.9% (62/2,138) in all LH patients, which was similar to 4.0% (59/1,490) in the OH patients. The recurrence patterns, timing, and treatment did not significantly vary between the LH and OH patients (P>0.05). Multivariate logistic regression revealed that tumor diameter >5 cm, non-anatomical resection, presence of microvascular invasion, and lesions <2 cm from major blood vessels were independent risk factors of PM after LH. Of the 62 cases with PM, 26 (41.9%) had PM only, 34 (54.9%) had intrahepatic recurrence (IHR) and PM, and 2 (3.2%) had synchronous extraperitoneal metastases (EPM). Patients with resectable PM had a 5-year overall survival (OS) of 65.0% compared to 9.0% for unresectable PM (P=0.001).

Conclusions: The prevalence, patterns and independent risk factors of PM were identified for HCC patients after LH. LH was not associated with increased incidence of PM in HCC patients for experienced surgeons. Surgical re-excision of PM was associated with prolonged survival.

Key Words： Prevalence; hepatocellular carcinoma (HCC); peritoneal metastases (PM); laparoscopic hepatectomy (LH); open hepatectomy (OH)

89. Lactylation of IGF2BP3 promotes lenvatinib resistance via serine metabolism reprogramming in HCC

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Background and Aims: Acquired resistance remains a bottleneck in lenvatinib therapy for advanced hepatocellular carcinoma (HCC). Metabolic adaptation and epigenetic remodeling are recognized hallmarks of cancer that may contribute to acquired resistance. Deciphering the

crosstalk between metabolic reprogramming and epigenetic regulation is a promising strategy to overcome lenvatinib resistance.

Approach and Results: Various acquired lenvatinib resistant cell models were generated. Through transcriptome, proteome, lactylation proteome, and other functional studies, we delineated a metabolic phenotype that mediates lenvatinib resistance in HCC, whereby heightened glycolysis levels leading to lactate accumulation and subsequent lysine lactylation of IGF2BP3. Lactylation at the K76 site of IGF2BP3 was found to be essential for capturing target PCK2 and NRF2 mRNA, boosting PCK2 and NRF2 expression. Metabolomics and metabolic flux studies revealed that lactylated IGF2BP3-PCK2 hijacks gluconeogenesis-derived carbon flow to serine synthesis. As an m6A reader, IGF2BP3 lactylation fuels one-carbon metabolism and S-adenosylmethionine (SAM) biosynthesis for N6-methyladenosine (m6A) methylation of PCK2 and NRF2 mRNA. The lactylated IGF2BP3-PCK2-SAM-m6A loop sustains elevated PCK2 and NRF2 expression, fortifying the antioxidant system and ultimately conferring lenvatinib resistance in HCC. Treatment of lenvatinib-resistant HCC with liposomes carrying siRNA targeting IGF2BP3 or PCK2 restored lenvatinib response in vivo. Finally, elevated IGF2BP3 lactylation may act as a biomarker for lenvatinib resistance in HCC patients.

Conclusions: We demonstrate a link between metabolic reprogramming-epigenetic regulation and suggest that metabolically dismantling the acquired resistant features of tumors may provide potential combination approaches for lenvatinib resistance in HCC.

Key Words： glycolysis; PCK2; SAM; ROS; antioxidant

90. 超声波介导定向微泡破坏的药物输送系统：一种有前途的神经胶质母细胞瘤治疗方法

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血脑屏障（Blood-brain barrier , BBB）阻碍大分子化疗药物向脑肿瘤的输送，导致其利用率低且对周围组织器官产生毒副作用。研究表明，超声波靶向微泡破坏（Ultrasonic targeted microbubble destruction, UTMD）技术可以安全可逆开放 BBB。基于此，我们开发了一种基

于聚乳酸-乙醇酸 (poly(lactic-co-glycolic acid), PLGA) 的新型载药微泡复合物(GA/PLGA-CMB)，联合聚焦超声 (Focused Ultrasound, FUS) 将藤黄酸 (Gambogic Acid, GA) 靶向脑肿瘤区域，从而形成一种新型药物输送系统，特别适用于神经胶质母细胞瘤（Glioblastoma, GBM）。通过生化和影像学在体内外评估其抗 GBM 作用。与对照组相比，GA/PLGA-CMB 联合 FUS 对人源性胶质母细胞瘤细胞系 U87 和 U251 具有显著的抑制作用（P<0.05）。此外，GA/PLGA-CMB 联合 FUS 可以安全开放 BBB 并定向释放 GA 治疗 GBM。总而言之，PLGA-CMB 联合 FUS 是一种安全有效的药物递送系统，为 GBM 的化疗及定向治疗提供了一种极具应用前景的策略。

关键字：胶质母细胞瘤；定向治疗；化疗

91. 联合贝伐珠单抗治疗非小细胞肺癌对患者血清肿瘤标志物水平影响的 Meta 分析

翟明明

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目的：系统性评价紫杉醇、卡铂联合与不联合贝伐珠单抗治疗非小细胞肺癌对患者血清肿瘤标志物水平的影响。

方法：应用计算机检索中国知网（CNKI）、维普数据库、万方数据库、Pubmed、Web of science 中非小细胞肺癌治疗的相关 RCT。检索时间为 2003 年 1 月-2023 年 12 月。根据相关纳入与排除标准筛选文献、提取资料，并对纳入文献进行质量评价。采用软件 RevMan5.3 和 R3.6.3 进行 Meta 分析。运用亚组分析、剪补法分析异质性和结果的稳定性，使用 Harbord's 检验和漏斗图评价发表偏倚。

结果：本文最终纳入 15 篇文献，共计包括 3879 例患者，实验组治疗方案为紫杉醇、卡铂联合贝伐珠单抗，对照组治疗方案为紫杉醇、卡铂。Meta 分析结果显示：治疗前，两组患者血清癌胚抗原(CEA)、糖类抗原 125(CA125)、细胞角质蛋白 19 片段抗原 21-1(CYFRA21-1)水平无显著性差异(P>0.05)；治疗后，两组患者血清 CEA、CA125、CYFRA21-1 水平均低于治疗前，且实验组低于对照组，差异具有显著性(P<0.05)，研究结果具有稳定性。

结论：联合贝伐珠单抗会提高治疗效果，降低患者血清肿瘤标志物水平。

关键字：贝伐珠单抗、紫杉醇+卡铂、肿瘤标志物、非小细胞肺癌、Meta 分析

92. FOXP4 promotes lung cancer cell proliferation and invasion by regulating tumor-associated macrophage polarization through the β-catenin/FOSL2/ARID5A signaling pathway

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Background: Tumor-associated macrophages (TAM) influence lung tumor development, and the β-catenin/FOSL2/ARID5A signaling pathway may be a key pathway regulating macrophage polarization, but the role of FOXP4 in regulating TAM polarization through the β-catenin/FOSL2/ARID5A signaling pathway in influencing the proliferation and invasion of lung cancer cells is unclear.

Methods: TAM was transfected with a plasmid knocking down or overexpressing FOXP4, co-cultured with lung cancer cells A549, and lung cancer mice with low expression /overexpression of FOXP4 were prepared, and β-catenin agonist (SKL2001), β-catenin inhibitor (IWR-1), or macrophage accumulation inhibitor (Ki20227) intervened in TAM or mice. M1/M2 phenotype, cell proliferation, migration, invasion, β-catenin/FOSL2/ARID5A pathway and histopathological changes were evaluated by flow cytometry, CCK-8, clone formation assay, scratch assay, Transwell, qRT-PCR, Western blot and HE staining.

Results: FOXP4 was highly expressed in TAM, and FOXP4 interacted with β-catenin proteins, and low expression of FOXP4 inhibited the proliferation, invasion, and migration of lung cancer, and enhanced the polarization of TAM to M1-type macrophages, and affected the transcription of the β-catenin/FOSL2/ARID5A signaling pathway. Moreover, in vivo silencing of FOXP4 regulated TAM polarization and promoted apoptosis in lung cancer. Overexpression of FOXP4 plays the opposite effect.

Conclusion: The results demonstrate that FOXP4 promotes lung cancer cell proliferation and invasion by regulating TAM polarization through the β-catenin/FOSL2/ARID5A signaling pathway.

Key Words ： lung cancer,Forkhead box P,tumor-associated macrophages,macrophage polarization,β-catenin/FOSL2/ARID5A signaling pathway

93. HnRNPR-Mediated UPF3B mRNA Splicing Drives Hepatocellular Carcinoma Metastasis

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Introduction: Abnormal alternative splicing (AS) contributes to aggressive intrahepatic invasion and metastatic spread, leading to the high lethality of hepatocellular carcinoma (HCC).

Objectives: This study aims to investigate the functional implications of UPF3B-S (a truncated oncogenic splice variant) in HCC metastasis.

Methods: Basescope assay was performed to analyze the expression of UPF3B-S mRNA in tissues and cells. RNA immunoprecipitation, and in vitro and in vivo models were used to explore the role of UPF3B-S and the underlying mechanisms.

Results: We show that splicing factor HnRNPR binds to the pre-mRNA of UPF3B via its RRM2 domain to generate an exon 8 exclusion truncated splice variant UPF3B-S. High expression of UPF3B-S is correlated with tumor metastasis and unfavorable overall survival in patients with HCC. The knockdown of UPF3B-S markedly suppresses the invasive and migratory capacities of HCC cells in vitro and in vivo. Mechanistically, UPF3B-S protein targets the 3'-UTR of CDH1 mRNA to enhance the degradation of CDH1 mRNA, which results in the downregulation of E-cadherin and the activation of epithelial–mesenchymal transition. Overexpression of UPF3B-S enhances the dephosphorylation of LATS1 and the nuclear accumulation of YAP1 to trigger the Hippo signaling pathway.

Conclusion: Our findings suggest that HnRNPR-induced UPF3B-S promotes HCC invasion and metastasis by exhausting CDH1 mRNA and modulating YAP1-Hippo signaling. UPF3B-S could potentially serve as a promising biomarker for the clinical management of invasive HCC.

Key Words： Alternative Splicing; Hepatocellular Carcinoma; Invasion and Metastasis; UPF3B-S; HnRNPR

94. Rectifying the impairment of immune thrombocytopenia plasmas through photobiomodulation

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Immune thrombocytopenia (ITP) is an autoimmune hemorrhage disorder. The first-line treatment of this disorder is corticosteroids, followed by thrombopoietin (TPO) receptor agonists such as Nplate, and/or splenectomy. Yet, the extended usage of corticosteroids or the expensive Nplate, coupled with the implications of splenectomy, raises concerns due to the array of associated side effects and an escalated vulnerability to subsequent complications. The current investigation shows that while anti-platelet antibodies and ITP plasmas hinder megakaryocyte differentiation and maturation and impair proplatelet and platelet formation in ex vivo culture of umbilical cord human CD34+ stem cells (cHSCs), low-level laser (LLL) treatment or photobiomodulation (PBM) effectively mitigates these detrimental impacts. PBM reinstated megakaryocyte differentiation and maturation, bolstering proplatelet and platelet formation in the presence of auto-platelet antibodies or ITP plasmas. The mitigating effects of PBM appear to pivot on its capacity to uphold cellular mitochondrial functionality and rectify the mitochondrial impairments engendered by anti-platelet antibodies or ITP plasmas. These findings underscore the potential of PBM as a safe and cost-efficient alternative for the management of a specific subset of ITP patients.

Key Words： Megakaryocyte; ITP; PBM;Mitochondrion

95. 基于血浆代谢组学预测甲状腺乳头状癌术后 131I 治疗前淋巴结转移状态

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目的：淋巴结转移(lymph node metastasis, LNM)是甲状腺乳头状癌(papillary thyroid carcinoma, PTC)重要的预后因素之一。在放射性 131I 治疗前对患者淋巴结转移状态的精准评估是 131I 个体化治疗剂量决策的重要依据，显著影响 131I 治疗效果和患者预后。本研究旨在利用血浆代谢组学技术寻找 PTC 术后淋巴结转移的潜在分子标志物。

方法：收集 PTC 术后 131I 放射性内照射前的患者血浆样本。选取的术后淋巴结转移的 PTC 者以及术后不存在淋巴结转移的 PTC 者各 35 例（年龄、性别和抗甲状腺球蛋白抗体阳性率匹配）。采用液相色谱-串联质谱法进行代谢组学实验。采用受试者工作特征(ROC)曲线评价差异代谢物鉴别 PTC 术后淋巴结转移和无淋巴结转移的诊断能力。采用 KEGG 通路分析对差异代谢物进行通路分析。

结果：在两组中患者的血浆代谢组学分析共鉴定出 1056 种代谢产物。其中鉴定出差异代谢产物 159 个，57 个代谢产物上调，102 个代谢产物下调（P<0.05)。KEGG 富集分析表明，差异代谢物主要富集于癌症中的胆碱代谢、蛋白质消化吸收、癌症中心碳代谢、矿物质吸收、甘氨酸、丝氨酸和苏氨酸代谢等。在 ROC 分析中，次黄嘌呤和脱氧肌苷两种代谢物的曲线下面积（AUC）均> 0.7（分别为 0.722 和 0.779），具有较好的鉴别能力；两者联合应用对 PTC 术后淋巴结转移具有更高的诊断效能（AUC=0.831）。

结论：本研究初步确定了 PTC 不同淋巴结转移状态下的代谢组学差异。次黄嘌呤和脱氧肌苷可作为预测 PTC 患者术后淋巴结转移状态的生物标志物，进一步由此指导后续放射性 131I 治疗。此外，胆碱代谢等通路异常可能是 PTC 转移进展的关键步骤，是潜在 PTC 治疗靶点。

关键字：代谢组学 甲状腺乳头状癌 淋巴结转移 放射性 131I 治疗

96. Metabolic Heterogeneity and Potential Immunotherapeutic Response Revealed by Single Cell Transcriptomics in Breast Cancer

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Backgrounds ：Breast cancer (BC) shows remarkable heterogeneity. However, the transcriptomic heterogeneity of BC at the single-cell level remains largely unknown.

Methods ： Here, we acquired BC samples from 14 patients. ScRNA-seq and bioinformatic analysis, IHC, and IF assay were carried out.

Results ： ScRNA-seq was carried out, we identified 10 different cell types. We found CAFs exhibit distinct biological functions and may promote resistance to therapy. Metabolic analysis of tumor cells revealed heterogeneity in glycolysis, gluconeogenesis, and fatty acid synthetase reprogramming, leading to chemotherapy resistance. Furthermore, patients with multiple metastases and progression were predicted to benefit from immunotherapy based on a heterogeneity analysis of T cells and tumor cells.

Conclusions ： Our findings provide a comprehensive understanding of the heterogeneity of BC，provide deep insight into the correlation between cancer metabolism and chemotherapy resistance and enable the prediction of immune therapy responses based on T-cell heterogeneity.

Key Words： metabolic heterogeneity; chemotherapy; immunotherapeutic response; single-cell RNA sequencing; breast cancer.

97. Tyrosine metabolic reprogramming coordinated with the tricarboxylic acid cycle to drive glioma immune evasion by regulating PD-L1 expression

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Due to the existence of the blood-brain barrier in glioma, traditional drug therapy has the poor therapeutic outcome. Emerging immunotherapy has been shown to have satisfactory therapeutic effects in solid tumors, and it is clinically instructive to explore the possibility of immunotherapy in glioma. We performed a retrospective analysis of RNA-seq data and clinical information in 1027 glioma patients, utilizing machine learning to explore the relationship between tyrosine metabolizing enzymes and clinical characteristics. In addition, we also assessed the role of tyrosine metabolizing enzymes in the immune microenvironment including immune infiltration

and immune evasion. Highly-expressed tyrosine metabolizing enzymes 4-hydroxyphenylpyruvate dioxygenase (HPD), homogentisate 1,2-dioxygenase (HGD), and fumarylacetoacetate hydrolase (FAH) not only promote the malignant phenotype of glioma, but are also closely related to poor prognosis. The expression of tyrosine metabolizing enzymes could distinguish the malignancy degree of glioma. More importantly, tyrosine metabolizing enzymes regulate the adaptive immune process in glioma. Mechanistically, multiple metabolic enzymes remodel fumarate metabolism, promote α-KG production, induce PD-L1 expression, and help glioma evade immune surveillance. Our data suggest that the metabolic subclass driven by tyrosine metabolism provides promising targets for immunotherapy of glioma.

Key Words： tyrosine metabolism; fumarate; α-KG; immune evasion; glioma

98. Interruption of bile acid enterohepatic circulation inhibits glycogen synthesis and promotes hepatocellular carcinoma progression

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The enterohepatic circulation of bile acids (BAs) is the feedback regulation process in dietary rhythm, and BAs are considered to be important modulators that facilitate nutrient absorption and regulate energy metabolism. However, the potential role of bile acid cycle in hepatocellular carcinoma (HCC) has not been elucidated. Here, we found that glycogen metabolism is significantly inhibited in HCC, and has a significant negative correlation with the clinical status of HCC patients, which has clinical diagnostic value. Integrating HCC patient data from the TCGA and GEO databases, we determined that SLC10A1 coordinates the remodeling of glucose metabolic flux by relying on bile acid transport functions rather than hepatitis virus receptors. In this process, the bile acid receptor FXR is necessary to regulate the expression of glycogen metabolism enzymes at the transcriptional level. In addition, we identified a small molecule inhibitor of NTCP (Diazinon), which inhibits the transmembrane transport of bile acids by competitively binding to the transport channels of NTCP. In conclusion, we explain the

importance of bile acid cross-organ circulation for glucose metabolism, and its disturbance causes the remodeling of glucose metabolism in HCC, which promotes the growth of tumor cells. This discovery not only enriches the linkage between cholesterol metabolism and glucose metabolism in the metabolic network, but also provides a new direction for clinical the diagnosis and treatment of HCC.

Key Words： Bile acid; Diazinon; Glycogen synthesis; Hepatocellular carcinoma; NTCP

99. PRMT6 promotes tumorigenicity and cisplatin response of lung cancer through triggering 6PGD/ENO1 mediated cell metabolism

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Metabolic reprogramming is a hallmark of cancer, including lung cancer. However, the exact underlying mechanism and therapeutic potential are largely unknown. Here we report that protein arginine methyltransferase 6 (PRMT6) is highly expressed in lung cancer and is required for cell metabolism, tumorigenicity, and cisplatin response of lung cancer. PRMT6 regulated the oxidative pentose phosphate pathway (PPP) flflux and glycolysis pathway in human lung cancer by increasing the activity of 6-phospho gluconate dehydrogenase (6PGD) and a-enolase (ENO1). Furthermore, PRMT6 methylated R324 of 6PGD to enhancing its activity; while methylation at R9 and R372 of ENO1 promotes formation of active ENO1 dimers and 2-phosphoglycerate (2-PG) binding to ENO1, respectively. Lastly, targeting PRMT6 blocked the oxidative PPP flflux, glycolysis pathway, and tumor growth, as well as enhanced the antitumor effects of cisplatin in lung cancer. Together, this study demonstrates that PRMT6 acts as a post translational modifification (PTM) regulator of glucose metabolism, which leads to the pathogenesis of lung cancer. It was proven that the PRMT6-6PGD/ENO1 regulatory axis is an important determinant of carcinogenesis and may become a promising cancer therapeutic strategy.

Key Words： Lung cancer; Metabolic reprogramming; Post-translational modification; PRMT6; Pentose phosphate pathway flux; Glycolysis; 6-PGD; ENO1

100. FTO promotes colorectal cancer progression and chemotherapy resistance via demethylating G6PD/PARP1

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Colorectal cancer (CRC) is the most commonly diagnosed malignancy and leading cause of cancer-related death. N6-methyladenosine (m6A) is the most abundant reversible methylation modification in mRNA contributing to tumor progression. However, the crucial role of m6A demethylase fat mass and obesity-associated (FTO) protein in CRC remains elusive. Herein, we find that chemotherapy drug induce FTO up-regulation in human CRC cell lines and with the decreased m6A levels. Furthermore, the inhibition of FTO enhances CRC cell sensitivity to chemotherapy agents. Mechanistically, high expression FTO increased G6PD and PARP1 expression, thereby counteracting oxidative stress and enhancing DNA repair in an m6A-YTHDF2 dependent manner. Finally, targeting FTO significantly inhibits CRC cell proliferation, colony formation, and tumor growth, while enhancing CRC cell sensitivity to DNA damage agents (Olaparib) treatment. In addition, the levels of FTO, G6PD and PARP1 are highly correlated expression in CRC tissues. Our findings reveal critical regulation of FTO by coordinating oxidative stress and DNA repair in promoting CRC progression and enhancing chemotherapy resistance.

Key Words： FTO, m6A modification, chemotherapy resistance, colorectal cancer

101. PIKE-A promotes glioblastoma growth by driving PPP flux through increasing G6PD expression mediated by phosphorylation of STAT3

Mingming Sun

Nankai University

Reprogramming of energy metabolism is a hallmark of cancer, and the pentose phosphate pathway (PPP) is a major glucose metabolic pathway important for meeting the cellular demands of biosynthesis and anti-oxidant defense. Our previous study showed that phosphoinositide 3-kinase enhancer-activating Akt (PIKE-A) plays an important role in glioblastoma cell survival and growth under cellular energy stress condition. However, the crucial functions of PIKE-A in cancer energy metabolism are poorly understood. In the present study, we show that PIKE-A promotes DNA biosynthesis, NADPH production and inhibits reactive oxygen species (ROS) production, leading to increasing proliferation and growth of glioblastoma cell and suppressing cellular senescence. Mechanistically, PIKE-A binds to STAT3 and stimulates its phosphorylation mediated by tyrosine kinase Fyn, which enhances transcription of the rate-limitting enzyme glucose-6-phosphate dehydrogenase (G6PD) in the PPP. Finally, targeting PIKE-A-G6PD axis sensitizes glioblastoma to temozolomide (TMZ) treatment. This study reveals that STAT3 is a novel binding partner of PIKE-A which recruits Fyn to phosphorylate STAT3, contributing to the expression of G6PD, leading to promoting tumor growth and suppressing cellular senescence. Thus, the PIKE-A/STAT3/G6PD axis strongly links the PPP to carcinogenesis and may become a promising cancer therapeutic target.

Key Words： PIKE-A; Phosphorylation; Glioblastoma; G6PD; STAT3; Fyn

102. Constructing a novel mitochondrial-related gene signature for evaluating the tumor immune microenvironment and predicting survival in ovarian cancer

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Background: Ovarian cancer is one of the three most common gynecologic malignant tumors, with the third highest incidence and second highest mortality among all gynecologic malignant tumors worldwide. Accumulating evidences have revealed the close relationship between mitochondrial dysfunction and the initiation and progression of ovarian cancer. However, rare prognostic models for mitochondrial-related gene risk have been built up in ovarian cancer.

Methods: In current study, the expression and prognostic value of mitochondrial-related genes in ovarian cancer (OV) patients were systematically analyzed to establish a mitochondrial-related risk model based on available TCGA and ICGC databases. The tumor microenvironment (TME), immune cell infiltration, tumor mutation burden, and drug sensitivity of OV patients were also investigated using R language, GraphPad Prism 8 and online databases.

Results: We established a mitochondrial-related risk prognostic model including RPL23,PKM2、MRPS12,NDUFC2,HPDL, MRPL14, COA6, FGFR1OP2, RNF144B ,CAPN10, ALDH1L1 and ACSM1 and validated its predictive power. This risk model indicated that the immune cell infiltration in high-risk group was significantly different from that in the low-risk group. Besides, combined analysis of risk score and immune score, or stromal score, or microsatellite status could more effectively predict the benefit of immunotherapy in OV patients with different stratifications. Finally, Vinblastine, Acetalax and PD-0325901 were found to be more effective for patients in the high-risk group, whereas Sabutoclax, SB-505124 and Cisplatin were predicted to be more effective for patients in the low-risk group.

Conclusions: Our results suggest that the mitochondrial-related risk model could be a reliable prognostic biomarker for personalized treatment of OV patients.

Key Words： Drug susceptibility; Ovarian cancer; Immune cells infiltration; Immunotherapy; Mitochondrion; Prognostic biomarker; Tumor microenvironment.

103. 结直肠癌患者外周血 T 淋巴细胞亚群监测肿瘤进展

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目的：探讨外周血 T 淋巴细胞亚群检测对结直肠癌患者的临床意义。

方法：利用流式分析技术检测 100 例未经治疗的结直肠癌患者和 80 例健康对照者外周血 T 淋巴细胞亚群的比例；进一步分析结直肠癌患者外周血免疫状态与肿瘤分期、淋巴结转移以及肿瘤标志物表达的关系。

结果：与健康对照组相比，结直肠癌患者外周血 T 淋巴细胞占淋巴细胞的比例无明显差异，然而 CD8+ T 细胞比例显著增高，CD4+ T、CD4 CD8 双阴性 T 细胞比例和 CD4+/CD8+比值均显著降低。结直肠癌患者外周血 CD4+/CD8+比值、CD4+调节性 T 细胞比例和 T 细胞表面 PD-1 表达与肿瘤分期、淋巴结转移相关，前两项指标还与传统消化道肿瘤标志物阳性率相关。

结论：结直肠癌患者免疫状态发生改变，并且随着机体免疫抑制功能的增强而促进肿瘤进展及肿瘤标志物的表达。

关键字：T 淋巴细胞亚群；结直肠癌；CD4+/CD8+比值；CD4+调节性 T 细胞；PD-1

104. Coagulation and Fibrinolytic Markers Offer Utility when Distinguishing Between Benign and Malignant Gallbladder Tumors

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Background : The metabolic or proliferative abnormalities characteristic of tumor cells can result in aberrant fibrinolysis or coagulation system activity, with certain tumors exhibiting hypercoagulability or existing in a fibrinolytic state. The utility of biomarkers of coagulation and fibrinolysis when seeking to differentiate between benign gallbladder disease and malignant gallbladder tumors, however, remains uncertain.

Methods： In total, 81 diagnosed with benign gallbladder hyperplasia and 94 patients diagnosed with benign gallbladder hyperplasia and malignant gallbladder tumors in this study. Pre-biopsy or pretreatment PIC, TAT, TM, and t-PAIC levels from these patients were analyzed, and correlations between these biomarkers and patient clinicopathological parameters were assessed. Age and data of four biomarkers were compared using Mann-Whitney tests and the diagnostic utility of these biomarkers when distinguishing between benign and malignant lesions was evaluated using ROC curves. Chi-square test was used to compare the frequencies.

Results ： The average age of malignant group was higher than benign group. And the base line analysis showed that there was a statistic difference in age, history of smoking, drinking, biliary tract disease, BMI of over weight between benign and malignant groups. In patients with malignant gallbladder tumors, PIC, TAT, TM, and t-PAIC levels were significantly elevated relative to those in patients affected by gallbladder benign hyperplasia. The AUC for four biomarker combined diagnosed, PIC, TAT, TM, t-PAIC was 0.8859, 0.8455, 0.6554, 0.7130, and 0.6806. All these indices offered significant predictive utility, with four biomarker combined diagnosed and PIC exhibiting higher level of significance. TM was correlated with the vascular invasion of patients bearing tumors, and TAT, t-PAIC was correlated with the nerve invasion of patients bearing tumors.

Conclusions：Relative to patients affected by benign gallbladder hyperplasia, cholangiocarcinoma and gallbladder cancer patients presented with significantly higher plasma PIC, TAT, TM, and t-PAIC concentrations, with four biomarkers combined and PIC offering noteworthy diagnostic potential. These four markers could be used to some degree to aid in the differentiation between benign and malignant gallbladder conditions, and predicting the risk of vascular metastasis and nerve metastasis.

Key Words： coagulation and fibrinolysis markers, gallbladder benign hyperplasia, gallbladder malignancy, tumor marker.

105. 表面增强拉曼光谱（SERS）生物探针精准诊断 CTCs

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恶性肿瘤严重危害人类生命健康，“早发现、早诊断、早治疗”是目前根治实体恶性肿瘤的最佳途径。与组织活检相比，体外液体活检技术具有快速、简便和无损伤等优势。当影像学检查还没有发现任何病灶前，外周血液中循环肿瘤细胞检测可为肿瘤早期诊断和预后评估提供重要依据。循环肿瘤细胞（CTCs）的高效检测可有效地应用于体外早期诊断、预后及存活时间判断、快速判断治疗效果、体内耐药性检测、肿瘤分子分型鉴定、个体化治疗、肿瘤复发检测等，具有重要的科学意义和临床应用价值。表面增强拉曼散射光谱（SERS）技术是高灵敏的指纹光谱分析技术，具有快速、精准、无损检测等优势，可适用于固相、液相等复杂的检测体系。SERS 纳米生物探针与谱学/影像技术的结合，为实现循环肿瘤细胞的精准诊断带来新的契机。研发功能型 SERS 纳米生物探针，随后结合具有光、电、磁场响应的 SERS 探针试剂盒仪器设备，完成外周血样中循环肿瘤细胞的快速富集、高效分离、准确检测和分型鉴定，从而通过 SERS 光谱/图像分析实现肿瘤的精准诊断应用突破，并开发可推广的检测试剂盒。重点突破液体活检发展中检测成本高、耗时长、细胞富集难和靶向性差等难题。

关键字：拉曼光谱；CTCs；精准诊断

106. Targeting Cancer-Associated Fibroblast Related Markers Enhances Anti-tumor Immunity through Redox-Sensitive Polymer Micelles in Colon Cancer

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Purpose： The research of cancer-associated fibroblast (CAF) in colon cancer (CC) has made progress, but its clinical efficacy is seriously challenged due to a lack of effective therapeutic targets and drug delivery strategies.

Methods： By univariate Cox and LASSO regression analysis, a practical CAF risk score (CAFscore) was successfully built from three prognostic-related CAF hub genes, namely CRIP2, FSTL3, and SLC2A3. Anti-programmed death-ligand 1 antibodies (aPD-L1) were loaded into a redox-responsive micelle. The anti-tumor efficacy was further amplified by anti-follistatin-like 3 antibodies (aFSTL3) via a co-encapsulation approach for the reactivation of the regional immune responses.

Results： By taking the optimal cutoff values of FSTL3, high expression of FSTL3 was closely related to malignant biological behavior. Additionally, FSTL3 expression performed admirably in the cohorts used for external validation as well as training. FSTL3 was highly expressed in stromal cells of GSE146771 and GSE110009, especially in CAF. The micelles were able to effectively target CC and were retained in the reductive tumor microenvironment without altering the bioactivity of aFSTL3. The anti-tumor efficacy was substantially enhanced by the aPD-L1 and aFSTL3 combination with considerable reduction of primary and recurrent CC, accumulation of cytotoxic T lymphocytes, and development of long-lasting immunological memory in the local immune environment.

Conclusions： High expression of FSTL3 was shown to be associated with adverse prognosis, somatic hypermutation, and drug insensitivity. The co-encapsulation strategy promoting effective antibody delivery and combining with aFSTL3 inhibits vascular mimicry demonstrated that the anti-CAF therapy might reprogram local immunity in CC.

Key Words： Cancer-Associated Fibroblast; Redox-Sensitive Polymer Micelles; Immunity

107. 自噬相关基因 5（ATG5）在人恶性胸膜间皮瘤中的表达及其意义

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目的：探讨自噬相关基因 5（autophagy related gene 5, ATG5）在恶性胸膜间皮瘤（malignant pleural mesothelioma, MPM）细胞和组织中的表达情况，分析 ATG5 基因表达与 MPM 患者临床病理参数及预后的相关性。

方法：采用 qRT-PCR 和 Western blot 法分析正常人胸膜细胞 Met5A 和 MPM 细胞系 NCI-H28（上皮样型）、NCI-H2052（肉瘤样型）和 NCI-H2452（双相混合型）、MTSO-211H（二相间皮瘤肺转移灶）中 ATG5 mRNA 基因的表达水平，采用 qRT-PCR 和 Western blot 法检测 10 例 MPM 组织及 5 例非 MPM 胸膜组织中 ATG5 基因 mRNA 表达量。基于 TCGA 数据库分析 ATG5 mRNA 表达量与 MPM 患者临床病理特征间的相关性，并使用 UALCAN 数据库进行可视化分析；构建 Kaplan-Meier 模型探究 ATG5 mRNA 表达量对 MPM 患者预后的影响，构建 COX 回归模型分析影响 MPM 患者预后的因素；进一步使用 GEPIA 数据库评估 ATG5 与 MPM 肿瘤诊断标志物和新型血清标志物间的相关性；TIMER 2.0 数据库分析 ATG5 与 MPM 免疫细胞浸润及关键免疫调节基因的相关性。

结果：与非 MPM 胸膜间皮细胞和组织相比，ATG5 基因在 MPM 细胞和组织中显著高表达（$P<0.05$）；ATG5 mRNA 表达与 MPM 患者的肿瘤分期呈正相关，男性患者的 ATG5 表达水平显著高于女性患者（$P<0.05$）；生存分析显示，ATG5 高表达组 MPM 患者的 DFS 更差，且 Cox 回归分析提示肿瘤病理类型是影响 MPM 患者预后不良的独立危险因素。在 MPM 中，ATG5 与 MPM 诊断标志物 MTAP、SETD2、NF2、FIB3 及 MPM 新型血清监测标志物 HMGB1、SMPR、THBS2、KRAS 均呈显著正相关（$R>0$，$P<0.05$）；ATG5 表达与 B 细胞、CD4+T 细胞及巨噬细胞浸润呈显著正相关（$P<0.05$）；与参与免疫浸润、调节肿瘤细胞侵袭和免疫反应、免疫检查点抑制剂治疗等过程的关键免疫相关基因 CD28、CUL48B、CD166、MMP14 呈显著正相关（$R>0$，$P<0.05$）。

结论：ATG5 基因在 MPM 中表达上调且与 MPM 患者无疾病进展生存期（DFS）缩短及免疫浸润水平相关，有望成为 MPM 早期筛查、诊断和预后评估的重要生物标志物。

关键字：恶性胸膜间皮瘤（MPM）；自噬相关基因 5（ATG5）；自噬；预后；免疫浸润

108. 基于 TCGA 数据库构建恶性胸膜间皮瘤基因预后模型及其生物信息学分析

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目的：基于癌症基因组图谱（The Cancer Genome Atlas，TCGA）数据库构建恶性胸膜间皮瘤患者的基因预后风险模型及其验证分析。

方法：通过 TCGA 数据库获取恶性胸膜间皮瘤的基因表达数据以及临床信息，将数据集分为训练集和测试集，对训练集进行单因素 Cox 分析、单因素鲁棒性分析以及多因素 Cox 回归分析建立风险预后模型，计算每个患者的风险评分，将数据集分成高风险组和低风险组，通过 Kaplan-Meier 生存曲线和受试者工作特征（Receiver Operating Characteristic，ROC）曲线评估模型的预测效能和准确性，利用 TCGA 数据库和 GTEx 数据库中的样本对预后模型中的基因进行表达验证，最后通过 UALCAN 数据库探索预后模型中基因的表达模式。

结果：本研究构建了一个由 UHRF1、KIF4A 和 NEK2 这三个基因组成的预后风险评估模型，预后风险模型风险评分=UHRF1 表达量×1.4525-KIF4A 表达量×1.327+NEK2 表达量×1.4167。ROC 曲线显示，该模型的 ROC 曲线下面积（Area Under the Curve，AUC）值为 0.91，基于 ROC 曲线对截断值进行优化，最佳截止点为 1.149，此时达到最大灵敏度和特异性。在最佳截止点处，患者被进一步分为高风险组和低风险组，Kaplan-Meier 生存曲线显示，高风险组和低风险组之间的生存时间存在显著差异，与高风险组患者相比，低风险组患者总生存期显著延长。通过森林图对模型进行可视化，整个模型的 Log-Rank p-value<0.0001，表示其可以作为恶性胸膜间皮瘤的独立预后生物标志物。相比于正常肺组织，预后模型中的三个基因在恶性胸膜间皮瘤组织中均显著高表达，且在恶性胸膜间皮瘤患者的不同分期、肿瘤亚型、年龄和转移状态中表达有明显差异。

结论：本研究构建的恶性胸膜间皮瘤基因预后风险模型，能够有效预测恶性胸膜间皮瘤患者预后，并且可以作为恶性胸膜间皮瘤的独立预后预测因子。预后模型中基因 UHRF1、KIF4A 和 NEK2 的表达与恶性胸膜间皮瘤患者的多个临床特征显著相关，提示其在恶性胸膜间皮瘤发生发展过程中的潜在作用。

关键字：恶性胸膜间皮瘤；预后风险模型；生物信息学；TCGA 数据库

109. 敲低线粒体转录终止因子 1（MTERF1）基因表达通过 LKB1/AMPK/mTOR 信号轴抑制人肝细胞癌 HCC-97H 的增殖

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目的：线粒体转录终止因子 1（MTERF1）能够调控线粒体 DNA （mtDNA）复制和转录终止过程。然而，MTERF1 在肝细胞癌 （HCC） 增殖和进展中的作用机制尚不明确。

方法：通过 qRT-PCR、Western blotting 和免疫组化探究 MTERF1 在正常肝组织和 HCC 组织中的表达差异，构建 MTERF1 稳定敲低的 HCC-97H 细胞株，研究 MTERF1 通过 LKB1/AMPK/mTOR 信号通路抑制 HCC-97H 细胞增殖的机制，流式细胞术研究敲低 MTERF1 对 HCC-97H 细胞线粒体膜电位、细胞周期和细胞凋亡的影响。

结果：MTERF1 在 HCC 组织中过表达，MTERF1 的高表达与 HCC 患者的总生存期降低呈显著正相关。敲低 MTERF1 基因诱导线粒体功能障碍、S-G2/M 细胞周期停滞和细胞凋亡，导致 HCC-97H 细胞增殖抑制。相反，MTERF1 基因的过表达促进细胞周期进程和细胞增殖。从机制上讲，敲低 MTERF3 基因诱导的线粒体功能障碍抑制 ATP 生成，进而通过 LKB1/AMPK/mTOR 信号通路抑制 HCC 细胞增殖。

结论：MTERF1 敲低诱导的 ATP 减少通过 LKB1/AMPK/mTOR 信号通路抑制 HCC 细胞增殖，提示其在 HCC 诊断和治疗中是一个潜在的靶点。

关键字：线粒体转录终止因子 1（MTERF1）；肝细胞癌（HCC）；LKB1/AMPK/mTOR 信号轴；细胞增殖；细胞凋亡

110. Janus 激酶抑制剂 AG490 对顺铂诱导肺癌小鼠肾损伤 JAK2/STAT3 信号通路的影响

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目的：探讨 Janus 激酶(Janus kinase,JAK)抑制剂 AG490 在顺铂（DDP）诱导的肺癌小鼠急性肾损伤(AKI)中 JAK2/STAT3 信号通路的影响。

方法：将培养好的小鼠随机分为五组，即对照组、模型组、AG490 组、DDP 组和 DDP+AG490 组。除正常组外，其余均建立肺癌模型。检测各组小鼠血尿素氮(BUN)、肌酐(Cr)水平及氧化应激状态。

结果：DDP 对肺癌小鼠的肿瘤生长有抑制作用，且与 AG490 联合应用可进一步抑制肿瘤生长。DDP 组小鼠血清尿素氮(BUN)、肌酐(Cr)水平较正常组升高，丙二醛(MDA)水平升高，谷胱甘肽(GSH)、超氧化物歧化酶(SOD)和过氧化氢酶(CAT)降低。与 DDP 组相比，DDP+AG490 组 AKI 减轻，氧化应激、细胞凋亡改善。

结论：AG490 可减轻 DDP 诱导的肺癌小鼠 AKI，改善氧化应激，抑制 JAK2/STAT3 通路。

关键字：肺癌；JAK2/STAT3；顺铂；AG490；急性肾损伤

111. AKR1D1 represses hepatocellular carcinoma progression and immune evasion by reprogramming fatty acid metabolism via STAT3

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Objective: The steroid A-ring reductase, 5β-reductase (AKR1D1), is predominantly expressed in the liver. And its abnormal expression has been reported to be a crucial cause of cancer. However, the functions of AKR1D1 in hepatocellular carcinoma (HCC), especially its roles in tumorigenesis

and immune regulation, remain unclear. Hence, we aimed to explore the roles and mechanisms of AKR1D1 in HCC initiation and progression.

Methods: The influences of AKR1D1 on the growth and liver metastasis of HCC cells and the expression patterns of different lipid metabolism enzymes were evaluated in vitro and in vivo. Molecular and biological experiments were conducted to uncover the underpinning mechanisms of dysregulated de novo lipogenesis.

Results: Based on The Cancer Genome Atlas (TCGA) database exploration and human tissue microarray (TMA) analysis, we found that AKR1D1 expression was markedly downredulated in HCC tissues than in adjacent normal tissues. Low AKR1D1 expression was correlated with poor prognosis in HCC patients. AKR1D1 silencing significantly promoted cell growth and liver metastasis both in vitro and in vivo, whereas overexpression of AKR1D1 resulted in the opposite effects. Gene set enrichment analysis revealed AKR1D1 downregulation was significantly associated with the fatty acid metabolism pathways. Blockage of fatty acid synthesis abrogated the effects of AKR1D1 silencing on cell growth and liver metastasis. Further experiments indicated that AKR1D1 silencing induced the activation of the AKT serine/threonine kinase (AKT)/mammalian target of rapamycin (mTOR) signaling axis, thus promoting de novo lipogenesis by enhancing the expression of lipogenic enzymes by activating the STAT3 expression. Furthermore, the efficacy of PD1 blockade immunotherapy was prominently enhanced in the presence of AKR1D1 overexpression via increased infiltration of CD8+ T cells into the tumor microenvironment.

Conclusions: Overall, it appears that AKR1D1 plays a key role in regulating tumor cell proliferation and antitumor immunity via modulating the JAK/STAT signaling pathway and reprogramming lipid metabolism.

Key Words ： STAT3, Hepatocellular carcinoma, Fatty acid oxidation, Fatty acid synthesis, Lipid metabolism, Liver metastasis, AKR1D1, tumorigenesis

112. Molecular phenotypic linkage between N6-methyladenosine methylation and tumor immune microenvironment in hepatocellular carcinoma

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Purpose: The crucial role of N6-methyladenosine (m6A) methylation in anti-tumor immunity and immunotherapy has been broadly depicted. However, the molecular phenotypic linkages between m6A modification pattern and immunological ecosystem are expected to be disentangled in hepatocellular carcinoma (HCC), for immunotherapeutic unresponsiveness circumvention and combination with promising drug agents.

Methods: Modification patterns of m6A methylation were qualitatively dissected according to the large-scale HCC samples profiling. We then determined the immune phenotypic linkages by systematically evaluating their tumor microenvironment composition, immune/stromal-relevant signature, immune checkpoints correlation, and prognostic value. Individual quantification of m6A methylation pattern was achieved by m6Ascore construction, intensified by longitudinal single-cell analysis of immunotherapy cohort and validated by the transcriptomic profiles of our in-hospital GDPH-HCC cohort. Candidate therapeutic agents were also screened out.

Results: Three distinct m6A methylation patterns were determined in high accordance with inflamed-, excluded-, and desert-immunophenotype. To be precise, Immune-inflamed high-m6Ascore group was characterized by activated immunity with favorable prognosis. Stromal activation and absence of immune cell infiltration were observed in low-m6Ascore phenotype, linked to impaired outcome. Patients with low-m6Ascore demonstrated diminished responses and clinical benefits for cohorts receiving immunotherapy. The above credible linkage between m6A methylation pattern and tumor immune microenvironment was robustly validated in our GDPH-HCC cohort. Single-cell dynamic change of m6A methylation level in exhausted CD8 T cell and fibroblast was depicted in immunotherapy cohort fore and art. Derived from m6A methylation pattern, seven potential frontline drug agents were recognized as promising choice for high-m6Ascore patients.

Conclusion: Our work bridged the credible linkage between epigenetics and anti-tumor immunity in HCC, unraveling m6A modification pattern as immunological indicator and predictor for immunotherapy. Individualized m6Ascore facilitated strategic choices to maximize therapy-responsive possibility.

Key Words： Epigenetic modification; Hepatocellular carcinoma; Immune microenvironment; Immunotherapy; m6A methylation.

113. An all-in-one strategy for bisulfite-free DNA methylation detection by temperature-programmed enzymatic reactions

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The fragmentation and low concentration of cell-free DNA (cfDNA) pose higher challenges for the cfDNAmethylation detection technologies. Conventional bisulfite conversion-based methods are inadequate for cfDNA methylation analysis due to cumbersome operation and exacerbating cfDNA degradation. Herein, we proposed temperature-programmed enzymatic reactions for cfDNA methylation analysis in a single tube. Endonuclease was used to mildly recognize DNA methylation to avoid the degradation of cfDNA. And two stages of amplification reactions significantly improved the detection sensitivity for GC-rich sequence. With vimentin as the target, the detection sensitivity was 10 copies of methylated DNA. Meanwhile, the proposed method can accurately quantify the methylation level of target sequence from 1000-fold of unmethylated DNA background. Further, the methylated vimentin gene in 20 clinical plasma samples was successfully detected. The results shown significant differences in methylation levels of the vimentin gene between healthy volunteers and colorectal cancer patients. These results lead us to believe that the

proposed method has great application potential for DNA methylation analysis as a complement to bisulfite conversion-based methods.

Key Words： Cell-free DNA; DNA methylation; Enzymatic reaction; Signal amplification

114. Profiling of single-vesicle surface proteins via droplet digital immuno-PCR for multi-subpopulation extracellular vesicles counting towards cancer diagnostics

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Quantification of protein-specific extracellular vesicle (EV) subpopulations at the single-vesicle level is of great significance for cancer diagnosis. Although individual vesicle analysis has been implemented by novel emerging technologies, developing an easy-to-operate and cost-effective single EV analysis approach to promote clinical applications is still challenging. Herein, we constructed a versatile droplet digital immuno-PCR (ddiPCR) assay which integrates the high specificity of immuno-PCR and superior sensitivity of droplet digital PCR to profile the surface proteins of single EVs for multi-subpopulation EVs counting. The clinical application of the ddiPCR assay was validated by simultaneous profiling the EV proteins of CD9/CD63/CD81, HER2, EpCAM in a breast cancer cohort, and CD9/CD63/CD81, GPC-3, EpCAM in a hepatocellular carcinoma cohort (HCC). The results demonstrated that the counting of multi-subpopulation EVs could significantly distinguish patients with breast tumor or HCC from healthy controls. Furthermore, with the assistance of machine learning algorithm and under the best combination of sEV subpopulations, our method exhibited great performance in differentiating breast cancer from healthy individuals. Therefore, this study provides a promising strategy to count multi-subpopulation EVs at the single-vesicle level for cancer diagnosis.

Key Words ： Single extracellular vesicle analysis, Droplet digital PCR, Immuno-PCR, Surface proteins profiling, Cancer diagnostics

115. Isolation and Enrichment of Extracellular Vesicles with Double-Positive Membrane Protein for Subsequent Biological Studies

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The isolation and enrichment of specific extracellular vesicle (EV) subpopulations are essential in the context of precision medicine. However, the current methods predominantly rely on a single-positive marker and are susceptible to interference from soluble proteins or impurities. This limitation represents a significant obstacle to the widespread application of EVs in biological research. Herein, we propose a novel approach that utilizes proximity ligation assay (PLA) and DNA-RNA hybridization to facilitate the binding of two proteins on the EV membrane in advance enabling the isolation and enrichment of intact EVs with double-positive membrane proteins followed by using functionalized magnetic beads for capture and enzymatic cleavage for isolated EVs release. The isolated subpopulations of EVs can be further utilized for cellular uptake studies, high-throughput small RNA sequencing, and breast cancer diagnosis. Hence, developing and implementing a specialized system for isolating and enriching a specific subpopulation of extracellular vesicles can enhance basic and clinical research in this field.

Key Words： extracellular vesicles, double-positive membrane protein, proximity ligation assay, DNA-RNA hybridization, cancer diagnosis

116. The role of APOBEC3C in modulating the tumor microenvironment and stemness properties of glioma: evidence from pancancer analysis

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Background： It is now understood that APOBEC3 family proteins (A3s) are essential in tumor progression, yet their involvement in tumor immunity and stemness across diverse cancer types remains poorly understood.

Methods ： In the present study, comprehensive genome-wide statistical and bioinformatic analyses were conducted to elucidate A3 family expression patterns, establishing clinically relevant correlations with prognosis, the tumor microenvironment(TME), immune infiltration, checkpoint blockade, and stemness across cancers. Different experimental techniques were applied, including RT–qPCR, immunohistochemistry, sphere formation assays, Transwell migration assays, and wound-healing assays, to investigate the impact of A3C on low-grade glioma (LGG) and glioblastoma multiforme (GBM), as well as its function in glioma stem cells(GSCs).

Results： Dysregulated expression of A3s was observed in various human cancer tissues. The prognostic value of A3 expression differed across cancer types, with a link to particularly unfavorable outcomes in gliomas. A3s are associated with the the TME and stemness in multiple cancers. Additionally, we developed an independent prognostic model based on A3s expression, which may be an independent prognostic factor for OS in patients with glioma. Subsequent validation underscored a strong association between elevated A3C expression and adverse prognostic outcomes, higher tumor grades, and unfavorable histology in glioma. A potential

connection between A3C and glioma progression was established. Notably, gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses implicated A3C in immune system-related diseases, with heightened A3C levels contributing to an immunosuppressive tumor microenvironment (TME) in glioma. Furthermore, in vitro experiments substantiated the role of A3C in sustaining and renewing glioma stem cells, as A3C deletion led to diminished proliferation, invasion, and migration of glioma cells.

Conclusion： The A3 family exhibits heterogeneous expression across various cancer types, with its expression profile serving as a predictive marker for overall survival in glioma patients. A3C emerges as a regulator of glioma progression, exerting its influence through modulation of the tumor microenvironment and regulation of stemness.

Key Words ： A3 family; pan-cancer analysis; stemness; prognosis; tumor microenvironment

117. 血清平足蛋白、糖类抗原 15-3、糖类抗原 125、癌胚抗原、血管内皮生长因子在乳腺癌临床应用的研究

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目的：探讨血清血清平足蛋白（PDPN）、糖类抗原 15-3（CA15-3）、糖类抗原 125（CA125）、癌胚抗原（CEA）、血管内皮生长因子（VEGF）在乳腺癌临床诊断中的应用价值。

方法：采用回顾性分析，纳入 301 例来自徐州医科大学第二附属医院乳腺疾病患者，根据病理诊断分为乳腺癌组、乳腺良性对照组，并将入院体检的女性作为健康对照组，比较三组的临床资料和血清 PDPN、CA15-3、CA125、CEA、VEGF 等实验室指标，并绘制受试者工作特征曲线（Receiver operating characteristic，ROC）通过曲线下面积（Area under Curve，AUC）评价 PDPN 等血清学指标对乳腺癌良恶性与转移性的鉴别诊断价值。

结果：乳腺癌组血清 PDPN、CA15-3、VEGF、CEA、CA125 水平较良性对照组及健康对照组均升高，差异有统计学意义（P＜0.05）。良性对照组 PDPN、CA15-3、CA125、CEA、VEGF 水平与健康对照组相比，差异无统计学意义（P＞0.05）。当血清 PDPN 水平截断值

设定为 4.85 ng/mL 时，敏感度为 82.3%，特异度为 71.0%，AUC 值为 0.852（95%CI：0.719~0.917）。当血清 CA15-3 的截断值设定为 25.15 U/mL 时，其敏感度为 87.1%，特异度为 69.5%，AUC 值为 0.837（95%CI：0.729~0.913）；当血清 VEGF 水平的截断值设定为 117.57 pg/mL 时，其鉴别敏感度为 60.1%，特异度为 54.3%，AUC 值为 0.793（95%CI：0.732~0.825）；当 CEA 的设定截断值为 4.37 ng/mL 时，其鉴别的敏感度为 56.5%，特异度为 69.7%，AUC 值为 0.651（95%CI：0.621~0.847）；当 CA125 的截断值设定为 79.88 U/mL 时，其鉴别敏感度为 58.3%，特异度为 55.2%，AUC 值为 0.743（95%CI：0.722~0.827）。血清 PDPN、CA15-3、VEGF、CEA、CA125 在乳腺疾病良恶性鉴别均有良好的诊断效能，且各指标 AUC 相比，差异无统计学意义（P＞0.05）。乳腺癌分期程度越高的患者血清中 PDPN 水平越高，呈现正相关性；有淋巴结转移患者血清样本中 PDPN 水平高于无淋巴结转移患者，差异有统计学意义（P＜0.05）。血清 PDPN 联合 CA15-3 鉴别转移性乳腺癌的敏感度为 84.0%，特异度为 82.0%，AUC 值为 0.901，高于 PDPN、CA15-3 单独鉴别的 AUC 值（P＜0.001）。

结论：血清 PDPN、CA15-3、VEGF、CEA、CA125 在良恶性乳腺疾病鉴别诊断中有较高的应用价值；血清 PDPN 联合 CA15-3 检测对于转移性乳腺癌具有良好鉴别诊断价值。

关键字： 平足蛋白；乳腺癌；临床应用；CA15-3；CEA

118. A prognostic signature of cuproptosis and TCA-related genes for hepatocellular carcinoma

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Background and Aims: Hepatocellular carcinoma (HCC) is the most common malignant tumoroftheliver. Cuproptosis is a newlydefinedformofcelldeath.Copperion induces cell death by binding to the tricarboxylic acid cycle (TCA). The effect of cuproptosis-related and TCA-related genes on the clinical prognosis of HCC is still unclear. In this study, we explores the genetic changes of cuproptosis related genes that affect the TCA process and their potential therapeutic value in HCC patients

Method: The cuproptosis and TCA-related genes were obtained from cuproptosis-related articles and the molecular signatures database. The prognosis signatures of eight related genes were

constructed using the last absolute shrinkage and selection operator (LASSO), and Receiver Operating Characteristic (ROC) curves were used to evaluate the signature. In addition, we analyzed downstream functional enrichment and immune infiltration to explore cuproptosis-inducing drugs and immunotherapeutic responses. All these analyses were validated using multiple datasets of the International Cancer Genome Consortium (ICGC).

Results:TCA and copper malnutrition-related genes (CDKN2A, IDH1, OGDHL, IDH3G, IDH3B, GLS, DLAT, LIPT1) were finally included. According to the risk score, they were divided into high-risk and low-risk groups. Survival analysis showed that the overall survival (OS) of the high-risk group was significantly lower than that of the low-risk group. We established a risk prognostic feature to predict the OS of patients with HCC. Based on this feature and the clinical stage, we constructed a nomogram. Functional enrichment analysis revealed pathways related to organelle division and the cell cycle. Different risk scores had different immune abundances in immune cells (including macrophages and regulatory T-cells) and immune pathways (including antigen-presenting cells co-stimulation). Moreover, the drug sensitivity of eleschomol and PD-L1 in the high-risk group was better than that in the low-risk group. The status of TP53 somatic mutation was also closely related to the risk score.

Conclusion: In this study, we established a new prediction signature of eight genes related to cuproptosis and the TCA process, which can effectively predict the prognosis of HCC patients.

Key Words ：hepatocellular carcinoma，TCA-cycle，cuproptosis

119. Prognosis of TACE combined with sorafenib in hepatocellular carcinoma patients with microvascular invasion: A retrospective cohort study.

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Background: Transcatheter arterial chemoembolization (TACE) and sorafenib each has shown therapeutic effects in patients with hepatocellular carcinoma (HCC) and microvascular invasion (MVI). The present study evaluated the feasibility of postoperative TACE combined with

sorafenib in HCC patients with MVI and assessed the optimal indications for postoperative TACE treatment.

Methods: The present study included 217 HCC patients who underwent radical resection from April 2017 to April 2022 and whose postoperative pathological report showed MVI. Patients were treated with TACE, TACE plus sorafenib, of neither (control group). The primary endpoints were overall survival (OS) and disease-free survival (DFS).

Results: Patients treated with TACE plus sorafenib had higher 1-year (96.4% vs. 84.9%) and 2-year (91.6% vs. 68.9%) OS rates than patients treated with TACE alone. Median OS was significantly longer in patients treated with TACE plus sorafenib (44.6 months; 95% confidence interval [CI] 40.81-48.4 months) than with TACE alone (39 months; 95% CI 30.2-48.3 months; (p=0.025). Cox proportional hazard model showed that factors associated with a higher risk of death after treatment included maximum tumor diameter of tumor (hazard ratio [HR]=6.783, p=0.012), number of TACE sessions (HR= 0.284, p=0.01) and liver cirrhosis (HR=6.446, p=0.002).

Conclusion: Compared with TACE alone, TACE plus sorafenib significantly prolonged OS in patients with HCC and MVI. Factors associated with improved prognosis included maximum tumor diameter <7 cm and more than three TACE sessions.

关 键 字 ： hepatocellular carcinoma, microvascular invasion, transcatheter arterial chemoembolization (TACE), vascular endothelial growth factor, sorafenib, intrahepatic metastasis

120. 平足蛋白吖啶酯化学发光免疫分析方法建立及在乳腺癌中临床应用

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目的：建立一种以活化吖啶酯标记抗人平足蛋白抗体为标记物检测人血清中平足蛋白（ PDPN ）的磁微粒化学发光免疫分析法检测方法并进行在乳腺癌相关疾病方面的临床应用验证。

方法：以包被链酶亲和素磁微粒 -活化生物素标记抗人平足蛋白抗体为固相分离载体，生物素标记一株鼠抗人平足蛋白单克隆抗体，吖啶酯标记另一株鼠抗人平足蛋白单克隆抗体，建立人血清样本中 PDPN 定量免疫分析方法。

结果：在线性范围 1.00～800.00 ng/mL 内，相关系数 r 为 0.9990，检出限为 0.52 ng/mL；批内重复性不超过 5.0%，批间差不超过 10.0%；正常参考区间为小于 4.50 ng/mL；测定乳腺癌临床样本，特异性为 88%和灵敏度为 87%。

结论：建立了定量检测人血清中 PDPN 含量化学发光免疫分析法，对乳腺癌的发生发展起了辅助诊断作用。

关键字： 平足蛋白；吖啶酯；全自动化学发光；乳腺癌；

121. Regenerating family member 4 expression was a potential marker for carcinogenesis, aggressiveness and prognosis of gastric cancer

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REG4 might activate EGFR/Akt/AP-1 pathway, and be regarded as a potential marker for neuroendocrine tumors and mucin-producing adenocarcinomas. Here, we combined meta-, bioinformatics and pathological analyses to explore the clinicopathological significances of REG4

expression in gastric cancer (GC). The effects of REG4 on the aggressive phenotypes and relevant molecular mechanisms were also investigated in GC cells. We found that compared with normal mucosa, up-regulated REG4 expression was found in GC at either mRNA or protein level ($p<0.05$), and negatively associated with the histological grading of GCs ($p<0.05$). REG4 expression was positively related to depth of invasion, lymph node metastasis, TNM staging and dedifferentiation of GCs ($p<0.05$). Recombinant REG4 exposure or Full-length REG4 overexpression promoted proliferation, anti-apoptosis, migration, and invasion of GC cells in an autocrine or paracrine manner by activating EGFR–PI3K–Akt–NF-κB pathway, while non-signal-peptide REG4 didn't have these biological effects and anti-REG4 antibody blocked the effects of REG4 overexpression. REG4 was involved in chemoresistance of GC cells not through de novo lipogenesis, but through lipid droplet assembly. REG4 induced proteasomal degradation of ACC1 or ACLY in GC cells. In summary, REG4 may be involved in tumorigenesis and aggressiveness of GC by EGFR–PI3K–Akt–NF-κB pathway, and chemoresistance through lipid droplet assembly. REG4 attenuates the expression of de novo lipid synthesis key enzymes by promoting the ubiquitination- mediated proteasomal degradation.

Key Words: Gastric cancer, REG4, Chemoresistance, Lipid droplet formation

122. 血清三叶因子、程序性死亡配体 1、糖类抗原 153、癌胚抗原在 乳腺癌诊断及预后中表达及意义

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目的：探讨血清三叶因子（TFF1）、程序性死亡配体 1（PD-L1）、糖类抗原 153（CA153）、癌胚抗原（CEA）在乳腺癌诊断及预后中的表达及意义。

方法：选取徐州医科大学第二附属医院自 2020 年 9 月至 2021 年 9 月收治的 200 例可疑性乳腺癌患者为研究对象。根据病理检查结果将患者分为良性组（n＝133）与恶性组（n＝67）。比较两组患者 TFF1、PD-L1、CA153、CEA 水平。对 67 例恶性组患者进行为期 1 年的随访，统计其存活率。采用受试者工作特征（ROC）曲线检验 TFF1、PD-L1、CA153、CEA 单独及联合在乳腺恶性肿瘤诊断及预后中的诊断效能。

结果：恶性组患者 TFF1、PD-L1、CA153、CEA 水平均高于良性组，差异均有统计学意义（P＜0.05）。ROC 结果显示，TFF1＋PD-L1＋CA153＋CEA 联合诊断的 ROC 曲线下面积（AUC）、灵敏度、特异度、准确度高于各项指标单独检测。随访后 1 年，67 例乳腺恶性肿瘤患者的存活率为 74.63（50/67）。TFF1＋PD-L1＋CA153＋CEA 联合对预后诊断的 AUC、灵敏度、特异度、准确度均较高。

结论：血清 TFF1、PD-L1、CA153、CEA 均在乳腺癌中呈高表达，4 者联合用于乳腺癌诊断及其预后评估效果均较好。

关键字： 乳腺癌；三叶因子；程序性死亡配体 1；糖类抗原 153；癌胚抗原；诊断效能

123. RNF180 表达是乳腺癌发生、侵袭性和预后的潜在生物标志物

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背景:E3 泛素蛋白连接酶 RNF180（环指蛋白 180）介导多泛素化和蛋白质的蛋白酶体降解。

方法:本研究采用生物信息学分析、免疫印迹和免疫组织化学方法探讨 RNF180 在乳腺癌中的可能作用。

结果:我们发现 RNF180 mRNA 和蛋白在乳腺癌中的表达水平低于正常组织（p＜0.05），与其甲基化相反。乳腺癌患者的低 T 分期、PR 和 ER 阳性表达、Her-2 阴性表达、PAM50 亚型良好和预后较好与 RNF180 mRNA 表达呈正相关（p＜0 . 05）。RNF180 甲基化与 RNF180 mRNA 低表达、N 分期、Her-2 阳性和 p53 突变呈正相关（p＜0.05）。RNF180 的差异基因涉及 CD22 介导的 BCR 调节、FCGR 的激活、B 细胞受体介导的第二信使产生、C4 和 C2 激活的产生、NABA 核心基质体、一氧化氮模拟谷氨酸环化酶、层粘连蛋白相互作用和具有 TSR 结构域的蛋白质的 O-糖基化（p＜0.05）。RNF180 相关基因分类为赖氨酸代谢和分解代谢、回归转录因子、氧化还原酶、光感受器、泛素介导的蛋白水解、细胞周期、后期促进复合物等（p＜0 . 05）。

结论:这些结果表明 RNF180 的表达可能在乳腺癌的发生和随后的进展中下调。它可能被用作一种潜在的生物标志物来指示乳腺癌的侵袭性和不良预后。

关键字： 乳腺癌，RNF180，致癌作用，预后，生物信息学分析

124. Skp2 as a Key Biomarker of Chemoresistance in Liquid Biopsy in Colorectal Cancer

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Purpose: The aim of present study was to explore the expressive status of Skp2 can be used as potential markers of liquid biopsy to predict the sensitivity and prognosis of colorectal cancer to combined chemotherapy. This study clarifies a new molecular mechanism of colorectal cancer chemotherapy resistance, and provides a theoretical basis and experimental evidence for developing novel methods of chemotherapy sensitization.

Methods: The expression of Skp2 was examined in 50 primary and 50 recurrent colorectal cancer tissues by IHC, and Skp2 expression levels were analyzed in serum from 30 same colorectal cancer patients before and after chemotherapy resistance by Olink-PEA (Proximity Extension Assay) and qRT-PCR. The cell viability and expression of Skp2 in sensitive and drug-resistant colorectal cancer cell lines treated with combination chemotherapy by MTS analysis and Western Blot, the stability of Skp2 protein changes in HCT116R in combination chemotherapy-resistant cells by CHX assay.

Results: The protein expression and mRNA of Skp2 was markedly up-regulated in the tumor tissues ($p<0.001$) and serum ($p<0.001$) of colorectal cancer to combined chemotherapy resistance. The expression level of Skp2 in serum after chemotherapy resistance was significantly higher than before ($p<0.01$). Colorectal cancer cells HCT116, HT29 and SW620 were used to establish 5-Fu+ irinotecan in combination with chemotherapy HCT116R, HT29R and SW620R. The half-life of Skp2 protein in HCT116R in chemotherapy-resistant cells was significantly extended, and the protein stability of Skp2 was enhancer.

Conclusions: The shRNA library screening targeting deubiquitinating enzymes found that the stability of the Skp2 protein and thus enhance the resistance of colorectal cancer cells to 5-Fu

combined with irinotecan. The molecular mechanism to promote chemotherapy resistance in vitro and in vivo, and to determine Skp2 can be used as potential markers of liquid biopsy to predict the sensitivity and prognosis of colorectal cancer cases to combined chemotherapy.

Key Words： Liquid Biomarker; Colorectal cancer; Skp2; Chemoresistance

125. 肿瘤患者念珠菌血症病原学特点与死亡危险因素分析

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目的：探讨肿瘤患者念珠菌血症病原菌分布特点、耐药情况、预后危险因素及实验室相关检测指标的临床诊断价值，为疾病预防和合理诊治提供有效依据，以期改善预后及提高生存率。

方法：回顾性队列研究纳入某肿瘤医院 2013 年 1 月至 2022 年 12 月期间所有念珠菌血症患者，对其疾病谱及临床分离株的微生物学数据进行统计分析。根据预后情况分为死亡组和生存组，采用单因素分析、logistic 回归及受试者工作特征（ROC）曲线分析死亡相关危险因素。

结果：念珠菌血症患者共 67 例，死亡 26 例，病死率 38.8%。感染患者以胰腺癌(25.4%)、结直肠癌(16.4%)、食管癌(16.4%)为主。共检出念珠菌 68 株，以白念珠菌（44.1%）、近平滑念珠菌（20.6%）、光滑念珠菌（11.8%）为主；体外药敏试验结果显示，念珠菌 98.4%为两性霉素 B 野生型，90.9%是伊曲康唑野生型。单因素分析结果显示，原发肿瘤远处转移、合并 3 种及以上基础疾病、血液透析、气管切开、机械通气、合并细菌血流感染、中心静脉导管相关真菌感染均为影响患者预后的危险因素（P＜0.05）；Logistic 回归分析模型显示，原发肿瘤远处转移（P=0.003）以及机械通气（P=0.019）是患者死亡的独立危险因素。共计 43 例患者送检(1,3)- β-D 葡聚糖，阳性率为 48.8%。死亡组患者与生存组患者血清 C-反应蛋白（CRP）（P=0.039）、降钙素原（PCT）（P=0.006）、血小板（PLT）（P=0.001）、血浆纤维蛋白原（FIB）（P=0.023）、D-二聚体（D-Dimer）（P<0.001）、纤维蛋白原降解产物（FDP）（P=0.001）水平比较差异有统计学意义，全血白细胞水平（WBC）、活化部分凝血活酶时间(APTT)、凝血酶原时间（PT）、凝血酶时间（TT）比较无明显差异。PLT 预

测念珠菌血流感染患者死亡的 ROC 曲线下面积（AUC）为 0.751，高于其他指标，具有一定的临床应用价值；D-Dimer 的敏感性显著高于其他指标，而 PCT 的特异性最优。

结论：肿瘤患者发生念珠菌血症预后差，感染以白念珠菌为主，两性霉素 B 野生型菌株占比高。原发肿瘤远处转移及机械通气与患者死亡率密切相关，(1,3)- β-D 葡聚糖联合血培养送检有助于早期诊断，血清 CRP、PCT、PLT、FIB、D-Dimer、FDP 水平可一定程度预测患者预后，PCT 及 D-Dimer 具有较高的生存预测价值。

关键字：念珠菌血症；肿瘤患者；脓毒症；凝血功能障碍；(1,3)-β-D 葡聚糖；C 反应蛋白；降钙素原；死亡率；危险因素

126. CDK5RAP2 作为 Wnt 通路靶基因可促进口腔鳞状细胞癌干细胞活性和的肿瘤进展

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Background: Head and neck squamous cell carcinoma (HNSCC) is a highly aggressive and frequently lethal malignancy. The 5-year survival rate of patients with HNSCC has remained low due to the tumor recurrence, metastasis, and treatment resistance. CDK5RAP2 is a microtubule regulatory protein. The role and underlying molecular mechanism of CDK5RAP2 in HNSCC are unknown.

Methods: CDK5RAP2 expression was examined using qRT-PCR and database analysis, and the biological role of CDK5RAP2 in HNSCC were investigated using colony formation assays, transwell assays, sphere formation assays, and in vivo tumorigenesis assays. Drug treatment,

chromatin immunoprecipitation, and luciferase reporter assays were used to determine the regulation of CDK5RAP2 expression by the Wnt signaling pathway. Moreover, the gene expression profiles of CDK5RAP2-depleted cells were identified through RNA-sequencing and bioinformatics analyses. Lastly, spindle orientation was investigated through immunostaining.

Results: CDK5RAP2 expression was upregulated in HNSCC tumor tissues and cells, and CDK5RAP2 knockdown inhibited cell tumorigenesis and migration. CDK5RAP2 expression was found to be regulated by the Wnt signaling pathway. Moreover, CDK5RAP2 depletion altered the cancer stem (-like) cell (CSC) signature of HNSCC cells. Notably, CDK5RAP2 was found to regulate spindle orientation in mitotic cells.

Conclusions: CDK5RAP2 is identified here as a potential CSC marker of HNSCC that is regulated by the Wnt signaling pathway. CDK5RAP2 plays an indispensable role in HNSCC development and regulates the CSC signature of HNSCC by controlling spindle orientation during mitosis.

Key Words： Head and neck squamous cell carcinoma (HNSCC); Wnt signaling pathway; Cancer stem (-like) cell (CSC); CDK5RAP2; Spindle orientation

127. 白桦茸多糖治疗肝癌的网络药理学研究

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研究目的：本研究旨在探究白桦茸多糖对肝癌的网络药理研究。

材料与方法：利用 chemdraw 构建化合物的 3d 结构文件，并获取对应的 smiles 号。利用 PharmMapper、SwissTargetPrediction、TargetNet 获取化合物的靶点。利用 CTD、GeneCards、PharmGKB、DisGeNET 获取肝癌的相关靶点。利用 Venny 网站取化合物靶点和疾病靶点交集。STRING 数据库用于蛋白互作网络构建。用 Rstudio 的 clusterprofiler 包对基因进行 GO 和 KEGG 富集分析。

结果：白桦茸多糖筛选出靶点 174 个，肝癌靶点 926 个。将白桦茸多糖靶点与肝癌相关靶点经过 Venn 分析，得到白桦茸多糖治疗肝癌的交集靶点 65 个。将 65 个治疗基因导入 STRING 数据库，cytoscape3.8.0 可视化并分析，分别计算节点基因的 degree、betweenness、

closeness 其中关联度前 10 的关键靶点有 ALB、EGFR、TP53、ESR1、SRC、CASP3 等。GO 富集分析显示核受体活性、蛋白酪氨酸激酶活性、激素受体结合等；KEGG 信号通路富集包括 PI3K-Akt 信号通路、VEGF 信号通路、FoxO 信号通路等。

结论：白桦茸多糖可能通过以上信号通路靶点对肝癌起到治疗作用。

关键字：白桦茸；桦褐孔菌；白桦茸多糖；肝癌；网络药理学

128. Non-homologous spectral data fusion for the discrimination of single base mutation in KRAS gene fragment through different active cells

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Current diagnosis of the KRAS gene mutation in colorectal cancer (CRC) lack enough sensitivity and the poor detection efficacy resulted in poor prognosis. Therefore, it is very important to develop a rapid, accurate and low-cost method to distinguish the metabolic characteristics induced by single base mutations in KRAS gene fragments. Four colon cancer cell lines were chosen to represent different status of KRAS mutation, including wild-type cells DKS-8 and HEK-3 and their respective mutant cells DLD-1 and HCT-116. The nuclear magnetic resonance (NMR) and laser tweezers Raman spectroscopy (LTRS) were used to investigate the metabolomics signatures of these mutant and wild-type cells. Various statistical techniques were used to investigate the specific changes according to both NMR and LTRS data sets and their fusion data sets. The results

demonstrated that there were significant differences between mutant and wild-type cells. Four metabolites include taurine, glucose, phosphorylcholine and tyrosine were screened as characteristic metabolites. Common altered metabolic pathways due to single base mutations in KRAS gene fragments include D-glutamine and D-glutamate metabolism, alanine, aspartate and glutamate metabolism, and arginine biosynthesis. It is also noted that the fusion of NMR and LTRS data sets exhibit superior performance. Thus, the combination of non-homologous spectral data fusion would enhance reliability of the single source-derived characteristic markers. The proposed strategy will be helpful for congeneric researches in the biomedical field.

Key Words： colorectal cancer; KRAS; laser tweezers Raman spectroscopy; nuclear magnetic resonance; metabolomics; data fusion

129. Elevated neutrophil extracellular traps by HBV-mediated S100A9-TLR4/RAGE-ROS cascade facilitate the growth and metastasis of hepatocellular carcinoma

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Background: Neutrophil extracellular traps (NETs) are considered significant contributors to cancer progression, especially metastasis. However, it is still unclear whether NETs are involved in hepatitis B virus (HBV)-related hepatocarcinogenesis and have potential clinical significance during evaluation and management for hepatocellular carcinoma (HCC). In this study, we aimed to investigate the functional mechanism of NETs in HBV-related hepatocarcinogenesis and their clinical significance.

Methods: A total of 175 HCC patients with and without HBV infection and 58 healthy controls were enrolled in this study. NETs were measured in tissue specimens, freshly isolated neutrophils and blood serum from these patients, and the correlation of circulating serum NETs levels with malignancy was evaluated. The mechanism by which HBV modulates NETs formation was

explored using cell-based studies. In addition, in vitro and in vivo experiments were further performed to clarify the functional mechanism of NETs on the growth and metastasis of HCC.

Results: We observed an elevated level of NETs in blood serum and tissue specimens from HCC patients, especially those infected with HBV. NETs facilitated the growth and metastasis of HCC both in vitro and in vivo, which were mainly dominated by increased angiogenesis, epithelial-mesenchymal transition (EMT)-related cell migration, matrix metalloproteinases (MMPs)-induced extracellular matrix (ECM) degradation and NETs-mediated cell trapping. Inhibition of NETs generation by DNase 1 effectively abrogated the NET-aroused HCC growth and metastasis. In addition, HBV-induced S100A9 accelerated the generation of NETs, which was mediated by activation of toll-like receptor (TLR4)/receptor for advanced glycation end products (RAGE)-reactive oxygen species (ROS) signaling. Further, circulatory NETs were found to correlate with viral load, TNM stage and metastasis status in HBV-related HCC, and the identified NETs could predict extrahepatic metastasis, with an area under the ROC curve (AUC) of 0.83 and 90.3% sensitivity and 62.8% specificity at a cutoff value of 0.32.

Conclusions: Our findings indicated that activation of RAGE/TLR4-ROS signaling by HBV-induced S100A9 resulted in abundant NETs formation, which subsequently facilitated the growth and metastasis of HCC cells. More importantly, the identified circulatory NETs exhibited potential as an alternative biomarker for predicting extrahepatic metastasis in HBV-related HCC.

Key Words ：Neutrophil extracellular trap, hepatocellular carcinoma, hepatitis B virus, metastasis, S100A9

130. Establishment of oxidative stress-related prognostic models for endometrial cancer based on machine learning

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Abstract: Background: Endometrial cancer (EC) is the sixth most common cancer among women with poor prognosis and high recurrence rate. Establishing prognostic models contribute to the precise treatment of EC; however, an effective prognosis prediction method is lacking.

Methods: Oxidative stress-related genes were derived from the GeneCards website, and prognostic genes of EC were identified using the TCGA database. Then, we took the intersection of these two gene sets and selected key oxidative stress-related genes with prognostic value using Lasso, Xgboost, and random forest algorithms. We split the data into train and test sets with a 7:3 ratio and integrated 20 machine learning algorithms, including LASSO, Enet, Random Survival Forest, Survival Support Vector Machine, Stepwise Cox, plsRox, and SuperPC, along with their combinations for model fitting. According to the prognostic model, the EC patients were divided into high- and low-risk groups, and the survival outcome and immune cell infiltration of the EC patients in the two groups were compared.

Results: Oxidative stress is closely related to the progression of EC. We retrieved 567 oxidative stress-related genes from GeneCards and identified 184 prognostic genes of EC. We identified six key oxidative stress-related genes with prognostic value: ASS1, FN1, DRD2, FMO3, CCL2, and EDN1 prior to modeling. The predictive model utilizing the plsRox algorithm ranked first with an average C-index value of 0.682 in the train set and test sets. The AUCs of the model were 0.76, 0.73, and 0.75 for one-year, three-year, and five-year survival rates in the training set. The corresponding AUCs of the model were 0.75, 0.68, and 0.65 in the test set. Significant differences were observed in the survival outcome and immune cell infiltration of EC patients between the high- and low-risk groups.

Conclusion: We established an effective prognostic model for EC, offering valuable support for EC treatment.

Key Words： Endometrial Cancer; Oxidative Stress; Machine Learning; Prognostic Model

131. Comprehensive pan-cancer analysis of CD274 as a prognostic and immunomarker

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Purpose: CD274 (B7-H1) is a member of the B7 co-inhibitory molecule family, and its expression is closely related to poor prognosis or malignant tumor grade, but its significance is far more than that. The aim of this study was to perform pan-cancer analysis of CD274 by bioinformatics methods.

Methods: Multiple online databases were used to analyze the association of CD274 with prognosis, genomic instability, tumor stemness, DNA repair, and immune infiltration. In addition, single-cell database and TIMER online database were used to verify the correlation between CD274 expression and M1 macrophages. Finally, single-cell function analysis and functional enrichment analysis of co-expressed genes of CD274 were performed.

Results: Prognostic analysis indicated that CD274 may be an independent prognostic factor for KIRC, SKCM and LGG. High CD274 was associated with higher genomic stability. Then we found that high CD274 was associated with high expression of mismatch repair genes, stemness and homologous repair gene features in more than five cancers. Estimates and cytokine analysis showed that CD274 was associated with immunosuppression. In addition, we validated CD274 as a marker of M1 macrophages and showed its association with other immunosuppressive cells, and finally single-cell functional analysis showed that CD274 was negatively associated with DNA damage and DNA repair in some tumors.

Conclusion: We found that CD274 is not only an important member of MMR and HRR, and further found that CD274 may be a potential biomarker for STAD， COAD and READ genome stabilization, but also has potential value in tumor immunity and may be an M1 macrophage biomarker in many cancers. It is expected to be a prognostic marker for specific cancers.

Key Words ： CD274; Prognosis; Immune cell infiltration; pan-cancer

132. The proposal of New China Climate Changes Prevention Law

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Background and objective: In southern China, in 2021, there have been being in hot Summer in more than 67 cities, counties or areas, with the hot temperature 30 degrees Celsius and more than 30 degrees Celsius with the highest as 34 degrees Celsius.After the Chinese lunar year and the 24 Solar Term, the beginning of winter has passed 5 days. And there have 23 cities, counties or areas which the temperature have reached the highest 34 degrees Celsius. Which all are rare in the weather history in China in the aspects of the highest temperature as 34 degrees Celsius and in large part of southern China in early Winter.

As the World Health Organization, the United Nations and the world have been striving for preventing and curing the climate changes. And have been paying special attention to the health impacts by the climate changes. In China, after the history hottest Summer suffered from by the Chinese in 2022. The Chinese have been continuing to suffer from the hottest temperature like Summer in the early winter. So the weather in China is not normal comparing to the post years. And it is sure that the climate changes impacts on Chinese in China in 2022 have been evidenced.

As I have been being a senior doctor treating and preventing patients and promoting the public health more than 35 years. I have the duty and the motive to do something to prevent and cure the climate changes and their impacts on public health. So in this research I especially create and propose a new draft law, the China climate changes prevention law, to speed, administrate and guard China doing well in preventing climate changes in China and the world.

Methods: Summarized the public health promotion and environment protection in China and in author own doing. Referenced the present new situation of climate changes in China and the world. Created the China climate changes prevention law in draft and in central strategies.

Results: The China climate changes prevention law in central strategies as follows:

1. In order to prevent and cure the climate changes and their impacts on public health and mankind, the China climate changes prevention law must be created as soon as possible.

2. All Chinese people and every government department and any unit must pay special attention to the climate changes and their impacts on public health and mankind. And must be consider it as the first doing job among the all works in any unit.

3. China own scientific research must be done as early as possible and as deeply as possible to find the etiology and mechanism of the climate changes and their impacts on public health and mankind. When the etiology and mechanism research have gained achievements. The application must be done as soon as possible.

4. The present achievements of etiology and mechanism of the climate changes and their impacts on public health and mankind must be applied as soon as possible.

5. All the policies of the United Nations and its organizations for controlling the climate changes must be signed and applied totally and completely as soon as possible.

6. China should be the leader of controlling the climate changes in the world. The significant China strategies must be contributed to the world for controlling the climate changes as soon as possible as China is the biggest country in population.

7. From birth and kindergarten to the time before death,the knowledge of environment protection and climate changes prevention, cure must be educated constantly to every Chinese.

8. The precondition for organizing any new unit and old unit must pass the exam of climate changes prevention. The concrete policies must be created and documented.

9. All over the China, the inspection stations must be built to monitor the climate changes wrongly doing.

10. Regulations and their process must be built to punish any anti law doers who promote the the climate changes. Also, reward any people and units who have contributed significantly to the prevention of climate changes.

11. Cooperation with internationals must be indispensable.

12. As the village of the Earth, open policies must be built to let internationals to inspect, learn,study and cooperation,etc. in China.

13. As the climate changes impacts on the Chinese and the mankind, the medical support, research, prevention, treatment, education and other health promotion policies must be created and built to protect the Chinese and the mankind from harming by the climate changes. The universities, hospitals, institutes should operate the climate changes impacts medical science.

14. Summarizing the doings of the climate changes prevention constantly to make progress further.

15. Liberating the thoughts of the leaders and the ordinary people, throwing away any selfish doing of only pursuing own country economic development at the price of world climate changes impact worse in the Earth and the space.

Conclusion: The China climate changes prevention law in draft comes from the candid invention of the author by summarized the present situation of climate changes impacts in China and the world. The 15 paragraphs of the new China climate changes prevention law is valuable, as up to now, China has not built this kind of law. This proposal of the new China climate changes prevention law is worthwhile to referenced by China lawmakers, world countries lawmakers, the UN and its organizations and related others.

Key Words ： Climate changes; Climate changes impacts; Health promotion; Prevention; Law-making; Climate emergency.

133. Computational identification and clinical validation of a novel risk signature based on coagulation-related lncRNAs for predicting prognosis, immunotherapy response, and chemosensitivity in colorectal cancer patients

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Background ： Coagulation is critically involved in the tumor microenvironment, cancer progression, and prognosis assessment. Nevertheless, the roles of coagulation-related long noncoding RNAs (CRLs) in colorectal cancer (CRC) remain unclear. In this study, an integrated

computational framework was constructed to develop a novel coagulation-related lncRNA signature (CRLncSig) to stratify the prognosis of CRC patients, predict response to immunotherapy and chemotherapy in CRC, and explore the potential molecular mechanism.

Methods ： CRC samples from The Cancer Genome Atlas (TCGA) were used as the training set, while the substantial bulk or single-cell RNA transcriptomics from Gene Expression Omnibus (GEO) datasets and real-time quantitative PCR (RT-qPCR) data from CRC cell lines and paired frozen tissues were used for validation. We performed unsupervised consensus clustering of CRLs to classify patients into distinct molecular subtypes. We then used stepwise regression to establish the CRLncSig risk model, which stratified patients into high- and low-risk groups. Subsequently, diversified bioinformatics algorithms were used to explore prognosis, biological pathway alteration, immune microenvironment, immunotherapy response, and drug sensitivity across patient subgroups. In addition, weighted gene coexpression network analysis was used to construct an lncRNA–miRNA–mRNA competitive endogenous network. Expression levels of CRLncSig, immune checkpoints, and immunosuppressors were determined using RT-qPCR.

Results ： We identified two coagulation subclusters and constructed a risk score model using CRLncSig in CRC, where the patients in cluster 2 and the low-risk group had a better prognosis. The cluster and CRLncSig were confirmed as the independent risk factors, and a CRLncSig-based nomogram exhibited a robust prognostic performance. Notably, the cluster and CRLncSig were identified as the indicators of immune cell infiltration, immunoreactivity phenotype, and immunotherapy efficiency. In addition, we identified a new endogenous network of competing CRLs with microRNA/mRNA, which will provide a foundation for future mechanistic studies of CRLs in the malignant progression of CRC. Moreover, CRLncSig strongly correlated with drug susceptibility.

Conclusions ： We developed a reliable CRLncSig to predict the prognosis, immune landscape, immunotherapy response, and drug sensitivity in patients with CRC, which might facilitate optimizing risk stratification, guiding the applications of immunotherapy, and individualized treatments for CRC.

Key Words： Colorectal cancer, coagulation, long noncoding RNA, prognostic signature, tumor microenvironment, immunotherapy, chemosensitivity

134. Bulk RNA-seq revealed molecular mechanisms behind differences in clinicopathologic characteristics of hepatocellular carcinoma patients with different tumor marker combinations

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Objective: Hepatocellular carcinoma (HCC) is the fourth most common malignant tumor and the second leading cause of tumor death in China. Efficient biomarkers are needed to guide precision therapy to improve patient prognosis and 5-year survival. Alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) are now commonly used tumor markers for HCC. This study aimed to mainly investigate whether HCC patients with different AFP and DCP combinations had distinct clinical phenotypes and their underlying molecular mechanisms.

Methods: The medical data of consecutive HCC patients undergoing hepatectomy from Nanjing Drum Tower Hospital (NJDTH) and The First Affiliated Hospital of Nanjing Medical University (FAHNJMU) from January 2020 to August 2023 were retrospectively reviewed. Based on whether AFP and DCP were preoperative positive (≥ 10 ng/mL and ≥ 40 mAu/mL), patients were divided into four groups: both AFP & DCP negativities (Group 1), only AFP positivity (Group 2), only DCP positivity (Group 3), and both AFP & DCP positivities (Group 4). The Welch test and Pearson χ^2 test were used to compare whether there were differences in each continuous and categorical variable among the four groups, respectively. Twelve HCC tissues (three in each group) were collected, and bulk RNA-seq was conducted. Then, differentially expressed genes between groups were identified by the R package "DESeq2". Clinical information for HCC obtained from The Cancer Genome Atlas (TCGA) dataset was used for Kaplan-Meier (KM) survival analysis.

Finally, gene set enrichment analysis (GSEA) and gene set variation analysis (GSVA) were conducted to detect specific signaling pathway activation in each group.

Results: 370 and 350 patients from NJDTH and FAHNJMU were included according to the inclusion criteria. Among them were 93 patients (12.9%) in Group 1, 87 (12.1%) in Group 2, 185 (25.7%) in Group 3, and 355 (49.3%) in Group 4. First, DCP showed a higher positive rate in detecting resectable HCC (75.0% vs. 61.4%, $p < 0.001$). Second, the four groups of HCC patients had significantly different clinicopathologic phenotypes. For instance, Group 4 patients were characterized by worse HCC differentiation, larger tumor sizes, more tumor numbers, as well as higher probability of occurring micro- and macro-vascular invasion and satellite nodules. Furthermore, states of hepatic function, inflammation, and fibrosis differed between groups. Third, bulk RNA-seq revealed specific gene expression landscapes of each group. Subsequently, GSEA and GSVA manifested that Group 1 patients retained better liver metabolic functions, while carcinogenic-related signaling pathways were activated in the other three groups. Integrated analyses found that Group 2, Group 3, and Group 4 were featured with Wnt/beta-catenin signaling, cytokine-mediated signaling, and cell cycle signaling.

Conclusion: Different preoperative AFP and DCP combinations represented distinct clinical phenotypes and long-term prognoses of HCC patients. Revealing underlying molecular mechanisms provided the theoretical basis and therapeutic strategies for future precision therapy.

Key Words : hepatocellular carcinoma, alpha-fetoprotein, des-γ-carboxy prothrombin, clinicopathologic phenotypes, bulk RNA-seq, molecular mechanisms

135. MAP3K4 Kinase Action and Dual Role in Cancer

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It is generally accepted that the MAPK pathway is involved in translating environmental inputs, the downstream regulation, and maintaining the intrinsic dynamic balance. There have been multiple major components and regulatory processes in this critically important cascade. MAP3K4

belongs to serine/threonine kinases, playing significant roles in the whole life cycle, such as governing apoptosis and autophagy. Besides, it has the ability to bind with critical partners like GADD45 and regulates growth and development of organisms. Noteworthy, MAP3K4 serves as both tumor promotor and suppressor, activated by various factors and initiating different down-streams to govern cancer developments in different ways. The aim of this study is to provide a brief overview of physiological functions of MAP3K4 and elucidate its dual role in tumorigenesis.

Key Words ： MAP3K4; MAPK pathways; binding partners; organism development; cancer

136. Prognostic, Immunological, and Mutational Analysis of MTA2 in Pan-Cancer and Drug Screening for Hepatocellular Carcinoma

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Background:Metastasis-associated protein 2 (MTA2) is a member of the metastasis-associated transcriptional regulator family and is a core component of the nucleosome remodeling and histone deacetylation complex. Despite growing evidence that MTA2 plays a crucial role in the tumorigenesis of certain cancers, no systematic pan-cancer analysis of MTA2 is available to date. Therefore, the aim of our study is to explore the prognostic value of MTA2 in 33 cancer types and to investigate its potential immune function.

Methods: By comprehensive use of databases from TCGA, GTEx, GEO, UCSC xena, cBioPortal, comPPI, GeneMANIA, TCIA, MSigDB, and PDB, we applied various bioinformatics approaches to investigate the potential role of MTA2, including analyzing the association of MTA2 with MSI, prognosis, gene mutation, and immune cell infiltration in different tumors. We constructed a nomogram in TCGA-LIHC, performed single-cell sequencing (scRNA-seq) analysis of MTA2 in

hepatocellular carcinoma (HCC), and screened drugs for the treatment of HCC. Finally, immunohistochemical experiments were performed to verify the expression and prognostic value of MTA2 in HCC. In vitro experiments were employed to observe the growth inhibition effects of MK-886 on the HCC cell line HepG2.

Results: The results suggested that MTA2 was highly expressed in most cancers, and MTA2 expression was associated with the prognosis of different cancers. In addition, MTA2 expression was associated with Tumor Mutation Burden (TMB) in 12 cancer types and MSI in 8 cancer types. Immunoassays indicated that MTA2 positively correlated with activated memory CD4 T cells and M0 macrophage infiltration levels in HCC. ScRNA-seq analysis based on the GEO dataset discovered that MTA2 was significantly expressed in T cells in HCC. Finally, the eXtreme Sum (Xsum) algorithm was used to screen the antitumor drug MK-886, and the molecular docking technique was utilized to reveal the binding capacity between MK-886 and the MTA2 protein. The results demonstrated excellent binding sites between them, which bind to each other through Π-alkyl and alkyl interaction forces. An immunohistochemistry experiment showed that MTA2 protein was highly expressed in HCC, and high MTA2 expression was associated with poor survival in HCC patients. MK-886 significantly inhibited the proliferation and induced cell death of HepG2 cells in a dose-dependent manner.

Conclusions: Our study demonstrated that MTA2 plays crucial roles in tumor progression and tumor immunity, and it could be used as a prognostic marker for various malignancies. MK-886 might be a powerful drug for HCC.

Key Words ： MK-886; MTA2; immune cell infiltration; immunohistochemistry; pan-cancer analysis.

137. Single-cell transcriptome sequencing of B-cell heterogeneity and tertiary lymphoid structure predicts breast cancer prognosis and neoadjuvant therapy efficacy

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Background: Breast cancer (BC) is a highly heterogeneous disease, and although immunotherapy has recently increased patient survival in a number of solid and hematologic malignancies, most BC subtypes respond poorly to immune checkpoint blockade therapy (ICB). B cells, particularly those that congregate in tertiary lymphoid structures (TLS), play a significant role in antitumour immunity. However, B-cell heterogeneity at single-cell resolution and its clinical significance with TLS in BC need to be explored further.

Methods: Primary tumour lesions and surrounding normal tissues were taken from 14 BC patients, totaling 124,587 cells, for single-cell transcriptome sequencing and bioinformatics analysis.

Results: Based on the usual markers, the single-cell transcriptome profiles were classified into various clusters. A thorough single-cell study was conducted with a focus on tumour-infiltrating B cells (TIL-B) and tumour-associated neutrophils (TAN). TIL-B was divided into five clusters, and unusual cell types, such as follicular B cells, which are strongly related to immunotherapy efficacy, were identified. In BC, TAN and TIL-B infiltration are positively correlated, and at the same time, compared with TLS-high, TAN and TIL-B in TLS-low group are significantly positively correlated.

Conclusions: In conclusion, our study highlights the heterogeneity of B cells in BC, explains how B cells and TLS contribute significantly to antitumour immunity at both the single-cell and clinical level, and offers a straightforward marker for TLS called CD23. These results will offer

more pertinent information on the applicability and effectiveness of tumour immunotherapy for BC.

Key Words： B cells; breast cancer; single cell sequencing; tertiary lymphoid structures; treatment.

138. Pan-Cancer Analysis of the Prognostic and Therapeutic Role of BUB1

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Background: BUB1 mitotic checkpoint Serine/Threonine Kinase (BUB1) plays a pivotal role in mitosis and is associated with multiple types of cancer, such as colorectal cancer, neuroblastoma and gastric adenocarcinoma. However, so far there has been no systematic pan-cancer analysis of BUB1.

Methods: Comprehensively incorporating data from The Cancer Genome Atlas (TCGA), Genotype-Tissue Expression Project (GTEx), Cancer Cell Line Encyclopedia (CCLE), Gene Expression Omnibus (GEO), cBioPortal, TIMER and so on, we conducted a series of analyses to excavate BUB1' s potential value in prognosis and clinical therapy, analyses that entailed gene expression analyses, Kaplan-Meier plotters, pathological, TME, CNV, stemness, and drug response analyses.

Results: BUB1 expression was markedly higher in most tumor types versus normal tissues and its high expression was correlated with worse Overall Survival (OS), Disease Free Survival (DSS), Disease-Free Interval (DFI), and Progression-Free Interval (PFI). Moreover, BUB1 demonstrated remarkable co-expressions with certain immune cells, checkpoint genes, RNA modification genes, mitotic-related genes, DNAss and RNAss; it also displayed evident relationships with higher TIDE, ImmuneScore, ICB response, and paclitaxel sensitivity.

Conclusion: Via scrupulous reflections on all the results, we confirmed the value of BUB1 in pan-cancer and concluded that BUB1 might be an auxiliary biomarker.

Key Words： BUB1 mitotic checkpoint Serine/Threonine Kinase (BUB1); pan-cancer; single-cell sequencing; stemness; immunotherapy; targeted therapy

139. Heterogeneity of 68Ga-Prostate-specific membrane antigen positron emission tomography/computed tomography in metastatic castration-resistant prostate cancer: genomic characteristics and association with abiraterone response: an international multi-center cohort study

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Purpose: In prostate cancer, both 68Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and circulating tumor DNA (ctDNA) could act as a dynamic tool for 'real-time' reflection of tumor characteristics. The aim of this study was to evaluate the impact of spatial heterogeneity of the PSMA uptake on the ctDNA characteristics and response rate to new hormonal agent (NHA) treatment.

Methods: This international multi-center cohort study included 153 patients with metastatic castration-resistant prostate cancer (mCRPC) undergoing 68Ga-PSMA PET/CT and 72 targeted genes ctDNA sequencing with a less than 2-week interval. Patients with >1 PSMA-positive lesions were eligible for SUVhetero (as measured by the variance of average SUV) calculation. Patients receiving abiraterone treatment after enrollment and with complete follow-up record were included into prostate-specific antigen (PSA) response rate analysis and PSA-PFS. PSA response was defined as a reduction of greater than 50% from baseline. Correlations and comparisons by Spearman and Mann-Whitney tests, respectively.

Results: Overall, 118 patients were eligible for SUVhetero calculation. The ctDNA detection rate was 65% (100/153). Higher SUVhetero value contributed to higher ctDNA% (Spearman's rho = 0.278, $p < 0.002$). Compare to patients with higher SUVhetero value, patients with NA SUVhetero had a higher PSA response rate (52% vs. 90%, $p = 0.036$) post NHA treatment. We further discovered a higher SUVmax-mean value was strongly correlated with higher SUVhetero (Spearman's rho = 0.833, $p < 0.0001$). Patients with higher SUVmax-mean value also had a higher PSA response rate compared to patients with lower SUVmax-mean value (83.3% vs. 53.3%, $p = 0.024$) and shorter PSA-PFS ($p < 0.01$). An external cohort (from University Hospital of Liège, Liège, Belgium) confirmed baseline SUVmax-mean value was associated with NHA treatment response rate ($p = 0.038$). Patients with alterations in AR, DNA damage repair pathway, TP53, and WNT pathway had higher SUVmax-mean value compared to those without ($p < 0.05$).

Conclusion: SUVhetero and SUVmax-mean, which was associated with ctDNA characteristics and showed predictive ability in NHA treatment response rate analysis, both reflect the spatial heterogeneity of the PSMA uptake. Our findings supported the implementation of 68Ga-PSMA PET/CT testing in clinical management of NHA-treated patients with mCRPC.

Key Words ： Heterogeneity; PSMA PET/CT; ctDNA; mCRPC; biomarker

140. Targeting MMP9 in CTNNB1 mutant hepatocellular carcinoma restores CD8+ T cell-mediated antitumor immunity and improves anti-PD-1 efficacy

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Objective: The gain of function (*GOF*) CTNNB1 mutations (CTNNB1*GOF*) in hepatocellular carcinoma (HCC) cause significant immune escape and resistance to anti-PD-1. Here, we aimed to

investigate the mechanism of CTNNB1*GOF* HCC-mediated immune escape and raise a new therapeutic strategy to enhance anti-PD-1 efficacy in HCC.

Design: RNA sequencing was performed to identify the key downstream genes of CTNNB1*GOF* associated with immune escape. An in vitro coculture system, murine subcutaneous or orthotopic models, spontaneously tumorigenic models in conditionally gene knocked out mice and flow cytometry were used to explore the biological function of matrix metallopeptidase 9 (MMP9) in tumor progression and immune escape. Single-cell RNA sequencing and proteomics were used to gain insight into the underlying mechanisms of MMP9.

Results: MMP9 was significantly upregulated in CTNNB1^{GOF} HCC. MMP9 suppressed infiltration and cytotoxicity of CD8^{+} T cells, which was critical for CTNNB1*GOF* to drive the suppressive tumor immune microenvironment (TIME) and anti-PD-1 resistance. Mechanistically, CTNNB1*GOF* downregulated sirtuin 2 (SIRT2), resulting in promotion of β-catenin/lysine demethylase 4D (KDM4D) complex formation that fostered the transcriptional activation of MMP9. The secretion of MMP9 from HCC mediated slingshot protein phosphatase 1 (SSH1) shedding from CD8^{+} T cells, leading to the inhibition of C-X-C motif chemokine receptor 3 (CXCR3)-mediated intracellular of G protein-coupled receptors (GPCRs) signaling. Additionally, MMP9 blockade remodeled the TIME and potentiated the sensitivity of anti-PD-1 therapy in HCC.

Conclusions: CTNNB1*GOF* induces a suppressive TIME by activating secretion of MMP9. Targeting MMP9 reshapes TIME and potentiates anti-PD-1 efficacy in CTNNB1*GOF* HCC.

Key Words ： Hepatocellular carcinoma; Mutations; Cancer immunobiology; Immunotherapy

141. 转移性去势抵抗性前列腺癌中 68Ga-PSMA PET/CT 异质性对二代抗雄治疗响应率及基因组特征预测作用的研究：一项国际多中心队列研究

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目的：探讨前列腺特异性膜抗原（prostate-specific membrane antigen，PSMA）摄取的空间异质性对循环肿瘤 DNA（circulating tumor DNA，ctDNA）特征及雄激素受体信号抑制剂（new hormonal agent，NHA）治疗的响应率的影响。

方法：本回顾性研究纳入 153 例转移性去势抵抗性前列腺癌（metastatic castration-resistant prostate cancer，mCRPC）患者，这些患者接受 68Ga-PSMA PET/CT 和 72 个基因的 ctDNA 靶向测序，两种检测时间间隔小于 2 周。SUVhetero 定义为患者体内每个 PSMA 阳性病灶 SUVmean 值的方差；SUVmax-mean 定义为每个患者 SUVmean 值与 SUVmax 值的差值。在 68Ga-PSMA PET/CT 和 ctDNA 测序检测后接受阿比特龙治疗，并且有完整随访记录的患者被纳入前列腺特异性抗原（prostate-specific antigen，PSA）响应率分析。PSA 响应被定义为较基线减少 50%以上。

结果：ctDNA 检出率为 65%（100/153）。68Ga-PSMA PET/CT 和 ctDNA 测序检测之间中位间隔期为 5（IQR 3-8）天。SUVhetero 值与 ctDNA%（Spearman's rho = 0.278, $p < 0.002$）、PSA （Spearman's rho = 0.320, $p < 0.001$）、肿瘤总体积（Spearman's rho = 0.218, $p = 0.017$）和较高的病灶总摄取强度（Spearman's rho = 0.364, $p < 0.0001$）之间存在相关性。预后分析中，中位随访时间为 19.3 个月（IQR 16.2-23.2）。与 SUVhetero 值较高的患者相比，NA SUVhetero 患者的 PSA 应答率更高（52% vs. 90%，$p = 0.036$）。SUVmax-mean 值越高，SUVhetero 值越高（Spearman's rho = 0.833, $p < 0.0001$）。SUVmax-mean 值较高的患者 PSA 响应率也高于 SUVmax-mean 值较低的患者（83.3% vs. 53.3%，$p = 0.024$）。来自比利时列日大学医学院的外部队列证实，高 SUVmax-mean 值患者在接受恩杂鲁胺治疗后，3 个月时发生进展的概率更高（50.0% vs 12.5；$p = 0.038$）。基线 SUVmax-mean 值与恩杂鲁胺治疗响应率相关。高 SUVmax-mean 值患者 AR 基因、DNA 损伤修复通路、TP53 基因、AR 相关通路、细胞周期通路或 WNT 通路的突变率显著高于低 SUVmax-mean 值患者（$p < 0.05$）。

结论：能反映 PSMA 摄取空间异质性的 SUVhetero 和 SUVmax-mean 水平与 ctDNA 特征相关，并能预测 NHA 治疗响应率。我们的研究结果支持在转移性去势抵抗性前列腺癌（mCRPC）患者的临床管理中应用 68Ga-PSMA PET/CT 检测。

关键字： 异质性; PSMA PET/CT; ctDNA; mCRPC; 肿瘤预后标志物

142. 3q 扩增（AMP）在种族多样化的晚期肺鳞状细胞癌患者群体中的预后相关性

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背景：3q amplification（AMP） 是肺鳞状细胞癌 （LUSC） 中最常见的遗传改变，最常见的扩增区域是 3q26-3q28。它代表了 LUSC 和腺癌之间最显着的分子差异之一。我们通过分析癌症基因组图谱 （TCGA） 中 476 名 LUSC 患者的数据并从 cBioPortal 中提取拷贝数改变数据，确定了由 3q 染色体上大扩增子内的 25 个基因构成的 AMP 的最小共同区域 （minimal common region, MCR）。在 46.4%的病例中检测到完整的 25 个基因 MCR 的 AMP，并且与更好的疾病特异性生存期（NR vs 9.25 年，95%CI [5.24-NR]；P = 0.011）和无进展间期（8 年 vs 4.9 年，95% [3.5-NR]；P = 0.020）相关。TCGA 数据主要由白种人（69.7%）和早期肺鳞状细胞癌患者（98.7%）组成。我们进行了一项回顾性分析，以验证 MCR AMP 的预后价值，使用具有晚期 LUSC 的种族多样性队列。

方法：我们检索了 33 例 III 期或 IV 期 LUSC 患者的组织样本，并从电子病历中收集了回顾性数据。病理组织免疫组化以确保肿瘤组织的充分性。MCR AMP 通过实验室开发的跨越 MCR 区域的 FISH 探针进行评估。FISH 测试显示超过 4 个拷贝的信号簇被认为是阳性的;我们对 3p 臂使用了对照探针，该探针通常不会在 LUSC 中扩增。

结果：该队列的平均年龄为 69.1 岁，57.6% 为男性，39.4% 为非裔美国人 （AA），54.5% 为白种人，66.7% 为 3 期，33.3% 为 4 期。只有 6.1%的人从不吸烟，84.8%的人以前吸烟。在 54.5%（n = 18）的病例中检测到 MCR AMP。21 例（63%）病例处于 PD-L1 状态，6 例（3 例有 MCR AMP）为 PD-L1 阴性（TPS < 1%），15 例（9 例有 MCR AMP）为 PD-L1 阳性（TPS > 1%）。与 TCGA 队列中观察到的结果一致，与非扩增病例相比，MCR 扩增病例的总生存期（OS）有更好的趋势（1.74 年 vs 0.91 年；HR=0.57，95%CI

[0.26-1.24]，P = 0.15），无进展生存期（progression-free survival，PFS）呈改善趋势（0.90 年 vs 0.74 年；HR=0.88，95%CI [0.43-1.81]，P = 0.73）。

结论：该初步分析表明，MCR AMP 在种族多样化的晚期 LUSC 患者群体中具有预后价值，类似于我们在 TCGA 队列中的观察结果。需要在大量样本中进行进一步验证。

关键字： 3q 扩增，最小共同区域，肺鳞状细胞癌，种族多样性。

143. Screening and verification of new metastasis related immune biomarkers in breast cancer

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Objective: Distant metastasis remains the primary cause of death among breast cancer (BRCA) patients. Many mechanisms including the failure of the immune system, are involved in the process of cancer metastasis. However, all genes involved in immune function have not been fully revealed. This study aims to explore the immune biomarkers associated with breast cancer metastasis.

Methods: We obtained 1623 BRCA samples including transcriptome sequencing and clinical information using GEO (GSE102818, GSE45255, GSE86166) and TCGA-BRCA dataset. Subsequently weighted correlation network analysis (WGCNA) was performed using the GSE102818 dataset to identify the most relevant module to the metastasis of BRCA. We used ConsensusClusterPlus to divide TCGA-BRCA patients into two subgroups (G1 and G2). Meanwhile, LASSO regression analysis was used to construct a MRIGs_score to predict metastasis and progression. Importantly, we validated the expression of vital genes through RT-qPCR and IHC.

Results: The expression pattern of 76 metastasis-related immune genes (MRIGs) screened by WGCNA divide TCGA-BRCA patients into two subgroups (G1 and G2), and the prognosis of G1 group was worse. We also found G1 had a higher mRNA expression-based stemness index score and TIDE score. In addition, higher MRIGs_score represented the higher probability of

progression in BRCA patients. It was worth mentioning the patients in the G1 have a high MRIGs_score at the same time. Importantly, the results of RT-qPCR and IHC demonstrated FEZ1 and IGF2R were risk factors, while IL1RN was a protective factor.

Conclusion: Our study revealed a prognostic model composed of eight immune related genes that can predict the metastasis and progression of BRCA. High scores represented higher metastasis probability. Meanwhile, the consistency of key genes in BRCA tissue and bioinformatics analysis results from mRNA and protein levels was verified.

Key Words ：breast cancer; metastasis; immune genes; weighted correlation network analysis; prognostic model

144. ADH1B 和 ALDH2 在肺腺癌中的预后作用

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背景：乙醇脱氢酶（ADH）和乙醛脱氢酶（ALDH）是参与致癌乙醛代谢的主要酶，分别将醇转化为乙醛，将乙醛解毒为无害的乙酸。为了研究 ADH 同工酶和 ALDH 同工酶在肺腺癌（LUAD）发展中的作用，我们对基因表达进行了回顾性分析。

方法：从癌症基因组图谱 （TCGA） 数据库获得来自 497 个肿瘤样本和 54 个相邻正常样本的 RNA 测序数据。通过 Wilcoxon 试验比较肿瘤组织与邻近正常组织之间 ADH 和 ALDH 家族基因的转录水平。该结果在 111 名肺癌患者的转录组数据中得到了验证，这是先前研究的一部分。通过 TCGA 数据库的生存分析和列线图进一步研究 ADH 和 ALDH 家族基因的诊断和预后价值。通过基因集富集分析（GSEA）深入了解了作用机制。

结果：许多 ADH 和 ALDH 家族基因在肿瘤和邻近正常组织之间显示出显著差异表达。ADH1B 和 ALDH2 的表达水平在肿瘤组织中显示出显著抑制。ADH1B 和 ALDH2 的低表达与较差的总生存期相关，这些基因的组合比 TCGA 数据库中这些基因的单独累加效应提供更大的预后价值。ADH1B 和 ALDH2 转录水平与代谢、细胞周期、DNA 修复和癌症相关通路的调节有关。建立了预测 LUAD 预后的风险评分模型，在预测 1 年、3 年和 5 年总生存期（OS）方面显示出良好的性能。与 TCGA 结果一致，我们的 111 名患者数据集显

示，ADH1B 的肿瘤特异性抑制最明显，低表达与血管、胸膜和淋巴浸润有关。此外，吸烟状况和/或累积吸烟史并不能提供直接的、临床可及的影响肿瘤 ADH1B 或 ALDH2 表达。

结论：ADH1B 和 ALDH2 的组合是 LUAD 的潜在预后标志物，可能作为评估 LUAD 预后的独立临床因素。

关键字： ADH1B，ALDH2，LUAD，预后标志物

145. CD73/腺苷通路相关基因特征在肺腺癌预后中的肿瘤内异质性和免疫浸润研究

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背景：腺苷是一种免疫抑制分子，可以抑制免疫细胞，特别是 T 细胞的活性，促进肿瘤生长。CD73，也称为胞外-5'-核苷酸酶，是一种细胞表面酶，在腺苷途径中发挥作用，可以催化 AMP 转化为腺苷。建立和评估基于 CD73/腺苷通路的预后模型将有助于了解肺腺癌（LUAD）的生物学机制，并为患者的治疗提供更准确的预测。

方法：RNA 测序（RNA-seq）、全外显子组测序（WES）和临床数据来自 TCGA 的 LUAD 转录组与临床数据。通过筛选 CD73 STRING 网络（置信度=0.9，相关作用≤50 个）和 KEGG 嘌呤代谢通路基因列表（map00230）中的基因来鉴定 CD73/腺苷通路相关基因。进行最小绝对收缩和选择算子 （LASSO） 回归以得出 CD73/腺苷通路相关风险评分 （CD73RS）。在 LUAD-TCGA 队列中进行时间依赖性 ROC 曲线和生存分析，以验证 CD73RS 的预测性能。使用 R 包“maftools”和“math.score”函数计算 MATH（突变等位基因肿瘤异质性）ITH 分数以评估 LUAD-TCGA WES“maf”文件中的肿瘤内异质性 （ITH）。采用 TIMER 2.0 数据库（http://timer.cistrome.org/）对肿瘤微环境进行估计，以进一步了解 CD73RS 的分子特征。使用独立队列 （GSE72094） 验证 CD73RS 的预后效果。

结果：采用 LASSO 回归法建立基于 21 个 CD73/腺苷通路相关基因的预后预测模型。LUAD-TCGA 队列风险模型的 Kaplan-Meier 生存分析显示，高危组的预后明显更差（HR=3.298，P=1.26e-08）。1 年、3 年和 5 年时，时间依赖性 ROC 曲线的曲线下面积（AUC）分别为 0.794、0.722 和 0.686。验证集在高危组中也显示预后较差（HR=1.473，p=0.0403）。

与低风险组相比，高危组的 ITH 评分较高（p = 0.0094），B 细胞（p = 7.23e-15）、CD4+ T 细胞（p = 0.003）、巨噬细胞（p = 0.016）和髓样树突状细胞（p = 0.037）的浸润水平较低。

结论：我们建立并验证了 CD73/腺苷通路风险模型，该模型对 LUAD 患者的预后表现出强大的预测性能。CD73/腺苷通路已被证明在肿瘤内异质性 （ITH） 等自我驱动的基因组变化以及免疫微环境适应等非自主过程中发挥作用，这些过程有助于肿瘤的可塑性和发展。

关键字： CD73，腺苷，LUAD，免疫浸润，肿瘤内异质性

146. 基于基因组测序的透明细胞肾细胞癌预后、突变分析和生存率

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目的：透明细胞肾细胞癌（ccRCC）是最普遍的泌尿生殖系统癌，预后较差。关于 ccRCC 的全基因组测序、预后预测系统和总生存期的信息有限。虽然 VHL 的缺失通常与 ccRCC 有关，但其他癌症中指示的两个基因 SDHD 和 ARID1A 关于它们与 ccRCC 相关性的文献有限。因此，我们旨在分析 ccRCC 的基因组特征、流行病学特征和总生存期。

方法：我们利用 cBioPortal 癌症基因组学 [癌症基因组图谱（TCGA）泛癌图谱、TCGA Firehose Legacy 和 TCGA Nature 2013] 来研究与 ccRCC 相关的基因突变。评估了流行病学特征和遗传特征，并生成了一个查询以计算最常见突变的 5 年和 10 年生存率。采用 log-rank 检验和 Kaplan-Meier 估计器分析生存函数。具有两个或更多重叠突变的患者（72）被排除在外。

结果：我们确定了 761 例 ccRCC 患者，其中 442 例患有原发性 ccRCC，并提供所有人口统计学详细信息。65.8%为男性，58.1%为白种人，7.2%为非裔美国人。大多数患者（199 例）年龄在 50-65 岁之间。286 人（64.7%）还活着，156 人（35.3%）死亡。与生存率降低相关的常见突变是 VHL、BAP1、SDHA、SDHD 和 ARID1A。VHL、BAP1、SDHA、SDHD、ARID1A 突变患者的中位生存期分别为 118.85 个月、93.04 个月、40.70 个月、2.04 个月和 6.02 个月，而未改变突变组（78.44 个月）则为 118.85 个月、93.04 个月、40.70 个月、2.04 个月和 6.02 个月（p < 0.0001）。（表 1）SDHD [2.04 个月] 和 ARID1A [6.02 个月] 的

生存率最低。（p = 3.26e-10）。在生存分析中，SDHD 和 ARID1A 在 60 个月（图 1）和 120 个月（图 2）的初始诊断后生存率最低。（p = 2.592e-3）。

结论：我们的研究发现，SDHD、ARID1A 和 SDHA 基因与 ccRCC 的最差预后相关，中位生存期分别为 2.04、6.02 和 40.70 个月。本研究可为 ccRCC 的靶向治疗提供思路，改善这些患者的预后。

关键字： ccRCC，SDHD，ARID1A，预后，突变分析

147. 卵巢肿瘤患者核酸内切酶检测方法的建立及其临床应用

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背景与目的：卵巢癌是严重威胁女性健康的恶性肿瘤之一，临床上发现多处于晚期，尚缺乏卵巢肿瘤的早期血清学筛查方法。探究核酸内切酶活性的检测方法，可为卵巢肿瘤的辅助诊断提供科学依据。

方法：调整酶反应条件和加样量，尝试建立核酸内切酶检测方法，并用卵巢癌细胞 A2780 验证。对入组的临床卵巢肿瘤患者进行检测，并进行统计分析。实验组分为卵巢恶性肿瘤组（n = 97）、卵巢良性肿瘤组（n = 49）和健康对照组（n = 36）；比较其中卵巢癌患者（n = 31）化疗前后核酸内切酶活性的变化。

结果：成功建立了检测外周血单个核细胞中核酸内切酶的检测方法。检测并比较三组之间的核酸内切酶活性，恶性组较良性组和健康组的酶活性均显著增高（P < 0.001）。根据 ROC 曲线得出 R 值临界点为 0.24 时，对卵巢癌诊断的灵敏度为 92.38%，特异度为 72.46%。经单因素方差分析，核酸内切酶活性是患者发生卵巢肿瘤的独立危险因素。化疗后患者的酶活性水平显著下降（P < 0.001），且符合酶活性随化疗次数增加逐渐降低的趋势。

结论：建立了一种检测核酸内切酶活性的方法，该方法可应用于卵巢肿瘤的辅助诊断和化疗后的疗效评估。

关键字： 卵巢肿瘤，单个核细胞，核酸内切酶，辅助诊断，疗效评估

148. Influence of Age and Tumor Location on Long-Term Survival of Colorectal Cancer Patients Undergoing Laparoscopic or Open Surgery: A Retrospective Study Based on Propensity Score Matching

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Purpose: This study aimed to compare the long-term outcomes of laparoscopic and laparotomy surgeries in colorectal cancer (CRC) patients, examining differences in various factors, including tumor locations and ages. The goal was to identify suitable subgroups for laparoscopic surgery and determine an optimal age cutoff.

Methods:A retrospective study included 2014 CRC patients undergoing radical surgery. Patients were categorized into laparoscopy and laparotomy groups, with propensity-score-matching (PSM) performed. Kaplan–Meier analysis, Log-rank test, and Cox regression models were utilized for survival analysis and identification of independent factors affecting CRC OS.

Results: Before PSM, the laparoscopy group demonstrated higher survival rates, but after PSM, no significant difference in mean overall survival (OS) was found between the two groups. Cox regression analysis identified various factors influencing CRC OS, with age, T staging, nodal involvement, poorly-differentiated adenocarcinoma, ascites, preoperative intestinal obstruction, and local tumor dissemination as independent risk factors. Family history was a protective factor, and surgical modality did not independently impact CRC OS. Subgroup analysis highlighted the advantages of laparoscopic surgery in specific subgroups.

Conclusion: In conclusion, laparoscopic and laparotomy surgeries exhibited similar mid-term and long-term prognoses for CRC patients. Laparoscopic surgery showed better outcomes in certain subgroups, particularly in patients aged over 60 and those with right-sided colon carcinoma. The study suggested that > 64 years might be the optimal age cutoff for laparoscopic surgery.

Key Words： Colorectal cancer; Laparoscopic surgery; Laparotomy; Overall survival, Subgroup analysis; Right-sided colon carcinoma

149. Metabolomic landscape of overall and common cancers in the UK Biobank: a prospective cohort study

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Abstract: Information about the NMR metabolomics landscape of overall, and common cancers is still limited. Based on a cohort of 83,290 participants from the UK Biobank, we used multivariate Cox regression to assess the associations between each of the 168 metabolites with the risks of overall cancer and 20 specific types of cancer. ·Then, we applied LASSO to identify important metabolites for overall cancer risk and obtained their associations using multivariate cox regression. We further conducted mediation analysis to evaluate the mediated role of metabolites in the effects of traditional factors on overall cancer risk. Finally, we included the 13 identified metabolites as predictors in prediction models, and compared the accuracies of the our and traditional models. We found that there were commonalities among the metabolic profiles of overall and specific types of cancer: the top 20 frequently identified metabolites for 20 specific types of cancer were all associated with overall cancer; most of the specific types of cancer had common identified metabolites. Meanwhile, the associations between the same metabolite with different types of cancer can vary based on the site of origin. We identified 13 metabolic biomarkers associated with overall cancer, and found that they mediated the effects of traditional factors. The accuracies of prediction models improved when we added 13 identified metabolites in models. This study is helpful to understand the metabolic mechanisms of overall and a wide range of cancers, and our results also indicate that NMR metabolites are potential biomarkers in cancer diagnosis and prevention.

Significance: There were commonalities among the metabolic profiles of overall and specific types of cancer. Meanwhile, the associations between the same metabolite with different types of cancer can vary from site to site.

Key Words： overall cancer; NMR-metabolomics; commonalities; biomarkers; mediation analysis.

150. Guanosine diphosphate–mannose enhances the efficacy of DNA-damaging agents and anti-PD-1 therapy in triple-negative breast cancer

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Background: Triple-negative breast cancer (TNBC) patients with high HRD scores benefit from poly (ADP-ribose) polymerase (PARP) inhibitors, while those with low HRD scores still lack therapeutic options. Homologous recombination deficiency (HRD) induction is an effective strategy to broaden the indications of PARP inhibitors. Metabolic reprogramming is a critical feature of TNBC. In this study, we aimed to explore novel metabolic biomarkers for HRD and new strategy for sensitizing PARP inhibitors.

Methods: We utilized TNBC metabolomics to systematically evaluate metabolites that were correlated with HRD. A crucial metabolite, GDP-mannose (GDP-M), that impedes homologous recombination repair (HR) and sensitizes PARP inhibitors was identified and functionally validated. We further explored the detailed mechanism and proposed a potential treatment strategy utilizing GDP-M for TNBC in preclinical models.

Results: Systematic metabolomic analysis revealed that GDP-mannose (GDP-M) was significantly enriched in basal-like tumors with HRD. GDP-M promoted cisplatin-induced DNA double-strand breaks by inducing HRD. Mechanistically, the low expression of the upstream enzyme GMPPA led to the endogenous upregulation of GDP-M, which further promoted the ubiquitin-mediated degradation of BRCA2 to inhibit HR. GMPPA expression and GDP-M could

serve as predictive biomarkers for HRD and the response to PARP inhibitors. Therapeutically, we validated that the combination of GDP-M and PARP inhibitors synergistically inhibit tumor growth in multiple preclinical models. Moreover, GDP-M supplementation plus PARP inhibition activated STING-dependent antitumor immunity and further augmented the efficacy of anti-PD-1 antibodies.

Conclusions: GDP-M promotes the degradation of BRCA2 and thus enhances the sensitivity of PARP inhibitors in TNBC. The combination of GDP-M, PARP inhibitors and anti-PD-1 immunotherapy may be a potential treatment strategy for TNBCs with low HRD scores.

Key Words： Guanosine diphosphate–mannose, PARP inhibitors，anti-PD-1 therapy，triple-negative breast cancer，BRCA2

151. 通过综合生物信息学分析和机器学习算法的增强 MRI 影像组学模型无创性预测 NRG1 的诊断乳腺癌的研究

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目的：乳腺癌是全球女性最常见的恶性肿瘤，据 2023 年全球癌症统计报告显示，女性乳腺癌已超过肺癌成为最常见的恶性肿瘤，其发病和死亡均位居女性恶性肿瘤的首位，本研究提出通过增强 MRI 影像组学无创性预测乳腺癌组织中 NRG1 的 mRNA 表达；同时整合生信分析，探讨影像组学背后潜在的分子机制与免疫微环境的关联。

方法：根据排除标准，从 TCGA-BRCA 数据库中筛选出原发实体肿瘤且有 RNA-seq 的样本（n = 840）,从 TCIA-BRCA 中得到与 TCGA-BRCA 数据有交集的增强 MRI 影像数据（n = 98）。影像数据按随机数字表法（5：5）分为训练集（n =70）和测试集（n = 28），使用筛选出的特征子集，通过 SVM（support vector machine）算法，在训练集中构建模型。使用（receiver operating characteristic，ROC）曲线评价模型的预测效能，通过绘制校准曲线和进行 Hosmer-Lemeshow 拟合优度检验，评价影像组学预测模型的校准；通过 Brier score，量化影像组学预测 ，通过绘制决策曲线（DCA）展示影像组学预测模型的临床获益度。并应

用验证集对模型进行外部验证。利用 LR 影像组学模型计算出样本的影像组学评分（Radiomics score），将其划分为 Low/High 二分类变量 RS。然后根据高低表达进行 KEGG 通路分析、免疫相关基因的差异性分析和基因突变分析。

结果：通过 ICC 值≥0.75 获得 1810 个影像组学特征，再通过 mRMR(Maximum relevance，minimum redundancy)方法选出前 30 个特征，最后利用 RFE（Recursive feature elimination）算法进一步筛选出最佳 7 个特征子集。SVM 模型具有良好的预测效果：如 ROC 曲线所示，模型在训练集的 AUC 值为 0.822；验证集的 AUC 值为 0.779。校准曲线和 Hosmer-Lemeshow 拟合优度检验显示影像组学预测模型对基因是否高表达的概率和真实值一致性好（P > 0.05）;DCA 显示模型有较高的临床实用性。

结论：结合机器学习与影像组学特征构建的模型 NRG1 可无创性预测乳腺癌治疗预后，并具有较好的泛化能力。

关键字： 乳腺癌，NRG1，MRI，机器学习

152. LncRNA SNHG17 reprograms energy metabolism by activating mitochondrial DNAs to promote breast cancer progression

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In most solid tumors, aerobic glycolysis dominates cellular energy metabolism and meets its large demand for biomacromolecules at the expense of lower efficiency of ATP production. However, it is not yet fully understood how these rapidly growing malignant cells are supplied with sufficient energy in this inefficient ATP production state. In this study, we found that high expression of a long non-coding RNA (lncRNA) SNHG17 correlated with poor prognosis in breast cancer (BCa) and promoted BCa cells growth by increasing triphosadenine (ATP) production in mitochondria.

Mechanistically, SNHG17 directly bond to the transcription factor NF-κB/P65 (P65) in both the cytoplasm and mitochondria and enhanced the settlement of P65 in mitochondria, leading to transcriptional activation of mitochondria DNAs (MT-DNAs) encoded ETC genes (MT-DNAs (including MT-ND1, MT-ND2, MT-ND4, MT-ND5, MT-ND6, MT-CO1, MT-CO3, MT-CYB and MT-ATP6). Accordingly, anti-sense oligonucleotide (ASO) targeting SNHG17 significantly reduced BCa tumor growth both in vitro and in vivo. Overall, our results define a role for SNHG17 in promoting BCa progression by increasing ATP production in mitochondria and provide insight into our understanding on the reprogramming of energy metabolism in solid tumors.

Key Words ： breast cancer, energy metabolism, lncRNA, SNHG17, MT-DNAs

153. miR-143/145 基因簇在口腔鳞癌细胞信号通路调控中的研究进展

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口腔鳞状细胞癌（oral squamous cell carcinoma, OSCC）是口腔颌面部最常见的恶性肿瘤，由于缺乏特异性治疗手段，传统的手术切除仍是主要的治疗策略，但随之而来的口腔颌面部缺损对患者的生活质量造成了严重影响。因此阐明调控 OSCC 发生发展的分子机制俞显必要。越来越多的报道提示 miR-143、miR-145 在 OSCC 组织和细胞株中异常表达，并深入参与其发生演进，且与临床结局相关。研究 miR-143、miR-145 在 OSCC 中的表达及靶基因调控作用有助于进一步阐明其分子机制，明确二者作为生物标志物和分子靶标的价值，从而为 OSCC 临床诊疗提供新思路。

关键字： miR-143；miR-145；口腔鳞癌；信号通路；靶基因

154. Identification of regulatory factors associated with disease-free survival of triple-negative breast cancer based on GEO and transcription factor databases

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Objective: The objective of this study is to identify the transcription factors associated with the disease free survival (DFS) of triple negative breast cancer (TNBC), and to analyze and validate the clinical significance of transcription factors in TNBC progression.

Materials and Methods: We downloaded the dataset GSE97342 from the Gene Expression Omnibus (GEO) database and identified the modules related to DFS of TNBC via weighted gene co-expression network analysis (WGCNA). Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes Genomes (KEGG) pathway analysis were used to explore the biological functions of these modules. The modules were intersected with Human Transcription Factor Database (HumanTFDB), and univariate COX regression analysis was performed for the overlapping transcription to select the hub transcription factors. Through bioinformatics analysis, we evaluated the prognostic value of hub transcription factors, explored their target genes and associations with tumor immune cells in TNBC. Finally, the levels of hub transcription factors were validated by immunohistochemical (IHC) staining and qRT-PCR.

Results: By WGCNA analysis, we extracted three modules related to DFS status of TNBC patients. GO and KEGG analyses demonstrated the biological functions of genes within the three modules. Three hub transcription factors FOXD1, ARNT2, and ZNF132 were identified by survival analysis. Higher FOXD1 was significantly associated with poorer prognosis in TNBC patients, while ARNT2 and ZNF132 were significantly associated with better prognosis in patients with TNBC. IHC staining and qRT-PCR confirmed the expression levels of the identified hub transcription factors.

Conclusion: We identified three hub transcription factors (FOXD1, ARNT2, and ZNF132) associated with the DFS of TNBC, which may be the potential prognostic predictors for TNBC patients.

Key Words ： Transcription factors, Disease free survival (DFS), Triple negative breast cancer, WGCNA, GEO, TCGA

155. Research progress on serum biomarkers for early diagnosis of hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a common malignant tumor, and early diagnosis is of great significance for improving cure rates and improving patient prognosis. This article reviews the research progress of serum biomarkers for early diagnosis of HCC in recent years, including traditional and novel biomarkers. The performance characteristics of various biomarkers are compared in order to provide more choices and basis for early diagnosis of HCC. Collect research literature on serum biomarkers for early diagnosis of HCC by searching relevant domestic and foreign databases. Screen literature based on inclusion and exclusion criteria, and review and analyze various serum biomarkers. The inclusion criteria include: (1) research papers publicly published in well-known journals; (2) The research content is related to serum biomarkers for early diagnosis of HCC; (3) Ability to obtain full text or related data. Exclusion criteria include: (1) conference papers, abstracts, comments, etc; (2) Non English or Chinese literature; (3) Repetitive studies or studies with incomplete data. Early diagnosis is of great value for the treatment and prognosis of HCC, which can significantly improve the survival rate and quality of life of patients. Therefore, finding reliable early diagnostic serum biomarkers is a hot topic in current research.

Objective: This review aims to systematically summarize and evaluate the research progress of serum biomarkers for early diagnosis of HCC in recent years, including traditional and novel

biomarkers, and compare the performance characteristics of various biomarkers, in order to provide more choices and basis for early diagnosis of HCC.

Method: Collect and organize relevant literature at home and abroad, and review and analyze various serum biomarkers. This includes traditional biomarkers such as AFP, CEA, CA19-9, as well as novel biomarkers such as microRNA, CTC, GP73, etc. Compare and analyze the sensitivity, specificity, and AUC values of various biomarkers.

Result:5.1 Traditional landmarks AFP is currently one of the most widely used serum biomarkers for early diagnosis of HCC, with high specificity and sensitivity. However, the expression level of AFP is relatively low in some HCC patients and may also be elevated in other liver diseases and reproductive system tumors, thus limiting its application value.CEA is a broad-spectrum tumor associated antigen that is upregulated in some HCC patients, but overall has lower sensitivity.

The expression level of CA19-9 is also increased in some HCC patients, but it is mainly used for the diagnosis and monitoring of pancreatic cancer.

5.2 New biomarkers

MicroRNA is an endogenous non coding RNA that plays an important role in various biological processes. In recent years, research has found that microRNA plays a crucial role in the occurrence and development of HCC, and has high specificity and sensitivity. Some studies have also found that combining microRNA with other traditional biomarkers can improve diagnostic accuracy.CTC stands for circulating tumor cells, which refer to the detection of cells from primary tumors in the bloodstream. In recent years, research has found that the expression level of CTC is elevated in some HCC patients and is related to tumor staging and prognosis. However, the sensitivity and specificity of CTC detection still need further validation.GP73 is a transmembrane protein that is upregulated in some HCC patients. Recent studies have found that GP73 has high specificity and sensitivity. Research has shown that combining GP73 with other biomarkers can improve diagnostic accuracy.

5.3 Comparative analysis

Comparative analysis of the sensitivity, specificity, and AUC values of various serum markers revealed that AFP had the highest sensitivity (70%) but lower specificity (80%) among single detection indicators; CEA has the highest specificity (90%) but lower sensitivity (40%). MicroRNA and GP73 have high specificity and sensitivity (microRNA: 85%/75%; GP73:

80%/70%), while CTC has relatively low sensitivity and specificity (60%/70%). Multiple studies have shown that joint detection of multiple biomarkers can improve diagnostic accuracy, with AFP+microRNA combined detection having the highest AUC value (AUC=0.90), followed by AFP+CEA+CA19-9 combined detection (AUC=0.85).

Conclusion: Early diagnosis of HCC is of great significance for improving the cure rate and improving patient prognosis. Traditional serum biomarkers such as AFP, CEA, CA19-9, etc. have certain application value, but there are problems with insufficient sensitivity and specificity. New serum biomarkers such as microRNA, CTC, GP73, etc. have high specificity and sensitivity, providing new choices and basis for early diagnosis of HCC. Joint detection of multiple biomarkers can improve diagnostic accuracy, but further clinical validation and research exploration are still needed.

Key Words： hepatocellular carcinoma, early diagnosis, serum markers, research progress

156. NSE 和 CA125 对肝癌的诊断性能及疗效评价

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摘要：本研究旨在探讨神经元特异性烯醇化酶(NSE)和糖类抗原 125(CA125)在肝癌诊断及疗效评估中的价值。通过对比分析肝癌患者与健康人群血清中 NSE 和 CA125 的水平，以及肝癌治疗前后 NSE 和 CA125 水平的变化，评估 NSE 和 CA125 对肝癌的诊断性能及疗效评价。

背景：肝癌是一种常见的恶性肿瘤，早期诊断对于提高治疗效果和改善患者预后具有重要意义。目前，肝癌的常用诊断方法包括影像学检查和肿瘤标志物检测。然而，一些常用的肿瘤标志物在肝癌早期诊断中的敏感性和特异性有限。因此，寻找新的肝癌诊断标志物是当前研究的热点。

目的：本研究旨在探讨 NSE 和 CA125 在肝癌诊断及疗效评估中的价值，以期为肝癌的早期诊断和治疗效果评估提供新的工具。

方法：采用酶联免疫吸附法(ELISA)检测肝癌患者和健康人群血清中 NSE 和 CA125 的水平，比较两组之间的差异。同时，检测肝癌治疗前后 NSE 和 CA125 水平的变化，评估 NSE 和 CA125 在疗效评价中的作用。

结果：研究发现，肝癌患者血清中 NSE 和 CA125 的水平显著高于健康人群，提示 NSE 和 CA125 可能作为肝癌诊断的潜在标志物。进一步分析发现，联合检测 NSE 和 CA125 可以提高肝癌诊断的敏感性和特异性。此外，肝癌治疗前后 NSE 和 CA125 水平的变化与治疗效果相关，可以作为疗效评价的参考指标。

结论：本研究表明，NSE 和 CA125 在肝癌诊断及疗效评估中具有一定的价值。然而，由于本研究样本量较小，尚需进一步验证和完善。未来可以通过扩大样本量、优化检测方法等方式，深入探讨 NSE 和 CA125 在肝癌诊断及疗效评估中的作用，为肝癌的早期诊断和治疗效果评估提供更多依据。

关键字：神经元特异性烯醇化酶(NSE)；糖类抗原 125(CA125)；肝癌；诊断性能；疗效评价

157. Blockage of CacyBP inhibits macrophage recruitment and improves anti-PD-1 therapy in hepatocellular carcinoma

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Background: Despite remarkable advancements in cancer immunotherapy, the overall response rate to anti-programmed cell death-1 (anti-PD-1) therapy in hepatocellular carcinoma (HCC) patients remains low. Our previous study has demonstrated the critical role of CacyBP/SIP (Calcyclin-Binding Protein and Siah-1 Interacting Protein) as a regulator of HCC development and progression. However, the possible impact of CacyBP on the tumor immune microenvironment has not yet been clarified.

Methods: The expressions of CacyBP and Myd88 in HCC cell lines and tissues was detected by bioinformatics analysis, real-time PCR (qPCR), western blotting and immunohistochemistry (IHC). The interaction between CacyBP and Myd88 was measured using co-immunoprecipitation

and immunofluorescence. In vitro and in vivo assays were used to investigate the regulation of CacyBP on tumor-associated macrophages (TAMs).

Results: We identified that CacyBP was positively correlated with Myd88, a master regulator of innate immunity, and Myd88 was a novel binding substrate downstream of CacyBP in HCC. Additionally, CacyBP protected Myd88 from Siah-1-mediated proteasome-dependent degradation by competitively binding to its Toll/interleukin-1 receptor (TIR) domain. Inhibition of CacyBP-Myd88 signaling subsequently diminished HDAC1-mediated H3K9ac and H3K27ac modifications on the CX3CL1 promoter and reduced its transcription and secretion in HCC cells. Moreover, by using in vitro and in vivo strategies, we demonstrated that depletion of CacyBP impaired the infiltration of TAMs and the immunosuppressive state of the tumor microenvironment, further sensitizing HCC-bearing anti-PD-1 therapy.

Conclusions: Our findings suggest that targeting CacyBP may be a novel treatment strategy for improving the efficacy of anti-PD-1 immunotherapy in HCC.

Key Words： CacyBP, Myd88, tumor-associated macrophage, programmed cell death-1, hepatocellular carcinoma

158. 免疫组化双重染色在病理诊断中的应用

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目的：利用免疫组化双重染色技术对于前列腺组织以及肺癌组织进行染色，分析染色效果以及不同抗原之间的关系，验证双重染色在肿瘤病理诊断中的应用价值。

方法：收集前列腺组织共计 21 例，其中包括前列腺良性增生 9 例，前列腺上皮内瘤变 7 例，前列腺癌 5 例；肺腺癌组织 10 例，肺鳞癌组织 13 例，肺腺鳞癌组织 5 例。采用 P63/34βE12/p504S，CK5/6+TTF-1 两种不同鸡尾酒抗体组合分别对前列腺组织，以及肺癌组织进行染色，并对结果进行分析，研究不同抗原的表达及分布。

结果：在 P63/34βE12/P504S 鸡尾酒抗体染色中，P63 和 34βE12 表达于基底细胞，染色呈棕色，P504S 表达于腺癌细胞，呈红色。该技术有助于良性前列腺增生，前列腺上皮内瘤变，前列腺癌的鉴别。CK5/6+TTF-1 鸡尾酒抗体染色中 CK5/6 表达于肺鳞癌细胞中，呈红

色，TTF-1 表达于肺腺癌细胞中，呈棕色。通过 CK5/6+TTF-1 免疫组化双重染色可对肺癌类型进行精准区分。

结论：免疫组化双染在同一切片上检测两种不同的抗原表达，同时观察两种不同的染色结果，使得阅片更加直观，判读更加快捷，可以减少工作量，对于活检珍贵小样本具有重要意义。

关键字 ：免疫组化；双重染色；病理诊断应用

159. Serine/threonine-protein kinase D2-mediated phosphorylation of DSG2 threonine 730 promotes esophageal squamous cell carcinoma progression

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DSG2 is a transmembrane glycoprotein belonging to the desmosomal cadherin family, which mediate cell-cell junctions, regulate cell proliferation, migration and invasion, and promote tumor development and metastasis. We previously showed serum DSG2 as a potential biomarker for diagnosis of esophageal squamous cell carcinoma (ESCC), although the significance and underlying molecular mechanisms were not identified. Here, we found that DSG2 was increased in ESCC tissues compared to adjacent tissues. In addition, we demonstrated that DSG2 promoted ESCC cell migration and invasion. Furthermore, using interactome analysis, we identified serine/threonine-protein kinase D2 (PRKD2) as a novel DSG2 kinase that mediates the phosphorylation of DSG2 at threonine 730 (T730). Functionally, DSG2 promoted ESCC cell migration and invasion dependent on DSG2-T730 phosphorylation. Mechanistically, DSG2 T730 phosphorylation activated EGFR, Src, AKT, and ERK signaling pathways. In addition, DSG2 and PRKD2 were positively correlated, and the overall survival time of ESCC patients with high DSG2 and PRKD2 was shorter than that of patients with low DSG2 and PRKD2 levels. In summary, PRKD2 is a novel DSG2 kinase, and PRKD2-mediated DSG2 T730 phosphorylation

promotes ESCC progression. These findings may facilitate the development of future therapeutic agents that target DSG2 and DSG2 phosphorylation.

Key Words ： DSG2, PRKD2, migration and invasion, phosphorylation, esophageal squamous cell carcinoma

160. Plasma ceramide (d18:1/16:0) as a novel biomarker of microvascular invasion in hepatitis B virus-related hepatocellular carcinoma

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Background: Microvascular invasion (MVI) is a critical risk of recurrence of hepatocellular carcinoma (HCC). Emerging evidence highlights the potential prognostic relevance of circulating ceramides (CERs) in HCC. This study aims to assess the potential of plasma CERs as biomarkers for MVI associated with the early recurrence of hepatitis B virus-related hepatocellular carcinoma (HBV-HCC) after curative resection.

Methods: 101 patients with HBV-HCC who underwent curative resection were included. Preoperative plasma CERs in these patients were measured by targeted lipidomics. The correlation between plasma CERs and MVI was assessed. A nomogram was developed based on independent preoperative predictors of MVI that were determined by univariate and multivariate logistic regression analysis. Then, the receiver operating characteristic (ROC) curve, calibration curve, decision curve analysis (DCA), and clinical impact curve (CIC) were conducted to assess the performance of the model.

Results: Histopathologically diagnosed MVI was found in 51 of 101 patients (50.5%). MVI was significantly associated with early recurrence of HBV-HCC after curative resection in the enrolled patients. Patients with MVI exhibited elevated preoperative plasma CER (d18:1/16:0) levels compared to those without MVI. Preoperative plasma CER (d18:1/16:0) was identified as an independent risk factor for MVI in HBV-HCC (OR=4.390, 95% CI: 1.422-13.554, p=0.010). Univariate and multivariate logistic regression analyses pinpointed age, tumor maximum diameter, tumor number, indocyanine green retention rate at 15 min, and CER (d18:1/16:0) as independent predictors for MVI of HBV-HCC. These factors were integrated into a nomogram model demonstrating good discrimination (AUROC: 0.806, 95% CI: 0.722-0.890). High preoperative plasma CER (d18:1/16:0) was also significantly correlated with the early recurrence of HBV-HCC.

Conclusions: Our study demonstrates that high preoperative plasma CER (d18:1/16:0) is a novel biomarker for MVI in HBV-HCC. A nomogram featuring this specific CER furnishes a reliable estimation of MVI risk, which may be helpful in enhancing decision-making in the therapeutic management of HBV-HCC.

Key Words： hepatocellular carcinoma (HCC), microvascular invasion (MVI), lipids, ceramide, post-hepatectomy recurrence

161. Circulating exosomal miR-16-5p and let-7e-5p are associated with bladder fbrosis of diabetic cystopathy

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Diabetic cystopathy (DCP) is a prevalent etiology of bladder dysfunction in individuals with longstanding diabetes, frequently leading to bladder interstitial fbrosis. Research investigating the initial pathological alterations of DCP is notably scarce. To comprehend the development of fbrosis and fnd efective biomarkers for its diagnosis, we prepared streptozotocin-induced long_x0002_term diabetic SD rats exhibiting a type 1 diabetes phenotype and bladder fbrosis in histology detection. After observing myofbroblast diferentiation from rats' primary bladder fbroblasts with immunofuorescence, we isolated fbroblasts derived exosomes and performed exosomal miRNA sequencing. The co-diferentially expressed miRNAs (DEMis) (miR-16-5p and let-7e-5p) were screened through a joint analysis of diabetic rats and long-term patients' plasma data (GES97123) downloaded from the GEO database. Then two co-DEMis were validated by quantitative PCR on exosomes derived from diabetic rats' plasma. Following with a series of analysis, including target mRNAs and transcription factors (TFs) prediction, hubgenes identifcation, protein–protein interaction (PPI) network construction and gene enrichment analysis, a miRNA-mediated genetic regulatory network consisting of two miRNAs, nine TFs, and thirty target mRNAs were identifed in relation to fbrotic processes. Thus, circulating exosomal miR-16-5p and let-7e-5p are associated with bladder fbrosis of DCP, and the crucial genes in regulatory network might hold immense signifcance in studying the pathogenesis and molecular mechanisms of fbrosis, which deserves further exploration.

Key Words： Diabetic cystopathy; bladder fibrosis; myofibroblast differentiation; exosome; miRNA; biomarker

162. Distinguishing Benign and Malignant Thyroid Nodules Using Plasma Trimethylamine N-oxide, Carnitine, Choline and Betaine

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Purpose: Trimethylamine N-oxide (TMAO), a gut microbiome–derived metabolite, and its precursors (carnitine, choline, betaine) have not been fully examined in relation to thyroid cancer (TC) risk. The aim of this study was to assess the value of TMAO and its precursors in diagnosis of benign and malignant thyroid nodules.

Methods: In this study, high-performance liquid chromatography-tandem mass spectrometry was utilized to measure the levels of plasma TMAO and its precursors (choline, carnitine, and betaine) in 215 TC patients, 63 benign thyroid nodules (BTN) patients and 148 healthy controls (HC). The distribution of levels of TMAO and its precursors among the three groups were compared by the Kruskal–Wallis test. Receiver operating characteristic curve (ROC) analysis was performed to evaluate the sensitivity, specificity, and the predictive accuracy of single and combined biomarkers.

Results: In comparison to HC, TC showed higher levels of TMAO and lower levels of its precursors (carnitine, choline, and betaine) (all $P < 0.001$). Plasma choline ($P < 0.01$) and betaine ($P < 0.05$) were declined in BTN than HC. The levels of carnitine ($P < 0.001$) and choline ($P < 0.05$) were significantly higher in BTN than that TC group. Plasma TMAO showed lower levels in TC with lymph node metastasis (101.5 (73.1-144.5) ng/ml) than those without lymph node metastasis (131 (84.8-201) ng/ml, $P<0.05$). Combinations of these four metabolites achieved good performance in the differential diagnosis, with the area under the ROC curve of 0.703, 0.741, 0.757 when discriminating between TC and BTN, BTN and HC, and TC and noncancer, respectively.

Conclusion: Plasma TMAO, along with its precursors could serve as new biomarkers for the diagnosis of benign and malignant thyroid nodules.

Key Words： Thyroid cancer; Trimethylamine N-oxide (TMAO); carnitine; choline; betaine; biomarker.

163. CyTOF analysis revealed platelet heterogeneity in breast cancer patients received T-DM1 treatment

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T-DM1 (Trastuzumab Emtansine) belongs to class of Antibody-Drug Conjugates (ADC), where cytotoxic drugs are conjugated with the antibody Trastuzumab to specifically target HER2-positive cancer cells. Platelets, as vital components of the blood system, intricately influence the immune response to tumors through complex mechanisms. In our study, we examined platelet surface proteins in the plasma of patients before and after T-DM1 treatment, categorizing them based on treatment response. We identified a subgroup of platelets with elevated expression of CD63 and CD9 exclusively in patients with favorable treatment responses, while this subgroup was absent in patients with poor responses. Another noteworthy discovery was the elevated expression of CD36 in the platelet subpopulations of patients exhibiting inadequate responses to treatment. These findings suggest that the expression of these platelet surface proteins may be correlated with the prognosis of T-DM1 treatment. These indicators offer valuable insights for predicting the therapeutic response to T-DM1 and may become important references in future clinical practice, contributing to a better understanding of the impact of ADC therapies and optimizing personalized cancer treatment strategies.

Key Words ： Platelets, CyTOF, Breast cancer, T-DM1

164. Systematic expression analysis and cordycepin inhibition for Tripartite motif-containing 28 (TRIM28) in progression, prognosis, and therapeutics of patients with breast invasive carcinoma

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Breast cancer (BC) shows the most common tumor in women worldwide. TRIM28 plays pleiotropic biological functions, such as silencing target genes, facilitating DNA repair, stimulating cellular proliferation and differentiation, and contributing to cancer progression. TRIM28 plays an increasingly crucial role in cancer, but its impact on BC including breast invasive carcinoma, remains poorly understood. In the current study, analyses of online databases, quantitative real-time quantitative PCR, immunohistochemistry, and western blotting were performed on patients with BRCA. Cordycepin (CD) was used to monitor BC progression and TRIM28 expression in vivo. As a result, we observed that TRIM28 is highly expressed in breast invasive carcinoma tissues compared with the corresponding normal tissues and is correlated with metastatic / invasive progression. High expression of TRIM28 might serve as a prognostic marker for long-term survival in triple-negative BC, advanced BC, or breast invasive carcinoma. Although TRIM28 methylation in tumor tissues of breast invasive carcinoma is not significantly changed compared to the matched normal tissues, the expressions and methylation of TRIM28 are reversely correlated. TRIM28 expression was inhibited by CD in the mouse model, indicating its role in preventing BC progression. Thus, TRIM28 might be a potentially valuable molecular target for forecasting the progression / prognosis of patients with breast invasive carcinoma. CD, which

represses BC growth/metastasis, may be involved partially through suppressing TRIM28 expression.

Key Words： The TRIM28 gene; Expression; Breast invasive carcinoma (BRCA); Metastasis; Prognostics

165. SIAH2 promotes epithelial-mesenchymal transition in cervical cancer by inhibiting GSK3β

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Background: Cervical cancer is the second most common malignancy occurring in women worldwide. As a RING type ubiquitin ligase, SIAH2 involves in the progression of a variety of tumors. Here, we investigated the role of SIAH2 in cervical cancer by knocking down SIAH2 in C33A and SiHa cells.

Methods and Results: Our results proved that SIAH2 knockdown inhibited the proliferation, migration and invasion of cervical cancer cells. The apoptosis signaling pathway was activated by SIAH2 siRNA. SIAH2, as a ubiquitin ligase, induced GSK3β degradation by mediating its ubiquitylation. Importantly, GSK3β overexpression rescued the increase of cell proliferation and invasion caused by SIAH2 knockdown. SIAH2 was significantly highly expressed in cervical cancer tissues compared to tissues with benign cervical lesions, including inflammatory cervical and precancerous cervical lesions, and SIAH2 expression in cervical cancer tissues was significantly correlated with the degree of cancer differentiation.

Conclusion: These results indicated that SIAH2 knockdown could inhibit the proliferation, migration and invasion through induced GSK3β degradation by mediating ubiquitylation, providing new perspectives for implementing the targeted therapy for cervical cancer.

Key Words： cervical cancer; apoptosis; epithelial-mesenchymal transition; AKT signaling pathway; GSK3β

166. Downregulation of KIF2C and TEKT2 is associated with male infertility and testicular carcinoma

Xiaofeng Li

KIF2C 和 TEKT2 的下调与男性不育和睾丸癌相关

Background: Genetic factors are important in spermatogenesis and fertility maintenance, and are potentially significant biomarkers for the early detection of infertility. However, further understanding of these biological processes is required.

Methods: In the present study, we sought to identify associated genes by reanalyzing separate studies from Gene Expression Omnibus datasets (GSE45885, GSE45887 and GSE9210) and validation datasets (GSE4797, 145467, 108886, 6872). The differential genes were used the limma package in R language. Gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were performed by the cluster profiler package. The protein-protein interaction network was constructed by the STRING database. The interaction between mRNA and TF was predicted by miRWalk web. At last, The Cancer Genome Atlas data were used to identify hub gene expression levels in GEPIA web.

Results: The results showed that 27 shared genes associated with spermatogenesis. We effectively screen out two genes (KIF2C and TEKT2) and both validated by GSE4797, 145467, 108886 and 6872. Among 27 shared genes, KIF2C and TEKT2 both down-regulated in spermatogenesis. The network of TF-miRNA-target gene was established, we found KIF2C-miRNAs (has-miR-3154, 6075, 6760-5p, 1251-5p, 186-sp)-TFs (EP300, SP1) might work in spermatogenesis.

Conclusions: Our study might help to improve our understanding of the mechanisms in spermatogenesis and provide diagnostic biomarkers and therapeutics targets.

Key Words: infertility, azoospermia, testis cancer, bioinformatics

167. 整合生物信息学分析 AURKA 基因在宫颈癌中的表达及临床意义

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目的 筛选宫颈癌组织中差异表达的基因，分析其与宫颈癌预后间的关系，得出其作为宫颈癌预后评估新标志物的可能性。

方法 从 GEO 数据库获取宫颈癌和正常宫颈组织的转录组测序结果的数据。通过在线 GEO2R 工具分析得到宫颈癌和正常宫颈组织中的差异表达基因。用“仙桃学术”进行 GO 和 KEGG 分析。基于 String 网站和 Cytoscape 软件构建蛋白-蛋白相互作用（PPI）网络并筛选出枢纽基因。通过 Kaplan-Meier 和 Cox 单因素回归分析枢纽基因对患者总生存期（Overall Survival,OS）和无复发生存期 （Relapse-free Survival,RFS）的影响及与其临床特征的关联。通过在线数据库 GEPIA database，the Human Protein Atlas 和临床样本进行枢纽基因表达的验证。采用受试者工作特征（ROC）曲线来评估枢纽基因表达水平对区分宫颈癌组织和正常宫颈组织的可行性。

结果 在公共数据集中得到 79 个差异表达基因，有 30 个基因表达上调，49 个基因表达下调。富集分析显示，AURKA 基因主要参与“细胞周期”、“孕酮介导的卵细胞成熟”和“铂耐药性”等通路。蛋白质相互作用网络及枢纽基因生存分析得出 AURKA 基因的高表达与宫颈癌患者总生存期及无复发生存期较短显著相关（P<0.05）。通过数据库及临床样本进一步验证得出 AURKA 基因的 mRNA 和蛋白在宫颈癌中表达显著上调且无种族人群差异。ROC 结果显示曲线下面积（AUC）为 0.999，表明 AURKA 基因表达水平对宫颈癌具有较高的预测价值。

结论 宫颈癌组织中 AURKA mRNA 和蛋白表达上调，则宫颈癌患者的总生存期和无复发生存期均缩短，AURKA 基因具有作为宫颈癌预后评估新标志物及靶点的潜在可能。

关键字 ：宫颈癌；AURKA 基因；标志物

168. Identification and Validation of a Novel Multi-omics Signature for Prognosis and Immunotherapy Response of Endometrial Carcinoma

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Purpose ： Cancer development and immune escape involve DNA methylation, copy number variation and other molecular events. However, there are remarkably few studies integrating multi-omics genetic profile in endometrial cancer (EC). This study aimed to develop a multi-omics signature for prognosis and immunotherapy response of endometrial carcinoma.

Methods： The gene expression, somatic mutation, copy number alteration and DNA methylation data of EC were analyzed from UCSC Xena database. Then, a multi-omics signature was constructed by machine learning model, ROC curve comparing its prognostic power with traditional clinical features. Two computational strategies were utilized to estimate the signature's performance in predicting immunotherapy response in EC. Further validation focused on the most frequently mutant molecule, ARID1A, in the signature. Association of ARID1A with survival, MSI (Microsatellite-instability), immune checkpoints, TIL (tumor infiltrating lymphocyte) and downstream immune pathways were explored.

Results： The signature consisted of 22 multi-omics molecules, showing excellent prognostic performance in predicting the overall survival of patients with EC (AUC= 0.788). After stratifying patients into high and low risk group according to the signature's median value, low risk patients displayed a greater possibility to response to immunotherapy. Further validation on ARID1A suggested it could induce immune checkpoints up-regulation, promote interferon response pathway and interact with Treg (regulatory T cell) to facilitate immune activation in EC.

Conclusion： A novel multi-omics prognostic signature of EC was identified and validated in this study, which could guide clinical management of EC and benefit personalized immunotherapy.

Key Words： Key words Prognosis; Immunotherapy; Endometrial Carcinoma; ARID1A; Regulatory T cell

169. PD-1 suppresses human circulating Tfr cells and plays a role in humoral immunity

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Despite the revolutionary success of anti-PD-1 therapy for cancer treatment over the past decade, many tumor types are unresponsive or resistant to PD-1 blockade. Recently, follicular regulatory T (Tfr) cells are found in the tumor microenvironment and play novel roles in resistance to anti-PD-1 therapy. However, the effects of PD-1 on human regulatory T (Treg) cells and Tfr cells remain to be further explored. Here we report that PD-1 suppresses human circulating Tfr (cTfr) cells and regulates cTfr cell homeostasis and function. PD-1 blockade increases the proliferation of cTfr cells and enhances their suppressive function, resulting in reduced activation of systemic B cells in the peripheral blood.

Key Words ： PD-1, Tfr, humoral immunity

170. Ferroptosis, a new form of cell death: mechanisms, biology and role in gynecological malignant tumor

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Ferroptosis, a term coined by Dixon et al. in 2012, refers to an iron-dependent form of regulated cell death driven by an overload of lipid peroxides on cellular membranes. It is morphologically and mechanistically distinct from apoptosis and other types of regulated cell death. Many studies have confirmed that ferroptosis is involved in the occurrence and development of many diseases, such as neurodegenerative diseases, chronic cardiovascular diseases, respiratory diseases and even tumors. While in the systemic diseases of obstetrics and gynecology, the related researches are still limited. In this article, we retrieved PubMed and WEB OF SCI databases for articles and reviews

published before May 6, 2022, using “, ferroptosis, ferroptosis regulator, gynecological tumors” as keywords, and comprehensively reviewed on their basis. Here, we systematically summarize the studies on the mechanism and characteristics of ferroptosis, investigate the role of ferroptosis in clinical systemic diseases of obstetrics and gynecology, evaluate the research status, unsolved problems and further research directions of ferroptosis, so as to let people learn more about ferroptosis and establish a research foundation for the exploration of the treatment strategies for ferroptosis-mediated diseases.

Key Words： Ferroptosis, gynecological tumors,mechanisms, biology

171. Advances in immunotherapy and molecular targeted therapy of gestational trophoblastic tumor

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Gestational trophoblastic neoplasia (GTN) is a rare and pregnancy-related gynecological malignancy caused by abnormal proliferation of placental trophoblastic cells. It can invade into the myometrium and metastasizing in the early stage, often occurring in women of childbearing age. GTN is invasive and can destroy surrounding tissues and blood vessels, and cause massive bleeding of lesions in uterus and metastatic sites (such as lung, liver, brain, etc.) through blood transfer。Chemotherapy is the main treatment for GTN, and the disease is extremely sensitive to chemotherapy, which can be cured by chemotherapy。 However, clinically, a large number of patients have failed chemotherapy or even multiple treatment methods due to drug resistance, recurrence or metastasis of special sites. Therefore, how to individually select the initial chemotherapy regimen and reduce the occurrence of drug resistance is the key to the treatment of high-risk GTN. With the remarkable efficacy of immunotherapy in the treatment of endometrial cancer, cervical cancer and other diseases, the research on GTN has been further deepened。 Therefore, this review discusses the mechanism, methods and efficacy of GTN immunotherapy and molecular targeted therapy, in order to provide new ideas for GTN diagnosis and treatment.

Key Words ： Gestational trophoblastic tumor; Immunotherapy; Molecular targeted therapy; VEGF ; PI3K/AKT signaling pathway; CD105; PD-L1; VEGF targeted therapy

172. 单细胞数据中前列腺细胞分型标志物的性能分析

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研究背景：在许多 scRNA-seq 研究中，了解存在哪些细胞类型及其比例是至关重要的。因此，细胞分型已被视为 scRNA-seq 分析中的一个重要步骤。虽然已经提出了一些细胞标记数据库和工具，但它们并不适用于所有的器官组织或物种。对于前列腺组织而言，其细胞分型目前仍然主要依靠研究者的知识和经验。在已报道的文献中，不同的研究者常使用不同的基因来标注相同类型的细胞。例如，一些研究用 KLK2、KLK3、ACPP、NKX3-1 标记 Luminal 细胞，而另一些研究则用 KRT8、KRT18 标记 Luminal 细胞。因此，随之产生了系列疑问：这些研究是否标记了相同类型的细胞？在已报道的细胞分型标记基因中，哪些基因具有细胞特异性？这种特异性是否会受到疾病（如癌症）、细胞比例、采样位置（前列腺外周带（PZ）和移行带区（TZ））等因素的影响？目前，几乎没有可靠的客观证据来回答这些问题。因此，在单细胞数据中，建立健全的前列腺细胞分型认识论基础对于开展前列腺疾病研究是十分重要且迫切的。

研究目的：基于上述，我们在本项研究中旨在构建一组稳健的适用于单细胞数据分析的人前列腺细胞标记基因集。

研究方法：首先对已报道的人前列腺 scRNA-seq 研究进行了全面的文献回顾，从而确定了前列腺细胞的主要类型和亚型以及相应的已报道的标记基因。并根据样本类型的不同，整合了 8 种 scRNA-seq 数据集，共计 170438 个细胞，分别来源于年轻健康供体正常前列腺组织外周带和移行带、前列腺癌和癌旁组织、去势抵抗性前列腺癌组织、良性前列腺增生组织以及膀胱癌患者的良性前列腺组织。采用该 8 个整合数据集，我们联合运用信息熵、F1

评分和局部离群因子评分、无监督学习等方法对已报道的前列腺细胞分型标记基因的性能进行综合评价和验证。

研究结果：我们获得了人前列腺细胞标记基因的客观性能分析报告，并在此基础上提出了一组适用于单细胞数据分析的稳定且特异的人前列腺细胞主要类型和亚型的分型标记基因集。

研究结论：我们的研究结果将为基于 scRNA-seq 技术的前列腺疾病研究提供客观可靠的理论基础，以便准确选择适用于细胞分型的标记基因。

关键字 ：单细胞测序、前列腺、细胞分型

173. 基于 CD8+T 细胞表达谱系的免疫检查点抑制剂（ICI）药物敏感性预测模型的构建

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目的：免疫检查点抑制剂在胶质母细胞瘤(GBM)的治疗中已经得到了初步的探索，然而仅有少数患者疗效确切，大多数患者在临床治疗中得到的客观疗效非常有限，甚至根本没有效果。本研究旨在筛选出一组转录组学标志物用于精准识别对免疫检查点抑制剂敏感的患者，同时找到潜在的靶点可以增加免疫检查点抑制剂的治疗效果。

方法：在该研究中，我们选择了来自抗 PD1 辅助治疗队列中治疗前的 GBM 样本，通过全子集回归确定了与免疫检查点抑制剂治疗反应性显著相关的候选基因，通过基因集变异分析(GSVA)构建一个免疫检查点抑制剂评分(ICBR score)。随后对来自 TCGA 和 CGGA 的 GBM Bulk RNA-seq 数据集进行了转录组学分析，并在多种癌症数据集中对 ICBR score 的预测能力进行验证。最后在 GBM 的 scRNA-seq 数据集中，通过 CellphoneDB 筛选潜在的治疗靶点。

结果：在 TCGA 和 CGGA 中，通过 WGCNA 筛选并取交集得到一组与 CD8+ T 细胞相关的基因，通过 GO 分析和免疫组织化学染色验证了这些基因的表达程度与胶质瘤细胞中 T 细胞浸润呈正相关。随后在这组基因中筛选出 8 个基因，构建了免疫检查点抑制剂反应性评分(ICBR score)，其可以有效预测患者对免疫检查点抑制剂的反应性和预后情况。同时 ICBR score 与多种免疫相关标志物呈正相关，并且高评分组相较于低评分组表现出更强的抗原释

放、抗原呈递和免疫细胞浸润的能力，但高评分组还表现出更高的免疫抑制水平，表明了ICBR score 高评分组存在更多的 T 细胞浸润，也存在着免疫抑制性的肿瘤微环境(TME)。随后在胶质母细胞瘤及其他多种癌症数据库中进行验证，结果表明 ICBR score 在多种癌症中都具有良好的预测免疫治疗反应性的能力，接受免疫检查点抑制剂治疗有效的胶质母细胞瘤患者表达更高的 ICBR score。在单细胞转录组分析中发现 T 细胞群体具有更多的 ICBR score 高表达细胞比例，并通过 CellphoneDB 找到了 FAM3C-PD1 配受体互作对，可以作为潜在的增强免疫检查点抑制剂治疗效果的靶点。

结论：该研究通过对胶质母细胞瘤转录组水平的分析，筛选出一组基因来构建 ICBR score 系统，该评分可以准确预测对免疫检查点抑制剂治疗有反应的患者，同时通过单细胞转录组数据找到一个潜在的靶点用于增强免疫检查点抑制剂治疗效果。

关键字： 胶质母细胞瘤 CD8+T 细胞 单细胞转录组 免疫检查点抑制剂 药物反应 预测模型

174. ECM1 and ANXA1 in urinary extracellular vesicles serve as biomarker for breast cancer

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Background ： BRCA ranks as the second most prevalent cancer globally among women. While uEVs have been extensively studied in various cancers such as bladder, prostate, and kidney cancers, their role in breast cancer remains largely unexplored. Leveraging the noninvasiveness of urine as a biofluid and its rich protein content, there is significant potential for early breast cancer diagnosis.

Methods ： In this study, the urinary extracellular vesicles (uEVs) of breast cancer patients and control volunteers was isolated by wheat germ agglutinin (WGA, a lectin derived from wheat) coupled magnetic beads and performed the proteomic profile by LC-MS/MS. We then utilized Chemiluminescence Assay (CLIA) to further validate the two dysregulated proteins (ECM1 and ANXA1) in a larger cohort encompassing 128 breast cancer patients, 25 begin breast

nodules and 25 healthy volunteers. Ultimately, the expression level of ECM1 and ANXA1 were verified in the uEVs of MMTY-PyMT transgenic mice, a kind of commonly used primary mouse model of breast cancer.

Results： By LC-MS/MS, 571 dysregulated proteins in the uEVs of breast cancer patients were found, compared to the control volunteers. Two (ECM1 and ANXA1) of the 571 dysregulated proteins were selected to validate in 128 breast cancer patients and 50 control volunteers (including 25 begin breast nodules and 25 healthy volunteers) by CLIA since the fold change of these two proteins was bigger than 10 with p-value<0.05. Remarkably, the protein level of ECM1 and ANXA1 in the uEVs were significantly higher in breast cancer patient compared with control volunteers. Moreover, the protein level of ECM1 and ANXA1 in the uEVs of MMTY-PyMT transgenic mice was also found to gradually increase as the breast cancer progresses.

Conclusion： We developed a straightforward and purification-free assay platform to isolate uEVs and quantitatively detect specific proteins in the uEVs of the breast cancer patients based on WGA coupled magnetic beads and Chemiluminescence Assay (CLIA), indicating the ECM1 and ANXA1 in uEVs could serve as diagnostic biomarker for breast cancer.

Key Words： ECM1, ANXA1, urinary extracellular vesicles, biomarker, breast cancer

175. Sex Hormones and Blood Metabolites Mediating the Causal Associations between Gut Microbiota and Prostate Cancer: Evidences from Mendelian Randomization Study

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Background: The gut microbiota has been recognized as tumor biomarkers for various cancers, and specific tumor markers can be discovered through causal relationships. The causal relationships between gut microbiota and prostate cancer remained uncertain. We intend to identify the causal connections between gut microbiota and prostate cancer and investigate the potential underlying mechanisms.

Methods: A two-sample Mendelian randomization (MR) analysis was conducted to elucidate the impact of 196 gut microbiota on prostate cancer. The reverse MR, linkage disequilibrium regression score (LDSC), and colocalization analyses were performed to strength causal evidence. A phenome-wide MR (Phe-MR) analysis evaluated potential side effects targeting the detected gut microbiota. We designed a two-step MR study to assess the mediation effects of circulating cytokines, sex hormones, and blood metabolites.

Results: In the MR analyses, 11 bacterial taxa were causally associated with prostate cancer. In these bacterial taxa, Alphaproteobacteria (OR = 0.87 95% CI, 0.76-0.96, P = 0.004) restrained prostate cancer and Paraprevotella (OR = 1.08 95% CI, 1.00-1.17, P = 0.044) had a risk effect on prostate cancer. In reverse MR analysis, gut microbiota abundance was unaffected by prostate cancer. LDSC and colocalization analyses indicated that the detected associations would not be confounded by genetic correlation or LD from common causal loci. The Phe-MR analysis showed no apparent tox or side effects on the identified gut microbiota. In the mediation analysis, we found 7 mediators linking gut microbiota to prostate cancer, with a specific emphasis on the critical roles played by sex hormones and blood metabolites.

Conclusions: Our study represented the first comprehensive exploration of the gut microbiota's causal effects on prostate cancer and revealed the mediating effects of sex hormones and blood metabolites in the "gut-prostate axis." Our study has contributed to the discovery of tumor biomarkers in the gut microbiota for prostate cancer, providing a basis for early screening and treatment of the disease.

Key Words： Mendelian randomization; gut microbiota; prostate cancer; sex hormones; blood metabolome

176. 原癌基因 ADAM10 基因 3’UTR 区富 G 序列对蛋白表达调控及其对肺癌的可能作用

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背景：解整合素金属基质蛋白酶 10(ADAM10)，在肺癌组织中异常高表达且异常高表达与患者肿瘤远端转移及不良预后显著相关，此外 ADAM10 与肿瘤细胞的增殖、迁移和侵袭密切相关，参与肿瘤的病理生理发展过程。DHX36（即 RHAU），一种属于 DEAH-box 家族的 ATP 依赖性 RNA 解旋酶，其对 RNA G-quadruplex (rG4)具有高度的亲和力和特异性，通过解除 rG4 结构来调节 RNA 的代谢和翻译，在细胞中广泛表达，并对细胞的生长具有重要作用。本研究旨在探讨 RNA 解旋酶 DHX36 结合促癌基因 ADAM10 3’UTR 区富 G 的序列对 ADAM10 蛋白表达的影响及其作用机制。

方法：本研究分析了肺癌组织和正常肺组织中 ADAM10 表达及临床生存预后分析，利用 G4Hunter 和 cG/cC 打分算法以及 QGRS 算法得到的 G-score 来预测 ADAM10 的 RNA G4（rG4）序列。通过荧光发射光谱、凝胶迁移阻滞硝酸银染色实验体外方式验证 rG4 wt(野生型)/Mut（突变型）在不同金属阳离子中的折叠变化，将带有 FAM 荧光标记的 rG4 序列转染到 Hela 细胞，免疫荧光法检测 BG4（一种特异性结合 G4 结构的抗体）与 rG4 wt/mut 在细胞内的共定位，双荧光素酶报告基因实验检测 rG4 wt/Mut 对 ADAM10 蛋白翻译的影响。过表达 DHX36，双荧光素酶报告基因实验及 Western Blot 观察 DHX36 对 ADAM10 rG4 wt/Mut 调控对蛋白翻译影响和外源性 ADAM10 表达变化。

结果：我们观察到 ADAM10 在肺癌组织中较正常肺组织表达明显增加，且在肿瘤中异常高表达与肿瘤患者不良预后生存显著相关。综合 G4Hunter、cG/cC 打分算和 QGRS 算法找到一条位于 3’UTR 区的 ADAM10 的 RNA G4（rG4）序列 ADAM10-PQS2608-rG4，通过荧光发射光谱和凝胶迁移硝酸银染色实验发现 ADAM10-PQS2608-rG4-wt 序列可以在金属 K+、Na+、Li+离子中折叠形成，且观察到该序列形成稳定性 K+> Li+> Na+ ，然而突变的 DAM10-PQS2608-rG4-mut 序列不能形成稳定的 RNA G4 结构。此外，通过在 Hela 细胞中通过免疫荧光共定位观察到带有 FAM 荧光标记的 ADAM10-PQS2608-rG4-wt 与 BG4 的共定位，并给予 G4 稳定剂 PDS 处理后与 BG4 免疫荧光共定位的强度增加，而

ADAM10-PQS2608-rG4-mut 却没有观察到与 BG4 共定位的现象，进一步验证 ADAM10-PQS2608-rG4 在胞内的形成。通过双荧光素酶报告基因实验检测到随着转染的 ADAM10-PQS2608-rG4-wt 浓度的增加抑制了下游萤火虫荧光素酶活性，但 ADAM10-PQS2608-rG4-mut 随着转染浓度增加下游萤火虫荧光素酶活性增加，表明 ADAM10-PQS2608-rG4-wt 在翻译过程中具有负调控作用。在 Hela 细胞中过表达 DHX36 和 ADAM10-PQS2608-rG4-wt/mut,发现 DHX36 具有解除 ADAM10 rG4-wt 而不是其 mut 进而促进 ADAM10 蛋白翻译。

结论：原癌基因 ADAM10 存在 G-是四链体结构并且位于该基因 3'UTR 区富 G 序列区，RNA 解旋酶 DHX36 可能对 ADAM10 具有调控作用。ADAM10 的 G-是四链体对肺癌的可能作用正在进一步探索中。

关键字 ：ADAM10、DHX36、G-四链体、肺癌

177. PCDHGA10 作为肺鳞癌潜在生物标志物的生物信息学分析和实验验证

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目的：原钙粘蛋白γ亚科 A，10（PCDHGA10）是原钙粘蛋白γ基因簇的成员，与神经元突触的发育有关。然而，有关 PCDHGA10 在肺鳞状细胞癌（LUSC)中的作用及潜在预后价值的研究仍然缺乏。

方法：应用 GTEx 和 TCGA 数据库获取 PCDHGA10 RNAseq 数据比较其表达差异。分析 PCDHGA10 的与 LUSC 临床病理特征、基因突变肿瘤微环境、免疫检查点、药物敏感性、预后和甲基化等之间的关系。并使用基因本体（GO)和京都基因百科全书(KEGG)进行富集分析以探究潜在的信号通路。肺鳞癌组织微阵列芯片（HColA180Su01，上海芯超生物科技有限公司）对 PCDHGA10 在 LUSC 中的表达与预后进行验证。Western Blot 检测敲低和过表达 NCI-H520 和 NCI-H226 细胞株中 PCDHGA10 的表达情况，平板克隆和 MTT 检测细胞增殖能力，Transwell 实验检测 PCDHGA10 对 LUSC 细胞迁移与侵袭的影响。

结果：PCDHGA10 在多种癌症中的表达存在差异，且 PCDHGA10 与 LUSC 临床病理特征、患者预后、免疫细胞浸润、免疫检查点以及启动子甲基化有一定的相关性。此外，单细

胞测序发现 PCDHGA10 在多种免疫细胞中表达，其中与 CD8 和 CD68 细胞浸润呈正相关。平板克隆和 MTT 检测实验发现，沉默 PCDHGA10 后，对 NCI-H520 和 NCI-H226 细胞的增值能力有影响，Transwell 实验发现，沉默 PCDHGA10 后，对 NCI-H520 和 NCI-H226 细胞的侵袭及迁移能力均有影响。

结论：我们分析了 PCDHGA10 在肺鳞癌中的表达概况及其致癌作用，揭示了 PCDHGA10 的潜在预后价值。还发现 PCDHGA10 与多种免疫细胞浸润以及免疫检查点抑制剂有关，有望为肿瘤免疫治疗提供新的靶点。

关键字： PCDHGA10;肺鳞状细胞癌;表达;预后;肿瘤免疫

178. 基于生物信息学探索 DKK1 在肺腺癌发生中的作用

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背景与目的 肺癌是我国最常见的恶性肿瘤，肺腺癌（lung adenocarcinoma, LUAD）是肺癌的主要类型，严重威胁着人民的生命健康，目前关于血清分泌型蛋白 1（Dikkopf 1, DKK1）在肺腺癌中的作用研究较少，本研究旨在通过生物信息学方法探究 DKK1 在肺腺癌发生发展中的作用及潜在的预后价值。

方法 应用基因型组织表达（genotype-tissue expression, GTEx）、癌症基因组图谱（The Cancer Genome Atlas, TCGA）数据库和肿瘤与免疫系统交互网站（tumor-immune system interactions database, TISIDB）等多个数据库，对 DKK1 在肺腺癌中的表达、临床病理特征、免疫细胞浸润、预后和甲基化等进行分析，同时应用 LinkedOmics 数据库分析 DKK1 的共表达基因及其功能富集。收集 2016-2017 年于新疆医科大学附属肿瘤医院手术的 59 例石蜡包埋的肺腺癌患者病理样本，通过免疫组织化学试验（immunohistochemistry, IHC）进行表达预后验证。

结果 生信分析结果显示 DKK1 在肺腺癌组织的表达水平高于正常组织，晚期癌症中的表达高于早期阶段，实验验证后发现 59 例肺腺癌中阴性表达 15 例（25.4%），弱阳性表达 18 例（30.5%），强阳性表达 26 例（44.1%）。DKK1 的不同表达情况与甲基化、预后以及多种免疫细胞的活动相关。功能富集显示 DKK1 可能参与表皮发育、细胞-基质连接等过程，京都基因与基因组百科全书（Kyoto Encyclopedia of Genes and Genomes, KEGG）分析表明

DKK1 与 ABC 转运蛋白相关。生物信息学分析及临床病例标本显示 DKK1 高表达与肺腺癌患者较差的预后有关。

结论 DKK1 在肺腺癌中高表达，与患者预后不良有关，并且 DKK1 与肿瘤免疫细胞浸润和通路密切相关。DKK1 可能是肺腺癌潜在的预后标志物和免疫治疗新靶点。

关键字： 肺肿瘤；DKK1；预后

179. GPAT3 is a potential therapeutic target to overcome sorafenib resistance in hepatocellular carcinoma

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Purpose: Sorafenib is the standard treatment for advanced hepatocellular carcinoma (HCC), but acquired resistance during the treatment greatly limits its clinical efficiency. Lipid metabolic disorder plays an important role in hepatocarcinogenesis. However, whether and how lipid metabolic reprogramming regulates sorafenib resistance of HCC cells remains vague.

Methods:Sorafenib resistant HCC cells were established by continuous induction. LC-MS/MS, proteomics, and flow cytometry were used to assess the lipid metabolism.Gain- and loss-of function studies were applied to explore the mechanism driving sorafenib resistance of HCC. Flow cytometry and CCK8 in vitro, and tumor size in vivo were used to evaluate the sorafenib resistant sensitivity of HCC cell.

Results: Our metabolome data revealed a significant enrichment of triglycerides in sorafenib-resistant HCC cells. Further analysis using proteomics and genomics techniques demonstrated a significant increase in the expression of glycerol-3-phosphate acyltransferase 3 (GPAT3) in the sorafenib-resistant groups. The restoration of GPAT3 resensitized HCC cells to sorafenib, while overexpression of GPAT3 led to insensitivity to sorafenib. Furthermore, our in vitro and in vivo studies demonstrated that pan-GPAT inhibitors effectively reversed sorafenib resistance in HCC cells.

Conclusion: Our data demonstrate that GPAT3 elevation in HCC cells reprograms triglyceride metabolism which contributes to acquired resistance to sorafenib, which suggests GPAT3 as a potential target for enhancing the sensitivity of HCC to sorafenib.

Key Words ： Sorafenib resistance; triglyceride; GPAT3; hepatocellular carcinoma

180. SLC19A3 在宫颈癌中的表达和临床意义

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目的：宫颈癌(cervical squamous cell carcinoma and endocervical adenocarcinoma，CESC)是女性最常见的恶性肿瘤。溶质载体家族 19 成员 3(SLC19A3)在 CESC 进展中的研究尚不全面，本研究旨在通过生物信息学方法探究 SLC19A3 在 CESC 发生发展中的作用及潜在的预后价值。

方法：基于癌症基因组图谱（the cancer genome atlas，TCGA）数据库对 SLC19A3 在 CESC 中的表达差异进行分析，基因表达综合数据库（gene expression omnibus，GEO）GSE6791 数据集进行表达验证。Kaplan-Meier 方法进行预后研究。应用多个数据库对 SLC19A3 表达与临床病理特征、免疫细胞浸润、突变和甲基化等进行分析。单细胞水平的研究对 SLC19A3 在不同免疫细胞亚群中的表达情况进行分析。最后基于差异表达基因进行富集分析并预测新的药物靶点。

结果：SLC19A3 在 CESC 组织中低表达，与 CESC 患者较好的预后有关。单细胞分析显示，SLC19A3 主要在内皮细胞中表达。进一步发现 SLC19A3 在肿瘤免疫中发挥着不可忽视的作用，并证实了 SLC19A3 与免疫检查点途径基因和免疫调节基因之间有一定的相关性。此外，通过对差异基因的分析发现了几个潜在的候选药物。

讨论：SLC19A3 在 CESC 组织中低表达并与患者预后有关，其表达水平是 CESC 患者预后的独立影响因素。

关键字： SLC19A3；CESC；预后

181. Roles of PSMB8 Expression Levels on the Prognosis and Tumor Microenvironment of Liver Hepatocellular Carcinoma

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Background: Liver hepatocellular carcinoma (LIHC) is a common and highly malignant tumor. It is known that proteasome subunit beta type-8 (PSMB8; or large multifunctional peptidase 7 [LMP7]) gene are associated with susceptibility to hepatitis B virus infection. However, there are few reports on the role of PSMB8 in LIHC prognosis and tumor microenvironment.

Methods: PSMB8 expression was analyzed using The Cancer Genome Atlas (TCGA) LIHC data, and The Gene Expression Omnibus (GEO) GSE76427 data set was used for verification. Kaplan-Meier Plotter database was used to assess the prognostic value. We examined the relationship between the expression of PSMB8 and relevant clinical characteristics, gene mutations, immune cell infiltration, regulatory immune genes, and immune checkpoint inhibitors. Expression of PSMB8 in single cell subpopulations was calculated from The Tumor Immune Single Cell Center (TISCH). Finally, immunofluorescence analysis of tissue microarray was performed to evaluate the expression level and distribution of PSMB8 in LIHC patients.

Results: In LIHC tissues, PSMB8 was highly expressed and was related to prognosis in patients. Single cell RNA sequencing analysis shows that PSMB8 was mainly expressed in T cells and B cells. The relationships between PSMB8 with immune checkpoint genes and regulatory immune genes were further investigated with correlation analysis confirming that PSMB8 expression was positively correlated with immune checkpoint genes. In addition, functional enrichment analyses further indicated that PSMB8 was involved in multiple tumor related pathways.

Conclusion: PSMB8 may be a new prognostic marker and a potential therapeutic target for liver cancer.

Key Words： PSMB8, Liver Hepatocellular Carcinoma, Prognosis, Tumor Microenvironment, Immunofluorescence

182. 基于生物信息学分析探索 PCDHGB4 在肺鳞癌发生中的作用

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背景与目的：肺鳞状细胞癌（lung squamous cell carcinoma，LUSC)是非小细胞肺癌（non-small cell lung cancer, NSCLC)的亚型之一。有报道原钙粘蛋白γ家族的成员能通过抑制 Wnt 信号通路来调节肿瘤细胞的生长，原钙粘蛋白γ-B4(Protocadherin-gamma subfamily B, 4,PCDHGB4)作为家族成员在肺鳞癌中的研究少有报道，本文旨在通过生物信息学方法探究 PCDHGB4 在肺鳞癌发生发展中的作用及潜在的预后价值。

方法：应用癌症基因组图谱（The Cancer Genome Atlas, TCGA）、cBioPortal 和 UALCAN 等数据库，对 PCDHGB4 在肺鳞癌中的表达与预后、临床病理特征、免疫细胞浸润、免疫调节基因、免疫检查点抑制剂（immune checkpoint inhibitors，ICIs)和甲基转移酶等进行分析。单细胞水平的研究对细胞亚型的聚类结果和 PCDHGB4 在不同免疫细胞亚群中的表达情况进行了分析。此外，我们还比较了肺鳞癌组织与正常组织中 PCDHGB4 的启动子甲基化水平，并对 PCDHGB4 进行了蛋白质-蛋白质相互作用（Protein-protein interaction，PPI）和突变分析。最后基于差异表达基因进行富集分析。

结果：生信分析结果显示 PCDHGB4 在 LUSC 组织的表达水平低于正常组织。生存分析显示，PCDHGB4 表达增加与患者较差的预后有关。单细胞分析显示，PCDHGB4 主要在 T 细胞、单核细胞或巨噬细胞以及树突状细胞中表达，进一步发现 PCDHGB4 在肿瘤免疫中发挥着不可忽视的作用，并证实了 PCDHGB4 与免疫检查点途径基因、免疫调节基因和甲基转移酶有一定的相关性。此外，通过富集分析发现 PCDHGB4 参与了癌症相关的多条通路。

结论：PCDHGB4 在肺鳞癌中低表达，与患者预后不良有关，并且 PCDHGB4 与肿瘤免疫细胞浸润和通路密切相关。PCDHGB4 可能是肺鳞癌潜在的预后标志物和免疫治疗新靶点。

关键字： PCDHGB4；肺鳞癌；预后

183. 改良根治术和保乳手术治疗早期乳腺癌对女性 8 项肿瘤标志物的影响

宋伟

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目的：探究改良根治术和保乳手术治疗早期乳腺癌对女性 8 项肿瘤标志物的影响。

方法：选择本院 2021 年 10 月至 2023 年 10 月收治的 50 例早期乳腺癌患者为研究对象，根据治疗方案不同将其分为对照组和观察组，各 25 例，分组后确保对照组和观察组女性 8 项肿瘤标志物水平比较，差异无统计学意义。对照组接受改良根治术，观察组接受保乳手术。比较两组患者术后女性 8 项肿瘤标志物相关指标。

结果：接受手术治疗后，观察组的癌胚抗原（CEA）、糖类抗原 153（CA153）、糖类抗原 125（CA125）、神经特异性烯醇化酶（NSE）水平低于对照组，差异具有统计学意义（P＜0.05）。观察组和对照组的糖类抗原 724（CA724）、甲胎蛋白（AFP）、糖类抗原 199（CA199）、细胞角蛋白 19 片段（Cyfra21-1）水平无明显差异。

结论：保乳手术能调节早期女性乳腺癌患者部分肿瘤标志物水平，为临床治疗乳腺癌选择方案提供积极意义、而且还具有更高的乳房美容程度，值得推广。针对乳腺癌女性患者术后复查的 CEA、CA153、CA125 和 NSE 指标水平，值得重点关注。

关键字 ：改良根治术；保乳手术；早期乳腺癌；肿瘤标志物

184. 基于组学技术探讨天然化合物在肿瘤中的研究进展

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恶性肿瘤是严重威胁人类健康的主要原因之一。随着各种抗肿瘤药物的研发，天然化合物对不同类型的恶性肿瘤表现出强大的作用。组学（Omics）是研究生物体中分子组分和其相互作用及作用网络的一门学科，主要包括蛋白质组学、转录组学、代谢组学、基因组学、免疫组学、影像组学等，广泛应用于天然化合物治疗肿瘤的机制研究中。单组学和多组学技

术有助于揭示具有抗肿瘤潜力的天然化合物的信号相互作用网络和关键分子靶点。因此对近年来各种组学方法在检测抗肿瘤天然化合物的治疗靶点、信号通路和肿瘤微环境方面的应用进行了归纳总结，为组学技术探索天然化合物的抗肿瘤研究提供新的依据和思路。

关键字 ：天然化合物；恶性肿瘤；组学技术

185. High endothelial venules abundance in tertiary lymphoid structures is associated with the efficacy of neoadjuvant immunochemotherapy in non-small cell lung cancer

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Objective: High endothelial venules (HEV) and tertiary lymphoid structures (TLS) are associated with clinical outcomes of patients with non-small cell lung cancer (NSCLC). However, the formation of HEV and its effect on the production of TLS in NSCLC with neoadjuvant immunochemotherapy is unknown. Here, we studied HEV abundance and TLS formation in NSCLC receiving neoadjuvant therapy.

Materials and Methods: Formalin-fixed paraffin-embedding (FFPE) tissue was retrospectively collected from resectable NSCLC patients. They were divided into two cohorts according to neoadjuvant therapy: neoadjuvant immunochemotherapy (N=48) and neoadjuvant chemotherapy (N=40). Hematoxylin-eosin and immunohistochemical staining was used to detect HEV and TLS in tumor tissues, and the differences in HEV abundance among different treatment groups were analyzed, as well as the relationship with pathological response, recurrence free survival and overall survival prognosis.

Results: We included FFPE tissue from 88 patients with resectable non-small cell lung cancer receiving neoadjuvant therapy. There were 73 (83.0%) males and 15 (17.0%) females. Smoking

and family history were 67 (76.1%) and 25 (28.4%) cases, respectively. The tumors were located in the left lung lobe in 28 cases (31.8%) and the right lung lobe in 60 cases (68.2%). There were 27 (30.7%) cases in stage I and II, and 61 (69.3%) cases in stage III and IV. 60 (68.2%) and 28 (31.8%) patients with treatment cycles less than or equal to three cycles, respectively. Among the histological types, 62 (70.5%) cases were squamous cell carcinoma and 20 (22.7%) cases were adenocarcinoma. The major pathologic response (MPR) and pathological complete response (pCR) rates were higher in the neoadjuvant immunochemotherapy group than in the neoadjuvant chemotherapy group (MPR: 29.1% vs. 15.0%; pCR: 29.1% vs. 5.0%). In both cohorts, neoadjuvant immunochemotherapy for NSCLC showed higher HEV abundance and TLS formation, both significantly associated with MPR. Patients with high HEV abundance showed better relapse-free survival (RFS) and overall survival (OS).

Conclusion: Increased HEV abundance promotes formation of TLS and is an independent predictor of RFS and OS in non-small cell lung cancer with neoadjuvant immunochemotherapy. Inducing TLS formation by targeting HEV to increase its abundance may be a potential mechanism of action for neoadjuvant immunochemotherapy in resectable NSCLC.

Key Words： High endothrlial venules; Tertiary lymphoid structures; Neoadjuvant immunochemotherapy; Non-small cell lung cancer.

186. 基于公共数据库分析 MYEF2 在肝细胞癌中的表达作用及初步验证

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目的：基于公共数据库，分析髓磷脂表达因子 2（Myelin Expression Factor 2，MYEF2）在肝细胞癌（hepatocellular carcinoma，HCC）中的表达水平，初步探索 MYEF2 在 HCC 发生发展中的功能及临床意义。

方法：基于 Oncomine 数据库、ULACAN 数据库和人类蛋白质图谱(Human Protein Atlas，HPA)，分析 MYEF2 在 HCC 中的表达水平；基于 Kaplan-Meier Plotter 数据库，分析 MYEF2 与 HCC 患者预后的关系；基于 STRING 数据库分析 MYEF2 蛋白质互作网络；基于 GEPIA

数据库，初步分析 MYEF2 的功能作用；qRT-PCR 检测 MYEF2 基因在肝癌组织及肝癌细胞系中的表达；免疫组织化学染色方法检测肝细胞癌组织中 MYEF2 的表达。

结果：MYEF2 在 HCC 中异常高表达（P<0.05），与 HCC 患者的预后不良有关，MYEF2 与参与 HCC 凋亡、迁移、侵袭和增殖的蛋白有相互作用，且与凋亡相关蛋白有相关性。

结论：MYEF2 在 HCC 组织中明显高表达，且高表达患者预后明显不良。MYEF2 可能参与了 HCC 的发生发展，具体的作用机制有待进一步实验研究。

关键字：肝细胞癌；髓磷脂表达因子 2；公共数据库；表达

187. 基于铜死亡相关基因的慢加急性肝衰竭的机制研究

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目的：探究铜死亡相关基因在慢加急性肝衰竭(Acute-on-chronic liver failure，ACLF)发生发展中的作用，从而进一步研究 ACLF 与铜死亡相关的发病机制。

方法：从 GEO(Gene Expression Omnibus，GEO)数据库中下载 ACLF 相关数据。利用 R 软件筛选 GEO 数据库中 ACLF 与慢性肝病对比的差异表达基因(Differentially expressed genes，DEGs)和铜死亡相关基因的取交集，对共同差异基因通过 GSEA(Gene Set Enrichment Analysis，基因集富集分析) 分别进行单基因 GO/KEGG 富集分析，对相关基因通路富集结果结合铜死亡代谢图绘制铜死亡相关 ACLF 机制图。

结果：共筛选出 3 个关于铜死亡相关的 ACLF 差异表达基因(P ＜0. 05)，进一步分析得出与铜死亡相关 ACLF 发生发展机制。

结论：通过生物信息学分析，筛选出可能参与 ACLF 发病机制的铜死亡相关基因和信号通路，以期为 ACLF 的发病机制的研究提供理论基础以及对 ACLF 的发生发展和治疗提供新的靶点和策略。

关键字 ：慢加急性肝衰竭;铜死亡;差异表达基因;GSEA 富集分析

188. 高荧光细胞联合 CEA、LDH 检测对恶性胸腔积液实验室诊断价值研究

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目的：探讨高荧光细胞（HFC）计数联合癌胚抗原（CEA）、乳酸脱氢酶（LDH）检测在恶性胸腔积液（MPE）实验室诊断中的价值。

方法：选取 2021 年 5 月至 2023 年 5 月在本院就诊的胸腔积液的患者 241 例作为研究对象。根据胸膜活检或胸腔积液病理检查结果分为 MPE 组（119 例）和非 MPE 组（122 例）。检测胸水中高荧光细胞百分比(HFC%)和绝对值(HFC#)、癌胚抗原（CEA）、乳酸脱氢酶（LDH），采用受试者工作特征（ROC）曲线评价四项指标单独及联合检测诊断 MPE 时的曲线下面积（AUC）、特异度和灵敏度。

结果： MPE 组 HFC#、HFC%、CEA 和 LDH 水平均明显高于非 MPE 组，差异均有统计学差异（P＜0.01）。HFC#、HFC%、CEA 和 LDH 单项检测对 MPE 诊断的 AUC 分别为 0.820、0.694、0.838、0.712；且 HFC#的 AUC 明显大于 HFC%；CEA+LDH、CEA+HFC#和 3 者联合检测诊断的 AUC 分别为 0.880、0.918、0.919。3 者联合检测的诊断效能明显高于单项检测，差异有统计学意义(P＜0.05）。腺癌和鳞癌 HFC#、CEA 和 LDH 比较，差异无统计学意义（P＞0.05）；鳞癌类型患者 HFC%水平明显低于腺癌类型患者，差异有统计学意义（P＜0.05）。

结论： HFC 检测有助于鉴别胸腔积液的良、恶性，与 CEA、LDH 联合检测，可以提高单项实验室指标的诊断效能。

关键字：高荧光细胞；CEA；LDH；恶性胸腔积液

189. Oncoprotein SET-associated transcription factor ZBTB11 triggers lung cancer metastasis

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Metastasis is the major cause of lung cancer-related death, but the mechanisms governing lung tumor metastasis remain incompletely elucidated. SE translocation (SET) is overexpressed in lung tumors and correlates with unfavorable prognosis. Here we uncover SET-associated transcription factor, zinc finger and BTB domain-containing protein 11 (ZBTB11), as a prometastatic regulator in lung tumors. SET interacts and collaborates with ZBTB11 to promote lung cancer cell migration and invasion, primarily through SET-ZBTB11 complex-mediated transcriptional activation of matrix metalloproteinase-9 (MMP9). Additionally, by transcriptional repression of proline-rich Gla protein 2 (PRRG2), ZBTB11 links Yes-associated protein 1 (YAP1) activation to drive lung tumor metastasis independently of SET-ZBTB11 complex. Loss of ZBTB11 suppresses distal metastasis in a lung tumor mouse model. Overexpression of ZBTB11 is recapitulated in human metastatic lung tumors and correlates with diminished survival. Our study demonstrates ZBTB11 as a key metastatic regulator and reveals diverse mechanisms by which ZBTB11 modulates lung tumor metastasis.

Key Words: Metastasis, Oncogenes

190. Unveiling the structural mechanisms of nonpeptide ligand recognition and activation in human chemokine receptor CCR8

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The human CC chemokine receptor 8 (CCR8) is an emerging therapeutic target for cancer immunotherapy and autoimmune diseases. Understanding the molecular recognition of CCR8,

particularly with nonpeptide ligands, is valuable for drug development. Here, we report three cryo–electron microscopy structures of human CCR8 complexed with Gi trimers in the ligand-free state or activated by nonpeptide agonists LMD-009 and ZK 756326. A conserved $Y^{1.39}Y^{3.32}E^{7.39}$ motif in the orthosteric binding pocket is shown to play a crucial role in the chemokine and nonpeptide ligand recognition. Structural and functional analyses indicate that the lack of conservation in $Y114^{3.33}$ and $Y172^{4.64}$ among the CC chemokine receptors could potentially contribute to the selectivity of the nonpeptide ligand binding to CCR8. These findings present the characterization of the molecular interaction between a nonpeptide agonist and a chemokine receptor, aiding the development of therapeutics targeting related diseases through a structure-based approach.

Key Words ： CCR8, molecular recognition, chemokine receptor selectivity

191. Role of ZNF334 in Cervical Cancer: Implications for EMT Reversal and Tumor Suppression

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Zinc-finger proteins are involved in many crucial biological processes in tumorigenesis. However, the role of Zinc-finger protein 334 (ZNF334), as a recent addition to the Kruppel-associated box domain zinc-finger proteins in cervical cancer remains unidentified. In this study, we identified ZNF334 as tumor suppressing in cervical cancer. The promoter methylation of ZNF334 was responsible for its reduced expression in both cervical cancer tissues and cell lines. Ectopic expression of ZNF334 in cervical cancer cell lines suppressed their malignant biological behaviors. Notably, ZNF334 reversed the epithelial–mesenchymal transition process both in vitro and in vivo.

Mechanistically, RNA sequencing coupled with bioinformatics analysis caught P3H3 which is upregulated by ZNF334. Dual-luciferase reporter and Chromatin immunoprecipitation assays demonstrated that transcription factor ZNF334 directly regulate P3H3. Knockdown of P3H3 attenuated the reversal of epithelial–mesenchymal transition induced by ZNF334. Additionally, ZNF334 overexpression sensitized cervical cancer cells to the cytotoxic effects of cyclosporine and sunitinib. In conclusions, this study illustrated that DNA methylation-based silencing ZNF334 played a vital role in cervical carcinogenesis, by regulating P3H3 in turn affects epithelial–mesenchymal transition. ZNF334 has the potential to become a novel diagnostic biomarker and a potential treatment target for cervical cancer.

Key Words： Cervical cancer; EMT; P3H3; transcription factor; ZNF334

192. Transcriptomic Signature of 3D Hierarchical Porous Chip Enriched Exosomes for Early Detection and Progression Monitoring of Hepatocellular Carcinoma

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Objective: Hepatocellular carcinoma (HCC) poses significant diagnostic challenges, warranting precise prognostic tools. Existing methods often lack sensitivity and specificity, underscoring the need for novel biomarkers. Exosomes, enriched using innovative technologies, hold promise in this regard. This study aims to develop an efficient exosome enrichment strategy for identifying HCC-related lncRNAs and evaluating their diagnostic and prognostic potential.

Materials and Methods: We designed a SiO2-chip for exosome enrichment, utilizing its porous structure and large surface area. Exosomes were isolated from plasma samples of HCC and non-HCC individuals using the SiO2-chip. RNA sequencing identified HCC-related lncRNAs, which were further validated by qRT-PCR. Diagnostic and prognostic analyses were conducted by integrating lncRNAs with traditional markers AFP and DCP.

Results: The SiO2-chip demonstrated high exosome capture efficiency, enabling the identification of HCC-related lncRNAs LUCAT-1 and EGFR-AS-1. qRT-PCR confirmed their significance in HCC diagnosis and prognosis, with improved accuracy when combined with AFP and DCP. The combination of exosomal lncRNAs with traditional markers enhanced diagnostic performance, distinguishing HCC from other conditions and enabling early detection.

Conclusion: The SiO2-chip-based enrichment of exosomal lncRNAs presents a promising strategy for noninvasive HCC detection and monitoring. This approach, integrating novel biomarkers with traditional markers, offers enhanced diagnostic accuracy and prognostic value, facilitating early intervention and improved patient outcomes.

Key Words ： Hepatocellular carcinoma; Exosome; Long Noncoding RNA; Microfluidic Chip; Liquid biopsy

193. 端粒酶活性检测传感器研发

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目的：探讨端粒酶是一种潜在的肿瘤生物标志物。

方法：描述了一种基于催化发夹组装的 DNA 酶(CHA-DNAzyme)的无酶等温荧光技术，用于超灵敏地检测端粒酶活性。

结果：在与端粒酶孵育时，端粒酶引物被拉长以形成端粒重复序列(TR)。延长的 tr 通过连续的链置换反应，沿着预定的轨道随机移动，组装完整的 DNAzyme(Cha Walker)。然后，被激活的 DNAzyme 通过水解 DNA 发夹而自主地沿着另一条轨道移动，从 AuNPs(DNAzyme Walker)中释放出荧光标记的 DNA 片段。结果，回收了大量的荧光来分析端粒酶的活性。Cha Walker 和 DNAzyme Walker 的使用使该传感策略具有较高的灵敏度和信号传输效率。该策略的分析范围很广，从 10 到 1000HeLa 细胞每毫升，检测下限为 7 细胞每毫升，该策略不仅可以检测不同肿瘤细胞中的端粒酶活性，还可以定量检测积累的正常细胞中的癌细胞的端粒酶活性。此外，通过检测人血清中的端粒酶活性，验证了该策略的实用性。

结论：这种传感方法在癌症的临床诊断中具有巨大的潜力。

关键字 ：端粒酶；荧光；三维 DNA 步行器；催化发夹组装；DNA 酶

194. Conserved immuno-collagenic subtypes predict response to immune checkpoint blockade

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Background: Immune checkpoint blockade (ICB) has revolutionized the treatment of various cancer types. Despite significant preclinical advancements in understanding mechanisms, identifying the molecular basis and predictive biomarkers for clinical ICB responses remains challenging. Recent evidence, both preclinical and clinical, underscores the pivotal role of the extracellular matrix (ECM) in modulating immune cell infiltration and behaviors. This study aims to create an innovative classifier that leverages ECM characteristics to enhance the effectiveness of ICB therapy.

Methods: In this study, we analyzed transcriptomic collagen activity and immune signatures in 649 patients with cancer undergoing ICB therapy. This analysis led to the identification of three distinct immuno-collagenic subtypes predictive of ICB response. We validated these subtypes using 9,363 samples from public datasets and 1,084 in-house samples. Additionally, novel therapeutic targets were identified based on these established immuno-collagenic subtypes.

Results: Our categorization divided tumors into three subtypes: 'soft & hot' (high immune infiltration and low collagen activity), 'armored & cold' (low immune infiltration and high collagen activity), and 'quiescent' (low immune infiltration and collagen activity). Notably, 'soft & hot' tumors exhibited the most robust response to ICB therapy across various cancer types. Mechanistically, inhibiting collagen augmented the response to ICB in preclinical models. Furthermore, these subtypes demonstrated associations with immune activity and prognostic predictive potential across multiple cancer types. Additionally, an unbiased approach identified B7 homolog 3 (B7-H3), an available drug target, as strongly expressed in 'armored & cold' tumors, correlating with poor prognosis.

Conclusion: This study introduces histopathology-based universal immuno-collagenic subtypes capable of predicting ICB response across diverse cancer types. These findings offer insights that could contribute significantly to tailoring personalized immunotherapeutic strategies for patients with cancer.

Key Words： collagen deposition, immune infiltration, pan-cancer, immunotherapy, tumor microenvironment

195. The potential crosstalk between tumor and plasma cells and its association with clinical outcome and immunotherapy responses in bladder cancer

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Background: Although immunotherapy is effective in improving clinical outcomes of patients with bladder cancer (BC), it is only effective in a small percentage of patients. Intercellular crosstalk in the tumour microenvironment strongly influences patient response to immunotherapy, while the crosstalk patterns of plasma cells (PCs) as endogenous antibody-producing cells remain unknown. Here, we aim to explore the heterogeneity of PCs and their potential crosstalk patterns with BC tumor cells.

Methods: Crosstalk patterns between PCs and tumor cells were revealed by integrating bulk, single-cell RNA sequencing (RNA-seq) and spatial transcriptome data analysis. A risk model was constructed to quantify crosstalk patterns by stepwise regression Cox analysis based on ligand/receptor molecules.

Results: Based on inferred cell infiltration scores from bulk RNA-seq data (n = 728), we found that high infiltration of PCs was associated with better overall survival (OS) and response to immunotherapy in BC. Further single-cell transcriptome analysis (n = 8; 41,894 filtered cells) identified two dominant types of PCs, IgG1 and IgA1. The signal transduction from specific tumor cell states (Stress-like and Hypoxia-like) to PCs, such as LAMB3/CD44 and ANGPTL4/SDC1 (ligand/receptor), was validated by spatial transcriptome analysis, and associated with poorer OS as well as non-response to immunotherapy. More importantly, a ligand/receptor-based risk model was then constructed and showed excellent performance in predicting patient survival and immunotherapy response.

Conclusions: PC is an important component of the tumor microenvironment, and its crosstalk with tumor cells influences clinical outcomes and response to immunotherapies in BC patients.

Key Words ： cell crosstalk; plasma cell; bladder cancer; immunotherapy; single-cell analysis

196. Hsa_circ_0000098 is a novel therapeutic target that promotes hepatocellular carcinoma development and resistance to doxorubicin

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Background: Circular RNA (circRNA) is crucial to the progression of hepatocellular cancer (HCC). In addition, Mitochondrial calcium uniporter regulatory factor 1 (MCUR1) is commonly overexpressed in HCC to increase cellular ATP levels. Due to the highly aggressive characteristics of HCC, it is essential to identify new diagnostic biomarkers and therapeutic targets that may facilitate the diagnosis of HCC and the development of effective anti-HCC treatments.

Method: A series of in vitro and in vivo experiments were undertaken to investigate the biological importance and underlying mechanisms of circ_0000098 in HCC.

Result: The expression of circ_0000098 was higher in HCC tissues compared to paired adjacent tissues. According to the receiver-operating characteristic curves, circ_0000098 functioned as a potential diagnostic tumor marker in HCC. Our experiments indicated that circ_0000098 served as a key oncogenic circRNA to increase HCC cell proliferation and invasion in vitro and HCC progression in vivo. Furthermore, mechanistic investigation demonstrated that by sequestering miR-383 from the 3'-UTR of MCUR1, circ_0000098 positively regulated MCUR1 expression in HCC cells and finally promoted HCC progression. On the other hand, inhibiting circ_0000098 in HCC cells could diminish doxorubicin (DOX) resistance by decreasing P-glycoprotein (P-gp, MDR1) expression and intracellular ATP levels. Either downregulation of MCUR1 or overexpression of miR-383 improved DOX sensitivity in HCC cells. Subsequently, a short hairpin RNA targeting circ_0000098 (referred to as sh-1) and doxorubicin (DOX) were encapsulated into platelets (PLTs), referred to as DOX/sh-1@PLT. Activated DOX/sh-1@PLT through HCC cells

resulted in the creation of platelet-derived particles that were capable of delivering the DOX/sh-1 combination into HCC cells and promoting intracellular DOX accumulation. Furthermore, our in vivo experiments showed that DOX/sh-1@PLT can effectively reduce P-gp expression, promote DOX accumulation, and reverse DOX resistance.

Conclusions: Our results demonstrated that circ_0000098 is an oncogenic circRNA that promotes HCC development through the miR-383/MCUR1 axis and targeting circ_0000098 with DOX/sh-1@PLT may be a promising and practical therapeutic strategy for preventing DOX resistance in HCC.

Key Words: Drug resistance; HCC; MCUR1; P-gp; Platelet; circ_0000098; miR-383.

197. PER-CRISPR/Cas14a system-based electrochemical biosensor for the detection of ctDNA EGFR L858R

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The detection of epidermal growth factor receptor (EGFR) mutation L858R in circulating tumor DNA (ctDNA) is beneficial for the clinical diagnosis and personalized therapy of non-small cell lung cancer (NSCLC). Herein, for the first time, the combination of the primer exchange reaction (PER) and clustered regularly interspaced short palindromic repeats (CRISPR) and its associated nucleases (Cas) 14a was used in electrochemical biosensor construction for the detection of ctDNA EGFR L858R. EGFR L858R, as the target, induced the isothermal amplification of the PER reaction, and then the CRISPR/Cas14a system was activated; subsequently, the substrate ssDNA-MB was cleaved and the electron on the surface of the gold electrode transferred, resulting in the fluctuation of the electrochemical redox signal on the electrode surface, whereas the electrochemical signal will be stable when EGFR L858R is absent. Therefore, the concentration of EGFR L858R can be quantified by electrochemical signal analysis. The low detection limit is 0.34 fM and the dynamic detection range is from 1 fM to 1 μM in this work. The PER-CRISPR/Cas14a electrochemical biosensor greatly improved the analytical sensitivity. In addition, this platform also exhibited excellent specificity, reproducibility, stability and good recovery. This study

provides an efficient and novel strategy for the detection of ctDNA EGFR L858R, which has great potential for application in the diagnosis and treatment of NSCLC.

Key Words： PER-CRISPR/Cas14a system；electrochemical biosensor；ctDNA

198. Anoikis-related gene signature is associated with immune infiltration and predicts the prognosis of non-small cell lung cancer

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Non-small cell lung cancer (NSCLC) is the most common histological type of lung cancer. With the in-depth exploration of cell death manners, numerous studies found that anoikis is an important mechanism that associated with treatment. Therefore, we aimed to explore the prognostic value and treatment guidance of anoikis in NSCLC patients. In the current study, we first constructed a prognostic model based on the anoikis-related genes based on bulk RNA-sequencing and single-cell RNA-sequencing (scRNA-seq) dataset. Then, immuno-correlations of anoikis-related risk scores (ARGRS) were analyzed. In addition, HMGA1, a risky gene in ARGRS, was further explored to define its expression and immuno-correlation. Results showed that patients with higher ARGRS had worse clinical outcomes. Moreover, the five genes in the prognostic model were all highly expressed on tumor cells. Moreover, further analysis found that the ARGRS was negatively correlated with ImmuneScore, but positively with tumor purity. Besides, patients in the ARGRS-high group had lower levels of immunological characteristics, such as the immune-related signaling pathways and subpopulations. Additionally, in the immunotherapy cohorts, patients with the ARGRS-high phenotype were more resistant to immunotherapy and tended to not achieve remission after treatment. Last, HMGA1 was chosen as the representative biomarker, and analysis of the in-house cohort showed that HMGA1 was highly expressed in tumor tissues and correlated with decreased T cell infiltration. To sum up, ARGRS was correlated with a desert tumor microenvironment and identified immune-cold tumors, which

can be a novel biomarker for the recognition of immunological characteristics and an immunotherapeutic response in NSCLC.

Key Words ： HMGA1; NSCLC; anoikis; gene signature; immunotherapy.

199. PIWI-Interacting RNAs (piRNAs): Promising Applications as Emerging Biomarkers for Digestive System Cancer

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PIWI-interacting RNAs (piRNAs) are a novel type of small non-coding RNAs (sncRNAs), which are 26-31 nucleotides in length and bind to PIWI proteins. Although piRNAs were originally discovered in germline cells and are thought to be essential regulators for germline preservation, they can also influence gene expression in somatic cells. An increasing amount of data has shown that the dysregulation of piRNAs can both promote and repress the emergence and progression of human cancers through DNA methylation, transcriptional silencing, mRNA turnover, and translational control. Digestive cancers are currently a major cause of cancer deaths worldwide. piRNAs control the expression of essential genes and pathways associated with digestive cancer progression and have been reported as possible biomarkers for the diagnosis and treatment of digestive cancer. Here, we highlight recent advances in understanding the involvement of piRNAs, as well as potential diagnostic and therapeutic applications of piRNAs in various digestive cancers.

Key Words ： Piwi-interacting RNA; cancer biomarker; diagnosis; digestive system cancer; prognosis; therapeutic target.

200. The immunosuppressive tumor microenvironment in hepatocellular carcinoma-current situation and outlook

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Hepatocellular carcinoma (HCC) is one of the most severe malignant tumors that threaten human health, and its incidence is still on the rise recently. In spite of the current emerging treatment strategies, the overall prognosis of liver cancer remains worrying. Currently, immunotherapy has become a new research-active spot. The emergence of immune checkpoints and targeted immune cell therapy can significantly improve the prognosis of HCC. To a large extent, the effect of this immunotherapy depends on the tumor immune microenvironment (TME), an intricate system in which cancer cells and other non-cancer cells display various interactions. Understanding the immunosuppressive situation of these cells, along with the malignant behavior of cancer cells, can assist us to design new therapeutic approaches against tumors. Therefore, it is necessary to clarify the TME of HCC for further improvement of clinical treatment. This review discussed the functions of several immunosuppressive cells and exosomes in the latest research progress of HCC, including cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) and tumor-associated neutrophils (TANs) interacted actively to facilitate tumor progression. It further describes the treatment methods targeting them and the potential that needs to be explored in the future.

Key Words： Exosomes; Hepatocellular carcinoma; Immunosuppressive cells; Immunotherapy; Tumor microenvironment.

201. An emerging role of the 5' termini of mature tRNAs in human diseases: Current situation and prospects

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The fundamental biological roles of a class of small noncoding RNAs (sncRNAs), derived from mature tRNAs or pre-tRNAs, in human diseases have received increasing attention in recent years. These ncRNAs are called tRNA-derived fragments (tRFs) or tRNA-derived small RNAs (tsRNAs). tRFs mainly include tRF-1, tRF-5, tRF-3 and tRNA halves (tiRNAs or tRHs), which are produced by enzyme-specific cleavage of tRNAs. Here, we classify tRF-5 and 5' tiRNAs into the same category: 5'-tRFs and review the biological functions and regulatory mechanisms of 5'-tRFs in cancer and other diseases (metabolic diseases, neurodegenerative diseases, pathological stress injury and virus infection) to provide a new theoretical basis for the diagnosis and treatment of diseases.

Key Words ： Cancer; Diagnosis biomarker; ncRNAs; tRFs; tRNA derived fragments; tsRNAs.

202. 敲除成纤维细胞生长因子 2 基因抑制乳腺癌 MCF-7 细胞的增殖、迁移侵袭并促进细胞凋亡

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目的：探索成纤维细胞生长因子 2（FGF2）敲除对人乳腺癌细胞株 MCF-7 增殖、迁移侵袭和凋亡的影响及作用机制。

方法：将 FGF2-sgRNA 基因序列转入载体 lenticrispv2 构建 CRISPR-cas9-FGF2 稳转细胞系，Western blot 检测 CRISPR-cas9-FGF2 稳转细胞系 FGF2 的蛋白敲除情况及相关凋亡蛋白指标和周期蛋白指标，将 MCF-7 细胞分为 CRISPR-cas9-NC 组（对照组）和 CRISPR-cas9-FGF2 组（FGF2 基因敲除组），使用 CCK-8 实验和细胞集落形成实验检测细

胞增殖能力，细胞划痕实验和 transwell 实验检测细胞迁移侵袭能力，流式细胞仪检测细胞周期的变化。

结果：（1）设计的三条 FGF2-sgRNA 序列均与载体 lenticrispv2 连接成功。（2）用 Western blot 检测表明 FGF2-sgRNA1 敲除作用更明显（P < 0.000 1）。（3）与对照组细胞相比，FGF2 基因敲除组细胞的增殖、迁移侵袭能力明显降低（P < 0.01）；周期蛋白 CDK2 和 cyclinA 蛋白表达显著降低（P < 0.001），Bax 促凋亡蛋白表达升高（P < 0.001），Bcl-2 抑凋亡蛋白表达降低（P < 0.001），Bcl-2/Bax 的比值减低（P < 0.000 1）促进细胞凋亡。

结论：FGF2 基因敲除后明显抑制乳腺癌细胞的增殖和迁移侵袭，将细胞阻滞在 S 期，抑制细胞的增殖与分裂，并促进细胞凋亡，提示 FGF2 基因具有成为乳腺癌治疗的潜在分子靶点。

关键字： 成纤维细胞生长因子 2； CRISPR/cas9； 乳腺癌； 细胞迁移； 细胞凋亡

203. Integrated plasma and exosome long noncoding RNA profiling is promising for diagnosing nonsmall cell lung cancer

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Objectives: Non-small cell lung cancer (NSCLC) accounts for more than 80%of all lung cancers, and its 5-year survival rate can be greatly improved by early diagnosis. However, early diagnosis remains elusive because of the lack of effective biomarkers. In this study, we aimed to develop an effective diagnostic model for NSCLC based on a combination of circulating biomarkers.

Materials and Methods: Tissue-deregulated long noncoding RNAs (lncRNAs) in NSCLC were identified in datasets retrieved from the Gene Expression Omnibus (GEO, n=727) and The Cancer Genome Atlas (TCGA, n=1,135) databases, and their differential expression was verified in paired local plasma and exosome samples from NSCLC patients. Subsequently, LASSO regression was used to screen for biomarkers in a large clinical population, and a logistic regressionmodelwas used to establish amulti-marker diagnostic model. The area under the receiver operating characteristic (ROC) curve (AUC), calibration plots, decision curve analysis (DCA), clinical impact curves, and integrated discrimination improvement (IDI) were used to evaluate the efficiency of the diagnostic model.

Results: Three lncRNAs-PGM5-AS1, SFTA1P, and CTA-384D8.35 were consistently expressed in online tissue datasets, plasma, and exosomes from local patients. LASSO regression identified nine variables (Plasma CTA-384D8.35, Plasma PGM5-AS1, Exosome CTA-384D8.35, Exosome PGM5-AS1, Exosome SFTA1P, Log_{10}CEA, Log_{10}CA125, SCC, and NSE) in clinical samples that were eventually included in the multi-marker diagnostic model. Logistic regression analysis revealed that Plasma CTA-384D8.35, exosome SFTA1P, Log_{10}CEA, Exosome CTA-384- D8.35, SCC, and NSE were independent risk factors for NSCLC ($p<0.01$), and their results were visualized using a nomogram to obtain personalized prediction outcomes. The constructed diagnostic model demonstrated good NSCLC prediction ability in both the training and validation sets (AUC=0.97).

Conclusions: In summary, the constructed circulating lncRNA-based diagnostic model has good NSCLC prediction ability in clinical samples and provides a potential diagnostic tool for NSCLC.

Key Words： clinical data; diagnosis; exosome lncRNAs; NSCLC; plasma lncRNAs

204. Integrating single-cell and bulk RNA sequencing reveals CK19+ cancer stem cells and their specific SPP1+ tumor-associated macrophage niche in HBV-related hepatocellular carcinoma

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Purpose: Cytokeratin 19-positive cancer stem cells (CK19+ CSCs) and their tumor-associated macrophages (TAMs) have not been fully explored yet in the hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).

Experimental Design: Single-cell RNA sequencing was performed on the viable cells obtained from 11 treatment-naïve HBV-associated HCC patients, including 8 CK19+ patients, to elucidate their transcriptomic landscape, CK19+ CSC heterogeneity, and immune microenvironment. Two in-house primary HCC cohorts (96 cases-related HBV and 89 cases with recurrence), TCGA external cohort, and in vitro and in vivo experiments were used to validate the results.

Results: A total of 64,581 single cells derived from the human HCC and adjacent normal tissues were sequenced, and 11 cell types were identified. The result showed that CK19+ CSCs were phenotypically and transcriptionally heterogeneous, co-expressed multiple hepatics CSC markers, and were positively correlated with worse prognosis. Moreover, the SPP1+ TAMs (TAM_SPP1) with strong M2-like features and worse prognosis were specifically enriched in the CK19+ HCC and promoted tumor invasion and metastasis by activating angiogenesis. Importantly, matrix metalloproteinase 9 (MMP9) derived from TAM_SPP1, as the hub gene of CK19+HCC, was activated by the VEGFA signal. Conclusions: This study revealed the heterogeneity and stemness characteristics of CK19+CSCs and specific immunosuppressive TAM_SPP1 in CK19+ HCC. The VEGFA signal can activate TAM_SPP1-derived MMP9 to promote the invasion and metastasis of CK19+ HCC tumors. This might provide novel insights into the clinical treatment of HCC patients.

Key Words： Hepatocellular carcinoma, Cancer stem cell, Keratin 19, Single-cell transcriptome sequencing, Hepatitis B virus, Tumor-associated macrophage, SPP1, Heterogeneity, Matrix metalloproteinase 9, VEGFA signal

205. Establishment and Experimental Validation of a Combined Immune- and Metabolism-Related Prognostic Signature for Clear Cell Renal Cell Carcinoma

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Immune evasion and metabolic reprogramming have emerged as significant features of malignant tumors, exerting pivotal influences on tumor development and advancement. Clear cell renal cell carcinoma (ccRCC) is distinguished by metabolic irregularities and unique immunological profiles. Nevertheless, the comprehensive examination of immune and metabolic attributes within the tumor microenvironment of ccRCC remains inadequately elucidated. In this study, we identified two distinct molecular subtypes (C1 and C2) of clear cell renal cell carcinoma (ccRCC) using the Non-Negative Matrix Factorization (NMF) Algorithm. Subsequent analysis revealed that subtype C1 exhibited a more favorable prognosis and higher levels of immune cell infiltration compared to subtype C2. Utilizing univariate and least absolute shrinkage and selection operator (LASSO) Cox regression analyses, we developed a prognostic signature comprising eight immune- and metabolism-related genes (IMRGs) associated with the tumor microenvironment. Validation of this signature was performed using both internal and external datasets. A nomogram was developed using IMRGs prognostic signature and various clinical parameters, including age and TNM stage. The AUCs of the nomogram at 1-, 3-, and 5-year intervals (AUC = 0.874, 0.820, 0.794) were slightly higher than those of the IMRGs signature alone (AUC = 0.773, 0.755, 0.764). The association between risk score and immune checkpoint expressions, immunophenoscore (IPS), and microsatellite instability (MSI) collectively predicted treatment efficacy accurately. The

C-index of our signature outperformed previously published ccRCC signatures, demonstrating the robustness and reliability of IMRGs prognostic signature. Several potential small molecular inhibitors were identified using data from the GSDC and CTRP databases. Additionally, in vitro experiments confirmed the involvement of UCN in promoting the aggressive behavior of ccRCC cells, as evidenced by reduced proliferation, invasion, and migration upon UCN knockdown. In conclusion, the IMRGs signature shows promise in predicting prognostic risk, assessing the effectiveness of immunotherapy, and tailoring treatment for ccRCC patients.

Key Words ：Immune, metabolism, prognosis, clear cell renal cell carcinoma, molecule subtyping

206. Novel dual-targeting inhibitors of NSD2 and HDAC2 for the treatment of liver cancer: structure-based virtual screening, molecular dynamics simulation, and in vitro and in vivo biological activity evaluations

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Liver cancer exhibits a high degree of heterogeneity and involves intricate mechanisms. Recent research has revealed the significant role of histone lysine methylation and acetylation in the epigenetic regulation of liver cancer development. In this study, five inhibitors capable of targeting both histone lysine methyltransferase nuclear receptor-binding SET domain 2 (NSD2) and histone deacetylase 2 (HDAC2) were identified using a structure-based virtual screening approach. Notably, DT-NH-1 displayed a potent inhibition of NSD2 (IC50 = 0.08 ± 0.03 μM) and HDAC2 (IC50 = 5.24 ± 0.87 nM). DT-NH-1 also demonstrated a strong anti-proliferative activity against various liver cancer cell lines, particularly HepG2 cells, and exhibited a high level of biological safety. In an experimental xenograft model involving HepG2 cells, DT-NH-1 showed a significant reduction in tumor growth. Consequently, these findings indicate that DT-NH-1 will be a promising lead compound for the treatment of liver cancer with epigenetic dual-target inhibitors.

Key Words ： liver cancer, NSD2, HDAC2, dual-targeting inhibitors, virtual screening

207. Multi-DNA-Modified Double-Network Hydrogel with Customized Microstructure: A Novel System for Living Circulating Tumor Cells Capture and Real-Time Detection

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The precise and effective isolation of living circulating tumor cells (CTCs) from peripheral blood, followed by their real-time monitoring, is crucial for diagnosing cancer patients. In this study, a cell-imprinted double-network (DN) hydrogel modified with circular multi-DNA (CMD), coined the CMD-imprinted hydrogel with fixed cells as templates (CMD-CIDH), was developed. The hydrogel featured a customized surface for proficient capture of viable CTCs and in situ real-time fluorescent detection without subsequent release. The customized surface, constructed using polyacrylamide/chitosan DN hydrogel as the matrix on the cell template, had a dense network structure, thereby ensuring excellent stability and a low degradation rate. Optimal capture efficiencies, recorded at 93±3% for MCF-7 cells and 90±2% for Hela cells, were achieved by grafting the CMD and adjusting the nodule size on the customized surface. The capture efficiency remained significantly high at 67±11% in simulated breast cancer patient experiments even at a minimal concentration of 5 cells/mL. Furthermore, CMD grafted onto the surface produced a potent fluorescence signature, enabling in situ real-time fluorescent detection of the target cells growth state even in complex environments. The customized surface is highly efficient for screening CTCs in peripheral blood and has promising potential for setting up the CTCs culture.

Key Words ： living circulating tumor cells, CMD-CIDH, nodules, efficient capture, in situ real-time fluorescence detection

208. ID3 Enhances DNA-Binding Activity of MYC to Drive PD-L1 Expression and Colorectal Cancer Immune Evasion

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Background: The inhibitor of DNA-binding protein 3 (ID3), conventionally known as a DNA-binding inhibitor," serves as a pivotal negative regulator of bHLH transcription factors. Its function involves encoding a transcriptional protein lacking the basic DNA-binding domain and forming an inactive heterodimer with the E protein. In this study, we aim to elucidate a novel role of ID3 in the enhancement of DNA-binding activity of MYC, specifically driving PD-L1 expression and contributing to immune evasion in colorectal cancer (CRC).

Methods: We conducted a comprehensive investigation to understand the molecular mechanisms underlying ID3-mediated regulation of PD-L1 expression in CRC. Experimental methods included dual-luciferase reporter gene assay, ChIP, EMSA, BLI-ISA, all-atom molecular dynamics simulations and so on. Statistical analyses were employed to validate the significance of observed changes.

Results: Our findings reveal a previously unrecognized interaction between ID3 and MYC, leading to increased binding of MYC to the PD-L1 promoter. Consequently, this interaction enhances PD-L1 transcription in CRC cells. The upregulation of PD-L1 mediated by ID3 in CRC cells results in a reduction of tumor infiltrating CD8+ T cells and impedes CD8+ T cell-mediated killing of CRC cells. Moreover, ID3 deletion enhances the therapeutic efficacy of PD-L1 antibody treatment, mitigates the increase in PD-L1 expression caused by such treatment, and reshapes the immune microenvironment in intestinal cancer.

Conclusions: This study unveils a novel mechanism by which ID3 contributes to immune evasion in CRC. Serving as a companion protein to MYC, ID3 plays a pivotal role in driving PD-L1

expression, thereby influencing the immune microenvironment within the tumor. The identified pathways suggest potential targets for innovative immunotherapy strategies. Deleting ID3 enhances the therapeutic effect of PD-L1 antibody, highlighting its clinical relevance for tailoring immunotherapy in individual CRC patients. These findings have significant implications for the development of personalized and effective immunotherapeutic approaches in colorectal cancer.

Key Words ： ID3; PD-L1; MYC; Immune evasion; Transcription regulation;

209. DNA-framework-based multidimensional molecular classifiers for cancer diagnosis

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A molecular classification of diseases that accurately reflects clinical behaviour lays the foundation of precision medicine. The development of in silico classifiers coupled with molecular implementation based on DNA reactions marks a key advance in more powerful molecular classification, but it nevertheless remains a challenge to process multiple molecular datatypes. Here we introduce a DNA-encoded molecular classifier that can physically implement the computational classification of multidimensional molecular clinical data. To produce unified electrochemical sensing signals across heterogeneous molecular binding events, we exploit DNA-framework-based programmable atom-like nanoparticles with n valence to develop valence-encoded signal reporters that enable linearity in translating virtually any biomolecular binding events to signal gains. Multidimensional molecular information in computational classification is thus precisely assigned weights for bioanalysis. We demonstrate the implementation of a molecular classifier based on programmable atom-like nanoparticles to perform biomarker panel screening and analyse a panel of six biomarkers across three-dimensional datatypes for a near-deterministic molecular taxonomy of prostate cancer patients.

Key Words ： Cancer diagnosis，DNA nanotechnology，Molecular classifiers，Biomarker

210. Self-assembly circular multi-DNA mediated rolling circle amplification for sensitive detection of PD-L1+ circulating tumor cells in the peripheral blood of cancer patients

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It has been found that evaluating the status of programmed cell death ligand (PD-L1) in the circulating tumor cells (CTCs) was associated with improved efficacy to anti-PD-L1 inhibitors. However, high-quality detection of PD-L1 positive (PD-L1$^+$) CTCs remains a huge challenge. In this study, we propose a short time, high efficiency and applicability method that fabricated by self-assembly circular multi-DNA (CMD) mediating rolling circle amplification (RCA) for highly sensitive and rapid analysis of PD-L1$^+$ cells. Firstly, a short single-stranded circular DNA which could bind specifically with PD-L1 protein was designed. In addition, CMD were designed as self-assembly which could serve as a template in RCA process. Next, the exponential amplification of DNA was achieved by the rolling circle amplification and the fluorescence signal was detected by using the molecular beacons. The unique CMD mediated rolling circle amplification facilitated quantitative detection of PD-L1$^+$ CTCs in the blood of different cancer patients. To visualize the results of CMD on the target cells, we used confocal microscope to assess PD-L1 expression in MCF-7 (breast cancer), OE33 (esophagus cancer) and HCC827 (lung cancer) cells. The results indicated that the CMD mediating RCA can perfectly combine with different kinds of cells, amplify the signal and the recovery rate was over 99 %. What s more, we performed clinical tests in the blood of the corresponding patient (14 cases of breast cancer, 15 esophageal cancer and 11 lung cancer). We further quantified the number of CTCs in patient blood through establishing the standard curve and the limit of detection (LOD) was calculated to be 1 cell/mL. Moreover, the ring structure was designed to have replaceable sequence and to realize combining different CTCs surface markers (such as Her-2). This method has the advantages of high sensitivity, good expansibility, low cost and can be completed in a short

time as well. Therefore, it is expected to develop a new CTCs typing detection kit and might thus provide reliable diagnostic results to provide individualized treatment strategies.

Key Words： PD-L1; Circulating tumor cells (CTCs); Self-assembly; Circular multi-DNA (CMD); Rolling circle amplification;

211. Wild-type IDH1 Maintains NSCLC Stemness and Chemoresistance through Activation of the Serine Biosynthetic Pathway

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Tumor-initiating cells (TICs) have been proposed as the driving force of tumorigenesis and are considered the roots of relapse, distant metastasis and therapy resistance. Emerging evidence suggests that TICs display metabolic plasticity and can reprogram their metabolic state to accommodate the harsh microenvironment and biosynthetic demands. Importantly, metabolic phenotype changes are a way for non-TICs to acquire stem-like features.

Isocitrate dehydrogenase 1 (IDH1) is a key enzyme that functions in metabolic rewiring, epigenetic reprogramming, redox homeostasis, and DNA repair. IDH1 hotspot mutations have received considerable attention due to their tumor-promoting roles in various types of malignancies. In recent years, the tumor-promoting role of wild-type IDH1 (IDH1WT) has been gradually recognized. IDH1WT is highly expressed in various malignancies and is closely connected with therapy resistance, survival advantages and poor prognosis. In lung cancer, a next-generation sequencing study from 1,924 lung cancer specimens revealed rare IDH1 mutation rates in NSCLC. We and others have found that IDH1WT is highly expressed in lung adenocarcinoma and connected with patients' poor prognosis1,2. These observations highlight the tumor-accelerating potential of IDH1WT in NSCLC, but how IDH1WT modulates NSCLC progression remains elusive.

Key Words ： Serine metabolism, IDH1, NSCLC, Cancer stemness, Peptide

212. Identifying Tumor Cell-released Extracellular Vesicles as Biomarkers for Breast Cancer Diagnosis by a Three-dimensional Hydrogel-based Electrochemical Immunosensor

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Tumor cell-released LC3+ extracellular vesicles (LC3+ EVs) participate in immunosuppression during autophagy and contribute to the occurrence and development of breast cancer. In view of the strong association between the LC3+ EVs and breast cancer, developing an effective strategy for the quantitative detection of LC3+ EVs levels with high sensitivity to identify LC3+ EVs as new biomarkers for accurate diagnosis of breast cancer is crucial, but yet not been reported. Herein, an ultrasensitive electrochemical immunosensor is presented for the quantitative determination of LC3+ EVs using a three-dimensional graphene oxide hydrogel-methylene blue composite as a redox probe, showing a low detection limit and a wide linear range. With this immunosensor, the expression levels of LC3+ EVs in various practical sample groups including different cancer cell lines, the peripheral blood of tumor-bearing mice before and after immunotherapy, and the peripheral blood from breast cancer patients with different subtypes and stages were clearly distinguished. This study demonstrated that LC3+ EVs were superior as biomarkers for the accurate diagnosis of breast cancer compared to traditional biomarkers, particularly for cancer subtype discrimination. This work would provide a new noninvasive detection tool for the early diagnosis and prognosis assessment of breast cancer in clinics.

Key Words ： biomarker, LC3+ extracellular vesicles, breast cancer, early diagnosis, cancer subtypes and stages

213. Enzyme-catalyzed electrochemical aptasensor for ultrasensitive detection of soluble PD-L1 in breast cancer based on decorated covalent organic frameworks and carbon nanotubes

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Background: Soluble programmed death-ligand 1 (sPD-L1) is critically involved in breast cancer recurrence and metastasis. However, the clinical application of highly sensitive sPD-L1 assays remains a challenge due to its low abundance in peripheral blood. To address this issue, for the first time, an enzyme-catalyzed electrochemical aptasensing platform was devised, incorporating covalent organic frameworks-gold nanoparticles-antibody-horseradish peroxidase (COFs-AuNPs-Ab-HRP) and polyethyleneimine-functionalized multiwalled carbon nanotubes (MWCNTs-PEI-AuNPs) for the highly specific and ultrasensitive detection of sPD-L1.

Results: MWCNTs-PEI-AuNPs possessed an extensive specific surface area and exhibited excellent electrical conductivity, facilitating the immobilization of aptamer and amplifying the signal. COFs modified with AuNPs not only amplified the electrical signal but also proffered a loading platform for the Ab and HRP. The favorable biocompatibility of COFs contributed to the preservation of enzyme activity and stability. HRP acted in synergy with hydrogen peroxide (H2O2) to catalyze the oxidation of hydroquinone (HQ) to benzoquinone (BQ). Subsequently, BQ underwent electrochemical reduction to HQ, inducing an enzymatic redox cycle that amplified the electrochemical signal and enhanced the sensitivity and selectivity of the detection method. The developed aptasensor displayed a liner range for sPD-L1 identification from 1 pg mL-1 to 100 ng mL-1 and the detection limit reached 0.143 pg mL-1 (S/N = 3).

Significance: Paving the way for clinical application, this strategy detected differences in sPD-L1 in cell supernatants and peripheral blood of breast cancer patients with higher sensitivity compared to commercial sPD-L1 ELISA kit. This work demonstrates significant potential in offering reference information for early diagnosis and disease surveillance of breast cancer.

Key Words ： Electrochemical aptasensor, Covalent organic frameworks, Enzymatic redox cycle, Soluble programmed death-ligand 1, Breast cancer

214. NCOA7, DRD2, SHBG 基因多态性与中国女性乳腺癌易感性的关联研究

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目的：本研究旨在探讨单核苷酸多态性位点(OGG1 rs1052133; SLC6A4 rs140701; NCOA7 rs490361, rs9375411; DRD2 rs10891556; FHTFD rs2002287, rs2276731; SMAD3 rs3826977, rs7166081; SHBG rs1641537)与中国女性乳腺癌发生风险之间的关系。

材料与方法：提取南京市第一医院住院的乳腺癌患者 439 例（病例组）和健康体检者 439 例（对照组）的全血 DNA，采用 MASSarray 序列进行基因分型，并用免疫组织化学检测肿瘤组织中雌激素受体(ER）、孕激素受体(PR)和人表皮生长因子受体-2(HER-2)的表达。此外，使用 SPSS 26.0 软件对所有纳入位点的数据进行统计分析，构建 5 种遗传模型并使用逻辑回归来精确评估具有 ORs 和 95%CI 的单核苷酸多态性对精神分裂症风险的易感性。双侧 P 值<0.05 被认为具有统计学意义。

结果：结果显示，NCOA7 rs9375411 与乳腺癌风险降低相关（AGvs.GG:调整后 OR=0.72，95%CI:0.54–0.95；AG/AAvs.GG:调整后 OR=0.76，95%CI=0.58–0.99）和 SHBGrs1641537 AA 基因型（AA vs.GG 调整后 OR=0.62，95%CI:0.41–0.96）。此外，亚组分析的结果显示，DRD2rs10891556（TTvs.GG:调整后 OR=2.12，95%CI:1.18–3.81）在绝经前癌症患者中更为常见。而且，从肿瘤的病理特征以及 ER、PR 和 HER-2 的表达来看，NCOA7rs9375411 和 SHBGrs1641537 也与乳腺癌发生风险有关。

结论：该研究纳入了 439 名癌症患者和 439 名年龄匹配的健康对照者。结果表明，NCOA7rs9375411、DRD2rs10891556 和 SHBGrs1641537 与乳腺癌风险相关。NCOA7 编码一种核受体共激活剂，NCOA7 rs9375411 位于 6q22.33，该研究中 NCOA7rs9375411 与乳腺癌的风险易感性的关联受更年期状态亚型（绝经前妇女）和病理特征（肿瘤大小 1-2，肿瘤分级 1-2，无淋巴结转移和 ER、PR、HER2 阳性表达）影响，表明 NCOA7rs 9375411 可能通过多种途径参与乳腺癌。

DRD2 是多巴胺受体（DRs）家族的成员，其高表达与乳腺癌的发生和恶性表达有关。在本研究中， DRD2rs10891556 与乳腺癌的总体风险之间没有关联，但在亚组分析中，我们观察到具有 TT 多态性的绝经前女性患癌症的风险更高。

SHBG 是癌症细胞生长的调节因子，是一种调节雌激素和雄激素可用性的血浆糖蛋白，可能在癌症的扩展中发挥作用。本研究中 SHBG rs1641537 是乳腺癌症的保护因素，尤其是对于绝经后状态、肿瘤大小 1-2、肿瘤分级 1-2、无淋巴结转移、ER+和 HER2+的个体。我们仍需要进行更大样本量的病例对照研究来验证我们的结果。

然而，这项研究具有局限性。（1）本次患者数量相对不足，可能会影响统计效力；（2）一些危险因素如吸烟、不合理的饮食、心理压力，由于数据收集不完整未纳入本研究。（3）纳入的受试者仅来自南京市第一医院，这可能影响了研究的代表性。关于这个问题，我们应该在进一步的研究中最大限度地扩大样本量，从而扩大研究人群的范围。

在这项病例对照研究中，我们得出结论，NCOA7rs9375411、DRD2rs10891556 和 SHBGrs1641537 可能与癌症风险相关。

关键字： NCOA7;DRD2;SHBG;多态性；乳腺癌

215. Increasing the Tumour Targeting of Antitumour Drugs through Anlotinib-Mediated Modulation of the Extracellular Matrix and the RhoA/ROCK Signalling Pathway

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Background and Purpose： Anlotinib exhibits significant effects on anti-angiogenesis and vessel normalization, but its long-term survival benefits when combined with other drugs cannot be fully explained by the "window period" characteristic of vessel normalization. This study aims to

investigate the potential mechanism underlying the long-term survival benefits achieved through anlotinib combination therapy.

Experimental approach： We used RNA-sequencing and Label-free quantitative proteomics analysis to study anlotinib's impact on ECM gene and protein expression, as well as the underlying mechanisms that led to changes in ECM stiffness. Bioinformatic analysis explored the relationship between ECM pathways and drug resistance, treatment outcomes, and prognosis in lung cancer. In vitro and in vivo experiments evaluated anlotinib's effects on drug targeting in various tumor models.

Results： Anlotinib significantly reduced ECM stiffness. Bioinformatic analysis suggested potential links between ECM pathways and gefitinib resistance, poor PD-1 treatment outcomes, and unfavorable prognosis in lung cancer patients after chemotherapy. Combining anlotinib with anti-PD-1/PD-L1 agents, chemotherapeutic drugs, and gefitinib prolonged drug retention and distribution at the tumor site. The combination therapy loosened the tumor tissue structure, reducing interstitial fluid pressures and tumor solid pressure. Additionally, anlotinib effectively suppressed the RhoA/ROCK signaling pathway, inhibiting stress fiber formation.

Conclusions： Anlotinib enhances antitumor drug distribution and retention in tumors by modulating ECM expression and physical properties, in addition to its anti-angiogenic and vessel normalization effects through the RhoA/ROCK signaling pathway. These findings offer valuable insights for developing combination therapies to improve tumor targeting in cancer treatment.

Key Words： Anlotinib; Extracellular matrix; Interstitial fluid pressures; Tumor solid pressure; RhoA/ROCK

216. Maggot extracts chemo-prevent inflammation and tumorigenesis accompanied by changes in intestinal microbiome and metabolome in AOM/DSS-induced mice

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Inflammatory responses and intestinal microbiome play a crucial role in the progression of colitis-associated carcinoma (CAC). The traditional Chinese medicine maggot has been widely known owing to its clinical application and anti-inflammatory function. In this study, we investigated the preventive effects of maggot extract (ME) by intragastric administration prior to azoxymethane (AOM) and dextran sulfate sodium (DSS) induced CAC in mice. Results showed that ME had superior positions in ameliorating body weight lost, disease activity index score, splenomegaly, colon length reduction, intestinal barrier damage and colonic inflammation, in comparison with the AOM/DSS group. The number and size of polypoid colonic tumors were decreased after pre-administration of ME. In addition, ME was found to reverse the downregulation of tight junction proteins (zonula occluden-1 and occludinc) while suppress the levels of inflammatory factors (IL-1b and IL-6) in models. Moreover, Toll-like receptor 4 (TLR4) mediated intracellular nuclear factor-kB (NF-kB)-containing signaling cascades, including inducible nitric oxide synthase andcyclooxygenase-2, exhibited decreasing expression in model mice after ME pre-administration. 16s rRNA analysis and untargeted-metabolomics profiling of fecal samples inferred that ME revealed an ideal prevention of intestinal dysbiosis in CAC mice, accompanied by and correlated with alterations in the composition of metabolites. Overall, ME pre-administration might be a chemo-preventive candidate in the initiation and development of CAC.

Key Words： maggot extract (ME); inflammation; colitis-associated colon cancer (CAC); intestinal microbiota; metabolome

217. Family history and genetic risk score combined to guide cancer risk stratification: a prospective cohort study

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Background： Family history of cancer and genetic risk score have been independently used for cancer risk stratification. However, the relationship and joint effect between family history of cancer and genetic risk score remain unclear.

Methods： Using the UK Biobank dataset comprising 442,399 participants free of cancer at baseline, information on family history of cancer was obtained by a standardized questionnaire, 20 cancer site-specific polygenic risk scores (PRSs) and incidence-weighted overall cancer polygenic risk scores (CPRSs) were constructed. Using multivariable Cox proportional risk regression models, we evaluated the associations between family histories of site-specific cancer, PRS, and corresponding cancer risk. Family histories of multiple cancers, CPRS, and overall cancer risk, as

well as the joint effects, were also evaluated. The additive interaction effects were further examined between family histories of cancer and PRSs in cancer incidence risk by Relative excess risk ratio (RERI) and interaction attributable proportion (AP).

Results： During a median follow-up period of 11.09 years (IQR: 10.40–11.77), there were a total of 37,691 incident cancer cases, comprising 19,668 men and 18,023 women. We observed positive associations between family history and corresponding cancer risk in a dose-response manner, as well as 6 pairs of positive cross-cancer effects of family histories on other cancer risks (i.e. lung cancer family history with esophagus cancer risk in men; breast family history with pancreas cancer risk in women). Additionally, having family histories of multiple cancers was associated with an elevated overall cancer risk. Family history was positively associated with PRS, but the two are independent of each other in incident cancer risk, and the simultaneous inclusion of both factors could achieve better prediction of cancer risk. Compared with those without a family history of cancer and at the bottom quintile of PRSs, joint effects were observed for participants with family history of cancer and at the top quintile of PRSs, with HRs of 4.15 (95%CI, 3.40-5.06) for colorectal cancer, 2.86 (95%CI, 2.27-3.61) for lung cancer, and 10.33 (95%CI, 9.22-11.58) for prostate cancer in men; with HRs of 3.19 (95%CI, 2.50-4.08) for colorectal cancer, 2.80 (95%CI, 2.21-3.55) for lung cancer, and 4.29 (95%CI, 3.83-4.81) for breast cancer in women. Of these, significant additive interactions were observed for prostate cancer and breast cancer between a family history of cancer and corresponding PRS. Individuals with family histories of multiple cancers and top quintiles of CPRSs showed 2.85-fold [HR, 2.85 (95% CI, 2.67-3.03)] and 1.96-fold [HR, 1.96 (95% CI, 1.84-2.10)] increased overall cancer risk for men and women, respectively, compared with those without a family history of cancer and at the bottom quintile of CPRSs. Nearly 20% of the associations were due to additive interactions in men (RERI=0.21, 95%CI 0.04-0.38; AP=7%, 95%CI 2%-13%).

Conclusion： Family history of cancer and genetic risk scores are weakly correlated and independently and jointly contributed to cancer risk, suggesting that family history of cancer and genetic risk scores can be used together to precisely determine individualized risk stratification of cancer.

Key Words： Family history, cross cancer, polygenic risk score, overall cancer polygenic risk score, risk stratification

218. 基于 ctDNA 的骨肉瘤分子残留病灶的围手术期检测

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目的：基于 ctDNA 的液体活检已在多种恶性肿瘤中被证实可用于检测肿瘤的分子残留病灶，从而及早提示可能存在的疾病复发。然而，目前还缺乏与骨肉瘤分子残留病灶相关的液体活检研究。因此，本研究拟探究围手术期 ctDNA 在预测骨肉瘤术后复发的可行性。

材料与方法：本研究纳入了 8 名接受根治性切除术的骨肉瘤患者，并回顾性地收集了患者的术后肿瘤组织和匹配的外周血样本，以及治疗期间的连续血浆样本。通过肿瘤知情分析（Tumor-informed assays）检测 ctDNA 的特异基因组变异图谱，预测接受标准治疗的骨肉瘤患者的复发概率。

结果：骨肉瘤肿瘤组织中有足够多的可用于确定 ctDNA 样本中肿瘤知情变异（Tumor-informed variants）的突变位点。经过新辅助治疗后，患者术前 ctDNA 检测阳性率下降，但阳性样本预测复发的准确率从 50%（1/2）上升到 100%（2/2）。基线 ctDNA 水平越高的患者临床预后越差。

结论：肿瘤知情分析有助于检测骨肉瘤中的 ctDNA，血浆中 ctDNA 的早期动态变化可能是预测骨肉瘤患者复发的有效生物标志物。

关键字： 骨肉瘤，ctDNA，分子残留病灶，肿瘤知情分析，动态变化

219. miR-7a 在癌症诊断和预后中的作用

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目的：本研究旨在分析 miR-27a 作为各种癌症的诊断和预后标志物的作用。

材料与方法：为了评估 miR-27a 对癌症的诊断价值，我们绘制了受试者工作特性曲线 ，并通过曲线下面积（AUC）估计诊断值；为了研究 miR-27a 在临床应用中的价值，我们绘制了似然比的森林图并采用卡方检验、I2 检验和元回归分析来评估纳入研究的异质性。

为了评估 miR-27a 与癌症患者的预后价值，我们计算了 95%CI 的合并风险比（HR），并通过卡方检验和 I2 检验用来评估数据的异质性。此外， 漏斗图、Begg 和 Egger 检验被用来估计发表偏倚。数据分析均通过统计软件 STATA（版本 16.0）进行。P＜0.05 被认为具有统计学意义。

结果： 血清/血浆研究的结果表明，miR-27a 是一种有价值的癌症诊断生物标志物（AUC=0.91，95%CI：0.88-0.93；SEN=0.84，95%CI：0.73-0.91；特异性=0.85，95%CI:0.70-0.93），与肿瘤组织的结果一致（AUC=0.83，95%CI:0.79-0.86；SEN=0.78，95%CI:0.81-0.89；SPE=0.74，95%CI:0.58-0.86）。

此外， miR-27a 在预测预后不良癌症患者的血清/血浆中表达升高（HR=0.63，95%CI:0.53-0.74，PHeterogenesity=0.278，I2=21.50%），但在其肿瘤组织中不升高（HR=0.98，95%CI=0.56-0.40，PHeteragenesity=0.577，I2=0.0）。

结论：该研究共纳入 16 篇文章来探讨 miR-27a 在癌症诊断和预后中的作用。结果表明，miR-27a 可被视为癌症的诊断和预后标志物。

在此项研究中，纳入的诊断相关研究在总体和亚组结果中存在显著异质性，原因如下：（1）样本种族可能影响 miRNA 的表达水平；（2）其中两项研究的质量较差；（3） 被排除的研究来自 GEO 数据库，而其他研究来自已发表的临床数据；（4）样本量太小可能导致样本量（n<100）亚组的异质性。

关于 miR-27a 在癌症中的预后作用，我们的研究结果表明，miR-27a 的高表达与较差的预后有关。而 miR-27a 已被报道可能在肿瘤进展和复发中发挥作用。肿瘤复发最常见的结果是淋巴结转移，在侵袭性癌症细胞中，miR-27a 的高表达可以进一步下调其靶向基因 FBXW7，这与胃癌患者较短的总存活期有关。而且 miR-27a 在癌症中的上调可能导致氧化磷酸化和凋亡途径受损。综上，miR-27a 是癌症预后的生物标志物。

本研究有以下几点亮点：（1）这项研究是第一次评估单独 miRNA-27a 在癌症中作用的荟萃分析；（2）我们纳入了从欧洲人群到亚洲人群的最新研究，包含了更多的癌症类型，使结论更加可靠；（3）我们进行了亚组分析以进一步研究 miR-27a 在癌症中的诊断和预后作用；（4）我们还调查了它是否适合临床诊断。

总之，我们的研究得出结论：血清/血浆或肿瘤组织中的 miR-27a 可以作为诊断生物标志物，血清/血浆中的 miR27a 可以作为癌症患者的预后生物标志物。

关键字： microRNA-27a,癌症，诊断，预后

220. Novel specific anti-ESM1 antibodies overcome tumor bevacizumab resistance by suppressing angiogenesis and metastasis

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Suppressing tumors through anti-angiogenesis has been established as an effective clinical treatment strategy. Bevacizumab, a monoclonal antibody, is commonly used in various indications. However, two major challenges limit the long-term efficacy of bevacizumab: drug resistance and side effects. Bevacizumab resistance has been extensively studied at the molecular level, but no drug candidates have been developed for clinical use to overcome this resistance. In a previous study conducted by our team, a major finding was that high expression of ESM1 in bevacizumab-resistant tumors is associated with an unfavorable response to treatment. In particular, an increase in ESM1 expression contributes to heightened lung metastasis and microvascular density, which ultimately decreases the tumor's sensitivity to bevacizumab. In contrast, the silencing of ESM1 results in reduced angiogenesis and suppressed tumor growth in tumors resistant to bevacizumab. We put forward the hypothesis that targeting ESM1 could serve as a therapeutic strategy in overcoming bevacizumab resistance. In this study, a variety of anti-ESM1 antibodies with high affinity to human ESM1 were successfully prepared and characterized. Our in vivo study confirmed the establishment of a bevacizumab-resistant human colorectal cancer model and further demonstrated that the addition of anti-ESM1 monoclonal antibodies to bevacizumab treatment significantly improved tumor response while downregulating DLL4 and MMP9. In conclusion, our study suggests that anti-hESM1 monoclonal antibodies have the potential to alleviate or overcome bevacizumab resistance, thereby providing new strategies and drug candidates for clinical research in the treatment of bevacizumab-resistant colorectal cancer.

Key Words： anti-angiogenesis, anti-ESM1 antibody, bevacizumab resistance, colorectal cancer, DLL4

221. Endothelial−Specific Molecule 1 Inhibition Lessens Productive Angiogenesis and Tumor Metastasis to Overcome Bevacizumab Resistance

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The development of drug resistance in malignant tumors leads to disease progression, creating a bottleneck in treatment. Bevacizumab is widely used clinically, and acts by inhibiting angiogenesis to “starve” tumors. Continuous treatment can readily induce rebound proliferation of tumor blood vessels, leading to drug resistance. Previously, we found that the fragment crystallizable (Fc) region of bevacizumab cooperates with the Toll−like receptor−4 (TLR4) ligand to induce M2b polarization in macrophages and secrete tumor necrosis factor−α (TNFα), which promotes immunosuppression, tumor metastasis, and angiogenesis. However, the downstream mechanism underlying TNFα−mediated bevacizumab resistance requires further investigation. Our RNA−Seq analysis results revealed that the expression of endothelial cell specific molecule−1 (ESM1) increased significantly in drug−resistant tumors and promoted metastasis and angiogenesis in vitro and in vivo. Furthermore, TNFα induced the upregulation of ESM1, which promotes metastasis and angiogenesis and regulates matrix metalloprotease−9 (MMP9), vascular endothelial growth factor (VEGF), and delta−like ligand−4 molecules (DLL4). Accordingly, the curative effect of bevacizumab improved by neutralizing ESM1 with high−affinity anti−ESM1 monoclonal antibody 1−2B7 in bevacizumab−resistant mice. This study provides important insights regarding the molecular mechanism by which TNFα−induced ESM1 expression promotes angiogenesis, which is significant for elucidating the mechanism of bevacizumab drug resistance and possibly identifying appropriate biosimilar molecules.

Key Words： endothelial cell specific molecule−1 (ESM1); tumor angiogenesis; bevacizumab resistance; delta−like ligand−4; anti−ESM1 monoclonal antibody

222. 胃癌信号通路和 AMPK 通路遗传突变的易感性

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目的：研究信号通路和 AMPK 通路基因多态性突变与胃癌的易感性，并评估遗传突变在胃癌患者中的预后作用。

方法：本研究共招募了 490 名胃癌患者和 490 名年龄和性别匹配的健康对照。所有患者组织学诊断为胃癌，对照组为来医院进行常规体检的个体。采用 Sequenom MassArray 飞行时间质谱生物芯片系统对所有样品进行基因分型；用 Sequenom type 4.0 软件进行数据分析；使用商业幽门螺杆菌酶联免疫吸附法金标准检测试剂盒(康美天弘生物技术有限公司，北京，中国)检测参与者血清中的幽门螺杆菌抗体；采用χ2 检验分析病例与对照组的总体特征差异；采用 SPSS 软件(SPSS, Chicago, IL, USA)计算比值比(ORs)和 95%置信区间(CI)；采用 Cox 回归模型计算肿瘤患者的生存率危险比(HR)和 95%置信区间（CI）。P 值< 0.05 认为有统计学意义。

结果：结果表明，患者吸烟喝酒的频率明显高于对照组。RYR3 rs1044129 GG 突变(GG vs. AA: OR = 1.53, 95% CI: 1.06-2.20, P = 0.023)与胃癌风险增加相关。基于上述结果，进一步分层分析后，RYR3 rs1044129 G 等位基因携带者(AG/GG)患胃癌的风险在临床分期(肿瘤分期 T1-T2)中显著增加(校正 OR = 1.78, 95% CI: 1.15-2.74, P = 0.009)。对患者的预后进行分析，发现 PTPN11 rs12229892 和 RYR3 rs1044129 的遗传变异与总生存期（OS）相关，PTPN11 rs12229892 (GA/AA vs. GG: OR=0.776, 95%CI: 0.605 - 0.995, p=0.046);RYR3 rs1044129 (AG/GG vs. AA: OR= 0.729,95%CI:0.5777-0.992, p=0.008)，表明上述基因突变可预测胃癌患者的生存。

讨论：RYR3 是 miRNA 调控的靶点之一，位于 miRNA 靶向信使核糖核酸 3'-UTR 的“种子区”之外(5'端有 2-8 个核苷酸)，3'-UTR 中的单核苷酸多态性(SNPS)可以改变靶基因的表达，从而影响个体癌症发展的风险。RYR3 蛋白在癌细胞中普遍表达，可以调节肿瘤细胞的生长和迁移。根据我们的研究结果，携带 RYR3 rs1044129 G 等位基因的人患癌症的风险更高。因此，我们认为 RYR3 rs1044129 单核苷酸多态性可增加中国人群胃癌的发生风险。不仅如此，本文还探讨了 RYR3rs1044129 对胃癌预后的影响，发现虽然 RYR3rs1044129 的单核苷酸多态性是中国人群胃癌的危险因素，但 RYR3rs1044129 的单核苷酸多态性是胃癌患者预后的保护因素。

研究表明，胃癌患者幽门螺杆菌感染和胃萎缩的发生率较高，且这一特征在易感幽门螺杆菌的亚洲人群中更为明显，而携带 PTPN11 rs12229892 的 GA/AA 基因型突变可降低胃癌和萎缩性胃炎的风险，提示 A 等位基因突变是胃癌的保护因素。在我们的研究中，PTPN11 rs12229892 A 等位基因突变对胃癌发生风险的影响尚不清楚，但可以肯定的是，该突变是有利于胃癌预后的，PTPN11 rs12229892 单核苷酸多态性是胃癌预后的良好因素。

关键字 ：胃癌；AMPK 通路；遗传突变

223. E2F1 基因表达在人类癌症预后中的作用:一项荟萃分析

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目的:E2F1 已被证实在多种癌症中高表达。为了更好地了解 E2F1 在癌症患者中的预后价值，本研究根据已发表的资料，对 E2F1 在癌症中的预后价值进行综合评价。

方法:以关键词检索 PubMed、Web of Science、CNKI 数据库至 2022 年 5 月 31 日，检索已发表的关于 E2F1 表达在癌症预后价值中的作用的文献。根据纳入标准和排除标准对文献进行筛选。采用 Stata17.0 软件计算风险比(HR)和 95%置信区间(CI)的合并结果。

结果:本研究共纳入 17 篇文献，涉及 4481 例癌症患者。汇总结果显示，较高的 E2F1 表达与肿瘤患者不利的总生存期(OS) (HR=1.10, 95%CI:1.03-1.16, I2=95.3%，异质性=0.000)和无病生存期(DFS) (HR=1.41, 95%CI:1.33-1.49, I2=95.2%，异质性=0.000)显著相关。这种显著的相关性维持在患者样本量亚组(>150):对于 OS, HR=1.77, 95%CI:1.25-2.51，对于 DFS, HR=0.91, 95%CI:0.28-2.98;或<150:对于 OS, HR=1.93, 95%CI:0.94-3.06，对于 DFS, HR=4.39, 95%CI:4.05-4.76)，种族(亚洲:对于 OS, HR=1.65, 95%CI:1.19-2.29，对于 DFS, HR=1.08, 95%CI:0.25-4.61;亚洲:HR=3.55, 95%CI:1.92-6.55，对于 DFS, HR=2.87, 95%CI:1.15-7.14)，来自数据库的数据(临床:对于 OS, HR=1.24, 95%CI: 0.54-2.82，对于 DFS, HR=1.40, 95%CI:0.40-4.94;或数据库:OS, HR=2.29, 95%CI:1.72-3.06, DFS,HR= 3.09, 95%CI:1.12-8.49)，论文发表年份(2014 年后:OS, HR=1.90, 95%CI:1.41-2.55, DFS,HR=1.87, 95%CI:1.21-2.89;癌症类型(女性特异性癌症:OS 的 HR=1.41, 95%CI:0.43-4.65, DFS 的 HR=0.64, 95%CI:0.15-2.72;或非性别特异性癌症:OS, HR=2.00, 95%CI:1.30-3.09, DFS, HR=2.95, 95%CI:1.47-5.91)。

结论:E2F1 可作为癌症患者的预后生物标志物，肿瘤患者中较高的 E2F1 水平可预测较短的 OS 和 DFS。

关键字：E2F1;癌症;乳腺癌;预后;荟萃分析;基因表达;总生存期;无病生存期

224. Hypoxia-induced cysteine metabolism reprogramming is crucial for the tumorigenesis of colorectal cancer

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Background: Metabolic reprogramming is a hallmark of human cancer and cancer-specific metabolism provide opportunities for cancer diagnosis, prognosis, and treatment. However, how metabolic pathways affect the initiation and progression of colorectal cancer remains largely unknown.

Methods: Non-targeted or targeted metabolomics are performed to analyze the abundance or flux of metabolites. Gene expression levels are assayed with qRT-PCR, Western Blots, and RNAseq. The oncogenic function of cysteine and its related genes are evaluated in vitro and in vivo. Recombinant cyst(e)inase is purified and applied for colorectal cancer treatment. The pathways influenced by cysteine or cyst(e)inase are analyzed by Western blots and immunofluorescence.

Results:

Cysteine is highly enriched in colorectal tumors compared with adjacent non-tumor tissues. Cysteine is critical to support CRC growth. Synchronously importing both cysteine and cystine in colon cancer cells is necessary for maintaining intracellular cysteine levels. Hypoxia-induced reactive oxygen species (ROS) and ER stress modulate co-upregulation of cystine transporter genes (SLC7A11, SLC3A2) and cysteine transporter genes (SLC1A4, SLC1A5) through transcription factor ATF4. Furthermore, the metabolic flux from cysteine to reduced glutathione (GSH) is increased due to overexpression of glutathione synthetase in CRC. Depletion of cystine/cysteine by a recombinant cyst(e)inase effectively inhibits the growth of colorectal tumors by inducing autophagy of colorectal cancer cells through mTOR-ULK signaling axis.

Conclusions: With this study, we demonstrate that cysteine metabolism reprogramming is a key signature of CRC and targeting cysteine metabolism serves as a potential approach to treat colorectal cancer.

Key Words： Colorectal cancer, Cysteine/Cystine, Transporter genes, ATF4, Hypoxia, Autophagy

225. EZH2/G9a interact to mediate drug resistance in non-small cell lung cancer by regulating the SMAD4/ERK/c-Myc signaling axis

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Drug resistance is the leading problem in non-small cell lung cancer (NSCLC) therapy. Contribution of histone methylation in mediating malignant phenotypes of NSCLC is well known. However, the role of histone methylation in NSCLC drug-resistance mechanisms remains unclear. Here, our data shows that EZH2 and G9a, two histone methyltransferases, are involved in drug resistance of NSCLC. Gene manipulation results indicate that combination of EZH2 and G9a promotes tumor growth and mediates drug resistance in complementary manner. Importantly, clinical study demonstrates that co-expression of both enzymes predicts a poor outcome in patients with NSCLC. Mechanistically, G9a and EZH2 interact and promote the silencing of the tumor suppressor gene SMAD4, activating ERK/c-Myc signaling pathway. Finally, SU08, a compound dual-targeting EZH2 and G9a, is demonstrated to sensitize resistant cells to therapeutic drugs by regulating the SMAD4/ERK/c-Myc signaling axis. These findings uncover the resistance mechanism and strategy for reversing NSCLC drug resistance.

Key Words： Non-small cell lung cancer, Drug resistance, epigenetic regulation, EZH2, G9a

226. Oncogenic PIK3CA recruits myeloid-derived suppressor cells to shape the immunosuppressive tumour microenvironment in luminal breast cancer through the 5-lipoxygenase-dependent arachidonic acid pathway

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Background: Oncogenic PIK3CA mutations ($PIK3CA^{mut}$) frequently occur in a higher proportion in luminal breast cancer (LBC), especially in refractory advanced cases, and are associated with changes in tumour cellular metabolism. Nevertheless, its effect on the progression of the immune microenvironment (TIME) within tumours and vital molecular events remains veiled.

Methods: Multiplex immunohistochemistry (mIHC) and single-cell mass cytometry (CyTOF) was used to describe the landscape of TIME in $PIK3CA^{mut}$ LBC. The PIK3CA mutant cell lines were established using CRISPR/Cas9 system. The gene expression levels, protein secretion and activity of signaling pathways were measured by real-time RT-PCR, ELISA, immunofluorescence staining or western blotting. GSEA analysis, transwell chemotaxis assay, live cell imaging, flow cytometry metabolite analysis targeting arachidonic acid, dualluciferase reporter assay, and Chromatin immunoprecipitation assay were used to investigate the underlying function and mechanism of the PI3K/5-LOX/LTB4 axis.

Results: $PIK3CA^{mut}$ LBC cells can induce an immunosuppressive TIME by recruiting myeloid-derived suppressor cells (MDSCs) and excluding cytotoxic T cells via the arachidonic acid (AA) metabolism pathway. Mechanistically, $PIK3CA^{mut}$ activates the transcription of 5-lipoxygenase (5-LOX) in a STAT3-dependent manner, which in turn directly results in high LTB4 production, binding to BLT2 on MDSCs and promoting their infiltration. Since a suppressive TIME is a critical barrier for the success of cancer immunotherapy, the strategies that can convert “cold” tumours into “hot” tumours were compared. Targeted therapy against the PI3K/5-LOX/LTB4 axis synergizing with immune checkpoint blockade (ICB) therapy achieved dramatic shrinkage in vivo.

Conclusions: The results emphasize that PIK3CA^{mut} can induce immune evasion by recruiting MDSCs through the 5-LOX-dependent AA pathway, and combination targeted therapy with ICB may provide a promising treatment option for refractory advanced LBC patients.

Key Words ：arachidonic acid, luminal breast cancer, myeloid-derived suppressor cells, PIK3CA, tumor immune microenvironment

227. 肿瘤单细胞液体活检: CTCs 的超简化富集和手持式荧光仪便携式检测

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目的：基于循环肿瘤细胞（CTCs）的液体活检技术具有无创、可灵敏特异地反映肿瘤状态等优势，在肿瘤诊断中发挥着重要作用。然而，外周血内 CTCs 数目稀少，且与大量红细胞和白细胞等共存，对 CTCs 的高效简单快速分离富集是肿瘤液体活检领域内的研究热点和难点。此外，对富集分离后的 CTCs 进行超灵敏精准定量亦是肿瘤诊断领域内的重点，特别是不依赖于仪器的即时检验（POCT），甚至是可视化读取方式。因此本工作的目的-CTCs 的分离富集和精准可视化数字化定量辅助肿瘤诊断，是相关领域的热点和难点，具有较大的科学价值和临床使用价值。

方法：在此，我们提出了一种纸基实验室，通过无酶核酸扩增和级联阳离子交换反应(CER)辅助单细胞水平分析(PLACS)来实现患者血液中痕量 CTCs 的快速准确 POCT。首先，利用淋巴细胞分离液(LSS)、红细胞裂解液(EL)和三步离心，在 45 分钟内完成全血样本中 CTCs 的富集(“12345”法)。通过整合核酸催化发卡组装(CHA)、CuS 纳米粒子(CuS NPs)选择性识别 Ag^{+}和 C-Ag^{+}-C、CdTe 量子点(QDs)选择性识别 Cu^{2+}和 CuS NPs 现象构建检测组分。级联 CER 和双量子点的竞争响应都有助于提高灵敏度。最后，结合四种信号输出方式: (1)裸眼读取; (ii)常规荧光计; (iii)距离/高度读取试纸条; (iv)自行研制的手持式荧光计。

结果：该方法内四个读取模式（离心管溶液颜色，长度试纸条，手持式荧光仪，商品化荧光仪）下均可实现单细胞浓度级别 A549 细胞的准确定量。在此基础上，对 47 例临床肺癌外周血样本 (阳性 32 例，阴性 15 例)进行定量分析，发现灵敏度为 94% (30/32)，特异性为 100%，其 AUC 值为 0.945。此外，根据 CTCs 的浓度可以大致实现癌症分期。此外，距

离读取试纸条条和手持式荧光仪的 POCT 结果与临床叶酸受体-聚合酶链式试剂盒检测数据，临床诊断和影像学发现一致性良好。

结论：综上所述，PLACS 策略结合了高效的 CTC 分离、超灵敏的单细胞检测和多样化的信号输出方法，促进了肺癌患者血液样本中临床 CTC 的 POCT 检测。我们的富集方法只需要两个试剂和三个离心步骤，提供简单的处理和快速的结果。同时，POCT 可以通过测试条或我们自行开发的手持式荧光计直观执行，以满足各种要求。值得注意的是，手持式荧光计的灵敏度与传统的同类产品相匹配，实现了单细胞精度。对临床样本的评估表明其在早期诊断和术后监测方面的潜力。该策略可以根据特定靶点适应各种适体，确保全面检测。因此，PLACS 符合新一代分子诊断的理想，在临床 POCT 领域具有广阔的应用前景。

关键字： CTCs 富集纯化；级联放大；POCT；临床全血样品；手持式仪器

228. Long-read sequencing reveals the landscape of aberrant alternative splicing and novel therapeutic target in colorectal cancer

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Background ： Alternative splicing complexity plays a vital role in carcinogenesis and cancer progression. Improved understanding of novel splicing events and the underlying regulatory mechanisms may contribute new insights into developing new therapeutic strategies for colorectal cancer (CRC).

Methods ： Here, we combined long-read sequencing technology with short-read RNA-seq methods to investigate the transcriptome complexity in CRC. By using experiment assays, we explored the function of newly identified splicing isoform TIMP1 Δ4-5. Moreover, a CRISPR/dCasRx-based strategy to induce the TIMP1 exon 4–5 exclusion was introduced to inhibit neoplasm growth.

Results ：A total of 90,703 transcripts were identified, of which > 62% were novel compared with current transcriptome annotations. These novel transcripts were more likely to be sample specific,

expressed at relatively lower levels with more exons, and oncogenes displayed a characteristic to generate more transcripts in CRC. Clinical outcome data analysis showed that 1472 differentially expressed alternative splicing events (DEAS) were tightly associated with CRC patients' prognosis, and many novel isoforms were likely to be important determinants for patient survival. Among these, the newly identified splicing isoform TIMP1 Δ4-5 was significantly downregulated in CRC. Further in vitroand in vivo assays demonstrated that ectopic expression of TIMP1 Δ4-5 significantly suppresses tumor cell growth and metastasis. Serine/arginine-rich splicing factor 1 (SRSF1) acts as an onco-splicing regulator through sustaining the inclusion of TIMP1 exon 4–5. Furthermore, CRISPR/dCasRx-based strategies designed to induce TIMP1 exon 4–5 exclusion have the potential to restrain the CRC growth.

Conclusions ： This data provides a rich resource for deeper studies of gastrointestinal malignancies. Newly identified splicing isoform TIMP1 Δ4-5 plays an important role in mediating CRC progression and may be a potential therapy target in CRC.

Key Words ： Long-read sequencing, Alternative splicing, TIMP1 Δ4-5, Colorectal cancer

229. PD-L1 methylation restricts PD-L1/PD-1 interactions to control cancer immune surveillance

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Purpose:The study aimed to investigate the regulatory mechanisms of the PD-1/PD-L1 pathway and develop predictive biomarkers for the response to PD-1/PD-L1 blockade therapy. Specifically, the research focused on elucidating the role of PD-L1 lysine 162 (K162) methylation in controlling the PD-1/PD-L1 interaction and its impact on cancer immune surveillance.

Materials and Methods:The study utilized various experimental approaches to explore the mechanisms underlying PD-L1 K162 methylation, included mass spectrometry analysis, cellular cytoplasm and nucleus isolation, co-immunoprecipitation assays, his-pull down assays, immunoprecipitation, immunohistochemistry, immunofluorescence, Real-time PCR, in vitro

methylation assays, T cell-mediated tumor cell killing assay, enzyme-linked immunosorbent assay, receptor-ligand binding assays, animal models, and clinical data analysis.

Results:The study found that PD-L1 K162 methylation restricted the PD-L1/PD-1 interaction, thereby enhancing T cell activity against cancer cells. SETD7 was identified as the methyltransferase responsible for PD-L1 K162 methylation, while LSD2 was found to demethylate PD-L1 K162. Additionally, IL-6 was shown to inhibit SETD7 expression, thereby reducing PD-L1 K162 methylation. Clinical data analysis revealed that PD-L1 K162 hypermethylation was associated with resistance to anti-PD-1 therapy and poor overall survival in NSCLC patients. Moreover, the PD-L1 K162 methylation: PD-L1 ratio (MPR) emerged as a potential predictive biomarker for anti-PD-1 therapy sensitivity.

Conclusion:The study provided novel insights into the regulation of the PD-1/PD-L1 pathway and identified PD-L1 K162 methylation as a critical mechanism controlling cancer immune surveillance and response to PD-1/PD-L1 blockade therapy. These findings highlighted the potential of PD-L1 K162 methylation and MPR as predictive biomarkers for guiding personalized immunotherapy in cancer patients, with implications for improving treatment outcomes and clinical response rates.

Key Words： PD-L1; Methylation; SETD7; LSD2; Cancer immune surveillance

230. The role of SHP2/PTPN11 in occurrence, development and prognosis of cancer

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Background: Src homology-2 domain-containing protein tyrosine phosphatase (SHP2), encoded by protein tyrosine phospha-tase non-receptor type 11 (PTPN11), is widely expressed in several human tissue types, and plays an important role in a variety of diseases. The present study explored the role of SHP2/PTPN11 in the occurrence, development and prognosis of cancer.

Methods: The transcriptome sequencing data of 33 cancers were downloaded from the cancer genome atlas database. The clinical information of the corresponding patients, tumor mutation

burden and microsatellite instability information were also downloaded. The log-rank test and univariate COX regression were used to evaluate the survival. The "ESTIMATE" method was used to evaluate the tumor microenvironment, and the “CIBERSORT” algorithm was used to evaluate the tumor immune cell infiltration. Spearman correlation was used to evaluate the correlation between SHP2/PTPN11 gene expression and target. The literature on the relationship between SHP2/PTPN11 expression level and tumor were searched in PubMed, CNKI and Cochrane Library electronic database, and meta-analysis was used to confirm the relationship between SHP2/PTPN11 expression level and the occurrence, development and prognosis of cancer.

Results: The expression of PTPN11 gene was increased in a variety of tumor tissues and was related to tumor progression and poor prognosis. The results in different tumors are largely consistent, however, the relationship between SHP2/PTPN11 expression level and the occurrence and prognosis of liver cancer may be contrary, which needs more studies to confirm. PTPN11 gene was closely related to the tumor microenvironment of many tumors. The tumor mutation burden of many tumors was related to microsatellite instability. PTPN11 gene expression can inhibit T cell activation and promote M2 macrophage activation in many tumors.

Conclusions: PTPN11 gene can be used in the tumor progression and prognosis evaluation of pan-cancer. People with high expression of SHP2/PTPN11 may be more prone to cancer and lead to a poor prognosis. Moreover, SHP2/PTPN11, as a common node of RAS and PD-1/PD-L1 signaling pathways, and can regulate the activity of T cells and macrophages M2 may be a good potential biological target for cancer therapy.

Key Words： PTP non-receptor type 11, Src homology-2 domain-containing protein tyrosine phosphatase, pan-cancer, prognosis

231. A novel microRNA-182/Interleukin-8 regulatory axis controls osteolytic bone metastasis of lung cancer

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Bone metastasis is one of the main complications of lung cancer and most important factors that lead to poor life quality and low survival rate in lung cancer patients. However, the regulatory mechanisms underlying lung cancer bone metastasis are still poor understood. Here, we report that microRNA-182 (miR-182) plays a critical role in regulating osteoclastic metastasis of lung cancer cells. We found that miR-182 was significantly upregulated in both bone-metastatic human non–small cell lung cancer (NSCLC) cell line and tumor specimens. We further demonstrated that miR-182 markedly enhanced the ability of NSCLC cells for osteolytic bone metastasis in nude mice. Mechanistically, miR-182 promotes NSCLC cells to secrete Interleukin-8 (IL-8) and in turn facilitates osteoclastogenesis via activating STAT3 signaling in osteoclast progenitor cells. Importantly, systemically delivered IL-8 neutralizing antibody inhibits NSCLC bone metastasis in nude mice. Collectively, our findings identify the miR-182/IL-8/STAT3 axis as a key regulatory pathway in controlling lung cancer cell-induced osteolytic bone metastasis and suggest a promising therapeutic strategy that targets this regulatory axis to interrupt lung cancer bone metastasis.

Key Words： microRNA-182，Interleukin-8，bone metastasis，lung cancer

232. 循环外泌体 miRNA 作为胃癌标志物

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目的：外泌体 miRNA 被认为是包括胃癌(GC)在内的多种癌症疾病诊断的标志物。本研究旨在鉴定血浆外泌体可以作为胃癌诊断和预后的 miRNAs。

方法：纳入 2020 年 10 月至 2022 年 5 月在常州市第二人民医院就诊的胃癌患者和健康人群。检测标本中外泌体中 miRNA 的表达水平，并进行比较分析。

结果：miR4488 在胃癌患者中高表达，miR4433b-3p 在晚期胃癌中表达量高于早期胃癌。miR4488、miR4429、miR4433b-3pmiR320c、miR320d、miR320e 表达随胃癌 TNM 分期越晚，表达越多。胃癌患者中 miR4429、miR320c、miR320d、miR320e、miR4433b-3p 高表达组比低表达有更少的生存时间。（P<0.05）

结论：我们鉴定了 6 种外泌体 miRNA 可作为潜在的胃癌诊断和预后标志物

关键字： 外泌体、miRNA、胃癌、预后

233. 循环外泌体 miRNAs 作为胃癌标志物

戴菡珏

常州市第二人民医院

目的：外泌体 miRNA 被认为是包括胃癌(GC)在内的多种癌症疾病诊断的标志物。本研究旨在鉴定血浆外泌体可以作为胃癌诊断和预后的 miRNAs。

方法：纳入 2020 年 10 月至 2022 年 5 月在常州市第二人民医院就诊的胃癌患者和健康人群。检测标本中外泌体中 miRNA 的表达水平，并进行比较分析。

结果：miR4488 在胃癌患者中高表达，miR4433b-3p 在晚期胃癌中表达量高于早期胃癌。miR4488、miR4429、miR4433b-3pmiR320c、miR320d、miR320e 表达随胃癌 TNM 分期越晚，表达越多。胃癌患者中 miR4429、miR320c、miR320d、miR320e、miR4433b-3p 高表达组比低表达有更少的生存时间。（P<0.05）

结论：我们鉴定了 6 种外泌体 miRNA 可作为潜在的胃癌诊断和预后标志物

关键字： 外泌体、miRNA、胃癌、预后

234. LDHA 和 LCN2 在甲状腺乳头状癌血清中的表达水平及其临床意义

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目的 探讨乳酸脱氢酶 A（LDHA）和脂质运载蛋白-2（LCN2）在甲状腺乳头状癌（PTC）患者血清中的表达及其临床意义。

方法 收集湖州市中心医院及浙江省肿瘤医院收治的甲状腺乳头状癌患者术前和术后配对样本 61 例、良性甲状腺结节 36 例。采用酶联免疫吸附法测定血液样本中 LDHA 和 LCN2 蛋白浓度。受试者工作特征（ROC）曲线分析 LDHA、LCN2 单独及联合检测对 PTC 的鉴别诊断及预后预测的价值。

结果 与良性结节组比较，PTC 组血清 LDHA、LCN2 表达显著增高（P<0．001）。与 PTC 患者术前组相比，术后组 LDHA、LCN2 表达明显下降（P<0.05）。通过 ROC 曲线分析，血清 LDHA、LCN2 分别区分甲状腺良恶性结节的检测灵敏度为 95.08%、85.25%，特异性为 78.69%、72.22%，ROC 曲线下面积（AUC）为 0.910、0.812。血清 LDHA、LCN2 分别区分术前术后的检测灵敏度为 78.69%、70.49%，特异性为 81.97%、44.26%，AUC 为 0.863、0.573。LDHA、LCN2 联合检测对 PTC 的预测价值与 LDHA 单独检测相比没有增强。

结论 本研究结果表明，血清 LDHA 表达水平在 PTC 患者的良恶性鉴别以及术后疗效评估和监测中具有潜在的临床应用价值。

关键字： 甲状腺乳头癌；LDHA；LCN2；血清标志物；酶联免疫吸附法

235. Clinical significance of serum LDHA and LCN2 expressions in patients with thyroid papillary carcinoma

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Objective ： To investigate the expression and clinical significance of lactate dehydrogenase A (LDHA) and Lipocalin-2(LCN2) in serum of patients with papillary thyroid carcinoma (PTC).

Methods ： 61 patients with thyroid papillary carcinoma and 36 patients with benign thyroid nodules were collected from Huzhou Central Hospital and Zhejiang Cancer Hospital before and after operation. The concentrations of LDHA and LCN2 in blood samples were determined by enzyme-linked immunosorbent assay. The value of receiver operating characteristic (ROC) curve analysis of single and combined detection of LDHA and LCN2 in differential diagnosis and prognosis of PTC.

Results ： The expression of serum LDHA and LCN2 in PTC group was significantly higher than that in benign nodule group (P<0.001). Compared with the preoperative group, the expression of LDHA and LCN2 in the postoperative group was significantly lower than that in the PTC group (P<0.05). By ROC curve analysis, the sensitivity of serum LDHA and LCN2 for differentiating benign and malignant thyroid nodules was 95.08% and 85.25%, respectively, and the specificity was 78.69% and 72.22%, with an area under the ROC curve (AUC) of 0.910 and 0.812. The sensitivity of serum LDHA and LCN2 for differentiating preoperative and postoperative was 78.69%, 70.49%, and the specificity was 81.97% and 44.26%, with an AUC of 0.863 and 0.573, respectively. The predictive value of combined detection of LDHA and LCN2 for PTC was not enhanced compared with that of LDHA alone.

Conclusion ： The results of this study show that the expression level of serum LDHA has potential clinical value in the differential diagnosis of benign and malignant PTC and in the evaluation and monitoring of postoperative curative effect.

Key Words： thyroid papillary carcinoma; LDHA;LCN2; serum marker;enzyme-linked immunosorbent assay

236. 16-hydroxydocosahexaenoic acid serve as diagnostic and prognostic markers for non-small cell lung cancer and influence radiosensitivity

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Background: Imbalance of long-chain polyunsaturated fatty acids (LCPUFA) plays crucial roles in the occurrence and development of lung cancer. Previous studies revealed that the intake of ω-3 rather than ω-6 LCPUFA is inversely associated with the incidence of non-small cell lung cancer (NSCLC). However, their oxidative metabolites and the underlying mechanisms remain to be investigated. This study aims to explore the diagnostic and prognostic values and regulatory effects of LCPUFA oxylipins in NSCLC.

Methods: Liquid chromatography and tandem mass spectrometry was performed to measure the levels of ω-3 and ω-6 LCPUFA, as well as their oxylipins, in the plasma of 39 NSCLC patients and 44 healthy controls. Univariate and multivariate analyses were conducted to demonstrate group separation. Receiver operating characteristic curve analysis was used to evaluate the diagnostic and prognostic values of each metabolite with significant changes. In vitro experiments were applied to confirm the regulatory effects and influenced pathways of 16-hydroxydocosahexaenoic acid (HDHA) on NSCLC cells.

Results: A total of 39 differential metabolites were identified based on variable importance in the projection > 1.0, P-value < 0.05, and fold change > 1.5 or < 0.667, including 18 upregulated and 21 downregulated metabolites. Survival analysis and multivariate Cox regression analysis showed a significant increase in overall survival in the ω-3 LCPUFA group (hazard ratio = 0.99, 95% confidence interval: 0.97-1.01, P-vale = 0.023). In addition, 15 metabolites were identified as prognostic markers for NSCLC. Five biomarkers were identified to simultaneously affect diagnosis and prognosis, including 9-hydroxyeicosapentaenoic acid (HEPE), 11-HEPE, 13-HDHA,

14-HDHA and 16-HDHA. In vitro experiments demonstrated that 16-HDHA inhibited NSCLC cell proliferation, induced cell death and enhanced radiosensitivity. Downregulation of peroxisome proliferator activated receptor (PPAR) γ partially attenuated the benefits of 16-HDHA.

Conclusion: The dysregulation of LCPUFA oxylipins is involved in the occurrence and development of NSCLC. Oxylipins of ω-3 LCPUFA improve the prognosis of NSCLC patients and provide potential targets for personalized therapy development. Further researches are required to elucidate the mechanisms of action of these biomarkers in anti-tumor effects and the molecular mechanisms as therapeutic targets in NSCLC.

Key Words： Non-small cell lung cancer; Radiosensitivity; 16-hydroxydocosahexaenoic acid; long-chain polyunsaturated fatty acid; peroxisome proliferator activated receptor

237. 肾透明细胞癌组织浸润 CD8+T 细胞中异质性胞核核糖核蛋白 A2B1 的表达及其临床意义

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目的：探讨异质性胞核核糖核蛋白 A2B1 （HNRNPA2B1）在肾透明细胞癌（ccRCC）组织浸润 $CD8^+$T 细胞中表达分布特征及其临床意义。

方法：利用基因表达综合数据库（GEO）分析 HNRNPA2B1 在 ccRCC 组织浸润免疫细胞以及 $CD8^+$T 细胞亚群中的表达分布；转录组测序技术（RNA-seq）差异分析高、低表达 HNRNPA2B1 ccRCC 患者高变免疫基因并富集相关通路。多标记免疫荧光染色（mIHC）检测 223 例 ccRCC 患者癌组织和癌旁正常组织浸润 $CD8^+$T 细胞中 HNRNPA2B1 的表达分布特征，采用 R 语言做统计分析，经单因素 Cox、最优子集回归和 LASSO 回归交叉验证筛选临床因素并纳入多因素 Cox 回归构建列线图预测模型。Wilcoxon 检验用于组间差异显著性分析，生存分析采用 Kaplan-Meier 法和 log-rank 检验。

结果：HNRNPA2B1 在 $CD8^+$T 细胞上高表达并参与抗原加工呈递、T 细胞增殖调节等多个信号通路。肾透明细胞癌患者肿瘤组织浸润 $HNRNPA2B1^+CD8^+$T 细胞比率高于癌旁正常组织[1.26%（0%，35.56%）比 0.28%（0%，13.35%），4.5，U=6287，P<0.001]。肿瘤组

织低浸润 HNRNPA2B1^{+}CD8^{+}T 细胞患者总体生存期（OS）显著差于高浸润患者[风险比（*HR*）=0.41；95%可信区间（*CI*）: 0.16~1.07，*P*<0.01）]。对单因素 Cox、最优子集回归筛选得到的年龄、病理分级、TNM 分期和 HNRNPA2B1^{+}CD8^{+}T 细胞浸润程度（*P*<0.05）构建列线图风险预测模型。公共单细胞数据分析结果表明 HNRNPA2B1 在增殖 CD8^{+}T 细胞上高表达。

结论：肾透明细胞癌组织浸润 CD8^{+}T 细胞 HNRNPA2B1 蛋白水平表达的降低表明其参与肾透明细胞癌的进展过程。

关键字： 肾透明细胞癌；异质性胞核核糖核蛋白 A2B1；CD8+T 细胞；预后

238. 食管癌组织中异质性细胞核核糖核蛋白 A2B1 的表达及临床意义

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目的：探讨食管癌组织中异质性细胞核核糖核蛋白 A2B1（HNRNPA2B1）的表达及临床意义。

方法：采用人食管癌组织芯片（含 114 例食管鳞状细胞癌组织和 66 例癌旁正常组织）收集患者临床病理资料，患者手术时间 2006 年 1 月至 2008 年 12 月，随访时间截至 2015 年 7 月；采用多色免疫组织化学染色检测食管癌组织芯片中细胞角蛋白（CK）、HNRNPA2B1 的表达情况，并进行多光谱组织成像。通过 GEO 数据库（GSE160269 数据集）下载食管癌单细胞数据，数据更新时间为 2020 年 11 月 29 日，分析 HNRNPA2B1 的表达情况。下载癌症基因组图谱（TCGA）数据库中食管癌转录组测序的 FPKM 定量数据（包含 173 例食管癌患者样本，其中 162 例为癌组织样本，11 例为癌旁正常组织样本）以及表型（phenotype）中的生存数据（survival data），通过 R4.3.0 survival 包和 survminer 包计算最佳临界值（cut-off 值），根据 cut-off 值将 173 例患者分为高表达组和低表达组，比较两组总生存（OS），采用 Cox 比例风险模型分析 OS 的影响因素。利用 TCGA 数据库中食管癌的 FPKM 定量数据进行分析，选取 HNRNPA2B1 相关度最高的前 250 个基因，通过 R4.3.0 clusterProfiler 包对选取的基因集进行 GO 及 KEGG 富集分析。将 TCGA 数据库中食管癌的 FPKM 定量数据导

入 CIBERSORTx 网站，获得免疫浸润细胞分值，分析 HNRNPA2B1 与免疫细胞浸润程度的相关性。

结果：GSE160269 数据集食管癌单细胞数据中，HNRNPA2B1 在肿瘤上皮细胞中的表达水平高于正常上皮细胞，在免疫细胞不同亚群中呈现高表达。mIHC 和多光谱组织成像分析结果显示，CK 主要表达在肿瘤细胞及正常食管上皮细胞胞膜，HNRNPA2B1 主要表达于肿瘤细胞及正常食管细胞胞核。根据 cut-off 值将患者分为高表达组（≥26%）和低表达组（<26%）。TNM 分期 III+IV 期患者中 HNRNPA2B1 高表达患者比例高于 I+II 期患者（$\chi 2=4.34$，P=0.04）。组织芯片和 TCGA 数据库结果显示，HNRNPA2B1 低表达食管癌患者比 HNRNPA2B1 高表达患者预后好（均 P<0.05）。Cox 回归多因素分析结果显示，年龄（HR=1.919，95%CI:1.158-3.182，P=0.011）、TNM 分期（HR=2.404，95%CI:1.374-4.207，P=0.002）、T 分期（HR=2.349，95%CI: 1.150-4.789，P=0.019）和肿瘤上皮细胞 HNRNPA2B1 的表达（HR=2.160，95%CI:1.280-3.647，P=0.004）是食管癌患者 OS 的独立影响因素。HNRNPA2B1 表达水平与活化 DC 细胞、M0 巨噬细胞、记忆性 CD4+T 细胞和滤泡辅助 T 细胞的浸润程度均呈正相关，与静息肥大细胞的浸润程度呈负相关。GO 富集分析显示 HNRNPA2B1 主要参与核分裂的生物学过程；细胞组分主要富集于染色体区域；分子功能主要富集于 ATP 水解活性。KEGG 富集分析显示 HNRNPA2B1 主要参与细胞周期、剪接体、DNA 复制等生物学过程。

结论：食管癌组织中 HNRNPA2B1 蛋白高表达可能参与食管癌的发生、发展，可作为食管癌预后评估的重要生物学标志。

关键字： 食管癌；异质性细胞核核糖核蛋白 A2B1；预后

239. Microwave ablation combined with PD-L1 blockade synergistically promotes Cxcl9-mediated anti-tumor immunity

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Background/Purpose: Microwave ablation (MWA) is an important curative therapy in colorectal cancer liver metastasis (CRLM), which also promotes tumor antigen-specific T-cell responses and enhances the effect of immunotherapy in preclinical settings. Although tumors are eliminated by MWA alone, recurrence still occurs clinically due to tumor-supportive immune microenvironment. Furthermore, our previous studies have shown that the expression of PD-L1 is upregulated following MWA, suggesting that MWA combined with anti-PD-L1 treatment can serve as a promising clinical therapeutic strategy against cancer.

Methods: Using MWA-treated preclinical mice models, we studied PD-L1 expression in myeloid cells and tumor cells. Furthermore, we examined the antitumor effects of MWA either alone or in conjunction with PD-L1 blockade on regulating tumor growth and survival in mice. Flow cytometry was used to analyze the number and function of tumor-infiltrating lymphocytes (TILs) and tumor cells among control, MWA alone, PD-L1 blockade alone, and MWA combined with the anti-PD-L1 antibody groups. We used single-cell RNA sequencing (scRNA-seq) data to analyze four $CD45^+$ immune cell and tumor cell infiltration groups. In addition, we also performed quantitative real-time PCR (qRT-PCR) to investigate IFN-γ stimulated MC38 cells in vivo and sorted tumor cells from four treatment groups. Finally, we evaluate the role of the Cxcl9 gene on the combined MWA plus PD-L1 blockade therapy using the Cxcl9 deficient MC38 cells or anti-CXCL9 antibodies.

Results: The expression of PD-L1 in myeloid cells and tumor cells was upregulated post-MWA treatment. MWA combined with αPD-L1 treatment decreased tumor growth and prolonged overall survival (OS). Furthermore, through flow cytometry and scRNA-seq analysis, we demonstrated

that the MWA plus αPD-L1 therapy significantly suppressed $CD8^+$T cell exhaustion and enhanced their effector function.

A significant increase in IFN-γ-stimulated transcription factors, specifically Stat1 and Irf1/8, was observed. This enhancement facilitated the polarization of tumor-associated macrophages (TAM1s and TAM2s) through the NF-κB/JAK-STAT1 signaling pathway. Furthermore, the combination therapy stimulated the production of CXCL9 by TAM1s and tumor cells, potentially increasing the chemotaxis of $CD8^+$T cells and Th1 cells. Knocking out of Cxcl9 in MC38 tumor cells or using CXCL9 blockade enhanced tumor growth of untreated tumors and shortened OS.

Conclusions: Our study showed that blocking the IFN-γ-Cxcl9-$CD8^+$T axis promoted tumor progression and discovered a potential involvement of IRF8-regulated TAMs in preventing T-cell exhaustion. Collectively, we demonstrated that the combination of MWA with anti-PD-L1 treatment holds promise as a therapeutic strategy to rejuvenate the immune response against tumors. This merits further exploration in clinical studies.

Key Words： Microwave ablation, Immune checkpoint inhibitors, PD-L1, Cxcl9, IRF8, Immunotherapy

240. IL1RN 在结直肠癌中的表达特征及其作为潜在生物标志物的应用研究

房章

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Interleukin-1 Receptor Antagonist (IL1RN)作为肿瘤标志物在结直肠癌中的研究备受瞩目。结直肠癌作为常见的恶性肿瘤，其早期诊断和治疗一直是医学研究的焦点。IL1RN，作为一种抗炎因子，最近被发现在结直肠癌中发挥着潜在的重要作用。

研究首先关注 IL1RN 的表达与结直肠癌发生和发展的关系。通过对患者组织样本的分析，发现 IL1RN 的表达水平在结直肠癌组织中显著上调。这提示了 IL1RN 可能参与了结直肠癌的病理生理过程，其表达水平可能与癌症的发生和进展阶段相关。

其次，IL1RN 可能通过调节免疫和炎症途径发挥作用。结直肠癌的发展与炎症状态密切相关，而 IL1RN 作为一个调节因子，可能通过抑制 IL-1 信号通路，对炎症反应产生调解作用。这一机制的理解为 IL1RN 作为治疗靶点提供了可能性。

在方法学上，为了准确评估 IL1RN 在结直肠癌中的表达，研究者采用了高灵敏的技术，包括免疫组化和分子生物学方法。这些方法的应用为未来在临床实践中使用 IL1RN 作为生物标志物提供了可行性。

最后，针对 IL1RN 作为结直肠癌标志物的潜在临床应用，相关的研究已经初具规模。IL1RN 可能不仅仅是一个用于癌症早期诊断的标志物，还可能成为制定治疗策略和预后评估的重要因素。

综合而言，IL1RN 作为结直肠癌肿瘤标志物的研究为我们提供了深入探讨其在癌症生物学中作用的机会。对于其潜在机制和临床应用的深入了解将为未来的癌症治疗研究提供新的方向。

关键字： IL1RN，肿瘤标志物，临床价值

241. Cordycepin remodels the tumor microenvironment of colorectal cancer by down-regulating the expression of PD-L1

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Purpose ： Colorectal cancer, as a common malignant tumor, poses a serious threat to human life. Cordycepin, derived from Cordyceps militaris extract, which was established as a capable inhibitor of tumor growth. Nevertheless, the precise antitumor mechanism of cordycepin in colorectal cancer cells remains elusive.

Methods ： Herein, our initial focus was to explore the tumor-suppressive impact of cordycepin through its influence on various biological functions in murine colorectal cancer cells, conducted by an in vitro setting. First, we investigated the tumor-suppressive effect of cordycepin on the regulation of biological functions in murine colorectal cancer cells in vitro. Furthermore, we

evaluated the in vivo antitumor potential of cordycepin using a mouse preclinical tumor model, and further explored the antitumor mechanism.

Results ：Our findings revealed that cordycepin effectively inhibit the proliferation, invasion, and migration of murine colon cancer cells. Moreover, there is a substantial reduction in the expression of PD-L1 observed in tumor cells, in response to cordycepin treatment. Collectively, these results demonstrate the significant tumor-suppressive attributes of cordycepin against colorectal cancer. Consequently, our study lays a solid foundation for the potential clinical utilization of cordycepin in cancer therapy.

Conclusion ：Cordycepin inhibits the biological functions of colorectal cancer cells and suppresses tumor growth by reducing the expression of PD-L1.

Key Words ：Cordycepin · Colorectal cancer · PD-L1 · Tumor microenvironment

242. IL-21 在促进人类肿瘤细胞免疫反应中的作用研究

伍悠

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背景：IL-21 是一种具有多种生物学功能的细胞因子，已显示出在调节免疫反应和抗肿瘤活性方面的潜力。本研究旨在深入探讨 IL-21 在促进人类肿瘤细胞免疫反应中的具体作用，以及其对肿瘤细胞增殖、凋亡和免疫细胞激活状态的影响。

方法：本实验选用人类黑色素瘤细胞株 A375 和人类肺癌细胞株 A549 作为研究对象，通过不同浓度的 IL-21 处理细胞，并采用 CCK-8 方法评估细胞增殖，Annexin V-FITC/PI 双染法检测细胞凋亡，以及流式细胞仪分析细胞表面免疫激活标志物的表达变化。

结果：研究结果显示，IL-21 能够显著抑制肿瘤细胞的增殖，并促进肿瘤细胞的凋亡。特别是在较高浓度（100 ng/mL）和较长时间（48 小时和 72 小时）处理后，这一效果更为显著。此外，IL-21 处理还显著提高了肿瘤细胞表面免疫激活标志物（如 CD80 和 CD86）的表达，表明 IL-21 可以有效激活肿瘤细胞的免疫应答。

结论：本研究证实了 IL-21 在抑制人类肿瘤细胞增殖、促进凋亡以及激活免疫应答方面的重要作用，为 IL-21 在肿瘤治疗中的应用提供了实验依据。这些发现强调了 IL-21 作为一

种潜在的肿瘤治疗策略的价值，同时为进一步研究其在肿瘤免疫治疗中的机制和应用潜力提供了基础。

关键字： IL-21 肿瘤治疗 免疫反应 黑色素瘤 肺癌

243. IL-33/ST2 作为早期结肠癌的潜在生物标志物

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背景和目的：结肠癌是全球发病率和死亡率较高的癌症之一，早期诊断对改善患者预后至关重要。IL-33 及其受体 ST2 在多种炎症和肿瘤过程中发挥作用，但其在早期结肠癌中的潜在应用尚未充分研究。本研究旨在评估血清中 IL-33 及其受体 ST2 表达水平作为早期结肠癌生物标志物的可行性和效能。

材料和方法：样本收集： 本研究收集早期结肠癌患者、非癌性结肠疾病患者及健康对照组的血清样本。分组： 将受试者分为三组：早期结肠癌组、非癌性结肠疾病组和健康对照组。检测方法： 使用酶联免疫吸附测定（ELISA）技术检测各组血清中的 IL-33 及其受体 ST2 的表达水平。统计分析： 采用方差分析和接受者操作特征（ROC）曲线评估 IL-33 及其受体 ST2 的诊断灵敏度和特异性。

结果：预期发现 IL-33 及其受体 ST2 在早期结肠癌患者中的表达水平显著高于非癌性结肠疾病患者和健康对照组。通过 ROC 曲线分析，预期确定 IL-33 及其受体 ST2 检测的最佳截断值，以实现早期结肠癌的高灵敏度和特异性诊断。

结论：本研究结果表明，血清中 IL-33 及其受体 ST2 的表达水平可作为早期结肠癌的潜在生物标志物，具有较高的诊断价值。这项研究的发现支持了进一步探索 IL-33 及其受体 ST2 在结肠癌早期筛查、诊断及治疗监测中的应用潜力，有望为结肠癌的早期诊断和治疗提供新的分子靶标。

关键字： 结肠癌、早期诊断、IL-33、ST2

244. The CXCL10/CXCR3 Pathway Contributes to the Synergy of Thermal Ablation and PD-1 Blockade Therapy against Tumors

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As a practical local therapeutic approach to destroy tumor tissue, thermal ablation can activate tumor-specific T cells via enhancing tumor antigen presentation to the immune system. In the present study, we investigated changes in infiltrating immune cells in tumor tissues from the non-radiofrequency ablation (RFA) side by analyzing single-cell RNA sequencing (scRNA-seq) data of tumor-bearing mice compared with control tumors. We showed that ablation treatment could increase the proportion of CD8+T cells and the interaction between macrophages and T cells was altered. Another thermal ablation treatment, microwave ablation (MWA), increased the enrichment of signaling pathways for chemotaxis and chemokine response and was associated with the chemokine CXCL10. In addition, the immune checkpoint PD-1 was especially up-regulated in the infiltrating T cells of tumors on the non-ablation side after thermal ablation treatment. Combination therapy of ablation and PD-1 blockade had a synergistic anti-tumor effect. Furthermore, we found that the CXCL10/CXCR3 axis contributed to the therapeutic efficacy of ablation combined with anti-PD-1 therapy, and activation of the CXCL10/CXCR3 signaling pathway might improve the synergistic effect of this combination treatment against solid tumors.

Key Words ： thermal ablation; microwave ablation; CXCL10; tumor microenvironment; cancer immunotherapy

245. 新型免疫检查点分子 VISTA 的研究进展

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肿瘤免疫监视理论认为机体的免疫系统可以监视突变细胞，并可以被免疫系统明确清除，以维持内环境的稳定。研究肿瘤的免疫逃逸机制对治疗肿瘤，尤其对免疫治疗具有重要意义。通过免疫检查点、信号传导和代谢的免疫抑制是肿瘤免疫逃逸的主要原因。因此，大量的研究被用于发现和鉴定这些免疫检查点受体的机制。B7 家族共抑制受体细胞毒性 T 淋巴细胞抗原-4 (CTLA-4)和程序性细胞死亡蛋白-1 (PD-1)是目前研究较全面的肿瘤免疫检查点阻断治疗。虽然针对 CTLA-4、PD-1 和 PD-L1 的药物已被研究和开发用于临床 III 期， 但存在响应率低、不良反应等情况。因此，新的免疫检查点靶点也亟待开发以改善当前的免疫治疗策略。最近的研究集中在寻找新的免疫检查点靶点，如程序性细胞死亡蛋白配体 2 (PD-L2)、淋巴细胞活化基因-3 (LAG-3)、T 细胞免疫球蛋白和黏蛋白结构域包含蛋白-3 (TIM-3)、T 细胞免疫球蛋白和 ITIM 结构域蛋白(TIGIT)、 T 细胞活化 V 域免疫球蛋白抑制因子(VISTA)，其中 VISTA 的相关研究相对较少。VISTA 是一种表达于初始 T 淋巴细胞(naïve T cell)上的 B7 家族抑制性受体，也被认为是临床潜力的新型检查点靶点。VISTA 能够参与维持 T 细胞静止和肿瘤免疫逃逸。本文介绍了 VISTA 的概念，总结了 VISTA 的最新研究，包括其与配体和受体的相互作用以及在肿瘤免疫治疗中的意义，旨为免疫检查点抑制剂治疗实体肿瘤提供新依据。包括以下几部分：

1 VISTA 的结构功能与表达：VISTA 作为 B7 家族受体，与 PD-1、PD-L1 存在结构上的相似，这使其可能拥有与其他 B7 家族免疫检查点蛋白类似的功能；VISTA 在髓系细胞高度表达，同时也在 T 细胞、肿瘤细胞上表达的表达规律也暗示其在肿瘤免疫中起到作用。

2 VISTA 及其配体生物学功能：VISTA 目前已确认存在两种配体 VSIG-3 和 PSGL-1。介绍他们之间的相互作用在免疫过程中扮演的角色。

3 VISTA 是肿瘤中髓系细胞的免疫抑制分子：VISTA 在髓系细胞中表达并且通过髓系细胞发挥部分免疫抑制分子的功能，帮助肿瘤细胞免疫逃逸。

4 VISTA 对 T 细胞的抑制作用：虽然 VISTA 在 T 细胞上的表达不如髓系细胞丰富，但它作为 T 淋巴细胞的抑制分子具有重要意义。介绍了研究中发现的 VISTA 对 T 细胞免疫功能的抑制情况。

5 VISTA 在各类肿瘤中的表达及其意义：VISTA 在各肿瘤细胞系中的表达以及他们对 T 细胞的免疫抑制作用。

5.1 VISTA 临床研究：介绍了 VISTA 相关的临床实验及其意义。

5.2 VISTA 拮抗剂的研究：总结目前处于临床实验阶段的 VISTA 拮抗剂以及小分子抑制剂。

关键字： V 型免疫球蛋白 T 细胞活化抑制因子；免疫检查点阻断治疗；肿瘤免疫治疗

246. NK 细胞表达的 XCL1 在结肠癌中的潜在作用及其作为肿瘤标志物的研究

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NK 细胞表达的 XCL1 在结肠癌中的表达情况及其与肿瘤相关的临床特征之间的关联，评估其作为结肠癌肿瘤标志物的潜在价值，为结肠癌的早期诊断和治疗提供新的思路和依据。在方法学上，本研究通过收集结肠癌患者的肿瘤组织样本和相应的癌旁正常组织样本。利用免疫组化技术检测并比较样本中 XCL1 的表达水平。分析 XCL1 的表达与结肠癌患者临床病理特征（如肿瘤大小、淋巴结转移、分期等）及预后指标（如生存期）的关联性。在结肠癌小鼠模型中验证 XCL1 作为肿瘤标志物的潜在价值。

通过对结肠癌患者样本进行免疫组化实验，发现在结肠癌组织中 XCL1 的表达水平显著升高，而在癌旁正常组织中表达较低或不表达。与此同时，统计分析结果显示，XCL1 的表达水平与结肠癌的临床病理特征以及预后指标呈显著相关性，表明其可能在结肠癌发生、发展及预后中发挥重要作用。

本研究结果提示 NK 细胞表达的 XCL1 在结肠癌中具有潜在的肿瘤标志物价值，可作为结肠癌的辅助诊断和预后评估的新指标。进一步的研究和临床验证将有助于深入了解 XCL1 在结肠癌发生发展过程中的作用机制，为结肠癌的个体化治疗和精准医疗提供理论支持和实践指导。

关键字： Xcl1，NK 细胞，结肠癌，标志物

247. TIGIT blockade reshapes the tumor microenvironment based on the single-cell RNA-sequencing analysis

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Immune checkpoint blockade therapy plays an important role in the treatment of malignant tumors, among which TIGIT is being widely studied as a new target for tumor immunotherapy. However, the immune microenvironment after TIGIT blockade treatment is not fully understood at present, so we performed single-cell sequencing on mice before and after anti-TIGIT treatment. We found that TIGIT is mainly expressed on T cells and NK cells. TIGIT blockade can inhibit the function of Treg cells by reducing the expression of FOXP3 and the secretion of immunosuppressive cytokines. In addition, TIGIT blockade can promote the activation of NK cells, increase the number of cells, and activate the TCR signal of $CD8^{+}$T cells by secreting XCL1 and FLT3 and promoting the maturation of DC1, thus enhancing the anti-tumor effect of $CD8^{+}$T cells. Our study provides new insights into the follow-up TIGIT-targeted therapy for cancer patients.

Key Words ： TIGIT, CD8+T cells, Treg, scRNA-seq, tumor microenvironment

248. IDH1/2 突变在结直肠癌诊断及预后评估中的应用价值研究

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研究目的：本研究旨在明确 IDH 突变在结直肠癌患者中的发生频率，探索其与患者临床特征及预后的相关性，并评估 IDH1/2 突变作为治疗靶点的潜力，为结直肠癌的分子靶向治疗提供新的策略。

材料与方法：患者样本与数据收集：回顾性分析 50 例结直肠癌患者的病理样本，并使用 PCR 和测序技术检测 IDH1 和 IDH2 的突变状态。临床数据分析：收集患者的临床路径数据，包括治疗历史、疾病进展情况和总生存期（OS），分析 IDH 突变与这些临床参数之间

的关系。统计方法：使用多变量 Cox 回归模型分析 IDH 突变状态对患者预后的影响，以及与治疗反应的相关性。体外实验：选取 IDH 突变型和野生型结直肠癌细胞株，进行细胞增殖、迁移、侵袭以及对化疗药物反应的实验，以评估 IDH 突变对肿瘤行为的影响。

预期结果：IDH1/2 突变在结直肠癌患者中具有一定的发生率，并可能与更高的肿瘤分期和较差的生存率相关联。统计分析预期显示 IDH1/2 突变是结直肠癌预后的独立预测因子。体外实验结果将揭示 IDH1/2 突变通过影响肿瘤细胞的代谢、增殖、迁移和侵袭能力来促进肿瘤进展，并可能减少化疗药物的敏感性。

结论：本研究将为理解 IDH1/2 突变在结直肠癌发病机制中的作用提供新的见解，并指出 IDH 突变可能作为预后因素和治疗靶点的潜力。这些发现有望促进针对 IDH 突变的结直肠癌患者的个性化治疗策略，提高治疗效果和患者生存质量。

关键字： IDH1/2 突变；结直肠癌；诊断；预后评估

249. MMP1 表达在食管鳞状细胞癌进展和预后关系分析

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目的：探讨基质金属蛋白酶-1（MMP1）在食管鳞状细胞癌（esophageal squamous carcinoma，ESCC)中的表达及意义，为 ESCC 患者预后的评价提供新角度。

方法：利用 GEO 公共数据库研究食管鳞状细胞癌组织浸润免疫细胞中 MMP1 的表达分布；RNA-seq 公共数据研究高、低表达 MMP1 的 ESCC 患者高变免疫基因及其相关富集通路。采用多标记免疫荧光染色检测 MMP1 在癌组织和癌旁正常组织的表达分布特征。通过 R 语言“survminer”包绘制不同表达程度的 MMP1 患者的 Kaplan-Meier 生存曲线。

结果：基于 GEO 数据分析结果显示，与食管鳞状细胞癌组织中其他细胞相比，MMP1 在成纤维细胞上高表达。食管鳞状细胞癌患者肿瘤组织中表达 MMP1 细胞占整个芯点所有细胞的比率显著高于癌旁正常组织。生存分析结果显示，肿瘤组织高浸润 MMP1 的细胞患者总生存期显著差于低浸润患者。对单因素 Cox、最优子集回归和 LASSO 回归交叉验证筛选得到的年龄、病理分级、TNM 分期和 MMP1 浸润程度进行相应的赋分，再依据得到的总分在列线图可以查到 1 年、3 年、5 年总体生存率。

结论：食管鳞状细胞癌肿瘤组织中 MMP1 的高表达与淋巴结转移、微血管密度及 TNM 分期密切相关，是评价食管癌患者预后的重要指标。

关键字： MMP1；食管鳞状细胞癌；数据库分析

250. Runt 相关转录因子 2 在人肾透明细胞癌组织的表达及其临床意义

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目的：探讨 Runt 相关转录因子 2(RUNX2)在肾透明细胞癌(ccRCC)中的表达及其与患者预后和临床病理特征之间的关系。

方法：基于肾癌肿瘤基因组图谱(TCGA)数据，分析 RUNX2 在癌和癌旁组织中的表达及其预后价值。采用多色免疫荧光标记(mIHC)技术分析 RUNX2 在癌和癌旁组织中的分布特征，并结合临床资料进行χ2 检验。单因素和拟合多因素 Cox 模型分析 RUNX2 及其他指标的预后价值。基于 TCGA 数据库，探讨 RUNX2 与免疫细胞浸润的相关性。

结果：TCGA 数据分析结果显示，RUNX2 在癌组织中的表达显著高于正常组织(P<0.001)。mIHC 结果表明 RUNX2 在癌组织表达水平高于癌旁组织(Z＝－2.123，P<0.05)，且其表达水平与患者总生存期呈负相关[P<0.01，风险比(HR)＝2.768，95%可信区间(CI)：1.120~6.838]。RUNX2 表达水平与患者美国癌症联合委员会(AJCC)临床分期明显相关(χ2＝4.505，P<0.05)。多因素 Cox 回归模型显示年龄(P<0.01，HR＝1.068，95%CI：1.024~1.113)、病理分级(P<0.05，HR＝2.171，95%CI：1.179~3.997)和 AJCC 分期(P<0.05，HR＝4.638，95%CI：1.086~19.793)均可以作为肾癌患者的独立预后因素。基于 TCGA 数据库分析，证实肾癌组织中 RUNX2 与多种免疫细胞的浸润程度相关。

结论：RUNX2 高表达与肾癌患者不良预后明显相关。

关键字： Runt 相关转录因子 2;肾透明细胞癌;预后;多标记免疫荧光

251. 雷帕霉素与氯法齐明联合治疗新进展

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多药物联合治疗对克服肿瘤耐药性，加强药物疗效，降低单药剂量毒性，以及扩大药物适应症等方面有很大的帮助。雷帕霉素（Rapamycin, Rapa），一种抗炎剂，主要用于器官移植患者避免免疫排斥，并且能够治疗多种不同类型的癌症。氯法齐明（Clofazimine, CFZ），一种抗生素药物，它作用于细胞壁，抑制细菌的生长和繁殖，以往主要应用于麻风病、银屑病、肺结核的基础研究及临床治疗。近期研究表明，Rapa 和 CFZ 联合治疗耐药性肺结核，显示出较强的协同促进保护性 Th1 反应，抑制 Th2 反应的作用，为抗肿瘤治疗提供了新思路。现就 Rapa 和 CFZ 治疗新进展展开详述。

关键字： 雷帕霉素；氯法齐明；联合治疗；

252. Gasdermins: a dual role in pyroptosis and tumor immunity

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The gasdermin (GSDM) protein family plays a pivotal role in pyroptosis, a process critical to the body's immune response, particularly in combatting bacterial infections, impeding tumor invasion, and contributing to the pathogenesis of various inflammatory diseases. These proteins are adept at activating inflammasome signaling pathways, recruiting immune effector cells, creating an inflammatory immune microenvironment, and initiating pyroptosis. This article serves as an introduction to the GSDM protein-mediated pyroptosis signaling pathway, providing an overview of GSDMs' involvement in tumor immunity. Additionally, we explore the potential applications of GSDMs in both innovative and established antitumor strategies.

Key Words： gasdermin, pyroptosis, caspase, granzyme, tumor immunity, immunotherapy

253. A colorimetric biosensor to track Trop-2 status of tumor cells for diagnosis of breast cancer

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The emergence of antibody-drug conjugates (ADCs) targeting trophoblast cell-surface antigen-2 (Trop-2) has reshaped the therapeutic landscape of advanced breast cancer. Accurate profiling of the Trop-2 status of tumor cells can facilitate the identification of patients who will benefit from Trop-2-targeting therapy; however limited analytical method has hindered this process. In this study, we have proposed a specific and sensitive biosensor for visual tracking of the Trop-2 status of breast cancer cells based on tetrahedral DNA nanostructure (TDN)-decorated Fe-based metal-organic framework nanoparticles (TDN-PCN-222 (Fe)). In the design, a dual-aptamer-assisted biomimetic capture strategy shows high capture efficiency while maintaining the viability and original phenotype of captured cells, ensuring the accurate profiling of the Trop-2 status. Meanwhile, by using the high intrinsic peroxidase activity and excellent targeting ability of Trop-2-specific aptamer-linked TDN-PCN-222 (Fe), specific detection of Trop-2-positive tumor cells can be achieved with a limit of detection (LOD) of 10 cells/mL, and the Trop-2 status of tumor cells can be visually tracked. Moreover, the proposed biosensor has been successfully used for tracking the Trop-2 status of tumor cells in breast cancer tissues, suggesting that our method has great promise for clinical applications.

Key Words： Colorimetric sensor, Trop-2, DNA tetrahedron, metal-organic framework, breast cancer

254. Tumor-derived Extracellular Vesicles as a Biomarker for Breast Cancer Diagnosis and Metastasis Monitoring

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Background: It is imperative to explore biomarkers that are both precise and readily accessible in the comprehensive management of breast cancer. The clinical significance of tumor-derived extracellular vesicle levels is unknown.

Methods: A multicenter cohort, including 512 breast cancer patients and 198 nonneoplastic individuals, was recruited to detect the level of tumor-derived extracellular vesicles using our method based on dual DNA tetrahedral nanostructures.

Results: The level of tumor-derived extracellular vesicles was significantly higher in newly diagnosed breast cancer patients than in nonneoplastic individuals at a cutoff value of 3.58 U/μL (AUC=0.872; sensitivity=73.97%; specificity=90.91%). Its efficacy of diagnosis was superior to that of traditional tumor markers (CEA: AUC=0.644, 95%; CA125: AUC= 0.527; CA15-3:

AUC=0.606). For postoperative metastasis monitoring, the level of tumor-derived extracellular vesicles was significantly higher in breast cancer patients with metastasis than in those without metastasis at a cutoff value of 3.91 U/μL (AUC=0.938; sensitivity=92.86%; specificity=95.2%). Its efficacy of metastasis monitoring was also superior to traditional tumor markers (CEA: AUC=0.773; CA125: AUC=0.779; CA15-3: AUC=0.749).

Conclusion: The tumor-derived extracellular vesicles served as a predictive biomarker for diagnosis and metastasis monitoring in breast cancer patients.

Key Words： breast cancer, tumor-derived extracellular vesicles, diagnosis, metastasis monitoring

255. The arachidonic acid metabolome reveals elevation of prostaglandin E2 biosynthesis in colorectal cancer

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Arachidonic acid metabolites are a family of bioactive lipids derived from membrane phospholipids. They are involved in cancer progression, but arachidonic acid metabolite profiles and their related biosynthetic pathways remain uncertain in colorectal cancer (CRC). To compare the arachidonic acid metabolite profiles between CRC patients and healthy controls, quantification was performed using a liquid chromatography-mass spectrometry-based analysis of serum and tissue samples. Metabolomics analysis delineated the distinct oxidized lipids in CRC patients and healthy controls. Prostaglandin (PGE2)-derived metabolites were increased, suggesting that the PGE2 biosynthetic pathway was upregulated in CRC. The qRT-PCR and immunohistochemistry analyses showed that the expression level of PGE2 synthases, the key protein of PGE2 biosynthesis, was upregulated in CRC and positively correlated with the CD68+ macrophage

density and CRC development. Our study indicates that the PGE2 biosynthetic pathway is associated with macrophage infiltration and progression of CRC tumors.

Key Words： Colorectal cancer, Arachidonic acid, metabolome, Prostaglandin

256. The Arachidonic Acid Metabolome Reveals Elevation of Prostaglandin E2 Biosynthesis in Colorectal cancer.

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Arachidonic acid metabolites are a family of bioactive lipids derived from membrane phospholipids. They are involved in cancer progression, but arachidonic acid metabolite profiles and their related biosynthetic pathways remain uncertain in colorectal cancer (CRC). To compare the arachidonic acid metabolite profiles between CRC patients and healthy controls, quantification was performed using liquid chromatography-mass spectrometry-based analysis of serum and tissue samples. Metabolomics analysis delineated the distinct oxidized lipids in CRC patients and healthy controls. Prostaglandin (PGE2)-derived metabolites were increased, suggesting that the PGE2 biosynthetic pathway was upregulated in CRC. The qRT-PCR and immunohistochemistry analyses showed that expression levels of PGE2 synthases, the key protein of PGE2 biosynthesis, was upregulated in CRC, and positively correlated with CD68+ macrophage density and CRC development. Our study indicates that PGE2 biosynthetic pathway is associated with macrophage infiltration and progression of CRC tumors.

Key Words： Colorectal cancer，Arachidonic acid，metabolomics, Prostaglandin

257. m6A 结合蛋白 HNRNPC 是胰腺癌患者的新型预后生物标志物

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目的：胰腺癌是目前已知的恶性度最高的肿瘤之一，也是常见的癌症相关死亡的主要原因之一。其发病率与死亡率接近，5 年生存率小于 6%。胰腺癌早期没有明显症状，一旦发现多数已经是晚期，在临床上没有很好的治疗手段，缺乏有效的靶向治疗药物。从胰腺癌的病理分型来看，胰腺导管腺癌(PDAC)占全部类型的 90%。而 KRAS 基因突变是 PDAC 发生的过程中最为常见的突变。发现新的胰腺癌生物标志物将有助于患者的早期诊断和更好的预后。最近，N6-甲基腺苷 (m^6A) 甲基化修饰及其调节剂常在许多癌症中表达失调，并且对于癌症的发生、发展、转移、耐药等至关重要。m^6A 甲基化修饰是一种具有代表性且经过长久探索的信使 RNA (mRNA) 修饰，广泛存在于哺乳动物、植物、原核生物和病毒中。在 mRNA 的转录、衰变、变性和翻译等 mRNA 代谢的各个方面都发挥着重要的调节作用。m^6A 由甲基转移酶复合体、去甲基酶以及相应的阅读器协同调控。HNRNPC 作为 m^6A 甲基转移酶，也叫写入器，用于催化 m^6A 的形成。另有研究表明，HNRNPC 可能是肺癌潜在的易感基因，在肝癌的发生发展中也起重要作用，但 HNRNPC 与胰腺癌的关系少有人研究。本文研究 RNA 甲基转移酶 HNRNPC 与胰腺导管腺癌的相互关联性，从分子水平探索 HNRNPC 对胰腺导管腺癌的影响和机制。

方法：使用 TCGA 数据库分析 HNRNPC 的 mRNA 水平；Log-rank 生存分析 HNRNPC 与患者总体生存期（Over survival, OS）的关系；Spearman 分析胰腺癌组织中 HNRNPC 与 KRAS 基因的相关性。

结果：首先我们使用 profile 分析研究了在泛癌中 HNRNPC 的表达情况。结果表明和正常组织相比，HNRNPC 在弥漫性大 B 细胞淋巴瘤、多形成性胶质细胞瘤、脑低级别胶质瘤、胰腺癌、睾丸癌和胸腺瘤中表达上调。接下来，我们研究该基因在胰腺癌中的预后作用。生存分析结果显示胰腺癌组织中 HNRNPC 高表达患者 OS 显著差于低表达患者（HR=1.8, P=0.0058）。随后，我们研究了 HNRNPC 的表达是否影响胰腺癌的临床分期。结果表明 HNRNPC 的表达未能影响胰腺癌的临床分期。最后，我们发现 HNRNPC 和 KRAS 基因正相关。

结论：我们的研究表明，食管癌组织中低表达 HNRNPC 可预测较好的患者预后，HNRNPC 可以作为一种新型的胰腺癌预后生物标志物。

关键字 ：N6-甲基腺苷；HNRNPC；胰腺癌；生物标志物

258. Integrated multi-omics approach to distinct molecular characterization and classification of early-onset colorectal cancer

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Incidence of early-onset colorectal cancer (EOCRC), defined by a diagnosed age under 50 years, is increasing, but its heterogeneous etiologies that differ from general CRC remain undetermined. We initially characterize the genome, epigenome, transcriptome, and proteome of tumors from 79 patients in a Chinese CRC cohort. Data for an additional 126 EOCRC subjects are obtained from the International Cancer Genome Consortium Chinese cohort and The Cancer Genome Atlas European cohort. We observe that early-onset tumors have a high tumor mutation burden; increased DNA repair features by mutational signature 3 and multi-layer pathway enrichments; strong perturbations at effects of DNA methylation and somatic copy-number alteration on gene

expression; and upregulated immune infiltration as hot tumors underlying immunophenotypes. Notably, LMTK3 exhibits ancestral mutation disparity, potentially being a functional modulator and biomarker that drives molecular alterations in EOCRC development and immunotherapies. This integrative omics study provides valuable knowledge for precision oncology of CRC.

Key Words： LMTK3; early-onset colorectal cancer; immunophenotype; multi-omics

259. 组蛋白 H3K79 甲基化转移酶 DOT1L 在结直肠癌中的研究进展

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结直肠癌（colorectal cancer, CRC）是全球最常见的恶性肿瘤之一，由遗传和表观遗传改变积累引起。CRC 表观遗传调控的破坏，特别是组蛋白甲基转移酶和去甲基化酶介导的异常组蛋白甲基化，引起了广泛的关注。类端粒沉默干扰体 1（disruptor of telomeric silencing 1-like, DOT1L）作为组蛋白 H3 第 79 位赖氨酸（H3K79）唯一的甲基化转移酶，通过多种途径作用于 CRC，导致 CRC 的恶性表型并影响其治疗反应。本文主要总结 DOT1L 的生物学功能及其在 CRC 中的作用机制，并讨论了靶向 DOT1L 治疗 CRC 的潜力，旨在为开发新型 CRC 治疗策略提供新思路。

关键字： DOT1L；H3K79 甲基化；组蛋白甲基化修饰；结直肠癌；表观遗传学

260. 肿瘤物理微环境协同ECAD介导混合EMT表型抵抗结直肠癌铁死亡的机制研究

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目的：肿瘤异质性，包括上皮-间质转化（EMT）的异质性，是导致耐药性的主要原因之一。诱导铁死亡有可能克服这种耐药性，提高疗效。然而，不同的 EMT 表型在铁死亡中的作用仍鲜为人知。

材料与方法: 本研究基于课题组前期建立的三维细胞软胶筛选结直肠癌（CRC）致瘤细胞模型，结合组学分析和生物力学研究手段，探索结直肠癌铁死亡与耐药的机制与干预靶点。

结果：本研究发现三维软纤维蛋白微环境赋予 CRC 混合 EMT 表型和对铁死亡的高度耐受性。组蛋白乙酰化和 WNT/β-catenin 信号的激活推动了三维 CRC 向混合 EMT 表型的转变，并通过谷胱甘肽过氧化物酶/铁蛋白信号轴进一步促进了对铁死亡的防御。此外，在三维而非二维的 CRC 中敲除 E-cadherin 会介导晚期混合 EMT 状态，并通过整合素介导的张力和线粒体重编程进一步增强对铁死亡的抵抗。抑制 WNT/β-catenin 信号传导和整合素αvβ3 可使三维 CRC 对铁死亡敏感。

结论：这项研究发现了混合 EMT 在铁死亡中的作用，而这一作用以前从未被认识到，它不仅能预测治疗效果，还能促进新靶向治疗策略的开发。

关键字： 异质性；物理微环境；EMT；铁死亡；

261. Targeting CD47 as a Novel Immunotherapy for Breast Cancer

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Nowadays, breast cancer has become the most commonly diagnosed cancer worldwide with high mortality rate. Immune checkpoint blockade holds great promise in tumor-targeted therapy, and CD47 blockade as one immune checkpoint therapy is undergoing various preclinical studies and

clinical trials to demonstrate its safety and efficacy in breast cancer. In this review, we summarize different therapeutic mechanisms to target CD47 and its prognostic role and therapeutic value in breast cancer.CD47 is a novel attractive target for the treatment of breast cancer. However, there are a series of biosafety problems with such treatments. Due to ubiquitous expression in normal cells, anti-CD47 antibodies could causes possible off-target effects, such as anemia, thrombocytopenia, and leukopenia. Moreover, the wide expression of CD47 creates an “antigen sink”, which means that larger initiation doses and/or frequenter administrations may be required to achieve effective blockade. Thus, there is an ongoing need to exploit safer solutions to overcome toxicities, and several strategies have been developed to address these issues by selectively binding to CD47 on tumor cells, including the identification of tumor-specific CD47 epitopes and the designs of bispecific antibody.

Key Words ： CD47, SIRPα, breast cancer, immunotherapy, immune checkpoint inhibitors

262. 胰腺癌的诊断及免疫治疗靶点的研究进展

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胰腺癌是临床死亡率高的恶性肿瘤之一，患者的整体生存期差，大部分患者就诊时已是中晚期。传统诊断方法检测早期胰腺癌困难，而影像学成像方式的创新、各种生物标志物的联合应用、活检技术的提高、肿瘤微生物的检测等手段可以提高胰腺癌早期诊断。肿瘤免疫疗法作为近年来新型的治疗方式，在胰腺癌治疗中有良好的应用前景。胰腺癌免疫治疗方式包括免疫检查点抑制剂/免疫反应调节剂、CAR-T 细胞免疫疗法和肿瘤疫苗等。本文概述了胰腺癌的诊断方法和基于疾病阶段的免疫治疗方法，以供临床参阅与借鉴。

关键字 ： 胰腺癌；诊断；肿瘤免疫疗法；CAR-T 细胞治疗

263. FOXO1-regulated lncRNA CYP1B1-AS1 suppresses breast cancer cell proliferation by inhibiting neddylation

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Purpose: Overactivated neddylation is considered to be a common event in cancer. Long non-coding RNAs (lncRNAs) can regulate cancer development by mediating post-translational modifications. However, the role of lncRNA in neddylation modification remains unclear.

Methods: LncRNA cytochrome P450 family 1 subfamily B member 1 antisense RNA 1 (CYP1B1-AS1) expression in breast cancer tissues was evaluated by RT-PCR and TCGA BRCA data. Gain and loss of function experiments were performed to explore the role of CYP1B1-AS1 in breast cancer cell proliferation and apoptosis in vitro and in vivo. Luciferase assay, CHIP-qPCR assay, transcriptome sequencing, RNA-pulldown assay, Mass spectrometry, RIP-PCR and Western blot were used to investigate the regulatory factors of CYP1B1-AS1 expression and the molecular mechanism of CYP1B1-AS1 involved in neddylation modification.

Results: We found that CYP1B1-AS1 was down-regulated in breast cancer tissues and correlated with prognosis. In vivo and in vitro functional experiments confirmed that CYP1B1-AS1 inhibited cell proliferation and induced apoptosis. Mechanistically, CYP1B1-AS1 was regulated by the transcription factor, forkhead box O1 (FOXO1), and could be up-regulated by inhibiting the PI3K/FOXO1 pathway. Moreover, CYP1B1-AS1 bound directly to NEDD8 activating enzyme E1 subunit 1 (NAE1) to regulate protein neddylation.

Conclusion: This study reports for the first time that CYP1B1-AS1 inhibits protein neddylation to affect breast cancer cell proliferation, which provides a new strategy for the treatment of breast cancer by lncRNA targeting neddylation modification.

Key Words： breast cancer, tumor marker

264. 一种超灵敏检测短片段游离 DNA 的技术

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Circulating tumor DNA (ctDNA), was short and rare, making the detection performance of the current targeted sequencing methods unsatisfying. We developed the One-PrimER Amplification (OPERA) system and examined its performance in detecting mutations of low variant allelic frequency (VAF) in various samples with short-sized DNA fragments. In cell line-derived samples containing sonication-sheared DNA fragments with 50-150 bp, OPERA was capable of detecting mutations as low as 0.0025% VAF, while CAPP-Seq only detected mutations of >0.03% VAF. Both single nucleotide variant and insertion/deletion can be detected by OPERA. In synthetic fragments as short as 80 bp with low VAF (0.03%-0.1%), the detection sensitivity of OPERA was significantly higher compared to that of droplet digital polymerase chain reaction. The error rate was 5.9×10-5 errors per base after de-duplication in plasma samples collected from healthy volunteers. By suppressing “single-strand errors”, the error rate can be further lowered by >5 folds in EGFR T790M hotspot. In plasma samples collected from lung cancer patients, OPERA detected mutations in 57.1% stage I patients with 100% specificity and achieved a sensitivity of 30.0% in patients with tumor volume of less than 1 cm3. OPERA can effectively detect mutations in rare and highly-fragmented DNA.

关键字 ：游离 DNA，文库构建，液态活检，突变，新一代测序

265. LncRNA LINC00969 promotes acquired gefitinib resistance by epigenetically suppressing of NLRP3 at transcriptional and posttranscriptional levels to inhibit pyroptosis in lung cancer

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Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment prolongs the survival of lung cancer patients harbouring activating EGFR mutations. However, resistance to EGFR-TKIs is inevitable after long-term treatment. Molecular mechanistic research is of great importance in combatting resistance. A comprehensive investigation of the molecular mechanisms underlying resistance has important implications for overcoming resistance. An accumulating body of evidence shows that lncRNAs can contribute to tumorigenesis and treatment resistance. By bioinformatics analysis, we found that LINC00969 expression was elevated in lung cancer cells with acquired gefitinib resistance. LINC00969 regulated resistance to gefitinib in vitro and in vivo. Mechanistically, gain of H3K4me1 and H3K27Ac led to the activation of LINC00969 expression. LINC00969 interacts with EZH2 and METTL3, transcriptionally regulates the level of H3K27me3 in the NLRP3 promoter region, and posttranscriptionally modifies the m6A level of NLRP3 in an m6A-YTHDF2-dependent manner, thus epigenetically repressing NLRP3 expression to suppress the activation of the NLRP3/caspase-1/GSDMD-related classical pyroptosis signalling pathways, thereby endowing an antipyroptotic phenotype and promoting TKI resistance in lung cancer. Our findings provide a new mechanism for lncRNA-mediated TKI resistance from the new perspective of pyroptosis via simultaneous regulation of histone methylation and RNA methylation. The pivotal role of LINC00969 gives it the potential to be a novel biomarker and therapeutic target for overcoming EGFR-TKI resistance in lung cancer.

Key Words ： LINC00969, histone methylation, m6A, pyroptosis, resistance.

266. Effects of Mediterranean and MIND Diets on Risks of Cancer, and the Mediating role of Metabolites

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Background: Research about the association of dietary adherence with cancer risk, especially overall cancer risk and the underlying mechanisms is still limited. This study aimed to investigate the associations of adherence to the MedDiet (Mediterranean Diet) and the MINDDiet (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet) with overall and 22 specific cancers, as well as the mediation effects of circulating metabolites based on the UKB data.

Methods: Based on the collected 24-h dietary information using Oxford WebQ, we quantified MedDiet and MINDDiet adherence using MedDiet Adherence Screener (MEDAS) score and MIND score, with a median follow-up of 13.2 years. Firstly, we used cox proportional hazard regression to obtain the associations of MEDAS/MIND scores with the incidences of overall and 22 specific cancers. Then, we identified cancer related metabolomic biomarkers from 168 metabolites using a combined method of cox hazard regression model, elastic net model (ENM) and gradient boost model (GBM). Finally, we conducted mediation analyses to determine the simple and multiple mediating effects of the identified metabolites on the associations between MEDAS/MIND scores and risk of overall cancer.

Result: Higher diet adherence is significantly associated with a lower risk of overall incident cancer with HR of 0.818 [95%CI: 0.789, 0.849] for MEDAS score and HR of 0.808 [95%CI: 0.784, 0.832] for MIND score. These associations exhibited robustness and consistency across 14 and 13 specific cancer types for MEDAS and MIND score, respectively. The top 10 ranked metabolites including total lipids in VLDL, total cholines, omega-3 fatty acids, tyrosine, glucose, citrate, creatinine, albumin, free cholesterol in IDL, and total lipids in large HDL were identified

to be associated with overall cancer risk using cox hazard regression model, ENM and GBM. Moreover, the proportion of simple mediation effect of these selected metabolites ranged from -4.5% to 19.7% in the association of MEDAS/MIND scores with overall cancer risk. Multiple mediation analyses revealed that the identified metabolites accounted for 19.7% and 20.8% of the total effect in the association between MEDAS/MIND scores and overall cancer risk.

Conclusion: Higher adherence to the MedDiet and MINDDiets is associated with a noteworthy reduction in the risks of overall cancer and specific cancer types. Identified metabolomic biomarkers independently and/or cumulatively mediate the associations between MEDAS/MIND scores and cancer risk. These findings contribute to our understanding of the intricate connections between diet, metabolites, and cancer development.

Key Words ： MedDiet, MINDDiet, Cancer, Metabolites, Mediating effect, UK Biobank

267. 基于肠道菌群调控 PD-1 单抗抑制肿瘤作用机制进展

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抗 PD-1/PD-L1 治疗作为重要的肿瘤免疫治疗方式，通过阻断 PD-1/PD-L1 相互作用增强免疫细胞的肿瘤杀伤活性。免疫检查点抑制剂的疗效已被证明取决于患者肠道中存在独特的有益细菌，肠道微生物组被证实可以影响肿瘤的发展和癌症治疗的疗效，菌群代谢物对 ICB 的抗肿瘤疗效有着一定的调节作用。在这篇文章中我们详细阐述了抗 PD-1 免疫治疗的机制，以及肠道菌群对免疫系统对调控作用。综述了肠道菌群对抗 PD-1 免疫治疗的调控作用，为肿瘤免疫治疗提供新的联合治疗思路与方法。

关键字 ： PD-1、anti-PD-1、肠道菌群、ICI、免疫治疗

268. 免疫细胞在口腔和咽喉癌中的因果作用

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背景：在过去的几十年里，头颈鳞状细胞癌（HNSCC）这一全球第六大常见癌症的治疗进展有限。其中，口腔癌和咽癌的发生、发展与免疫细胞密切相关，但二者之间的具体关系和潜在机制尚不清楚。

方法：对 3757 名欧洲人的 731 种免疫表型进行 GWAS 汇总统计，包括绝对细胞计数、表面抗原水平、形态学参数和相对细胞计数。口腔和咽癌的 GWAS 汇总统计数据(ieu-b-87、ieu-b-93 和 ieu-b-97)得到了口腔和口咽癌联盟的支持。GWAS 鉴定了低于全基因组显著性水平的独立 SNP。

结果：我们的研究揭示了与 $IgD^{-}CD38^{br}$ 细胞（浆细胞）上的 CD19 相关的口腔癌和咽癌风险的 OR：ieu-b-87 中为 1.27，ieu-b-93 中为 1.32，ieu-b-97 中为 1.23。这些数据表明，$IgD^{-}CD38^{br}$（浆细胞）上 CD19 的升高与口腔癌和咽癌的风险增加相关。此外，在 ieu-b-87 中，与 B 细胞上的 SSC-A 相关的口腔癌和咽癌风险的 OR 为 0.77，在 ieu-b-93 中，与 B 细胞上的 FSC-An 相关的 OR 为 0.76。 B 细胞上的 SSC-A 显示 OR 为 0.74，表明 B 细胞与总体口咽癌风险之间存在潜在负相关。

结论：我们的研究提供了遗传证据，表明 $IgD^{-}CD38^{br}$ 细胞（浆细胞）上的 CD19 与口腔癌和咽癌的总体风险呈正相关，而 B 细胞与口腔癌和咽癌的总体风险呈潜在负相关。

关键字： 口腔癌，咽喉癌，B 细胞，孟德尔随机化

269. Synergistic effect of CD47 blockade in combination with cordycepin treatment against cancer

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Cordycepin is widely considered a direct tumor-suppressive agent. However, few studies have investigated the effect of cordycepin therapy on the tumor microenvironment (TME). In our present study, we demonstrated that cordycepin could weaken the function of M1-like

macrophages in TME and also contribute to macrophage polarization toward M2 phenotype. Herein, we established a combined therapeutic strategy consisting of cordycepin and anti-CD47 antibody. By single-cell RNA sequencing (scRNA-seq), we showed that the combination treatment could significantly enhance the effect of cordycepin, which would reactivate macrophages and reverse macrophage polarization. In addition, the combination treatment could regulate the proportion of CD8+T cells to prolong the progression-free survival (PFS) for patients with digestive tract malignancy. Finally, flow cytometry validated the changes in the proportions of tumor-associated macrophages (TAMs) and tumor-infiltrating lymphocytes (TILs). Collectively, our findings suggested that the combination treatment of cordycepin and anti-CD47 antibody could significantly enhance tumor suppression, increase the proportion of M1 macrophages, and decrease the proportion of M2 macrophages. In addition, the PFS for patients with digestive tract malignancy would be prolonged by regulating CD8+T cells.

Key Words： Cordycepin, anti-CD47, macrophage, tumor microenvironment

270. 人参皂苷 Rb1 通过 ApoM/线粒体凋亡途径对肝癌的影响及机制研究

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目的：探究 ApoM/线粒体凋亡在肝癌中的作用及人参皂苷 Rb1（Ginsenoside Rb1，Rb1）通过 ApoM/线粒体凋亡途径影响肝癌可能的潜在机制。

方法：生物信息学分析筛选 ApoM 在肝癌中的差异性表达及临床验证；分子对接技术确定 Rb1 与 ApoM 的靶向结合，后体外培养人肝癌 HepG2 细胞，并予以 Rb1（CCK8 筛选最佳浓度)干预，克隆实验用于观察肝癌细胞的增殖情况，划痕实验用于观察 HepG2 细胞的迁移能力，采用 Western blot 法检测 ApoM 及线粒体凋亡相关蛋白表达及 Rb1 的干预情况，RT-qPCR 法检测 ApoM 及线粒体凋亡相关 mRNA 表达水平。

结果：生存分析发现 ApoM 低表达对肝癌具有更差预后，分子对接提示 Rb1 与 ApoM 之间具有较高亲和力，克隆及划痕实验提示 Rb1 有效抑制 HepG2 细胞增殖，Western blot 法及 RT-qPCR 验证 Rb1 可以干预线粒体凋亡相关蛋白表达。

结论：揭示了 ApoM/线粒体凋亡在肝癌中发挥重要作用，人参皂苷 Rb1 可能通过 ApoM/线粒体凋亡途径影响肝癌的可能潜在机制。

关键字： ApoM；人参皂苷 Rb1；线粒体凋亡；肝癌

271. 乳腺癌与免疫细胞之间的随机关系，一项孟德尔随机化研究

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Background: The composition and dysfunction of immune microenvironment may be one of the fundamental factors in the occurrence and development of breast cancer (BC). Many studies have reported that immune cells and cytokines play a crucial role in the regulation of tumor microenvironment. However, previous research on the association between immune inflammation with breast cancer have yielded inconsistent results.

Methods: We performed bidirectional two-sample Mendelian randomization (MR) analysis investigate the causal relationship between immune cell signatures and SCZ in this study. Inverse variance weighting method (IVW) was considered Four immune trait types (absolute count (AC), median fluorescence intensities (MFI), morphological parameter (MP) and relative count (RC)) were admitted into MR analysis. Reliability, heterogeneity, and horizontal pleiotropy of the results was checked by lateral sensitivity analysis.

Results: We identified casual effect of 21 immunophenotypes to be significantly associated with BC risk. The most prominent risk and protective portrait was CD127 on CD28+ CD45RA- CD8br (Treg panel, IVW, OR: 1.0258, 95% CI =1.0029 ~ 1.0492, P = 0.0272) and CD28- CD8br %CD8br (Treg panel, IVW, OR = 0.9529, 95% CI = 0.9185 ~ 0.9886, P = 0.0101). Through reverse Mendelian randomization analysis, we determined that BC morbidity was significantly associated with 17 immunophenotypes.

Conclusion: Our investigation demonstrated the causal associations between several immunophenotypes and BC by means of MR analysis bidirectionally, further elucidating the close correlation between Tregs, monocytes and breast cancer incidence and providing robust guidance for future clinical research and practice.

Key Words： Brest cancer, GWAS, Immune cell, MR analysis, Sensitivity

272. 杭州市 2023 年 41534 例健康体检人群肿瘤标志物检测结果分析

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目的：了解杭州迪安医学检验中心 41534 例健康体检人群肿瘤标志物血清抗原检测结果，探讨不同性别各种肿瘤标志物的差异。

方法：检测健康体检人群血清肿瘤标志物抗原，包括甲胎蛋白(AFP)、癌胚抗原(CEA)、糖类抗原(CA)125、细胞角蛋白 19 可溶性片段(CYFRA211)、神经元特异性烯醇化酶(NSE)、游离前列腺特异性抗原(FPSA)、CA199、CA724、血清胃泌素释放肽前体(ProGRP)、总前列腺特异性抗原(TPSA)、CA153、人附睾蛋白(HE4)，并对检测结果进行统计学处理。

结果：杭州市迪安医学检验中心 2023 年 41534 例健康体检人群中，男女共有的 10 项肿瘤标志物中异常比例较高的是 CA724(8.56%)，其次是 CEA(2.58%)，其余几种相对较低。男女之间 10 种肿瘤标志物异常比例比较，差异均有统计学意义(P<0.05)。

结论：杭州市 2023 年 41534 例健康体检人群 12 项肿瘤标志物男、女异常比例为分别为 23.35%、21.65%，性别对各种肿瘤标志物的异常比例均有影响。

关键字： 肿瘤标志物；健康体检；性别

273. 关于 AIM2 敲除联用免疫抑制剂对抗肿瘤治疗状况研究

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近年来，免疫治疗作为肿瘤治疗领域的一项重要突破备受关注。然而，尽管取得了显著进展，仍然有许多患者对免疫治疗反应不佳或存在抗药性。为了提高免疫治疗的效果，研究人员不断探索新的治疗策略。近期的研究表明，AIM2 基因敲除联合免疫抑制剂可能成为一种潜在的治疗方法。AIM2 基因敲除能够调节肿瘤微环境，促进免疫细胞的浸润和肿瘤细胞的凋亡，从而增强免疫治疗的疗效。这一发现为开发新的肿瘤治疗策略提供了重要的理论基础，为进一步的临床研究提供了新的方向。

研究发现，AIM2 基因敲除能够显著增强免疫治疗的抗肿瘤效应，通过调节肿瘤微环境，促进肿瘤细胞的凋亡和免疫细胞的浸润来提高治疗效果。与单一免疫治疗相比，AIM2 基因敲除联合免疫抑制剂能够显著延长患者的生存期，并提高治疗的整体有效率。这些发现为 AIM2 基因敲除联合免疫抑制剂作为新的肿瘤治疗策略提供了重要的理论依据和临床前景展望，但进一步的研究和临床验证仍然是必要的。

关键字： AIM2 免疫治疗

274. 间充质干细胞诱导的 NPRA 通过增强脂代谢促进胃癌干性和耐药的机制研究

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背景：以 CDDP 为基础的化疗是晚期胃癌(GC)患者的首选治疗策略。尽管化疗有效，但化疗耐药的发生是改善 GC 患者预后的主要障碍，其机制仍不清楚。越来越多的证据表明，间充质干细胞(mesenchymal stem cells, MSCs)在耐药中发挥重要作用。

方法：采用克隆形成、CCK-8、成球和流式细胞术观察 GC 细胞的耐药和干性。利用细胞系和动物模型研究相关功能。采用 Western blot、quantitative real-time PCR (qRT-PCR)和免疫共沉淀等方法探索相关通路。

结果：MSC 可增强 GC 细胞的干性和化疗耐药，是 GC 预后不良的原因。心房钠尿肽受体 A (NPRA)在 MSC 共培养的 GC 细胞中表达上调，敲低 NPRA 可逆转 MSC 诱导的干性和化疗耐药。此外，NPRA 通过脂肪酸氧化(FAO)促进干性和化疗耐药。在机制上，NPRA 保护线粒体融合蛋白 2 (Mfn2)免受蛋白质降解，促进其线粒体定位，从而增强 FAO。此外，etomoxir (ETX)抑制 FAO 可减轻 MSC 诱导的 CDDP 耐药。

结论：MSC 诱导的 NPRA 通过上调 Mfn2，增强 FAO 促进了干性和化疗耐药性。这些发现有助于我们更好地了解 NPRA 在 GC 预后和化疗中的作用， NPRA 有望成为克服化疗耐药的靶点。

关键字： 间充质干细胞、心房钠尿肽受体 A、脂代谢、胃癌

275. 基于机器学习开发并验证肺癌筛查模型：一项大规模、多中心呼吸气体生物标志物研究

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目标：肺癌是全球死亡率最高的肿瘤，目前由于缺乏有效的早期筛查方法，导致治疗效果不尽人意。本文旨在使用呼吸气体分析这种无创且非常简单的方法，来识别和验证用于肺癌筛查的呼吸气体生物标志物。

材料与方法：本研究共招募了来自两个中心的 2308 名参与者，使用质子转移反应飞行时间质谱（PTR-TOF-MS）进行在线呼吸气体分析。推导队列包括 1007 名原发性肺癌患者和 1036 名健康对照者，外部验证队列包括 158 名肺癌患者和 107 名健康对照者。我们使用极端梯度提升（XGBoost）来创建一组预测特征，并推导出一个预测模型来识别肺癌，最佳

特征数量由接收者操作特征（ROC）曲线下的最大面积（AUC）确定。并使用独立外部验证数据对模型的性能指标进行验证。

结果：本研究定义了六个特征作为检测肺癌的呼吸气体生物标志物组合。在训练数据集中，该模型的 AUC 为 0.963（95% CI，0.941–0.982），在阳性阈值为 0.5 时，其敏感性为 87.1%，特异性为 93.5%。该模型在独立验证数据集上的 AUC 为 0.771（0.718–0.823），敏感性为 67.7%，特异性为 73.0%。

结论：据我们所知，这是迄今为止同类研究中规模最大且使用区域外部验证的研究。本项大规模呼吸气体测试和机器学习的数据表明，呼吸气体分析技术可以作为医院就诊前筛查肺癌的有效方法。尽管呼吸气体生物标志物组合具有无创、快速和简单的优势，但仍需要在初级保健环境中进行前瞻性研究的进一步校准和验证。

关键字： 呼气分析技术；肺癌；机器学习；PTR-MS，标志物

276. Construction and Mechanism of IL-15-Based Coactivated Polymeric Micelles for NK Cell Immunotherapy

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Natural killer (NK) cells are an important contributor to cancer immunotherapy, but their antitumor efficacy remains suboptimal. While cytokine-based priming shows promise in enhancing NK-cell activity, its clinical translation faces many challenges, including coactivation of multiple cytokines, poor pharmacokinetics, and limited mechanistic understanding. Here, this work develops a polymeric micelle-based IL-15/IL-2 codelivery system (IL-15/2-PEG-PTMC) for NK-cell activation. In vivo studies demonstrate that half-life of IL-15 and IL-2 and the recruitment of NK cell within tumor tissue are significantly increased after PEG-PTMC loading. Coupled with the coactivation effect of IL-15 and IL-2 conferred by this system, it noticeably delays the growth of tumors compared to conventional NK-cell activation approach, that is free IL-15 and IL-2. It is

also surprisingly found that cholesterol metabolism is highly involved in the NK cell activation by IL-15/2-PEG-PTMC. Following stimulation with IL-15/2-PEG-PTMC or IL-15, NK cells undergo a series of cholesterol metabolism reprogramming, which elevates the cholesterol levels on NK cell membrane. This in turn promotes the formation of lipid rafts and activates immune synapses, effectively contributing to the enhancement of NK cell's antitumor activity. It is believed that it will open a new avenue for improving the efficacy of NK cell immunotherapy by regulating cholesterol metabolism.

Key Words ： NK Cells, Co-activated polymeric micelles, Cholesterol metabolism, IL-15, Immunotherapy

277. Single-cell transcriptomics provide insight into metastasis-related subsets of breast cancer

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Breast cancer metastasis is a complex, multi-step process, with high cellular heterogeneity between primary and met- astatic breast cancer, and more complex interactions between metastatic cancer cells and other cells in the tumor microenvironment. High-resolution single-cell transcriptome sequencing technology can visualize the heterogeneity of malignant and non-malignant cells in the tumor microenvironment in real time, especially combined with spatial transcriptome analysis, which can directly compare changes between different stages of metastatic samples. There- fore, this study takes single-cell analysis as the first perspective to deeply explore special or rare cell subpopulations related to breast cancer metastasis, systematically summarizes their functions, molecular features, and corresponding treatment strategies, which will contribute to accurately identify, understand, and target tumor metastasis-related driving events, provide a research basis for the mechanistic study of breast cancer metastasis, and provide new clues for its personalized precision treatment.

Key Words: Single-cell transcriptome sequencing, Breast cancer, metastasis

278. Multi-omics approaches identify malate dehydrogenase 2 (MDH2) as a tumor progression driver and druggable target in breast cancer

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The dysfunction of numerous metabolic enzymes is closely associated with the prominent metabolic dysregulation in breast cancer. As a vital enzyme of the tricarboxylic acid cycle, malate dehydrogenase 2 (MDH2) dysfunction has been linked to the development of several malignancies. However, the role of MDH2 in the tumorigenesis and progression of breast cancer remains obscure and warrants further investigation. Based on multi-omics approaches, it was determined that MDH2 plays an oncogenic role in the progression of breast cancer and could be used as a biomarker in the diagnosis, treatment, and prognosis of breast cancer patients. In vitro, MDH2 reduction inhibited breast cancer cell proliferation and migration, reversed the EMT process, and altered metabolic patterns (including glucose consumption and ATP production). In vivo, MDH2 overexpression facilitates the growth of xenograft breast cancer tumors. Transcriptomics revealed that MDH2 modifies the gene expression profile of breast cancer cells, including several genes implicated in the regulation of breast cancer metastasis. KEGG enrichment analysis reveals that the PI3K-Akt signaling pathway, which is implicated in tumor proliferation and metastasis, is the downstream regulatory pathway of MDH2. Untargeted metabolomics results indicated that MDH2 influences the production of 62 downstream differential metabolites, including the tumor immunomodulating metabolites adenosine and linoleic acid. In addition, we explored the potential of MDH2 as a novel druggable target in silico. These results shed new light on the function of metabolic enzymes in breast cancer development and metastasis. MDH2 could serve as a prospective target for developing novel cancer therapies that target cancer metabolism and tumor growth.

Key Words ： Breast cancer, Cancer metabolism, Malate dehydrogenase 2 (MDH2), Transcriptomics, Untargeted metabolomics, Druggable target

279. 7-AAB 联合高分辨率 CT 征象在 IA 期肺癌中的诊断意义

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目的：探讨 7 种肿瘤相关自身抗体（7-AAB）联合高分辨率 CT（HRCT）对在 IA 期肺癌中的诊断意义。

方法：回顾分析襄阳市中心医院医院自 2022 年 6 月至 2023 年 4 月经临床证实为 IA 期肺癌患者 169 例及同期良性肺结节患者 39 例，所有患者术前均行至少一次胸部 HRCT 检查及外周血 7-AAB 检测（包括 p53，GAGE7，PGP9.5，CAGE，MAGE A1，SOX2，GBU4-5）。采用 c2 检验和 Kruskal－Wallis 秩和检验比较IA 期肺癌组与良性组、IA 期肺癌各亚组间的 7-AAB 水平与影像学特征之间的关系，并计算 HRCT、7-AAB、HRCT+7-AAB 诊断肺癌的灵敏度、特异度。

结果：IA 期肺癌组的分叶征、毛刺征、胸膜凹陷征、血管聚集、亚实性比率及 7-AAB 检测的阳性率高于良性组（P 值均＜0.005）。IA1 期、IA2 期和IA3 期在分叶征、毛刺征、胸膜凹陷征及空气支气管征的阳性率差异均有统计学意义(P 值均＜0.001)，且随着分期的增高 CT 征象阳性率增高。HRCT+7-AAB 联合检测诊断肺癌灵敏度为 89.35%，特异度为 64.10%，高于任意一种单独诊断(P 值均＜0.001）。

结论：对于 IA 期肺癌，7-AAB 检测联合 HRCT 可以提高灵敏度，并且 7-AAB 阳性率与更晚的病理分期相关。

关键字 ：肺肿瘤；体层摄影术，X 线计算机；抗体

280. ACSL4——恶性前列腺癌的潜在标志蛋白

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研究目的：探究 ACSL4 作为恶性前列腺癌标志蛋白的可能性。

材料与方法：生信分析；WB 实验；MTS；Transwell；RT-qPCR；细胞转染。

结果：从 GEO、TCGA 中选取不同发展阶段的前列腺癌病例以及相关细胞系数据进行分析。细胞系分析显示，ACSL4 在 DU145 与 PC3 中的表达远超与 LNCaP、22RV-1。相关病例也表明 Gleason 评分越高的前列腺癌，ACSL4 表达越高，这都提示 ACSL4 在恶性前列腺癌中扮演重要的角色。在此基础上，选取 LNCaP、22RV-1、DU145、PC3 四株细胞系进项验证。根据 RT-qPCR 结果，我们发现 ACSL4 在两株高恶性前列腺癌中的表达是低恶性前列腺癌的数十倍，其中 ACSL4 在 PC3 中相对表达量最高，符合 PC3 恶性程度高的认知。随后，对上述四株细胞系进行 WB 验证，结果与 RT-qPCR 结果一致。这表明 ACSL4 有作为恶性前列腺癌潜在标志蛋白的可能性。

为了进一步验证 ACSL4 在恶性前列腺癌中扮演什么样的角色，我们对恶性程度高的两株细胞系进行干扰处理。首先，选用 ACSL4 相关抑制剂对细胞进行处理，并选取不同时间段的细胞进行吸光度测定，结果提示随着时间的推移，加药组的生长速度远远低于 Ctrl 组。随后对 DU145 和 PC3 进行细胞转染，从基因层面干扰 ACSL4 在细胞中的表达，并测定其在 490nm 处的吸光度值，结果发现在敲低 ACSL4 后，细胞活力受到极大的影响，细胞增殖速度也远远低于 Ctrl 组，以上结论均表明 ACSL4 对细胞的生长增殖产生促进作用。为求进一步探究 ACSL4 是否对细胞迁移产生影响，我们对两组细胞进行转染处理后，将其铺入 Transwell 小室中，在经过一段时间后对小室进行结晶紫染色，在显微镜下摄片。结果提示转染组在薄膜上的细胞数量远远低于 Ctrl 组，这表明在敲低 ACSL4 后，细胞的迁移能力受到一定程度的削弱。以上实验均说明 ACSL4 在促进前列腺癌细胞生长迁移中起到重要的作用。

结论：最新报道显示，前列腺癌发病率每年增加 2-3%1，因此利用肿瘤标志物来辨别前列腺癌恶性程度并早期干预已成为现下重要的研究方向。随着对前列腺癌研究的不断深入，ACSL4 在恶性前列腺癌中的部分影响也被探明 2。在此基础上，我们的研究结果均提示 ACSL4 高表达对恶性前列腺癌的生长，繁殖以及迁移都产生促进作用。因此，通过明确患者血清中 ACSL4 表达，对判断患者的预后，并早期干预产生积极影响。

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关键字 ：ACSL4　前列腺癌　标志蛋白

281. The Synthesis of Glutamine-Functionalized Block Polymer and Its Application in Triple-Negative Breast Cancer Treatment

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Triple-negative breast cancer (TNBC) is a highly malignant tumor. At present, there are still no targeted drugs for TNBC. Clinical chemotherapeutic drugs, such as doxorubicin (DOX), have the characteristic of nontargeted distribution in treatment of TNBC, causing severe side effects. Therefore, new target treatment strategies for TNBC are of urgent need. It was speculated that glutamine could be a potential target because it is in high demand by TNBC. In this study, we found that the transporter for glutamine, ASCT2 (solute carrier family 1 member 5 (SLC1A5)), is highly expressed in TNBC by analysis of data from The Cancer Genome Atlas (TCGA) and experiments in vitro. Based on this, glutamine was grafted onto a polymeric drug carrier in order to develop a tumor-targeting drug delivery system for treatment of TNBC. Firstly, pH-responsive glutamine-PEG5000-b-PAE10000 (Gln-PEG-b-PAE) copolymers were synthesized using Fmoc-PEG5000-b-PAE10000 (Fmoc-PEG-b-PAE) copolymers. Then, Gln-PEG-b-PAE@DOX micelles were prepared by loading DOX to Gln-PEG-b-PAE copolymer using a solvent casting technology. In vitro, Gln-PEG-b-PAE@DOX micelles exhibited pH-dependent micellization-decellularization behavior; namely, they can rapidly release DOX in acidic environment of pH 6.0 but release very slowly in physiological condition. Moreover, glutamine competition experiment showed that Gln-PEG-b-PAE@DOX micelles had the ability to target MDA-MB-231 cells. Compared to free DOX, Gln-PEG-b-PAE@DOX micelles had significantly greater cytotoxic effect and antiproliferative activity against MDA-MB-231 cells. In vivo, compared to free DOX and mPEG-b-PAE@DOX micelles, Gln-PEG-b-PAE@DOX micelles significantly inhibited tumor growth in tumor-bearing mice. Therefore, Gln-PEG-b-PAE@DOX micelles, as a tumor-targeting drug delivery system, may provide a new method for the treatment of TNBC.

Key Words ： triple-negative breast cancer, glutamine, copolymers

282. Mutational signature of mtDNA confers mechanistic insight into oxidative metabolism remodeling in colorectal cancer

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Rationale: Mitochondrial dysfunction caused by mitochondrial DNA (mtDNA) mutations and subsequent metabolic defects are closely involved in tumorigenesis and progression in a cancer-type specific manner. To date, the mutational pattern of mtDNA somatic mutations in colorectal cancer (CRC) tissues and its clinical implication are still not completely clear.

Methods: In the present study, we generated a large mtDNA somatic mutation dataset from three CRC cohorts (432, 1,015, and 845 patients, respectively) and then most comprehensively characterized the CRC-specific evolutionary pattern and its clinical implication.

Results: Our results showed that the mtDNA control region (mtCTR) with a high mutation density exhibited a distinct mutation spectrum characterizing a high enrichment of L-strand C > T mutations, which was contrary to the H-strand C > T mutational bias observed in the mtDNA coding region (mtCDR) ($P < 0.001$). Further analysis clearly confirmed the relaxed evolutionary selection of mtCTR mutations, which was mainly characterized by the similar distribution of hypervariable region (HVS) and non-HVS mutation density. Moreover, significant negative selection was identified in mutations of mtDNA complex V (ATP6/ATP8) and tRNA loop regions. Although our data showed that oxidative metabolism was commonly increased in CRC cells, mtDNA somatic mutations in CRC tissues were not closely associated with mitochondrial

biogenesis, oxidative metabolism, and clinical progression, suggesting a cancer-type specific relationship between mtDNA mutations and mitochondrial metabolic functions in CRC cells.

Conclusion: Our study identified the CRC-specific evolutionary mode of mtDNA mutations, which is possibly matched to specific mitochondrial metabolic remodeling and confers new mechanic insight into CRC tumorigenesis.

Key Words： mitochondrial DNA; somatic mutations; evolutionary selection; metabolic remodeling; colorectal cancer

283. 放化疗疗效预测标志物助力于泛鳞状细胞癌精准诊疗

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背景与目的：同步放化治疗是作为治疗不可切除食管癌的主要手段，但不同患者之间的治疗效果具有显著差异，仍有部分患者出现癌症复发和转移。放化疗抵抗是一大难题，阐明分子机制对于高效精准识别潜在受益患者及降低复发和远处转移具有重要意义。

材料与方法：对已建立的患者来源肿瘤移植模型进行放化疗处理，根据放化疗后肿瘤组织体积变化分为敏感组和抵抗组。对放化疗敏感和抵抗组肿瘤进行激光捕获显微切割联合转录组测序、微量蛋白质谱检测，分析两组之间显著差异表达的基因。免疫组化验证差异基因表达，用类器官、PDX 皮下移植实验验证放射、化疗药物敏感性。利用免疫组化和免疫荧光实验检测高表达蛋白在肿瘤组织中的表达水平和空间定位。使用 Student's t 等检验比较两组实验结果之间的差异是否显著。

结果：通过单细胞和空间转录组测序对食管癌中各类细胞的转录组特征及其相互作用进行了全面解析，多组学数据分析确定半鳞状分化是放化疗抵抗的显著特征，并在临床上、PDX 中证实半鳞状分化标志蛋白（KRT4/13，ANXA1，S100A8）在治疗后肿瘤中高表达，与复发转移密切相关。

结论：我们鉴定出能预测放化疗疗效的生物标志物；揭示了 KLF4、TFAP2A 驱动半鳞状分化的转录因子，并阐明功能分子 TGM1 促放、化疗抵抗机制；探究了靶向半鳞状分化药物半胱胺的临床价值，开展临床前实验评估药物联用方案的疗效。本研究聚焦于肿瘤细胞谱系可塑性，揭示放、化疗耐药新机制，助力于泛鳞状细胞癌精准诊疗。

关键字： 化学治疗，放射治疗，半鳞状分化，生物标志物，鳞状细胞癌

284. Dual-energy computed tomography quantitative parameter analysis of nasopharyngeal carcinoma cervical lymph node characteristics and prediction of radiotherapy sensitivity: A prospective study

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Background and purpose: Treatment efficacy may differ among patients with nasopharyngeal carcinoma (NPC) at a similar tumor–node–metastasis stage. Moreover, end-of-treatment tumor regression is a reliable indicator of treatment sensitivity. This study aimed to investigate whether quantitative dual-energy computer tomography (DECT) parameters can predict the sensitivity of neck-lymph node radiotherapy in patients with NPC.

Materials and methods: Overall, 388 lymph nodes were collected from 98 patients with NPC who underwent pretreatment DECT between September 2021 and December 2022. The patients were divided into complete response (CR) and partial response (PR) groups. Clinical characteristics and quantitative DECT parameters were compared between the groups, and the optimal predictive ability of each parameter was determined using the receiver operating characteristic (ROC) analysis. A nomogram prediction model was constructed and validated using univariate and binary logistic regression analyses.

Results: The DECT parameters were higher in the PR group than in the CR group. Iodine concentration (IC), normalized IC, Mix-0.6, λHU,Zeff,spectral Hounsfield unit curve slope, effective atomic number, and virtual monoenergetic images were significantly different between the groups. The area under the ROC curve (AUC) of the DECT parameters was (0.73-0.77) (P <0.001). Based on binary logistic regression, a column chart is constructed using 10 predictive factors, including age, sex,N stage, maximum lymph node diameter,arterial

phase NIC,λHU,70keVand venous phase NIC,IC,Mix-0.6.The AUC value of the constructed model was 0.84, with a sensitivity and specificity of 85.6% and 81.3%, respectively.

Conclusion: Quantitative DECT parameters can potentially predict the sensitivity of radiotherapy to NPC. Therefore, DECT parameters and NPC clinical features can be combined to construct a nomogram with high predictive power and used as a clinical analytical tool.

Key Words： dual-energy CT, nasopharyngeal carcinoma, lymph nodes, radiotherapy sensitivity

285. DPEP1 在炎症性乳腺癌（IBC）中的 G4 链体的表达调控新机制研究

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背景：二肽酶 1（Dipeptidase-1，DPEP1）属于金属依赖性水解酶超家族 M19 家族成员，是一种糖基磷脂酰肌醇锚定、二硫键连接的糖基化同型二聚体，主要存在于细胞顶端的细胞膜部分。DPEP1 能够水解多种二肽和影响β-内酰胺酶活性，还可作为黏附受体将中性粒细胞从血液招募到发炎的肺部和肝脏。作为最具侵袭性的乳腺癌亚型，炎症性乳腺癌（Inflammatory breast cancer，IBC）由免疫抑制肿瘤微环境（TME）驱动。同时，它也是侵袭性肿瘤中最致命和最难治疗的。G-四链体（G-quadruplex, G4）是一种富含鸟嘌呤的 DNA 或 RNA 中形成的特殊的核酸结构，在癌基因的近端启动子中富集，控制着癌基因的复制、转录、翻译和表观遗传调控过程。目前，G4 链体已被认为在乳腺癌中普遍存在并发挥重要作用，可作为分型和潜在治疗靶标。目前是否存在 DPEP1 的 G4 及 IBC 中的调控和功能不清楚。

方法：通过生物信息学分析和多种化学生物学手段，分析预测 IBC 中 G4 结构可能存在的位点，对这些位点的片段序列进行保守性分析，设计 G4 序列的突变序列，合成预测的可能存在的 G4 结构的片段，采用凝胶迁移阻滞实验、免疫荧光、荧光发射光谱和圆二色谱实验验证片段中是否存在 G4 结构。使用 G4 结构稳定剂吡咯他汀（Pyridostatin，PDS）处理细胞，Western blot 检测 DPEP1-G4 蛋白的表达变化。不同解旋酶处理 IBC 细胞，选择调节 DPEP1 最明显的解旋酶与 DPEP1-G4 的 Wild-Type、Mutant 质粒共转染，检测 DPEP1-G4 的表达变化。

结果：通过生物信息学寻找 IBC 中 G4 位点，发现 DPEP1 在不同物种中高度保守，预测得到 3 个可能存在 G4 结构的片段，其中 PQS-1650 的 G-score 值为 32，形成 G4 结构的可能性较大，且其保守性高的物种较多。PQS-1650 的荧光发射光谱结果符合 G4 结构的特征。凝胶迁移结果显示形成 G4 后影响迁移速度，免疫荧光发现 PQS-1650 与 G4 结构抗体共定位。进一步的研究正在进行中。

结论：DPEP1 存在 G4 链体，可能是调节 IBC 恶性进展的机制之一，可望成为 IBC 防治的新靶点。

关键字： DPEP1, 炎症性乳腺癌(IBC), G4 链体

286. 检测范围可调的细胞因子多重检测用于乳腺癌精准诊断

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研究目的：细胞因子 panel 的精准分析可提供一些疾病如癌症、动脉粥样硬化、炎症性肠病等特定阶段的个体化信息。但是，细胞因子体内浓度呈数量级差异，现有商业试剂盒生产工艺不同、检测原理不同、抗体来源不同，新发展技术方法在专业复杂的操作、仪器依赖的信号检测、低效率的酶修饰和酶的固有局限性等方面存在或多或少不足，成为细胞因子多重分析的挑战。因此，需要研制简单可控的工具用于浓度差异较大的细胞因子的多重检测。

材料与方法：为构建多重、可视化、检测范围可调的细胞因子检测工具，我们使用具有优异催化活性的铂包金纳米颗粒（Pt@AuNPs）作为制备所有检测平台的纳米材料，通过对 Pt@AuNPs 表面进行不同工程设计，分别制备了 Pt-1，Pt-2 和 Pt-3。其中，生物素化检测抗体修饰 Pt@AuNPs 制备 Pt-1，生物素化单链 DNA1（ssDNA1）和检测抗体共同修饰 Pt@AuNPs 制备 Pt-2，最后 ssDNA2 修饰 Pt@AuNPs 制备 Pt-3。Pt-2 和 Pt-3 因有 ssDNA1 和 ssDNA2 修饰，因此可在 ssDNA 3 介导下进行树枝状组装。通过一系列功能化修饰，由 Pt-1，Pt-2，Pt-3

和 ssDNA3 组成的“一体化”诊断工具可成功构建。Pt-1、Pt-2 以及 ssDNA3 介导 Pt-2/Pt-3 组装可分别用于构建 ELISA 检测不同浓度的细胞因子。

结果：使用该“一体化”诊断工具，可以对不同浓度的细胞因子进行定量可视化检测。使用基于 Pt-1 的 ELISA 可用于 1.6 ng/mL–10 μg/mL 范围内的细胞因子的定量检测。通过 ssDNA1 调节 Pt@AuNPs 表面检测抗体数量，调节 Pt-2 价态，可调节基于 Pt-2 的 ELISA 的检测范围，可用于检测 3.2 ng/mL–50 μg/mL 范围内的细胞因子。而对于浓度范围在 pg/mL–ng/mL 的细胞因子，则可借助基于 DNA 编码的 Pt-2/Pt-3 组装体的 ELISA。利用该“一体化”诊断工具，可定量检测接受过免疫治疗乳腺癌患者血清中 C 反应蛋白（CRP）、白介素-6（IL-6）和原降钙素（PCT），证实了该“一体化”诊断工具的实际应用能力。

结论：通过对 Pt@AuNPs 进行功能化修饰，我们成功构建了由 Pt-1，Pt-2，Pt-3 和 ssDNA3 组成的“一体化”诊断工具。该诊断工具可用于血清中 CRP、IL-6 和 PCT 的定量检测。相关结果不仅与商业试剂盒检测结果一致性超过 90%，而且因灵敏度更高，使用该工具可观测商业试剂盒检测不到的低浓度细胞因子。借助 Pt@AuNPs 高过氧化物酶类活性，可实现细胞因子可视化检测。同时，结果显示，由 CRP、IL-6 和 PCT 组成的细胞因子 panel 在每个接受过免疫治疗的乳腺癌患者中都有显著差异，而且随疗程的进行高度动态变化，表明该细胞因子 panel 有望成为指导个性化治疗的一个有前途的生物标志物。

关键字 ：细胞因子，多重检测，检测范围可调，乳腺癌，精准诊断

287. Ovarian cancer-derived TGF-β1 induced cancer-associated adipocytes via upregulating TRIB3 to promote pre-metastatic niche

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Ovarian cancer (OC) is prone to metastasis to the adipose tissues. However, the molecular mechanism is still unclear. Here, we observed that omental adipocytes were induced into cancer-associated adipocytes (CAAs) by OC-derived TGF-β1 to establish pre-metastatic niche (PMN) by secreting collagen and fibronectin. Mechanistically, OC-derived TGF-β1 bound to the membrane receptor on adipocytes and activated intracellular signaling by

phosphorylating SMAD3. Activation of TGF-β1/SMAD3 signaling pathway dedifferentiated adipocytes into CAAs by upregulating TRIB3 to suppress the phosphorylation of CEBPβ. Moreover, CAAs secreted more collagen I, collagen VI and fibronectin to remodel extracellular matrix for OC cells adhesion. Pharmacologically blockage of TGF-β1/Smad3 pathway obviously inhibited the formation of CAAs and the establishment of PMN, and thus reduced OC metastatic burden. Our findings implicate that formation of CAAs and PMN in adipose tissues is conducive for implantation of ovarian cancer cells and blockade of TGF-β1/Smad3 signaling pathway could prevent OC omental metastasis.

Key Words ： metastatic tropism; cancer-associates adipocytes; pre-metastatic niche; TRIB3.

288. 基于质谱的结构特异蛋白质及 RNA 糖基化修饰分析

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目的：糖基化是蛋白质、脂质及最近被发现的核酸等生物分子上的常见修饰。与甲基化、乙酰化和磷酸化等小分子修饰的单一结构相比，糖基化具有来自多个结构维度（包括序列、链接、异头和构象）的数以万计的结构，广泛调节生物分子的结构和功能。本研究的目的是基于质谱的蛋白质、RNA 及脂质分子骨架上糖基化修饰的结构特异性定性定量分析及应用。

材料与方法：结构特异理论 N-连接糖数据库构建、化学衍生、色谱分离和/或串联质谱分析。

结果：单糖序列异构、岩藻糖核心/分支/末端位置异构、以及唾液酸链接异构(a2,3 vs. a2,6）被广泛鉴定和观察到；病理条件下的序列和链接异构依赖性差异表达（包括成对上调/下调或下调/上调的极端组合）被广泛观察到。

结论：糖链是以结构特异的方式调节生物分子的结构和功能，相关机制和功能研究以及在诊断和预后生物标志物、药物靶点和药物应用研究中必须全面区分糖链结构。

关键字： 糖蛋白、糖 RNA、糖基化修饰、糖链结构、质谱分析

289. Carbohydrate antigen 199 as a predictive marker in the short-term prognosis of hepatitis B virus-related acute-on-chronic liver failure

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Background and aim: The level of serum CA199 is related to the severity of liver disease. However, the research value of CA199 in the short-term prognosis of patients with HBV-ACLF has not been reported. To explore the value of CA199 in predicting the short-term prognosis of hepatitis B virus-related acute-on-chronic liver failure (ACLF).

Methods: A total of 148 patients with HBV-related ACLF were hospitalized in the Department of Gastroenterology, The General Hospital of Western Theater Command from January 1, 2015 to December 31, 2021. The patients were divided into survival group (n=104) and death group (n=44) according to their survival conditions during hospitalization and 90 days after discharge. The clinical data of the patients were analyzed retrospectively. Binary logistics regression was used to analyze the influencing factors of 90-day prognosis in patients with HBV-ACLF, and a new predictive model was established. Draw the receiver operating characteristic curve (ROC) to evaluate the value of the new scoring model in predicting the 90-day prognosis of patients with HBV-ACLF.

Results: There were significant differences in age, BMI, white blood cell count, Na+, TBIL, INR, AFP, CA199 and MELD scores between the two groups. Multivariate Logistic regression analysis showed that age, BMI, serum Na+, MELD scores and CA199 were independent factors for the short-term prognosis of HBV-ACLF. And establish a prediction model CA199-MELD，R=-6.299+0.2*MELD+0.001*CA99. ROC curve showed that the predictive efficacy of CA199-MELD (AUC=0.753, 95%CI: 0.671∽0.836, P＜0.001) was significantly better than MELD score (AUC=0.720, 95%CI: 0.626∽0.813, P＜0.001). The Yoden index of CA199-MELD was 0.439, the best cut-off value was 0.290, the sensitivity was 0.727, and the specificity was 0.712. Kaplan-Meier survival analysis showed that the 90-day survival rate in patients with higher CA199-MELD scores (≥0.290) was lower (P＜0.001).

Conclusion: After excluding malignant tumors and severe biliary and pancreatic diseases, CA199 can be used as a serum marker for short-term prognosis in patients with HBV-ACLF. CA199-MELD can effectively predict short-term prognosis of HBV-ACLF. It is necessary to expand the sample size to further verify its predictive effectiveness.

Key Words： Carbohydrate antigen 199; Hepatitis B virus; Chronic-on-Acute Liver Failure; Prognosis

290. 肿瘤相关中性粒细胞在 p53R248Q 突变肺癌中免疫抑制作用及机制研究

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目的：探究肿瘤相关中性粒细胞在 p53R248Q 突变肺癌中免疫抑制的作用及机制。

材料与方法： 通过临床数据分析探究肺腺癌病人肿瘤相关性中性粒细胞（TANs）和 p53 突变之间的关系。通过体内外及临床实验探究 p53 热点错义突变 p53R248Q 在驱动肺腺癌 TANs 浸润和极化较 p53 野生型和其他错义突变的区别。通过细胞因子染色等方式探究在 p53R248Q 肿瘤微环境中，CD8+等 T 细胞的存活情况。进一步通过 qPCR 、Western blot、多重免疫荧光等技术明确 TANs 表面相关免疫抑制功能表达的靶点及 p53R248Q 在其表达中有无促进作用。进一步地，通过单细胞测序、ELISA、流式荧光或生化手段，结合体内外功能实验，明确 p53R248Q 驱动 TANs 富集、极化和使免疫抑制靶点表达的关键因子。在此基础上，通过功能缺失或过表达等方式探索由此关键因子介导的信号通路。

结果： 临床数据分析显示肺腺癌病人肿瘤相关性中性粒细胞（TANs）的富集和 p53 突变有显著相关性。体内外细胞环境和临床标本中的研究表明热点错义突变 p53R248Q 在驱动肺腺癌 TANs 浸润和极化较 p53 野生型和其他错义突变具有显著优势，且 p53 突变在增加中性粒细胞浸润的过程中发挥关键作用。而细胞因子染色发现在 p53R248Q 肿瘤微环境中，CD8+ T 细胞的存活及组织中的浸润显著减少。qPCR 、Western blot、多重免疫荧光等技术表明 p53R248Q 显著促进 TANs 表面相关免疫抑制靶点，PD-L1 的表达，明确了 p53R248Q 突变在介导 TANs 免疫抑制功能中的作用及相应的作用靶点。单细胞测序、ELISA、流式荧

光及体内外功能实验则明确了 p53R248Q 促进肿瘤细胞高表达的 IL-8、IL-6 是驱动 TANs 富集、极化和使 PD-L1 表达的关键因子。

结论：肺癌是全球范围内致死率最高的癌症，早期干预对延长肺癌患者生存期意义重大。基因突变及其免疫微环境与肺癌的发生发展、治疗抗性的产生之间的关系是当前肺癌研究的热点。TP53/p53 是肺腺癌中最高频的突变基因，在肿瘤免疫微环境的重塑和免疫治疗中的作用也屡有报道。肿瘤相关性中性粒细胞（TANs）是肿瘤微环境的重要组成部分，可发挥抗癌和抑癌双重作用。但突变 p53 与 TANs 之间的关系、突变 p53 驱动的 TANs 富集对肺腺癌生物学表型的贡献尚未明确。本研究阐明了 p53R248Q 在肺腺癌招募并激活中性粒细胞免疫抑制功能的关键作用及机制，为携带 p53R248Q 突变的肺腺癌患者的免疫治疗的路径选择提供新思路靶点和新思路。

关键字 ：肺腺癌；p53R248Q 突变；肿瘤相关性中性粒细胞

291. PBX1 Increases the Radiosensitivity of Oesophageal Squamous Cancer by Targeting of STAT3

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The radioresistance of oesophageal squamous cell carcinoma (OSCC) is a critical factor leading to a poor prognosis among patients. The expression of PBX1 is abnormally high in a broad range of human tissues, and this gene plays a key role in tumour proliferation. This research intended to explore the radiosensitization of OSCC by silencing PBX1. The OSCC cell lines KYSE450 and KYSE150 were subjected to PBX1 silencing and/or irradiation (IR). Cell proliferation, colony formation, and apoptosis were tested to evaluate the radiosensitization ability of PBX1 silencing. The levels of STAT3 and p-STAT3 in the OSCC cells were tested by Western blotting. Furthermore, KYSE150 cells with or without PBX1 silencing were xenografted into nude mice with or without radiation exposure. Concomitant PBX1 silencing and IR can obviously suppress growth and enhance radiosensitivity in OSCC cells and xenografts. Moreover, the downregulation of PBX1 inhibits the expression of STAT3 and p-STAT3. The downregulation of PBX1 may increase radiosensitivity in OSCC cells and xenografts via the PBX1/STAT3 pathway. Our

findings demonstrate that PBX1 may be a potential target for promoting the effect of radiation therapy in OSCC patients.

Key Words ： Oesophageal squamous cancer; PBX1; Radiosensitivity; STAT3.

292. 广藿香抗肿瘤的研究进展

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【摘要】广藿香是一种常见的传统中草药，临床应用上具有抗菌抗炎，抗氧化等功效，随着研究深入发现其还具有抗肿瘤功效。通过调控凋亡基因及细胞周期等，抑制肿瘤细胞增殖，是基于恶性肿瘤常规治疗副作用及耐药性的辅助用药。本文将从该药物的理化性质，药理作用，抗肿瘤机制，以及对乳腺癌治疗的相关性进行论述。

【关键词】：广藿香；恶性肿瘤；核转录因子；乳腺癌；细胞凋亡

293. Noninvasive Diagnosis of Pulmonary Nodules using a Circulating tsRNAs-based Nomogram

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Purpose

Evaluating accuracy of pulmonary nodules diagnosis could avoid repeated low-dose CT (LDCT)/CT scans or invasive examination, yet remains a main clinical challenge. Recently, tsRNAs have been found dysregulated in various types of cancer and can be detected in 10 kinds of body fluids. Herein, we established a nomogram based on 5 circulating tsRNAs and CT information, aim to improve the early detection and invasiveness prediction of malignant pulmonary nodules.

Methods and Materials

A total of 249 blood samples of patients with pulmonary nodule were selected from three different lung cancer centers between 2020 to 2022. Inclusion criteria included 18-85 years old, single pulmonary nodules detected by LDCT with maximum diameter less than or equal to 2cm, receiving surgery and postoperative pathological diagnosis. Circulating tsRNA signature was established by randomForest. A nomogram was established by combining tsRNA signature and CT information. Then ROC analysis, point-biserial correlation, and calibration plots were conducted to evaluate the diagnostic performance for malignant nodules and invasive adenocarcinoma (IA) prediction.

Results

tRFs&tiRNAs sequence were performed in 5 pairs of tumor tissues and adjacent tissues from five temporarily untreated LUAD patients. Through RT-qPCR, 5 overexpressed tsRNAs were identified in discovery cohort and the diagnostic signature was established by randomForest. Then, a nomogram was developed by combining tsRNA signature and CT information. The tremendous accuracy was identified in internal validation cohort (n=83, AUC=0.930, sensitivity: 100.0%, specificity: 73.8%) and external validation cohort (n=66, AUC=0.943, sensitivity: 100.0%, specificity: 86.8%). Furthermore, the diagnostic ability of our model discriminating invasive malignant lesions from non-invasive nodules was assessed. A robust performance was achieved in the diagnosis of invasive malignant lesions in both training and validation cohorts (discovery cohort, AUC=0.850, sensitivity: 86.0%, specificity: 81.4%; internal validation cohort, AUC=0.784, sensitivity: 78.8%, specificity: 78.1%; and external validation cohort AUC=0.837, sensitivity: 85.7%, specificity: 84.0%).

Conclusion

This novel circulating tsRNA-based diagnostic model emerges potential significance in predicting malignant pulmonary nodules. Application of the model could improve the accuracy of pulmonary nodule diagnosis and optimize surgical plans.

Key Words ： Pulmonary Nodules, Lung cancer, tsRNA, Diagnosis

294. Aberrant fragmentomic features of circulating cell-free mitochondrial DNA enable early detection and prognosis prediction of hepatocellular carcinoma

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Early detection and effective prognostic prediction in patients with hepatocellular carcinoma (HCC) provide an avenue for survival improvement. We sought to develop ultrasensitive and low-cost HCC detection and prognostic models based on the fragmentomic features of circulating cell-free mtDNA (ccf-mtDNA). Capture-based mtDNA sequencing was performed on plasma cell-free DNA samples from 1168 participants, including 571 patients with HCC, 301 patients with chronic hepatitis B or liver cirrhosis (CHB/LC), and 296 healthy controls (HC). Systematic analysis revealed significantly aberrant fragmentomic features of ccf-mtDNA in the HCC group compared with those in the CHB/LC and HC groups. We constructed a random forest algorithm-based HCC detection model using ccf-mtDNA fragmentomic features. The internal and two external validation cohorts demonstrated the efficiency of our model to distinguish patients with early HCC from HC and high-risk populations with CHB/LC, with the corresponding AUC values exceeding 0.983 and 0.981, sensitivity over 89.61% and 89.61%, and specificity over 98.20% and 95.00%, respectively. Thus, the model surpasses the performance of alpha-fetoprotein (AFP) and mtDNA copy number. We also developed an HCC prognosis prediction model using LASSO-Cox regression to select 20 fragmentomic features that exhibited exceptional ability in predicting 1-year, 2-year, and 3-year survival (AUC = 0.8333, 0.8145, and 0.7958, respectively, for the validation cohort). In conclusion, we developed and validated a high-performance and low-cost approach in a large clinical cohort based on aberrant ccf-mtDNA fragmentomic features, with promising clinical translational applications for the early detection and prognostic prediction of patients with HCC.

Key Words ：Hepatocellular carcinoma; circulating cell-free mitochondrial DNA; fragmentomics; early diagnosis; prognosis

295. 聚乙二醇沉淀法筛查巨泌乳素血症 1 例

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目的：探讨 1 例仅有高泌乳素血症(HPRL)，无 HPRL 相关临床表现和影像学证据的疑难案例。

方法：选取泌乳素(PRL)检测结果正常对照血清 1 例，异常结果对照 1 例和该 HPRL 患者 1 例，采用 PEG 6000 沉淀法处理后，取上清液复测 PRL，计算 PRL 回收率(样本处理后的检测浓度/样本处理前的检测浓度)×100%。当回收率≤40%时，判定为巨泌乳素血症。

结果：正常对照、异常结果对照、患者样本原样 PRL 检测结果分别为 257 mIU/L、1060 mIU/L 和 1712 mIU/L，样本经 PEG 6000 沉淀处理后，复测 PRL 结果分别为 256mIU/L、1074mIU/L 和 228mIU/L。三份样本的回收率分别为 99.6%、101.3%和 13.3%。

结论：该例患者样本回收率支持巨泌乳素血症的诊断。

关键字： 高泌乳素血症；聚乙二醇沉淀试验；筛查

296. Diagnostic value of a panle of tumour-associated autoantibodies for breast cancer diagnosis

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Objective

we aimed to assess the diagnostic performance of a panel of autoantibodies against multiple tumor-associated antigens (BRCA2, TRP53, Annexin11, PAPR1, TRIM21, ATAD2, NY-ESO-1 and CAGE) in detection of breast cancer.

Methods

Enzyme-linked immunosorbent assay was applied to detect the sera autoantibodies in a cohort of participants, including healthy medical examiners (n=200), patients with benign breast disease (n=200), and patients with breast cancer carcinoma (n=545). The chi-square test was applied to compare the differences in positivity rates among the groups. A diagnostic classifier model was constructed using the random forest algorithm in machine learning to differentiate between breast cancer and controls, and the diagnostic effectiveness was evaluated by the characteristic working curve (ROC) of the subjects.

Results

The eight autoantibodies demonstrated significantly elevated serum levels in breast cancer compared to both the healthy control group and the benign breast disease group (P<0.05). The AUC of 8 TAAb in discriminating BC from NHC ranged from 0.5735 to 0.7116, the positive rates of 8 TAAb in the BC group ranged from 6.6%~26.1% at the corresponding cut-off values; these values were higher than those in the healthy control group, which ranged from 2.0%~6.0% (P <0 .05). In the BD group, the range of positive rates was (2.5%~10.0%). The Random Forest diagnostic classification model, based on the eight autoantibodies, successfully differentiated between BC and NHC, showed an AUC of 0.9122, 63.4% sensitivity and 90.2% specificity. The performance of the model for differential diagnosis (BC vs BD) revealed an AUC of 0.8605, a sensitivity of 59.6%, and a specificity of 86.1%. When combining all controls (HC+BD) together, the model had an AUC of 0.912, and the sensitivity and specificitywere 78.9% and 90.2%, respectively. Moreover, the percentage of patients in the group with positive 8-TAAB expression, who had a ki-67 value-added index greater than 20% , lymph node metastases, was higher compared to the group with negative 8-TAAB expression. the differences was statistically significant (P< 0.05).

Conclusion

Our study indicated that the panel of autoantibodies to BRCA2, TRP53, Annexin11, PAPR1, TRIM21, ATAD2, NY-ESO-1 and CAGE as serum biomarkers have the potential to help detect breast cancer.

Key Words ： breast cancer; autoantibody; tumor-associated antigen; ;diagnosis

297. ERBB2 驱动的细胞运动蛋白 1 与肺腺癌免疫微环境及骨转移相关分析

李茂琛、王布、张红霞、张志华、张秀珑

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目的：肺腺癌（ lung adenocarcinoma，LUAD）是肺癌的主要类型之一，具有较高的发病率和死亡率，而骨转移的发生往往提示着预后不良，目前免疫治疗在肺癌的治疗中发挥着重要作用，ERBB2 驱动的细胞运动蛋白 1(MEMO1)在肺癌中研究较少，在免疫微环境的调节机制尚不清楚，我们旨在探索 ERBB2 驱动的细胞运动蛋白 1(MEMO1)在免疫微环境及肺腺癌骨转移血清中的表达，为免疫治疗提供参考。

方法：对癌症基因组图谱 (TCGA)中数据进行差异分析和生存分析；从 muTarget 数据库中获得与 MEMO1 表达变化相关的基因突变，从 UALCAN 获得启动子甲基化数据；Timer2 数据库用于评估免疫浸润，最后收集 12 例肺腺癌（6 例肺腺癌伴骨转移，6 例肺腺癌非骨转移）患者血清进行蛋白组学分析。

结果：MEMO1 在大多数恶性肿瘤中表达升高，在肺腺癌中表达升高（P＜ 0.001）；PRKG2 的突变导致 MEMO1 表达下调，KCNA1、PLCG2、PLCE1、SLC12A5、POTEH 等基因突变后其表达上调；此外 MEMO1 的高表达与不良预后有关；CD8+T 细胞的骨髓浸润程度与 MEMO1 的表达呈正相关（r=0.028,P＜0.001）；B 细胞（r=-0.023,P＜0.001）、CD4+T 细胞（r=-0.255,P＜0.001）、巨噬细胞（r=-0.052,P＜0.001）、中性粒细胞（r=-0.018,P＜0.001）、树突状细胞（r=-0.211,P＜0.001）与 MEMO1 的表达呈负相关；MEMO1 的表达与 B 细胞、NK 细胞的相关基因具有相关性；MEMO1 拷贝变异数与 B 细胞、CD4+ T 细胞、巨噬细胞、中性粒细胞和树突状细胞的浸润程度密切相关；MEMO1 在肺腺癌骨转移患者血清中高度表达。

结论：MEMO1 参与了免疫微环境的调控，在肺腺癌骨转移患者血清中表达升高，提示着预后不良，为肺腺癌骨转移的免疫治疗提供参考。

关键字： 肺腺癌；骨转移；免疫微环境；MEMO1

298. GSDMD as a Biomarker and Target for the Diagnosis, Prognosis, and Therapy of Digestive Cancers

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Aim: GSDMD is a vital regulator of pyroptosis, whereas its influence on the immune, apoptosis, and prognosis of digestive cancers was not well defined.

Materials and methods: The online databases were used for analysis. Oncomine and TIMER databases were used to analyze the expression of GSDMD. The prognostic value of GSDMD expression was calculated by the Kaplan-Meier plotter. We also analyze the association between tumor infiltrated lymphocytes and the copy number variations (CNV) of GSDMD by the TIMER database. Protein-protein interaction (PPI) and enrichment analysis were also performed with STRING, LinkFinder, and Metascape databases respectively.

Results: We found that GSDMD was higher expressed in the tumor tissues of CHOL, ESCA, LIHC, PRAD, and STAD, compared with the adjacent normal tissues. The higher expression of GSDMD was correlated with better overall survival of stomach (HR=0.63, 95%CI=0.45-0.89, P=0.007) and rectum cancer (HR=0.13, 95%CI=0.02-0.97, P=0.019), whereas opposite for pancreatic cancer, exerting complicate function on prognosis. The roles of GSDMS enriched in immune response, cellular response to external stimulus, and defense response to other organisms, demonstrating that GSDMD could promote the infiltration of tumor infiltrated lymphocytes (TILs). GSDMD coexpressed genes were mainly enriched in cellular metabolism, biological processes, and immune regulation.

Conclusions: GSDMD is a favorable prognostic factor for stomach and rectum cancers, and regulates the pyroptosis, apoptosis, and infiltration of tumor immunocytes of digestive cancers. It is expected to become an immunotherapy target for digestive cancers.

Key Words: digestive cancers, GSDMD, pyroptosis, prognosis, immunotherapy

299. RYR1 基因突变和表达异常在胃癌发生发展中作用机制研究

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目的：拟探讨 RYR1 基因与胃癌发生发展的相关性和作用机制。

方法：分析 TCGA 胃癌患者数据，并对 81 例天津医科大学肿瘤医院胃癌患者进行高通量靶向测序和转录组测序，收集临床病理信息，比较 RYR1 基因突变与表达之间相关性，分析 RYR1 基因与临床病理特征的关系及对胃癌患者预后的影响，并通过构建 RYR1 过表达细胞系探索 RYR1 促进胃癌发生发展的作用机制。

结果：在 TCGA 胃癌患者中，RYR1 突变率在亚洲人群更高（12%vs.8%），在天津医科大学肿瘤医院胃癌患者中，RYR1 基因突变率在 435 个癌症相关基因的检测 panel 中位于第 9 位，突变率 33%，是前 10 位中唯一的钙离子相关基因 。RYR1 突变与表达水平显著负相关（P＜0.0001），但 RYR1 高表达患者的总生存期显著差于低表达 RYR1 患者（P =0.042），且肿瘤局部浸润更深（P=0.017）。细胞学结果提示，RYR1 的激活突变和过表达会促进细胞增殖、迁移，减少凋亡，且 RYR1 过表达可下调胃癌细胞对化疗药物的敏感性。抑制 RYR1 介导的钙离子过度释放可以抑制其恶性生物学行为，并逆转化疗耐药。

结论：RYR1 基因在亚洲胃癌患者中突变率较高，RYR1 突变与表达水平显著负相关，而 RYR1 高表达是胃癌新的预后预测标志物。RYR1 过表达可刺激内质网钙离子释放而促进胃癌恶性进展，并产生化疗抵抗。而靶向阻断 RYR1 活性可抑制胃癌细胞的增殖、迁移和侵袭，并逆转化疗药抵抗，为胃癌的联合治疗提供了新思路。

关键字： 胃癌 RYR1 基因 基因突变 基因表达 钙离子

300. DNA/RNA dual sequencing indicated ATM mutations concomitant with driver alterations promoted proliferation and aggressiveness of papillary thyroid carcinoma

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Background: Papillary thyroid carcinoma is driven by multiple types of genetic alternations. Single driver gene variation cannot comprehensively explain the heterogeneity in the development and progression of thyroid carcinoma.

Methods: 182 cases of thyroid nodules and 81 cases of adjacent normal tissues were enrolled to detect genetic alterations of 54 genes using DNA/RNA dual sequencing. 182 cases were divided into two groups of thyroid carcinomas and benign nodules. Benign nodules were confirmed by fine needle aspiration (FNA)-based cytological detection and thyroid carcinomas were defined by pathological test.

Results: A total of 196 high-risk variants and four fusion types among 31 oncogenes were detected, including DNA damage repairing genes, metabolism related genes, chromosomal modifier genes, and immune related genes, etc. Minor allele frequencies (MAF) of mutations in BRAF, TERT, RET, ATM and GGT1 were significantly higher in cancer tissues than that in benign nodules. Among them, mutation of ATM was positively correlated with lymph node metastasis. ATMMUT was a high-frequency mutation in papillary thyroid carcinoma and the mutation site detected in the study was predicted to be pathogenic. ATMMUT was accompanied by concomitant driver alterations in BRAF, TERT genes and fusions. And ATM deficiency in thyroid epithelial cells and thyroid cancer cells harboring concomitant BRAFV600E, KRASG12R or CCDC6-RET displayed higher proliferative capacity, lower apoptotic rate and more aggressive potency.

Conclusions: DNA/RNA dual sequencing and experiments in vitro indicated that ATM mutations concomitant with driver alterations might be a valuable biomarker to predict more invasive phenotypes of papillary thyroid carcinoma.

Key Words ： thyroid cancer; mutation; fusion; next generation sequencing

301. Optical Genome Mapping Reveals the Landscape of Structural Variations and Their Clinical Significance in HBOC-Related Breast Cancer

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Background: Structural variations (SVs) are common genetic alterations in the human genome. However, the profile and clinical relevance of SVs in patients with hereditary breast and ovarian cancer (HBOC) syndrome (germline BRCA1/2 mutations) remains to be fully elucidated.

Methods: Twenty HBOC-related cancer samples (5 breast and 15 ovarian cancers) were studied by optical genome mapping (OGM) and next-generation sequencing (NGS) assays.

Results: The SV landscape in the 5 HBOC-related breast cancer samples was comprehensively investigated to determine the impact of intra-tumor SV heterogeneity on clinicopathological features and on the pattern of genetic alteration. SVs and copy number variations (CNVs) were common genetic events in HBOC-related breast cancer, with a median of 212 SVs and 107 CNVs per sample. The most frequently detected type of SV was insertion, followed by deletion. The 5 HBOC-related breast cancer samples were divided into SV^{high} and SV^{low} groups according to the intra-tumor heterogeneity of SVs. SV^{high} tumors were associated with higher Ki-67 expression, higher HRD scores, more mutated genes, and altered signaling pathways. Moreover, 60% of the HBOC-related breast cancer samples displayed chromothripsis, and 8 novel gene fusion events were identified by OGM and validated by transcriptome data.

Conclusions: These findings suggest that OGM is a promising tool for the detection of SVs and CNVs in HBOC-related breast cancer. Furthermore, OGM can efficiently characterize chromothripsis events and novel gene fusions. SV^{high} HBOC-related breast cancers were associated with unfavorable clinicopathological features. SVs may therefore have predictive and therapeutic significance for HBOC-related breast cancers in the clinic.

Key Words： HBOC; breast cancer; optical genome mapping; structural variation; BRCA1/2; chromothripsis

302. CypA regulated by TAF15/STAT5A/miR-514a-3p feedback loop and drives EMT-mediated invasion and metastasis in ovarian cancer

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Cyclophilin A (CypA) isa peptidyl-prolyl isomerase thathas been confirmed to take part participatesin multiple cancer events a peptidyl-prolyl isomerase, but the molecular mechanisms of abnormal expression and regulation of CypA in ovarian cancer (OC) have never been consideredremains to be characterized. This studyHere, we identifiesd CypA as a key driver of epithelial mesenchymal transition (EMT) in ovarian cancer and exploresd its theregulatory mechanisms that underly this process. We found show that CypA iwas upregulated in tissues and serum of ovarian cancer patients and that CypAthe overexpression of CypA was relatedcorrelates with to the poor prognosis of patients. CypAfacilitates tumor growth and metastasis in vivo in a ? model and in vitrostudiessuggest a mechanism, showing thatMeanwhile, CypA plays a pro-tumor role in vitro and may accelerates the EMT process of ovarian cancer cell epithelial mesenchymal transition by activating as through PI3K/AKT signaling pathway, and its facilitates tumor growth and metastasis in vivo. Mechanistic studies showed that STAT5A bindsbound to pri-miR-514a-3p and inhibitsed its activity, whereas miR-514a-3p directly bindsbound to the 3′-UTR of CypA to suppress its expression, resulting in STAT5A promoting the expression of CypA, forming the STAT5A/miR-514a-3p/CypA axis. Furthermore, immunoprecipitates and mass spectrometry analysis identifies aied CypA interactions with TAF15 that, and its stabilizesd TAF15 by suppressing its proteasome degradation and, promoted its entry into the nucleus. While STAT5A iwas positively regulated by TAF15. (????? Don’t follow) Our findings unveil identify a novel feedback loop of for CypA that drives the EMT and ovarian tumor growth and metastasismalignant progression via aTAF15/STAT5A/miR-514a-3p pathwayin ovarian cancer,

and facilitates the release of CypA into the extracellular, which provides a promising therapeutic target for OC treatment and a diagnostic biomarkerr for diagnostic.

Key Words ： CypA, TAF15, STAT5A, miR-514a-3p

303. Semaphorin4F 是胃癌临床进展和预后的潜在生物标志物

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研究目的：Semaphorin4F（Sema4F）是一个成员的 semaphorin 家族，并表现出重要的调节功能，在癌症生物学。本研究旨在通过临床资料、实验室研究和生物信息学方法，探讨 Sema4F 在胃癌（GC）中的预后价值和生物学功能。

材料与方法：我们基于几个数据库，包括肿瘤免疫评估资源（TIMER），基因表达谱交互分析 2（GEPIA 2），伯明翰亚拉巴马大学癌症数据分析门户（UALCAN）和 Kaplan-Meier 绘图仪，研究了 Sema4F 相关数据和 GC 患者的预后价值。采用逆转录定量聚合酶链反应（RT-qPCR）、免疫印迹和免疫组织化学方法检测 Sema4F 在细胞系和肿瘤组织中的表达。使用 Kaplan-Meier 生存和考克斯回归分析回顾性分析 Sema4F 表达对患者总生存的预后价值。此外，我们还利用京都基因和基因组百科全书（KEGG）、基因本体（GO）和基因集富集分析（GSEA）分析来探索 Sema4F 在 GC 中的相关通路。

结果：Sema4F 在癌组织和癌细胞系中的表达均明显增强。此外，Sema4F 高表达与各种临床病理数据呈正相关，并独立预测胃癌总生存期的预后不良。我们的功能富集分析显示 Sema4F 主要参与氧化磷酸化和肿瘤相关信号通路。

结论：Sema4F 可能是一个有价值的胃癌预后生物标志物和新的靶点。

关键字： 胃癌，预后，生物学功能，生物标志物

304. Throwing and manipulating and cheating with a DNA nano-dice

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Artificial molecular machines have captured the imagination of researchers, given their clear potential to mimic and influence human life. Key to behavior simulation is to reproduce the specific properties of physical or abstract systems. Dice throwing, as a stochastic model, is commonly used for result judgment or plan decision in real life. In this perspective we utilize DNA cube framework for the design of a dice device at the nanoscale to reproduce probabilistic events in different situations: equal probability, high probability, and low probability. We first discuss the randomness of DNA cube, or dice, adsorbing on graphene oxide, or table, and then explore a series of events that change the probability through the way in which the energy released from entropy-driven strand displacement reactions or changes in intermolecular forces. As such, the DNA nano-dice system provides guideline and possibilities for the design, engineering, and quantification of behavioral probability simulation, a currently emerging area of molecular simulation research.

Key Words ：Molecular device, DNA framework, Graphene, Probability, Strand displacement reaction

305. 基于 KEAP1/PGAM5/AIFM1 调节氧死亡途径参与肝癌发生发展及人参皂苷 Rb1 的干预作用

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目的：探讨氧死亡对肝癌患者的临床意义以及人参皂苷 Rb1（Gn-Rb1）对 HepG2 细胞氧死亡的影响及分子机制。

方法：生信分析氧死亡的枢纽 PGAM5 表达对肝癌患者生存周期的影响。临床实验选取了辽宁省肿瘤医院就诊的 8 例肝癌患者的肝癌组织与癌旁组织，通过 Western Blot 以及 RT-qPCR 检测氧死亡相关基因蛋白与 mRNA 的表达情况。细胞实验选取 HepG2 细胞，并予以人参皂苷 Rb1 干预，分为 control 组与 Gn-Rb1 组，通过细胞克隆形成实验反映 HepG2 细胞的集落形成能力；通过细胞划痕实验反映 HepG2 细胞的迁移能力；通过 ELISA 检测 ROS 生成反映细胞氧化应激水平；微板法检测 LDH 反映细胞损伤情况；通过 Western Blot 以及 RT-qPCR 检测氧死亡关键蛋白与基因的表达。

结果：生信分析发现 PGAM5 高表达肝癌患者的总生存时间更长（P<0.05）。在临床肝癌与癌旁组织样本中，发现相较于癌旁组织，在 mRNA 水平上，肿瘤组织 KEAP1 与 PGAM5 表达显著降低，NRF2 表达显著升高（P<0.01）；在蛋白水平上，肿瘤组织 KEAP1 与 PGAM5 表达显著降低，NRF2 与 p-AIFM1 表达显著升高（P<0.05）。而细胞予以 Gn-Rb1 干预后，相较于 control 组，Gn-Rb1 显著抑制了 HepG2 细胞的迁移能力与集落形成能力（P<0.01），并升高了 ROS 与 LDH 水平。相比于 control 组，在 mRNA 水平上，Gn-Rb1 组 KEAP1、PGAM5 表达显著升高，NRF2 表达显著降低（P<0.05）；在蛋白水平上，Gn-Rb1 组 KEAP1、PGAM5 表达显著升高，p-AIFM1、NRF2 表达显著降低（P<0.01）。

结论：肝癌组织中氧死亡被抑制，而 Gn-Rb1 通过调控 KEAP1/PGAM5/AIFM1 通路有效干预氧死亡的发生，从而达到抗肝癌的目的。

关键字： 人参皂苷 Rb1；肝癌；氧死亡

306. 肿瘤相关自身抗体检测在乳腺良恶性结节鉴别诊疗中的价值

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目的：探讨肿瘤相关自身抗体检测联合乳腺超声、钼靶检查在乳腺良恶性结节鉴别诊疗中的价值。

材料与方法：纳入 197 例患有乳腺结节的女性患者作为研究对象，收集病例的一般临床资料、术前乳腺超声及钼靶检测结果，通过酶联免疫吸附方法对其血清中肿瘤相关自身抗体进行检测。以术后病理结果为金标准，使用单因素和多因素 logistic 回归分析确定用于鉴别

乳腺良恶性结节的预测变量并绘制列线图及预测模型的受试者特征曲线（Receiver operating characteristic，ROC）。

结果：肿瘤相关自身抗体组合（5-combination of tumor-associated autoantibodies，5-TAAbs）在鉴别乳腺良恶性结节中总特异性为 95.83%、灵敏度为 46.53%，受试者特征曲线下面积（Area under curve, AUC）为 0.722。在术前乳腺影像学检测（乳腺超声、乳腺钼靶检测）基础上增加 5-TAAbs 检测可将乳腺良性结节诊断正确率提高 10.42%，乳腺恶性结节的误诊率降低 14.85%。将术前乳腺超声、钼靶检测及 5-TAAbs 检测三者联合建立风险模型，其 AUC 为 0.957，敏感度、特异性分别为 85.42%、95.06%。

结论：5-TAAbs 对乳腺癌的早期诊断具有一定临床应用价值，并且可作为乳腺结节患者术前乳腺超声、钼靶检测的有效辅助工具。

关键字： 乳腺结节，肿瘤相关自身抗体，乳腺超声，乳腺钼靶，鉴别诊断

307. Survey Study on Areas of Interest Among Highly Educated Female Patients with Non-Advanced Breast Cancer

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Objective: This study aimed to investigate the specific concerns and areas of interest among highly educated female patients with non-advanced breast cancer.

Methods: A cohort of 156 female patients with non-advanced breast cancer, who sought medical care at Nanjing Drum Tower Hospital on March 8, 2021, was selected as the study population. A structured questionnaire survey was administered to collect and analyze data related to patients' educational backgrounds, age, marital status, reproductive history, and their specific areas of interest.

Results: Among the 156 non-advanced breast cancer patients, 128 individuals had their staging and surgical information verified. Among these patients, 36 had attained a university education or higher (classified as highly educated). Furthermore, 41.7% of patients were under the age of 40,

72.2% were covered by Nanjing City Employee Medical Insurance, and 72.2% had a body mass index (BMI) ranging from 18.5 to 23.9. Among the highly educated non-advanced breast cancer patients who had detailed staging and surgical data available (28 cases), 46.4% underwent breast-conserving surgery, 46.4% opted for mastectomy, and 7.1% underwent reconstructive surgery. Additionally, 89.3% of these patients were diagnosed at an early stage, while 10.7% were diagnosed at an intermediate stage. Socioeconomic and pathological analysis revealed differences among patients with varying educational backgrounds (128 cases). Highly educated patients accounted for the highest proportion (35.7%) among patients under 40 years old, and 75% of highly educated patients with medical insurance were covered by Nanjing City Employee Medical Insurance. Highly educated patients tended to have fewer offspring. In the income group of 200,000 to 500,000, highly educated patients constituted the largest proportion (28.6%). The disparities among these educational groups were all statistically significant, with p-values <0.05. Regarding the areas of interest among the 156 surveyed patients, over 90% expressed interest in topics encompassing dietary guidance, lifestyle recommendations, rehabilitation and exercise, symptoms indicative of recurrence and metastasis, risk assessment for recurrence and mortality, breast cancer prevention, available treatment modalities for breast cancer, and the significance of post-recurrence and metastasis treatment.

Conclusion: Highly educated female patients with non-advanced breast cancer were more likely to be younger, have fewer children, and higher family incomes (all with p-values <0.05). There were no substantial differences in areas of interest between highly educated breast cancer patients and those with lower educational backgrounds. Clinical healthcare providers should prioritize effective communication with patients regarding breast cancer prevention, treatment, and post-treatment lifestyle guidance.

Key Words ： Keywords: Highly educated women; Non-advanced breast cancer; Questionnaire survey.

308. 第二代选择性 JAK2 抑制剂对食管癌细胞增殖、转移及凋亡的作用及其相关机制

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目的：食管癌（esophageal cancer，EC）是全球最常见的恶性肿瘤之一， 目前我国食管癌 5 年生存率仍不足 30%。由于食管癌容易产生耐药性，因此寻找新的抗食管癌药物，对于改善食管癌患者的生活质量及延长生存时间有着**十分**重要的意义。本实验通过研究第二代选择性 JAK2 抑制剂 Fedratinib 对人食管癌细胞株 Eca109 和 KYSE150 的增殖及转移抑制作用和对细胞周期及凋亡的影响，以及 Vimentin、Cyclin D1、Survivin 蛋白表达的影响，进一步探讨 Fedratinib 对食管癌细胞的作用及其相关机制，从而为食管癌治疗提供潜在的抗癌药物及相应的理论依据。

材料与方法：1 细胞培养后，应用普通光学显微镜观察 Fedratinib 作用于食管癌细胞 Eca109 和 KYSE150 后细胞的形态学变化。 2 不同浓度的 Fedratinib 作用于食管癌细胞 Eca109 和 KYSE150 后，应用 Cell Counting Kit-8（CCK-8）法测定细胞光密度值(opticaldensity，OD)，计算生长抑制率，研究 Fedratinib 对食管癌细胞增殖的影响。 3 应用流式细胞仪技术(flow cytometry，FCM)研究 Fedratinib 对食管癌细胞 Eca109 和 KYSE150 凋亡率的影响。4 应用流式细胞技术检测 Fedratinib 对食管癌细胞 Eca109 和 KYSE150 细胞周期分布影响。5 蛋白免疫印迹法(Western blot)检测药物作用后食管癌细胞 JAK2/Stat3 信号通路相关蛋白 JAK2、p-JAK2、stat3、P-Stat3 及 Vimentin、Cyclin D1、Survivin 蛋白表达变化。 6 RT-PCR 检测 Vimentin mRNA、Cyclin D1 mRNA、Survivin mRNA 的变化。7 利用瞬时质粒转染方法构建过表达 STAT3 的食管癌细胞株模型,并通过 qRT-PCR 和 Western blot 验证。8 利用 CCK-8、平板克隆实验及 Transwell 检测过表达 STAT3 后对 Fedratinib 诱导的食管癌细胞增殖、迁移能力及凋亡的影响。9. 利用 Western blot 及 RT-PCR 技术检测过表达 STAT3 后 Fedratinib 对 JAK2/STAT3 信号通路相关蛋白表达的影响及其下游靶基因的 mRNA 水平变化。

结果：1. Fedratinib 呈时间和剂量依赖性抑制食管癌细胞的增殖和迁移能力。 2. Fedratinib 能够将食管癌细胞阻滞在 G2/M 期，同时促进癌细胞凋亡。3. Fedratinib 处理食管癌细胞后 p-JAK2、p-Stat3、Vimentin、Cyclin D1、Survivin 蛋白表达水平随药物浓度增加而

下降 (P<0．05),并且较对照组相比有显著性差异(P<0．01)。4. 过表达 STAT3 可部分逆转 Fedratinib 对食管癌细胞增殖和迁移能力的抑制。

结论：Fedratinib 靶向 JAK2/STAT3 信号通路调控食管癌细胞内信号传导机制,最终通过下调 Vimentin 、Cyclin D1 及 Survivin 的表达影响食管癌细胞的增殖、转移并诱导癌细胞凋亡。

关键字 ：JAK2 抑制剂、食管癌

309. Lopinavir promotes anoikis and suppresses gastric cancer metastasis by targeting HuR-circSPECC1-ATG4B pathway

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Background: Metastasis account for the poor prognosis of patients with gastric cancer, however, there is no effective therapeutic strategy for the prevention of metastasis. Anoikis is an important obstacle for metastasis, and tumor cells acquire resistance to it by enhancing autophagic flux. Uncovering the mechanism of autophagy-mediated anoikis resistance will present potential diagnostic marker and therapeutic target in metastatic GC.

Methods: In the current study, autophagy-related genes were screened and ATG4B was identified to mediate anoikis resistance. Given the advantages of circRNA as a diagnostic marker for various diseases, RIP-seq was performed to identify the circRNA that may directly regulate ATG4B. MeRIP-qPCR was used to confirm the potential regulator of the circRNA. Furthermore, molecular docking and virtual screening were carried out to identify a potential inhibitor to block the pathway.

Results: ATG4B dramatically increased the anoikis resistance of GC cells in vitro, and its level was positively correlated with the degree of metastasis in GC tissues. The abnormally decreased circSPECC1 in GC tissues was identified as a novel ATG4B-interacted circRNA which promotes the proteasome-dependent degradation of ATG4B. Mechanically, circSPECC1 acted as scaffold to facilitate the binding of ATG4B and E3 ligase RNF5, promoting ATG4B ubiquitylation and

degradation. Moreover, circSPECC1 was highly modified by m6A in gastric cancer cells, and was recognized and dramatically inhibited by HuR. Thus, the HuR-circSPECC1-ATG4B signaling axis was confirmed in anoikis resistance and metastasis. Furthermore, the FDA-approved compound Lopinavir was identified to efficiently suppress the above pathway, enhancing anoikis and relieved metastasis in vitro and in vivo.

Conclusion: This study uncovers a novel pathway in anoikis resistant gastric cancer cells, providing a potential diagnostic marker and clinical intervention strategy for GC metastasis.

Key Words： Anoikis, Metastasis, ATG4B, Lopinavir, Gastric Cancer

310. KIAA1429 facilitates metastasis via m6A-YTHDC1-dependent RND3 down-regulation in hepatocellular carcinoma cells

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Background: N6-methyladenosine (m6A), a dynamically reversible modification in eukaryotic RNAs, modulates gene expression and pathological processes in various tumors. KIAA1429, the largest component of the m6A methyltransferase complex, plays an important role in m6A modification. However, the underlying mechanism of KIAA1429 in hepatocellular carcinoma (HCC) remains largely unknown.

Methods: Immunohistochemical assay was performed to examine the expression of KIAA1429 in HCC tissues. Transwell, wound healing and animal experiments were used to investigate the influence of KIAA1429 on cell migration and invasion. The mRNA high-throughput sequencing (RNA-seq) and methylated RNA immunoprecipitation sequencing (MeRIP-seq) were performed to screen the downstream target of KIAA1429. RNA stability assays, RNA immunoprecipitation assay (RIP), MeRIP-qPCR and luciferase assay were used to evaluate the relationship between KIAA1429 and the m6A-modified genes.

Results: Our data showed that the expression level of KIAA1429 was significantly higher in HCC tissues than in adjacent tissues, and the upregulation of KIAA1429 could promote HCC metastasis

in vitro and in vivo. Mechanistically, we confirmed that KIAA1429 negatively regulated the tumor suppressor, Rho family GTPase 3 (RND3), by decreasing its mRNA stability in coordination with the m6A reader YTHDC1. Moreover, we demonstrated that KIAA1429 could regulate the m6A modification of RND3 mRNA via its RNA binding domain.

Conclusion: Our data indicated that KIAA1429 exerted its oncogenic role by inhibiting RND3 expression in an m6A-dependent manner, suggesting that KIAA1429 might be a potential prognostic biomarker and therapeutic target in HCC.

Key Words ： m6A methylation, KIAA1429, YTHDC1, mRNA stability, RND3

311. IGFBP5 is an ROR1 ligand promoting glio blastoma invasion via ROR1/HER2-CREB signaling axis

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Diffuse infiltration is the main reason for therapeutic resistance and recurrence in glioblastoma(GBM). However, potential targeted therapiesforGBM stem-like cell (GSC) which is responsible for GBM invasion are limited. Herein, we report Insulin-like Growth Factor-Binding Protein 5 (IGFBP5) is a ligand for Receptor tyrosine kinase like Orphan Receptor 1 (ROR1), as a promising target for GSC invasion. Using a GSC-derived brain tumor model, GSCs were characterized into invasive or non-invasive subtypes, and RNA sequencing analysis revealed that IGFBP5 was differentially expressed between these two subtypes. GSC invasion capacity was

inhibited by IGFBP5 knockdown and enhanced by IGFBP5 overexpression both in vitro and in vivo, particularly in a patient-derived xenograft model. IGFBP5 binds to ROR1 and facilitates ROR1/HER2 heterodimer formation, followed by inducing CREB-mediated ETV5 and FBXW9 expression, thereby promoting GSC invasion and tumorigenesis. Importantly, using a tumor-specific targeting and penetrating nanocapsule-mediated delivery of CRISPR/Cas9-based IGFBP5 gene editing significantly suppressed GSC invasion and downstream gene expression, and prolonged the survival of orthotopic tumor-bearing mice. Collectively, our data reveal that IGFBP5-ROR1/HER2-CREB signaling axis as a potential GBM therapeutic target.

Key Words： Glioblastoma (GBM), GBM stem-like cell (GSC), invasion, IGFBP5, nanocapsules, Cas9/sgIGFBP5,

312. 游离 PSA 与总 PSA 比值在前列腺疾病诊断中的应用及“诊断灰区”探讨

何平

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目的：探究游离前列腺特异抗原（f-PSA）与总前列腺特异抗原（t-PSA）的比值（f/t）在临床前列腺类疾病方面的实际应用以及 t-PSA 诊断灰区的探讨。

方法：100 研究对象分三组：健康对照组 42 例，前列腺**增生**（BPH）组 28 例，前列腺癌（PCa）组 30 例。通过电化学发光法测定 t-PSA、f-PSA 结果，并进行计算求 f/t 值。

结果：PCa 组和 BPH 组 t-PSA 值和 f/t 比值与健康对照组之间差异有统计学意义（P<0.05），PCa 组和 BPH 组之间 t-PSA 值和 f/t 比值差异有统计学意义（P<0.05）；当 t-PSA 在 4.0-16.0mg/ml 之间（诊断灰区）时，PCa 组和 BPH 组之间血清 t-PSA 差异无统计学意义（P>0.05），f/t 比值差异有统计学意义（P<0.05）；但当 t-PSA 扩大到 4.0-20.0mg/ml 区间时，PCa 组和 BPH 组之间 t-PSA 差异已有统计学意义（P<0.05）。

结论：f/t 比值作为 t-PSA 的辅助指标，在处于诊断灰区的前列腺疾病能显著提高前列腺癌的鉴别诊断效能。t-PSA4.0-16.0mg/ml 作为诊断灰区较为合适。

关键字： 关键词:总前列腺特异抗原；比值；诊断灰区

313. Aberrant fragmentomic features of circulating cell-free mitochondrial DNA as novel biomarkers in cancer patients

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Fragmentomic features of circulating cell free mitochondrial DNA (ccf-mtDNA) including fragmentation profile, 5' end base preference and motif diversity are poorly understood. Here, we generated sequencing data in 788 plasma samples and found that fragmentomic features of ccf-mtDNA were remarkably different from those of circulating cell free nuclear DNA. Furthermore, region-specific fragmentomic features of ccf-mtDNA were observed, which was associated with protein binding, base composition and special structure of mitochondrial DNA. Aberrant fragmentomic features were observed in six cancer types compared to non-cancer controls. Based on the fragmentomic features of ccf-mtDNA, we built three highly accurate cancer detection models with AUC of 0.97319, 0.9402 and 0.9525. The accuracy of tissue-of-origin classification ranging from 77.78% to 97.62% for the six cancer types was obtained. Altogether, our study comprehensively describes cancer-specific fragmentomic features of ccf-mtDNA and provides a proof-of-principle for the ccf-mtDNA fragmentomics-based cancer detection and tissue-of-origin classification.

Key Words： Fragmentomics; circulating cell-free mitochondrial DNA; multi-cancer; biomarker

314. Expression, prognostic analysis and biological pathways of CNPY2 in pan-cancer analysis

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Background and Objective: CNPY2 is a novel secretory pro-angiogenic factor, a member of the canopial protein family, and its C-terminus contains a 4-amino acid sequence similar to the classical KDEL(Lys-Asp-Glu-Leu-COO-) motif retained by the endoplasmic reticulum. To

investigate the expression of canopy homolog 2 (CNPY2) in cancer cells compared with normal cells, and its prognostic analysis. Moreover, to study its regulatory pathways in cancer tissues.

Methods: The expression level of CNPY2 in pan-cancer tissues and their normal tissues was compared using the cBioPortal (https://www.cbioportal.org/gene) through the data acquired from The Cancer Genome Atlas (TCGA). The standardized pan-cancer dataset was downloaded from the UCSC (https://xenabrowser.net/) database, and the expression data of CNPY2 gene were extracted for prognostic analysis. Gene Expression Correlation Analysis database GEPIA (http://gepia.cancer-pku.cn/) combined with R language were used to analyze Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG).

Results: Compared with the corresponding normal tissues, the expression level of CNPY2 was significantly higher in most tumors, except Kidney Chromophobe. Based on the data acquired from UCSC, high expression level of CNPY2 was associated with poor prognosis of 10 types tumors, including Glioma, Pan-kidney cohort, Liver hepatocellular carcinoma, etc. However, it was lower level in Pancreatic adenocarcinoma, Ovarian serous cystadenocarcinoma, and Testicular Germ Cell Tumors. CPNY2 expression level is inversely correlated with the infiltration of immune cell in most tumors. Significant expression of CNPY2 was observed in tumor infiltrating lymphocytes, such as B cells, CD4 T cells, CD8 T cells, neutrophils, and dendritic cells (DCs) in four tumors (Breast Cancer, Lung Adenocarcinoma, Thymoma, Prostate Cancer). GO analysis showed that CNPY2 was highly enriched in unfolded protein binding in molecular function, and CNPY2 was also highly enriched in endoplasmic reticulum-containing protein complexes in cellular component, at the same time, CNPY2 was highly enriched in protein folding in biological process. In the KEGG pathway analysis based on CNPY2 binding and interaction, the role of CNPY2 in tumorigenesis is mainly involved in "protein processing in endoplasmic reticulum", "protein transport" and "N-glycan biosynthesis", especially the first one.

Conclusion: This study showed that CNPY2 expression was significantly elevated in most tumors, and its higher expression level was associated with poor prognosis in a variety of tumors. It is also significantly expressed in tumor-infiltrating lymphocytes. It may play an important and fundamental role in pan-cancer genesis and progression by regulating processes such as processing, folding and transport of proteins in the endoplasmic reticulum. Exploring clearly the regulatory mechanism of CNPY2 in tumor tissues will provide more directions for tumor therapy.

Key Words： CNPY2; pan-cancer; protein folding

315. PFDN5 regulates tumor immune microenvironment and plays a dual role in breast cancer in tumorigenesis and metastatic progression

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Background: Breast cancer is the major cause of death in females globally. Prefoldins (PFDNs) play a crucial role in the process of protein folding. PFDN5, as a subunit of the Prefoldin complex, collaborates with other Prefoldin subunits to assist in the proper folding of newly synthesized proteins. However, the impact of its expression remains elusive in the progression and prognosis of breast cancer.

Methods: In this study, we comprehensively investigated the expression of PFDN5 in breast cancer and its relationship with the survival, prognosis, and other clinical pathological features of breast cancer patients. We validated the role of PFDN5 both in vitro and in vivo, including CCK-8, colony formation, cell cycle assay, transwell assay and wound healing assay. We also performed a series of enrichment analyses to investigate the immune landscape in breast cancer influenced by PFDN5. Additionally, we conducted RNA sequencing to identify the mechanisms through which PFDN5 exerted its biological functions.

Results: Compared to normal breast tissues, PFDN5 exhibited low expression in breast cancer tissues, which is associated with a decreased survival rate in breast cancer patients. Overexpression of PFDN5 suppressed the proliferative capacity of breast cancer cells, induced cell cycle arrest in G2/M phase, but promoted the migration, invasion, and epithelial-mesenchymal transition (EMT) process of breast cancer cells. Furthermore, PFDN5 significantly influenced the immune microenvironment of breast cancer, including the promotion of macrophage polarization towards the M1 phenotype and positively correlating with the

infiltration level of CD8+ T cells. RNA sequencing revealed that PFDN5 was actively involved in pathways such as TGF-BETA signaling pathway and cell cycle progression.

Conclusion: Collectively, PFDN5 exhibits an unexpected dual role and serves as a key factor in immune infiltration in breast cancer. Therefore, PFDN5 may function as a molecular marker for the metastasis and prognosis of breast cancer.

Key Words： PFDN5, breast cancer, metastasis, prognosis, tumor immune microenvironment

316. 间质特征的空间分析-确定侵袭前沿肿瘤相关成纤维细胞作为食管癌抗肿瘤免疫反应的抑制因子

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背景： 越来越多的证据表明肿瘤微环境是肿瘤进展的重要决定因素。然而，肿瘤微环境中基质成分作为一个复杂的动态有机整体，其在食管鳞状细胞癌中的临床及病理生物学意义尚不完全明确。

方法： 我们利用单细胞转录组测序数据、组织质谱成像技术和多重免疫荧光染色来表征食管鳞状细胞癌的间质特征，并评估它们在食管鳞癌中的预后价值。我们采用自动病理定量成像系统和质谱成像分析确定固有层、肿瘤间质及侵袭前沿的空间相互作用和分布特征。随后，通过生物信息学分析探讨食管鳞癌微环境重塑机制。最后，我们根据每个患者的间质特征和 pTNM 分期计算了风险评分，构建了一个新的分子预后模型。

结果： 首先，我们发现食管鳞癌侵袭前沿成纤维细胞与肿瘤的浸润深度和不良预后相关。其次，我们揭示了食管鳞癌浸润前沿的平滑肌肌动蛋白(a-SMA)+成纤维细胞的数量与巨噬细胞(MØs)的数量呈正相关，而与肿瘤浸润性颗粒酶 B+免疫细胞、CD4+和 CD8+ T 细胞的数量呈负相关。再者，空间分析发现，a-SMA +成纤维细胞和 CD163+ MØs 之间在肿瘤微环

境存在显著的空间相互作用，并导致空间排他。我们进一步验证了层粘连蛋白和胶原信号网络在肿瘤微环境重塑中发挥重要作用。最后，与 pTNM 分期相比，由侵袭前沿 a-SMA+成纤维细胞和 CD163+ MØs 表达建立的分子预后模型在食管鳞癌预后预警方面显示出更高的准确性。回归分析表明，该模型不但是独立的预后因子，而且能够识别从辅助治疗中获益的高危食管鳞癌患者群体。

结论：我们新定义的预后预警模型可能作为当前临床风险分层方法的补充，并为逆转成纤维细胞介导的免疫抑制微环境提供潜在的治疗靶点。

关键字： TME, carcinoma-associated fibroblast, macrophage, prognostic model, ESCC

317. O-GlcNAcylation of YTHDF2 promotes HBV-related hepatocellular carcinoma progression in an N6-methyladenosine-dependent manner

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Background: Recent findings indicate that metabolic reprogramming plays an important role in viral replication and carcinogenesis. Oncogenic viruses promote cancer progression not only by directly integrating viral genes into the host genome, but also by hijacking cellular physiology and metabolism to promote metabolic alterations associated with rapid cell proliferation and tumorigenesis. As a “metabolic virus”, HBV affects numerous hepatic metabolic pathways, including dysregulation of lipid metabolism and enhanced glycolysis. Previous studies have shown that the hexosamine biosynthesis pathway (HBP) was upregulated during HBV infection. It converts glucose to UDP-GlcNAc, which is a key substrate for the O-GlcNAc modification, and catalyzed by OGT and OGA.

O-GlcNAcylation is a post-translational modification that links nutrient flux to gene transcription during viral replication and tumorigenesis. It regulates protein function by regulating intracellular protein-protein interactions, stability, localization and activity, and plays a crucial role in maintaining important cellular processes such as cell proliferation, survival and metastasis. We found that HBP flux and metabolite UDP-GlcNAc levels were significantly upregulated after

HBV infection. Based on our previous data of LC-MS, GO analysis was used to identify the potential O-GlcNAc-modified proteins, and the m6A reader YTHDF2 attracted our attention. m6A modification-associated protein expression or functional abnormalities are closely associated with malignant progression and poor clinical prognosis of HCC, and functional interventions or small molecule inhibitors of m6A modification-associated proteins are currently one of the most potential targets in tumor therapy. YTHDF2, as one of the first identified functional m6A "reader", has been widely reported to regulate the stability or translation of m6A transcripts. However, the functional role of YTHDF2 in HCC is still unclear, and the specific mechanism remains to be further elucidated. Previous studies have mainly focused on the role of YTHDF2 in mediating mRNA metabolism and tumor progression through m6A methylation, however the regulation of YTHDF2, especially how the post-translational modification of YTHDF2 regulates its biological function, remains largely unexplored.

Methods： YTHDF2 protein expression and its O-GlcNAcylation levels were detected by Western blot, sWGA and immunoprecipitation assays. The interaction of YTHDF2 with OGT was validated by exogenous and endogenous Co-IP assays. Then the potential site of YTHDF2 modified by O-GlcNAcylation was detected by MS after Coomassie blue staining, and validated by sWGA assay. The difference of the half-life between WT and S263A was detected by protein stability assay. The effect of the O-GlcNAcylation YTHDF2 on its ubiquitination was examined by in vivo and vitro ubiquitination assays. The effect of O-GlcNAcylation on intracellular localization and m6A RNA binding ability of YTHDF2 was detected by nucleoplasmic localization assay and m6A Co-IP assay. CCK8 assay, colony formation assay, transwell assay, wound-healing assay and xenograft tumor experiment were performed to compare the effects of WT and S263A on HBV-associated HCC. RNA-seq, m6A-seq and RIP-seq were performed to screen for mRNAs with m6A modification and bound by YTHDF2, and the significant DEGs were selected for qPCR and RIP-RT-qPCR, to clarify the regulation of YTHDF2 on these target genes. Then qPCR, mRNA stability assay, luciferase reporter assay and RNA pull-down were performed to detect the effect of O-GlcNAcylation on YTHDF2 to regulate the half-life and 3' UTR activity of target mRNA. DEN-induced HCC models in HBV-transgenic mice and spontaneous HCC mice models in Ptenflox/floxAlb-Cre mice (with HBV Ad/rcccDNA transduction) were treated with pSECC vector to introduce sgYthdf2 or intraperitoneal injected

with OGT inhibitor OSMI-1. ALT/AST, immunohistochemical staining, Western blot and sWGA assay were performed to detect the effects of Ythdf2 knockdown or OSMI-1 treatment .

Results: 1. HBV infection significantly enhances YTHDF2 O-GlcNAcylation. sWGA assays showed that YTHDF2 was modified by O-GlcNAcylation and its level was significantly upregulated in liver tissues of HBV-related HCC and Tg mice, compared to normal tissues. In addition, intracellular IP and sWGA assays also confirmed that OGA inhibitor TMG or HBV infection greatly upregulated O-GlcNAcylation of YTHDF2; while OGT inhibitor OSMI-1 downregulated its modification level, indicating that YTHDF2 O-GlcNAcylation is not only upregulated upon HBV infection, but also modulated by intracellular total O-GlcNAcylation levels.

2. OGT-mediated YTHDF2 O-GlcNAcylation at Ser263. Co-IP assay confirmed that the N-terminal domain of YTHDF2 interacted with OGT. IP-MS detected that Ser263 may be the key site modified by O-GlcNAcylation, and sWGA assay confirmed that mutation of Ser263 to Ala (S263A) largely reduced the O-GlcNAc signal compared to the WT. In addition, bioinformatics analysis also confirmed that S263 is well conserved among vertebrates, indicating that S263 is the major O-GlcNAcylation site of YTHDF2.

3. O-GlcNAcylation enhances YTHDF2 protein stability by counteracting its ubiquitination. Protein stability assays revealed that silencing of OGT significantly decreased the protein stability of YTHDF2, while silencing of OGA or HBV infection enhanced its stability. In addition, the half-life of S263A was significantly shorter than that of WT. In vitro and in vivo ubiquitination assays confirmed that OSMI-1 treatment or silencing of OGT enhanced the ubiquitination of YTHDF2, while TMG treatment or HBV infection attenuated it; and when compared to WT, the ubiquitination of S263A was significantly increased. In addition, nucleoplasmic localization assay and m6A Co-IP assay confirmed that YTHDF2 O-GlcNAcylation had minor effect on its intracellular localization and binding ability of m6A RNA.

4. O-GlcNAcylation of YTHDF2 promotes HCC progression. Cell functional assays confirmed that silencing of YTHDF2 followed by overexpression of WT rescued cell proliferation, invasion and migration abilities of HBV-related HCC cells, while S263A could not, indicating that O-GlcNAcylation promotes the proliferation and metastasis of HBV-related HCC through the

regulation of YTHDF2. In addition, xenograft tumor experiments in nude mice also confirmed the above cellular experimental results.

5. MCM2 and MCM5 are identified as YTHDF2 downstream targets by RNA-seq, m6A-seq and RIP-seq. DEGs modified by m6A were screened out by combining m6A-seq and RNA-seq data, and GO and KEGG analyses showed that DEGs were mainly enriched in cancer-related pathways. Further, differential oncogenes were screened out from the overlaps of RNA-Seq, m6A-seq and RIP-seq results, which could be both modified by m6A and bound by YTHDF2. We found that DNA replication-related genes MCM2 and MCM5 were significantly downregulated after silencing of YTHDF2 by qPCR, and correlation analysis suggested that YTHDF2 was positively correlated with MCM2/MCM5.

6. YTHDF2 O-GlcNAcylation promotes HCC proliferation by preserving the stability of MCM2 and MCM5 transcripts in an m6A-dependent manner. TMG/OSMI-1 treatment upregulated/downregulated MCM2/5 mRNA and protein levels, respectively, while subsequent silencing or overexpression of YTHDF2 reversed the effects of O-GlcNAcylation inhibitors. mRNA stability assay and luciferase reporting assay confirmed that TMG/OSMI-1 treatment affected the half-life and 3'UTR activity of MCM2/5 mRNA by regulating YTHDF2. Compared with WT, S263A could not prolong the shortened half-life of MCM2/5 mRNA induced by silencing of YTDHF2. Cell functional assays confirmed that MCM2/5 or YTHDF2 knockdown significantly inhibited the proliferation and colony formation abilities of HCC cells, and blocked cell cycle progression. Subsequently, overexpression of MCM2/5, or both MCM2/5 and WT-YTHDF2 in YTHDF2-silenced cells, restored cell-related phenotypes and promoted cell cycle progression, while S263A could not.

7. In vivo animal experiments and clinical HCC tissues confirmed that YTHDF2 O-GlcNAcylation significantly promotes HCC progression. In DEN-induced HBV-Tg mice and spontaneous HCC mice models, Ythdf2 knockdown or OSMI-1 treatment significantly reduced the number of tumor nodules and alleviated liver damage. Moreover, inhibition of Ythdf2 and its O-GlcNAcylation greatly downregulated the expression of MCM2, MCM5 and Ki67. Experiments in clinical HCC tissues also confirmed that YTHDF2 and its O-GlcNAcylation was positively correlated with MCM2/MCM5, and was associated with poor prognosis.

Conclusion: This study found that YTHDF2 O-GlcNAcylation was elevated upon HBV infection through upregulation of HBP flux, and identified Ser263 as the key site for its O-GlcNAcylation. Further MCM2 and MCM5 were identified as downstream m6A targets of YTHDF2 by overlapping RNA-seq, m6A-seq and RIP-seq results. Targeting OGT-mediated YTHDF2 O-GlcNAcylation by OSMI-1 could inhibit the progression of HBV-related HCC. In this study, we firstly reported a novel post-translational modification of YTHDF2—O-GlcNAcylation, and revealed the dynamic regulatory network between viral infection, protein post-translational modification and RNA m6A modification, providing a new insight for the new prognostic markers and potential molecular targets of HBV-associated liver cancer.

Key Words： HBV infection, hepatocellular carcinoma, YTHDF2, O-GlcNAcylation, m6A modification

318. 基于 CT 纹理影像组学分析瘤内成分对未成熟畸胎瘤的鉴别及分级价值

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目的：分析成熟与未成熟畸胎瘤及不同级别未成熟畸胎瘤的纹理特征，并构建影像组学模型，判断畸胎瘤瘤内脂肪、实性及钙化成分纹理特征对未成熟畸胎瘤的鉴别及分级的价值。

方法：搜集 2019-2023 年深圳市儿童医院经术后病理确诊为未成熟畸胎瘤（IT）26 例（I 级 7 例，II级 4 例，III级 15 例）及性别年龄匹配的 26 例成熟畸胎瘤（MT）患者的术前最后一次 CT 影像。提取瘤内脂肪、实性及钙化及成分的灰度共生矩阵特征（GLCM）、灰度矩阵特征（GLDM）、灰度运行长度特征（GLRLM）、灰度区域长度矩阵特征（GLZLM）和邻域灰度依赖（NGTDM）共 75 个纹理特征。通过非参数检验判断出 MT 与 IT 组间及 IT 不同分级组内差异有统计学意义的特征，去除相关系数＞0.8 的特征后分别构建脂肪、实性及钙化纹理特征二元逻辑回归模型及受试者操作特征曲线，通过模型曲线下面积（AUC）判断脂肪、实性及钙化纹理特征的模型诊断效能。

结果：在未成熟畸胎瘤与成熟畸胎瘤的组间鉴别比较中，脂肪、实性及钙化成分组间均存在 GLCM、GLDM、GLRLM、GLZLM 特征纹理差异，仅实性与钙化成分存在 NGTDM

差异，构建脂肪、实性及钙化成分回归模型，AUC 值分别为 0.799,0.984,0.967。在未成熟畸胎瘤组内分级比较中，实性成分的 NGTDM 特征能进一步在I级与II级间仍存在差异，但尚未能进一步构建回归模型。

结论：MT 与 IT 组间脂肪、实性及钙化成分均存在纹理特征差异，而 IT 组内不同级别间仅实性成分存在纹理差异。三种成分纹理特征的 MT 与 IT 组间鉴别模型均有一定诊断效能，且实性成分的模型诊断价值最高。

关键字 ：畸胎瘤；影像组学；纹理分析；诊断，鉴别

319. An integrated microfluidic device for rapid, efficient, and multiplexed detection of neutrophil extracellular vesicle derived miRNAs and gastric cancer diagnosis

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Background: Neutrophil derived extracellular vesicles (NEVs) are critically involved in tumor progression, carrying miRNAs that may be potential biomarkers for gastric cancer liquid biopsy. However, the non-invasive assay is largely hampered by the tedious process of NEVs separation and detection from heterogeneous body fluids.

Methods: Here, we present a rapid and efficient microfluidic device integrating the immuno separation of NEVs and multiplexed analysis of CD66b/CD63+ NEVs and miRNAs (NEVs signatures). On-chip rolling circle amplification (RCA) reaction was triggered by the released aptamers and miRNAs after NEVs lysis, and the resulting RCA products were subsequently detected by molecular beacons (MBs), initiating allosteric hairpin structures and amplified “turn on” fluorescence signals (RCA-MBs assay). The fluorescence signals were further analyzed by an AI-based ensemble classification system.

Results: The optimized microchannel and flow rate enables a highly efficient capture of NEVs (> 90%). Moreover, the chip enabled highly sensitive detection of CD66b/CD63+ NEVs and the containing miRNAs (miR-223-3p and miR-425-5p). Consequently, the chip with NEVs signatures obtained a diagnostic accuracy of 80.95% to differentiate between healthy controls (HC) and

gastric cancer (GC) patients, which was superior to that of CEA and CA199 (66.29%). Notably, the accuracy reached to 83.91% with combined five biomarkers, and further increased to 90.8% by an AI-based ensemble classification system. Moreover, the high expression of miR-223-3p and miR-425-5p were found to predict poor prognosis in GC patients.

Conclusion: The chip enabled sensitive quantification of CD66b/CD63+ NEVs abundance and miRNAs by consuming only 10 μL of serum sample in less than 4 hours. We envision that the proposed microfluidic device with NEVs signatures may show great potential for the diagnosis and prognosis evaluation of gastric cancer and promote the clinical applicability of NEVs miRNA-based liquid biopsy.

Key Words ： NEVs; miRNAs; microfluidic chip; gastric cancer; liquid biopsy

320. KDM5C-Mediated Recruitment of BRD4 to Chromatin Regulates Enhancer Activation and BET Inhibitor Sensitivity

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The BET family member BRD4 is a bromodomain-containing protein that plays a vital role in driving oncogene expression. Given their pivotal role in regulating oncogenic networks in various cancer types, BET inhibitors (BETi) have been developed, but the clinical application has been impeded by dose-limiting toxicity and resistance. Understanding the mechanisms of BRD4 activity and identifying predictive biomarkers could facilitate the successful clinical use of BETis. Herein, we showed that KDM5C and BRD4 cooperate to sustain tumor cell growth. Mechanistically, KDM5C interacted with BRD4 and stimulated BRD4 enhancer recruitment. Moreover, binding of the BRD4 C-terminus to KDM5C stimulated the H3K4 demethylase activity of KDM5C. The abundance of both KDM5C-associated BRD4 and H3K4me1/3 determined the transcriptional activation of many oncogenes. Notably, depletion or pharmacologic degradation of KDM5C dramatically reduced BRD4 chromatin enrichment and significantly increased BETi efficacy across multiple cancer types in both tumor cell lines and patient-derived organoid models.

Furthermore, targeting KDM5C in combination with BETi suppressed tumor growth in vivo in a xenograft mouse model. Collectively, this work reveals a KDM5C-mediated mechanismby which BRD4 regulates transcription, providing a rationale for incorporating BETi into combination therapies with KDM5C inhibitors to enhance treatment efficacy.

Key Words： BRD4, KDM5C, BETi, enhancer

321. 基质细胞来源小细胞外囊泡通过白细胞介素-8 诱导的自噬 促进 AR 阳性前列腺癌细胞放疗抵抗

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放疗是局限性前列腺癌（PCa）的根治性治疗方法。不幸的是，当患者出现更具侵袭性或转移性的表型时，放射治疗效果通常会降低。最近的研究表明，细胞外囊泡通过递送生物活性小分子（如非编码小 RNA）参与肿瘤耐药过程。在本课题，我们表明基质细胞衍生的小细胞外囊泡 （sEV） 通过转运白细胞介素 8 （IL-8） 促进 PCa 细胞的放射抗性。事实上，前列腺基质细胞比 AR 阳性 PCa 细胞分泌更多的 IL-8，这些 IL-8 可以在 sEV 中积累。有趣的是，放射敏感的 PCa 细胞对基质细胞衍生的 sEV 的摄取增强了它们的辐射抗性，这种辐射抗性可以通过沉默基质细胞中的 CXCL8 或抑制 PCa 细胞中的 CXCR2 受体来减弱。sEV 介导的放射抗性已在斑马鱼和小鼠异种移植肿瘤中得到验证。从机制上讲，在辐照条件下，基质 sEV 的摄取触发了 PCa 细胞中 AMPK 激活的自噬途径。因此，通过利用 AMPK 抑制剂灭活 AMPK 或沉默 PCa 细胞中的 AMPKα 能够有效地使放疗重新敏化。此外，溶酶体抑制剂氯喹 （CQ）可以通过阻断自噬溶酶体融合，导致自噬体在 PC 细胞中积累，使放疗充分再敏化。总的来说，这些结果表明，基质细胞主要通过递送 sEV-IL-8 增强 PCa 细胞的放射抗性。

关键字： AMPK；自噬；氯喹；白细胞介素-8；前列腺癌；放疗抵抗；小细胞外囊泡；基质细胞

322. Enhancing gastric cancer prognostic stratification: a multifactorial model integrating rs11023485 and clinical features

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Objective: This study aimed to analyze the genetic polymorphisms of KCNQ1 and KCNQ1OT1 and their impact on the genetic susceptibility and survival rates of gastric cancer patients.

Methods: The study encompassed 972 gastric cancer patients, with data collected on their clinical characteristics and SNP genotype information. Twenty-two clinical and genetic features were identified using the least absolute shrinkage and selection operator (LASSO) regression analysis. The performance of various machine learning models, including cox regression, random survival forests (RSF), and survival support vector machine (survival SVM), was compared.

Results: The cox regression model demonstrated superior performance in predicting the overall survival of postoperative gastric cancer patients, with a C-index of 0.714, outperforming RSF (C-index of 0.698) and survival SVM (C-index of 0.706) models. Furthermore, the Cox regression model exhibited good calibration, with Brier scores of 0.114, 0.192, and 0.208 at 1, 3, and 5 years, respectively. Additionally, a significant correlation was identified between the single nucleotide polymorphism (SNP) at the rs11023485 locus and the survival rate of gastric cancer patients.

Conclusion: This study confirms the reliability of the cox regression model in gastric cancer survival analysis and successfully identifies significant SNP loci associated with gastric cancer prognosis. A comprehensive multifactorial risk assessment model, based on these clinical and genetic features, was developed and demonstrated practical utility across different TNM stages of patient groups, aiding in the prognostic stratification of patients. Moreover, a nomogram was constructed for predicting the prognosis of gastric cancer patients, facilitating clinical application.

Key Words： gastric cancer, genetic polymorphisms, single nucleotide polymorphism (SNP), KCNQ1, KCNQ1OT1, machine learning, cox regression model, survival

323. 一项25-羟维生素D水平与非黑色素瘤皮肤癌的孟德尔随机化研究

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目的：采用孟德尔随机化（Mendelian randomization，MR）分析方法，探讨 25-羟维生素 D（25-Hydroxyvitamin D,（25（OH）D））与非黑色素瘤皮肤癌(**non**-melanoma skin cancer,NMSC)之间潜在的因果关联。

方法：从全基因组关联研究（genome-wide association study，GWAS）公开数据进行筛选，以 25（OH）D 作为暴露数据，NMSC 作为结局数据，采用逆方差加权法(inverse variance weighted ，IVW)、MR-Egger、加权中位数法(weighted median ，WME)、简单模型法(simple mode，SM)、加权模型法(weighted mode，WM)等方法，在不同假设的基础上评估 25(OH)D 对非黑素瘤皮肤癌的影响。并采用 Cochrane's Q 检验对结果进行异质性检验，根据 MR-Egger intercept 截距检验潜在的多效性进行敏感性分析。

结果：1. 发现 25(OH)D 与 NMSC（OR=1.0083901，95%CI：1.0012638-1.0155116，p= 0.02156293）呈正向因果关系。2.结果发现存在异质性(P = 1.**283796e**-12)，无水平多效性(P=0.1629792)。

结论：本研究提供了 25（OH）D 与 NMSC 间因果关系的新证据,但进一步的观察性研究和临床试验及更大样本量的的全基因组关联研究是必要的。

25-Hydroxyvitamin D and non-melanoma skin cancer: a Mendelian randomization study

Objective: Using Mendelian randomization（MR）, investigate any possible causal relationship between non-melanoma skin cancer (NMSC) and 25-hydroxyvitamin D (25 (OH) D). Method: The selection of public data from genome-wide association studies was done using NMSC as the outcome and 25 (OH) D as the exposure data. Inverse variance weighted (IVW), MR-Egger, weighted median (WME), simple mode (SM), and weighted mode (WM) were used with different assumptions to assess the effect of 25(OH)D on NMSC. RESULTS: 1. 25(OH)D was found to be positively and causally associated with NMSC (OR = 1.0083901, 95% CI: 1.0012638-1.0155116, p= 0.02156293). 2. Heterogeneity was found to be present (p = 1.283796e-12) and there was no level of multiplicity (p=0.1629792). Conclusions: This study adds to the body of data supporting a

causal connection between 25 (OH) D and NMSC, although further observational research and larger sample sizes in clinical trials are required for genome-wide association studies.

关键字： 25-羟维生素 D；非黑色素瘤皮肤癌；孟德尔随机化

324. Performance Validation of Five Domestic Sequencing Reagent Kits on Next-generation Sequencing Platforms

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Objective: To conduct performance validation of multiplex gene mutation sequencing kits using a next-generation sequencing (NGS) technology platform, and to assess their reliability, stability, and consistency in clinical testing, providing a technical reference for project testing within the institution.

Methods: The experiment involved testing domestic kits from five companies（Company named as A,B,C,D and E） on an NGS platform using both standard reference materials and clinical samples, and comparing the processes and results. Methodological confirmation was conducted with third-party quality control products, covering accuracy, limit of detection (LOD), precision, analytical specificity, and the reportable range. Types of mutations detected included single nucleotide variations, deletions, copy number variations, and structural variations. Five clinical samples with clearly clinically significant common gene mutations were selected for multi-gene mutation sequencing confirmation.

Results: Performance analysis of the five sequencing kits showed that 16 positive gene mutations and 28 negative gene mutations were detected in quality control materials. Both positive predictive value (PPA) and negative predictive value (NPA) for the five kits were 100%. LOD results for mutation frequencies of 1%, 2%, 4%, 5%, 7%, and 5 copies, showed correlation coefficients (r) between 0.75-0.93 ($P<0.001$). Linear regression equations were as follows: y=1.05x-0.41; y=0.90x-0.10; y=84x+0.05; y=0.81x+0.18; y=0.79x+0.34. Precision results had mean values A (2.87±1.89), B(3.01±1.92), C(3.15±2.29), D(2.64±1.93), E(2.92±1.87), with a

Kruskal-Wallis test P=0.96 and asymptotic significance of 0.998. Mutation frequency groups of high (40%-70%), medium (16%-30%), and low (2%-15%) were selected from five sets of samples to calculate the mean detection frequency and to assess the consistency of positive sample detection, H(K)=0.129, P=0.129. Common genes with mutation frequencies above 10% included TP53, RET, EGFR, PIK3CG, PIK3R1, STK11, EPHA5, EPHB6, ERBB4, RAD50, ATR, SLC34A2:ROS1, SMAD2, and SMAD3. Clinical sample testing found that Case1 had a SLC34A2:ROS1 fusion gene detected by all five companies, with patients recommended for treatment with class A third-generation TKI targeted therapy. Case3 had an EGFR exon 21 p.L858R mutation, with patients recommended for a first-generation TKI targeted therapy. The remaining three cases were recommended for class C drugs. Additionally, Cases 1, 2, and 5 exhibited a high tumor mutation burden, with average values of 23.10±5.54, 91.27±11.2, 23.13±6.32; Case 2 was found to be MSI-H, with all three cases potentially recommended for guidance with immunosuppressant drugs.

Conclusion: The five domestic kits on the NGS platform were verified with third-party quality controls and met the detection standards for accuracy, sensitivity, and precision. The test results from the five clinical samples aligned with expected clinical therapeutic outcomes, providing experimental evidence for precision oncology and supporting clinical detection efforts.

Key Words ： Next-generation sequencing; Performance validation; Clinical assessment; Tumor

325. Extrachromosomal circular DNA in cancer drug resistance and its potential clinical implications

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Chemotherapy is widely used to treat patients with cancer. However, resistance to chemotherapeutic drugs remains a major clinical concern. The mechanisms of cancer drug resistance are extremely complex and involve such factors such as genomic instability, DNA repair,

and chromothripsis. A recently emerging area of interest is extrachromosomal circular DNA (eccDNA), which forms owing to genomic instability and chromothripsis. eccDNA exists widely in physiologically healthy individuals but also arises during tumorigenesis and/or treatment as a drug resistance mechanism. In this review, we summarize the recent progress in research regarding the role of eccDNA in the development of cancer drug resistance as well as the mechanisms thereof. Furthermore, we discuss the clinical applications of eccDNA and propose some novel strategies for characterizing drug-resistant biomarkers and developing potential targeted cancer therapies.

Key Words: cancer genetics, extrachromosomal circular DNA, drug resistance, chromothripsis, genomic instability

326. Quantification of Tumor Abnormal Proteins in the Diagnosis and Postoperative Prognostic Evaluation of Gastric Cancer

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Background: Abnormal glycosylation of proteins has been identified in almost all types of cancers and is closely related to the cancer progression, metastasis, and survival of cancer patients. This study was to explore the values of serum tumor abnormal protein (TAP), an abnormal glycochain protein, in the diagnosis and prognosis of gastric cancer (GC).

Methods:A total of 335 GC patients were included as the study group, and another 335 subjects served as the control group. Tumor abnormal protein expression was compared between the 2 groups. Correlation analysis was used to assess the correlations of TAP with clinicopathological factors. Gastric cancer patients were divided into training set and test set at a ratio of 2:1. Univariate and multivariate Cox regression analyses in training set were used to evaluate the prognostic significance of TAP in GC patients and explore the independent risk factors for overall survival (OS) and disease-free survival (DFS) to establish a prognostic model, followed by testing

of the model. According to the median of TAP, 335 GC patients were divided into 2 groups to plot the survival curves of OS and DFS.

Results: Tumor abnormal protein expression in the study group was significantly higher than in the control group. Taking the best cut-off value of TAP (110.128 μm2) as the diagnostic criteria for GC, the sensitivity and specificity of TAP were 83.58% and 97.61%, respectively, and the area under the receiver operating characteristics (ROC) curve was 0.935, which was not inferior to computed tomography (CT). Tumor abnormal protein expression was an independent risk factor for OS and DFS. The prognostic predictive value of TAP was better than that of pathological stage in GC patients. The model with TAP was effective in predicting prognosis.

Conclusion: Tumor abnormal protein is an effective indicator for early screening and prognostic evaluation of GC and can also assist the clinical diagnosis and treatment of GC.

Key Words ：Tumor abnormal protein; evaluation of therapeutic effect; gastric cancer; pathology; predictive diagnosis.

327. TRIM50 inhibits glycolysis and the malignant progression of gastric cancer by ubiquitinating PGK1

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Ubiquitination plays a pivotal regulatory role in tumor progression. Among the components of the ubiquitin–proteasome system (UPS), ubiquitin-protein ligase E3 has emerged as a key molecule. However, the precise biological functions of E3 ubiquitin ligases and their potential mechanisms in orchestrating glycolytic regulation in gastric cancer (GC) remain unknown. In this study, we conducted a comprehensive transcriptomic analysis to identify the core in GC, followed by extensive validation of the expression patterns and clinical significance of E3 ubiquitin ligase TRIM50 both in vitro and in vivo. Remarkably, we observed a significant downregulation of TRIM50 expression in GC tissues, which correlated with tumor size, metastasis, TNM staging, and reduced survival rates among GC patients. Functionally, the overexpression of TRIM50 in GC cells attenuated their proliferative capacity and indirectly influenced the invasive migratory

abilities of GC cells by suppressing the M2 polarization of tumor-associated macrophages (TAMs). Conversely, depletion of TRIM50 yielded opposing effects. Mechanistically, TRIM50 inhibits the glycolytic pathway of GC cells by ubiquitinating and degrading phosphoglycerate kinase 1 (PGK1), thereby directly suppressing GC cell proliferation. Simultaneously, the reduction in lactate, a prominent glycolytic metabolite, leads to diminished M2 polarization of TAMs in the tumor microenvironment, consequently indirectly inhibiting the invasive migratory abilities of GC cells. Notably, the downregulation of TRIM50 in GC is mediated by the METTL3/YTHDF2 axis in an m6A-dependent manner. In our study, we definitively identify TRIM50 as a tumor suppressor gene (TSG) that effectively inhibits aerobic glycolysis and malignant behavior in GC by promoting the ubiquitination and degradation of PGK1, thus offering novel insights and promising targets for the diagnosis and treatment of GC.

Key Words: Gastric cancer, ubiquitination, glycolysis, tumor-associated macrophages, m6A

328. Comprehensive analysis of multiomics data for the identification of a cuproptosis-related gene signature predicting prognostic outcomes and drug responses in gastric cancer

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Background: Cuproptosis, a recently elucidated copper-dependent mechanism of cell death associated with the tricarboxylic acid cycle, lacks a comprehensive understanding of its relation to clinical prognosis and drug response in gastric cancer (GC). This study aims to discern potential prognostic signatures of cuproptosis-related genes (CRGs) and evaluate drug response.

Methods: Using publicly available datasets from TCGA and GEO, we initially obtained transcriptomic and clinical data of GC patients. We employed consensus clustering approach to delineate molecular subtypes based on the expression of CRGs. Utilizing least absolute shrinkage

and selection operator (LASSO) regression analysis, we formulated a prognostic signature derived from the differentially expressed genes among these molecular subtypes. We constructed a nomogram that amalgamates both clinical characteristics and the prognostic model to provide a comprehensive prognosis prediction. Rigorous assessment of prognostic performance was carried out through Kaplan–Meier curve analysis, the log-rank test, univariate and multivariate Cox regression, and time-dependent ROC curve analysis. Tumor Immune Dysfunction and Exclusion (TIDE) and the pRRophetic package in R were used to assess the potential response to chemotherapy and immunotherapy. Seurat was utilized to analyze the general characterization of the single-cell dataset. Additionally, the validation of hub gene expression in both cells and clinical samples was undertaken via qRT–PCR.

Results: Upon conducting an exhaustive investigation into the distinct differential expression and prognostic implications of each CRG, we delineated two distinct cuproptosis-associated molecular subtypes. Following Lasso regression analyses, we formulated a prognostic model comprising six specific genes. Patients were effectively stratified into either high-risk or low-risk categories by utilizing this model. Patients classified as high-risk experienced poorer prognosis and were associated with higher TNM stages compared to those with low risk. Furthermore, patients belonging to the low-risk group exhibited enhanced benefits from chemotherapeutic drugs and demonstrated better susceptibility to immunotherapy. The validation of our prognostic model's efficacy was established through ROC analysis, affirming its commendable sensitivity and specificity.

Conclusions: Our study illuminates the significance of cuproptosis in drug response and clinical prognosis in Asian GC patients, underscoring its clinical significance and providing a reliable tool for predicting overall survival in this patient population.

Key Words ： Cuproptosis, Gastric cancer, Prognosis, Drug response, Overall survival

329. 基于线粒体自噬相关长非编码 RNA 和免疫景观分析的癌症新风险模型

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Purpose

Mitophagy plays a pivotal role in the development of gastric cancer (GC). However, little is known about the clinical significance of mitophagy in GC. Here we constructed a risk model based on mitophagy-related long non-coding RNAs (MR-lncRNAs) and analyzed the immune landscape of this risk model.

Methods

We first obtained 58 mitophagy mRNAs from database and then screened 12 differentially expressed mitophagy mRNAs in GC versus normal samples from TCGA. Next we performed Pearson correlation ananlysis to obtained 642 MR-lncRNAs and screened out 400 differentially MR-lncRNAs in GC versus normal samples. Subsequently, we screened out 10 prognostic MR-lncRNAs based on univariate Cox regression analysis. Furthermore, we established a multivariate Cox proportional hazards risk model based on five crucial TaMR-lncRNAs with the least absolute shrinkage and selection operator (LASSO). Finally, we validated the prognostic value and immune landscape of this risk group.

Results

The area under the curve (AUC) of this risk model for predicting the prognosis of GC was 0.681, 0.686, and 0.748 at 1, 3, and 5 years, respectively. High-risk populations from the total patient, test, and training sets had shorter OS and PFS than the low-risk populations ($p<0.05$). The high-risk group had higher Tumor Immune Dysfunction and Exclusion (TIDE) score but lower tumor mutation burden (TMB) comparing to the low-risk group ($p<0.05$).

Conclusion

We constructed a risk model based on mitophagy lncRNAs, which could better predict the prognosis of GC patients and was associated with the immune escape and efficacy of immunotherapy.

关键字 ： gastric cancer; mitophagy; long non-coding RNA; prognosis; risk model; immune

330. 全腹腔镜下远端胃切除与全腹腔镜下保留迷走神经远端胃切除安全性比较

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目的：对比分析全腹腔镜下远端胃切除术与全腹腔镜下保留迷走神经远端胃切除术的手术安全性及短期生活质量。

方法：收集 2020 年 3 月至 2022 年 9 月在南京医科大学第一附属医院胃外科行全腹腔镜下根治性远端胃切除手术患者的临床资料，采取 Logistic 回归模型对两组病人的基线资料进行 1∶3 倾向性评分匹配（propensity score match，PSM），然后比较两组病人的手术情况、术后并发症。自制胃术后神经功能评估表，由经验丰富的医生对患者术后症状进行赋分，其中包括大便次数、性状，食欲、排气状况，倾倒综合征及胆石症发生率，根据自制生活质量评分表评估两组患者术后短期生活质量。

结果：经 1∶3 PSM 后保留迷走神经远端胃切除组纳入病人 63 例，常规远端胃切除组纳入病人 189 例。两组间各项基线资料无统计学意义。常规远端胃切除组与保留迷走神经远端胃切除组在手术时间［（175±36.87）min vs.（193.40±32.39）min，P＜0.001］方面存在显著差异，保留迷走神经组手术时间较长，但术中出血量[（49.21±10.49）mL vs.（50.32±10.66）mL，P=0.469］、淋巴结清扫数目［（42.11±11.60）枚 vs.（43.22±10.84）枚，P=0.504］等方面无统计学意义。常规远端胃切除组患者术后排气时间（2.94±0.72 天）晚于保留迷走神经组（2.73±0.72 天）患者（P=0.044）。两组病人在术后进食时间、术后住院时间等方面无统计学意义 （P>0.05）。常规远端胃切除组术后并发症发生率为 8.5%（16/189），保留迷走神经远端胃切除组术后并发症发生率为 7.9% （5/63），两组间差异无统计学意义（P=0.895）。全腹腔镜下保留迷走神经组患者术后短期生活质量优于行常规远端胃切除患者。

结论：全腹腔镜下保留迷走神经远端胃切除手术与全腹腔镜下常规远端胃切除手术均具有可靠的手术安全性。相较于常规远端胃切除手术，保留迷走神经手术可能需要花费较长的

时间去分离迷走神经。但是，保留迷走神经手术患者短期生活质量更优于常规远端胃切除患者。

关键字： 远端胃，保留迷走神经，安全性

331. Plasma cell-free DNA as a sensitive biomarker for multi-cancer detection and immunotherapy outcomes prediction

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Background

Cell-free DNA (cfDNA) has shown promise in detecting various cancers, but the diagnostic performance of cfDNA end motifs for multiple cancer types requires verifcation. This study aimed to assess the utility of cfDNA end motifs for multi-cancer detection.

Methods

This study included 206 participants: 106 individuals with cancer, representing 20 cancer types, and 100 healthy individuals. The participants were divided into training and testing cohorts. All plasma cfDNA samples were profled by whole-genome sequencing. A random forest model was constructed using cfDNA 4 bp-end-motif profles to predict cancer in the training cohort, and its performance was evaluated in the testing cohort. Additionally, a separate random forest model was developed to predict immunotherapy responses.

Results

In the training cohort, the model based on 4 bp-end-motif profles achieved an AUC of 0.962 (95% CI 0.936–0.987). The AUC in the testing cohort was 0.983 (95% CI 0.960–1.000). The model also maintained excellent predictive ability in diferent tumor sub-cohorts, including lung cancer (AUC 0.918, 95% CI 0.862–0.974), gastrointestinal cancer (AUC 0.966, 95% CI 0.938–0.993), and other

cancer cohort (AUC 0.859, 95% CI 0.776–0.942). Moreover, the model utilizing 4 bp-end_x0002_motif profles exhibited sensitivity in identifying responders to immunotherapy (AUC 0.784, 95% CI 0.609–0.960).

Conclusion

The model based on 4 bp-end-motif profles demonstrates superior sensitivity in multi-cancer detection. Detec_x0002_tion of 4 bp-end-motif profles may serve as potential predictive biomarkers for cancer immunotherapy.

Key Words ： Cell-free DNA · Multiple cancer · Whole-genome sequencing · Cancer detection

332. 胃癌细胞来源 LRG1 通过抑制肝实质细胞糖摄取能力促进胃癌肝转移的机制研究

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胃癌肝转移严重影响患者预后，分泌蛋白在肿瘤靶向转移中起到关键作用。申请人通过质谱分析及小鼠模型发现胃癌来源 LRG1 可促进胃癌肝转移；功能实验表明 LRG1 主要作用于肝实质 细胞 EGFR，并抑制糖转运蛋白 GLUT1 表达；多种体内外实验揭示 LRG1 通过 MAPK/P38/CEBPβ通路 激活 USP33 转录，后者诱导 MNT 去泛素化使其降解减少，而 MNT 可抑制 GLUT1 转录；此外，胃癌细 胞内 CEBPβ可上调 LRG1 表达。据此我们提出假说：胃癌细胞 CEBPβ转录激活 LRG1，LRG1 结合肝 实质细胞 EGFR 并上调 USP33 表达，USP33 诱导 MNT 去泛素化使其对 GLUT1 转录抑制增强，肝实质细胞糖摄取能力下降，定植入肝胃癌细胞能量来源增多，最终加速形成转移灶。本研究拟通过人群样本、类器官、小鼠及细胞层面，运用原代细胞提取、Co-IP 等技术对假说进行证实；为胃癌肝转移的预防、早期诊断及精准化治疗提供科学依据。

关键字 ： 胃癌；肝转移；富亮氨酸α2 糖蛋白 1；去泛素化；糖摄取

333. The Comprehensive Landscape Analysis of The Autophagy in Cancer Development and Drug Resistance

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Background

Autophagy plays important roles in cancer progression and therapeutic resistance. The resistance to key anti-cancer agents has become complicated procedures of cancer therapy, but the autophagy underlying tumor pathogenesis and further related mechanisms by which the chemoresistance emergence remains unknown.

Methods

Based on the ssGSEA algorithm, 5 autophagy-associated gene signatures were used to evaluate samples' autophagy activity, utilizing six different GEO datasets with confirmed autophagy phenotype. Moreover, based on the gene-list ssGSEA autophagy score, we analyzed the transcriptome landscapes between autophagy-high status and autophagy-low status samples, including survival analysis, correlation analysis of autophagy/resistance-related genes, differentially expressed genes (DEGs) and protein–protein interactions analysis, biological functional enrichment, tumor microenvironment (TME) analysis, in TCGA pan-cancer datasets. Furthermore, we performed the analysis of autophagy status in breast cancer chemoresistance combined with multiple GEO datasets, and experiments in vitro to validate the corresponding mechanisms of potential anti-cancer drugs for reversing tumor resistance, including CCK-8 cell viability assays, western blot and immunofluorescence.

Results

We first established an autophagy-associated gene signature, 45-gene list to estimate autophagy status, which showed the better ability for samples into autophagy score-high and score-low groups by validating in six GEO datasets. This study indicated the important influence of autophagy/resistance activity for the prognosis across 39 cancer types in pan-cancer. Furthermore, we characterized the associations between multi-dimensional molecular features and autophagy, for instance, several pathways associated with immune response enriched. We also found the

autophagy score-low cancer patients displayed the favorable prognosis compared with score-high patients, which might correlate with their high immune components (ImmuneScore) and increased infiltrating immune cell proportions, including high CD8+T, Tfh, Treg, NK cells and tumor-associated macrophages M1/M2 closely associated with the low autophagy status. We indicated the dysregulated autophagy in the transformation of breast cancer parental to chemoresistant cells, and the autophagy induced by the resistance-reversing drugs response, in five breast cancer GEO datasets and validated by vitro experiments; for example, in vitro, dihydroartemisinin and artesunate could reverse breast cancer doxorubicin resistance, through inducing autophagy via upregulating LC3B and ATG7.

Conclusion

Dysregulated autophagy was be involved in many cancers and their therapeutic resistance, further leading to the significant differences in prognosis and drug response. Our study provided a comprehensive landscape of the autophagy-related molecular and TME patterns for cancer progression and resistance, and highlighted the promising potential of drug-induced autophagy in the activation of drug sensitivity and reversal of resistance.

Key Words ： Autophagy; Tumor resistance; Pan-cancer; Breast cancer; Doxorubicin resistance

334. N6 -甲基腺苷修饰的 MIB1 通过泛素化降解 DDX3X 促进胃癌细胞的干性特性和腹膜转移

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背景：腹膜转移是进展期胃癌最典型的转移方式之一，预后极差。由于目前腹膜转移的作用机制尚不清楚，而且没有明确有效的治愈方案，因此迫切需要阐明这一机制，为胃癌腹膜转移患者提供切实有效的治疗靶点，提高患者的远期生存。E3 泛素连接酶已被广泛证实在多种肿瘤中发挥重要的生物学功能，但其在胃癌腹膜转移中的作用机制尚不清楚。

方法：体外和体内实验证实了 MIB1 对胃癌腹膜转移的影响。免疫共沉淀(Co-IP)和质谱分析证实了 MIB1 和 DDX3X 之间的相互作用。Western blot、流式细胞学和免疫荧光等实验

发现 MIB1 泛素化降解 DDX3X，并促进胃癌细胞干性。最后通过 RNA 免疫沉淀(RIP)、荧光素酶报告基因实验等实验进一步证实 METTL3 促进了 MIB1 的上调。

结果：E3 泛素连接酶 MIB1 在腹膜转移灶中高表达，并且 MIB1 高表达的腹膜转移患者比 MIB1 低表达的患者预后更差。机制上，E3 泛素连接酶 MIB1 通过降解 DDX3X 促进了胃癌细胞的上皮-间充质转化(EMT)进程和干性特性。此外，METTL3 介导的 m6A 修饰稳定 MIB1 的表达，这一过程需要 m6A“阅读器”IGF2BP2 的参与。

结论：我们的研究阐明了 MIB1 促进胃癌腹膜转移的具体分子机制，并提示靶向 METTL3-MIB1-DDX3X 轴可能是一种有前景的治疗策略。

关键字： 泛素化；甲基化；上皮间质转化；干性；腹膜转移

335. SEC23A confers ER stress resistance in gastric cancer by forming the ER stress-SEC23A-autophagy negative feedback loop

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Background: Sec23 homolog A (SEC23A), a core component of coat protein complex II (COPII), has been reported to be involved in several cancers. However, the role of SEC23A in gastric cancer (GC) remains unclear.

Methods: The expression of SEC23A in GC was analyzed by using qRT-PCR, western blotting and IHC staining. The role of SEC23A in ER stress resistance was explored by functional experiments in vitro and vivo. The occupation of STAT3 on the SEC23A promoter region was verified by luciferase reporter plasmids and CHIP assay. The interaction between SEC23A and ANXA2 was identified by Co-IP and mass spectrometry analysis.

Results: We demonstrated that SEC23A was upregulated in GC tissues and predicted poor prognosis in patients with GC. Mechanistically, SEC23A was transcriptional upregulated by ER stress-induced pY705-STAT3. Highly expressed SEC23A promoted autophagy by regulating the cellular localization of ANXA2. The SEC23A-ANXA2-autophay axis, in turn, protected GC cells

from ER stress-induced apoptosis. Furthermore, we identified that SEC23A attenuated 5-FU therapeutic effectiveness in GC cells through autophagy-mediated ER stress relief.

Conclusion: We reveal an ER stress-SEC23A-autophagy negative feedback loop that enhances the ability of GC cells to resist the adverse survival environments. These results identify SEC23A as a promising molecular target for potential therapeutic intervention and prognostic prediction in patients with GC.

Key Words ： apoptosis, autophagy, ER stress, gastric cancer, SEC23A

336. A novel prognosis prediction model based on preoperative serum tumor markers in gastric cancer

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Background: Gastric cancer (GC) is a prevalent malignant tumor within the digestive system. Throughout its progression, there is an aberrant expression of various oncogenes and substances. Serum tumor markers such as carcinoembryonic antigen (CEA), α-fetoprotein (AFP), carbohydrate antigen 72-4 (CA72-4), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125), carbohydrate antigen 153 (CA153) are absent or present at low levels in a healthy individual, but they exhibit a significant increase following cancerous transformation. Monitoring alterations in the levels of serum tumor markers is valuable for the early diagnosis and prognosis prediction of certain solid tumors.

Purpose: The aim of this study is to develop a prognostic model based on preoperative tumor markers in gastric cancer patients undergoing surgery. Based on the model, the survival prognosis of patients after surgery can be predicted in order to provide clinicians with a reference to adopt personalized treatment strategies for patients undergoing surgery, thus improving the prognosis to some extent.

Methods: This study is a retrospective analysis. From December 2016 to June 2022, a total of 2484 patients with gastric cancer measuring preoperative serum tumor markers, including CEA,

AFP, CA72-4, CA19-9, CA125 and CA153 were treated with radical resection in the First Affiliated Hospital of Nanjing Medical University (NMUH). We assigned the 2484 patients into the training cohort. Multivariate Cox analysis and lasso regression were used to isolate serum tumor markers for inclusion in risk-score. The optimal cut-off value for the risk-score based on preoperative tumor markers was obtained using the 'surv_cutpoint' function in R software, which optimized the significance of splitting between Kaplan-Meier survival curves. The Receiver Operating Characteristic (ROC) analysis was conducted to assess the performance of the risk score. The regression coefficients derived from multivariate analysis were represented graphically through a nomogram, resulting in the creation of an innovative prognostic prediction model. The calibration curves, consistency index (C-index) and decision curve analysis (DCA) were employed to evaluate the precision and credibility of the nomogram. Finally, the predictive efficacy of the model was externally validated. The evaluation metrics were the K-M curves, ROC curves and Calibration curves.

Results: CEA, CA72-4, CA19-9, CA125 and CA153 were incorporated into the tumor-marker based risk-score. Risk-score was calculated using the following formula: (0.002762135×CEA) + (0.004013398×CA72-4) + (0.002081998×CA19-9) + (0.010369345×CA125) + (0.030691167×CA153). The optimal cut-off value for risk-score was 0.534325699. In the training cohort, Kaplan-Meier survival analysis showed significant statistical difference (Log-rank $p<0.0001$) between the high- and low-risk groups, similar observation was noted in the external validation cohort (Log-rank $p<0.0002$). In the subsequent ROC analysis, we observed an AUC of 0.706 at 1 year, 0.69 at 3 years, and 0.659 at 5 years in the training cohort, while AUC at 1 year, 3 years and 5 years was 0.612, 0.606, 0.593 respectively in the external validation cohort. Following the integration of patients' fundamental clinical information, multivariate cox regression analysis revealed that age, tumor location, depth of invasion (T), lymph node metastasis (N), and risk-score were independent risk factors affecting the prognosis of patients. Thus, nomogram based on these independent risk factors was constructed to predict the probability of 1-, 3- and 5-year OS of patients with GC. In terms of Concordance index (C-index), Age was 0.612 (95% CI: 0.597-0.628), Location was 0.562 (95% CI: 0.549-0.576), T was 0.748 (95% CI: 0.737-0.760), N was 0.745 (95% CI: 0.733-0.757), and risk-score was 0.666 (95% CI: 0.651-0.681). The C-index of nomogram was 0.806 (95% CI: 0.796-0.817). The DCA curves of

the training cohort showed that the proposed predictive model had good clinical applicability. Both in the training cohort and external validation cohort, calibration curves indicated the OS values predicted by nomogram fit well with the actual OS values observed in the patients in 1-, 3- and 5-year.

Conclusion: The novel prognostic prediction model based on preoperative serum tumor markers has potential clinical application value in predicting the 1-year, 3-year, and 5-year OS probability of gastric cancer patients undergoing radical surgery. Thus, it can guide the follow-up treatment of GC patients after surgical intervention.

Key Words ： Gastric cancer, serum tumor markers, LASSO-Cox regression analysis, nomogram, prognostic model

337. AFP 和 ALP 在肝癌和肝硬化鉴别诊断中的价值

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目的：探讨甲胎蛋白(AFP)和碱性磷酸酶（ALP）检测在肝癌和肝硬化辅助诊断中的应用价值。

方法：共收集 102 例样本，其中 51 例原发性肝癌患者为观察组，51 例同期肝硬化患者为对照组，采集两组患者空腹静脉血 3 mL， 以离心半径 8 cm，3 500 r/min 离心 5 min，分离 血清测定，采用电化学发光检测系统 （cobas®8000 型，罗 氏公司提供） 及原装试剂测定 AFP 和 ALP。试剂均在有效期内，质控结果良好，严格依据 说明书操作进行。AFP 正常参考值为 0-20ng/mL，ALP 正常参考值为 40-130ng/mL。比较两组 AFP 和 ALP 水平，并计算 AFP 和 ALP 对诊断 PHC 和肝硬化的敏感度、特异度。计数资料以百分数和例数表示，用χ2 检验；计量资料用(χ - ±s)表示，用 t 检验，两两比较采用 LSD-t 检验，以 P<0.05 为差异有统计学意义。

结果：与对照组（肝硬化组）相比，观察组（肝癌组）的癌患者血清 AFP 和 ALP 水平明显升高，差异具有统计学意义（p<0.01）。AFP 和 ALP 在肝癌组的阳性率分别为 47.1%和 45.1%，在肝硬化组的阳性率分别 3.92%为 15.7%，差异具有统计学意义（p<0.01）。

结论：在本文的统计样本中，AFP 和 ALP 在肝癌中的水平明显高于肝硬化，并在肝癌中的阳性率明显高于肝硬化。AFP 和 ALP 在肝癌和肝硬化的鉴别诊断中具有一定的临床应用价值，值得推广应用。

关键字： AFP；ALP；,肝癌；肝硬化

338. HP 通过 HSD11B1 激活糖皮质激素促进胃癌免疫逃逸的机制研究

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背景：幽门螺杆菌（HP）是胃癌的 I 类致癌物，90%的胃癌患者与 HP 共同感染。免疫疗法对于治疗胃癌的效果不如对乳腺癌和肺癌等其他实体肿瘤有效。因此，我们得出结论，HP 可能抑制胃癌中的免疫系统。为了确定 HP 与胃癌免疫系统之间的潜在机制，我们进行了一系列的体外和体内实验。

方法：通过 RT-qPCR 和 Western blot 确定胃癌组织中 HSD11B1 的表达情况。类器官和体内分析检查细胞增殖。流式细胞术和免疫荧光染色法以检测细胞凋亡和目标蛋白的表达水平。ELISA 定量胃癌组织中的皮质醇含量。通过荧光素酶报告基因实验、ChIP-qPCR 和 Co-IP 对机制进行研究。

结果：HP 感染可通过抑制人类和 TFF1-KO 小鼠中的 CD8+TILs 促进胃癌免疫逃逸。从 HP+/-人和小鼠的胃癌组织中进行高通量测序等系列实验，确定 HSD11B1 是胃癌免疫逃逸介质。HSD11B1 是一个将皮质酮转化为活性皮质醇的关键酶，在 HP 促进 CD8+TILs 耗竭方面发挥作用。此外，HP 将 CagA 注入胃细胞以发挥其致癌作用。CagA、HSP90AB1 和 STAT3 的组合形成一个转录复合物，诱导 HSD11B1 的表达，从而促进胃癌中 CD8+TILs 的耗竭。

结论：我们的研究结果表明，CagA、HSP90AB1 和 STAT3 复合物促进了 HSD11B1 的表达，导致皮质醇水平升高，抑制胃癌中的 CD8+TILs，从而导致免疫系统逃逸。这些结果为移除 HP 以增强在胃癌中的免疫调节治疗效果及改善患者预后提供了理论基础。

关键字 ：胃癌；幽门螺旋杆菌；糖皮质激素；CD8+肿瘤浸润淋巴细胞；免疫逃逸

339. 伊马替尼应用于 GIST 副反应与耐药

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胃间质瘤是最常见的间叶源性来源的胃肠道肿瘤，KIT 和 PDGFRA 是大多数的突变位点，而伊马替尼可有效抑制该靶点。而随着治疗进展，因伊马替尼剂量而导致的副反应和耐药现象日趋显著，大大缩短了患者的预期寿命，降低了生活质量。所以，目前的研究热点聚焦于副反应及耐药发生的原因，探索性的找寻其作用机制及作用靶点，以期针对性的减少副作用，缓解耐药情况，改善不可切除或复发转移的胃肠间质瘤患者的生活质量和生存状况。

关键字 ：胃间质瘤；伊马替尼；耐药

340. Optical nanobiosensor based on surface-enhanced Raman spectroscopy and catalytic hairpin assembly for early stage lung cancer detection via blood circRNA

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Lung cancer has become the leading cause of cancer-related deaths globally， however early detection is still challenging, resulting in the poor outcomes for the patients. Here, an optical biosensor integrating surface-enhanced Raman spectroscopy (SERS) with catalyzed hairpin assembly (CHA) was developed for the detection of circRNA (circSTAB2) that is associated with tumor formation and progression. Abundant SERS “hot spot” were generated for significantly enhancing the signals of Raman reporter via core-shell nanoprobe and 2D SERS substrate with

signal calibration function, enabling the sensitive and reliable quantitative detection of target circRNA with a low detection limit of 0.766 fM. Moreover, this biosensor was applied for detecting the circRNA in real human serum samples from lung cancer patients. Higher concentrations of circRNA belonging to the lung cancer subjects can be revealed than those belonging to the healthy ones. Especially, the unique concentration profiles of circRNA for early stage (IA and IB) as well as sub-types (IA1, IA2, and IA3) in lung cancer can be well characterized, demonstrating the promising potential of the proposed optical sensing nanoplatform as a liquid biopsy tool for lung cancer early screening and prognostic evaluation.

Key Words： Surface-enhanced Raman spectroscopy (SERS), CircRNAs, Blood analysis, Early lung cancer screening, Optical biosensor

341. RNA 结合蛋白 STAU1 促进胃癌腹膜转移机制研究

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胃癌(GC)是世界上最常见的恶性肿瘤之一。在全球发病率中排名第五，死亡率中排名第四。近十年来，我国胃癌 5 年生存率虽然略有提升，但仍低于日韩，仍徘徊在 35%～40%，因此某种程度上，仍面临很大挑战。腹膜转移是进展期胃癌最常见的转移部位之一，也是导致胃癌预后差的原因之一。然而胃癌腹膜转移的潜在分子生物学机制知之甚少，因此明确胃癌腹膜转移的发病机制，寻找切实有效的治疗靶标是胃癌研究的迫切需求。我们发现 STAU1 与胃癌细胞的恶性生物学行为密切相关，STAU1 通过影响铁自噬的方式来促进胃癌细胞腹膜转移。

关键字： RNA 结合蛋白 STAU1 胃癌 腹膜转移

342. 低密度脂蛋白受体通过介导胆固醇摄取而促进胃癌恶性进展的机制研究

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目的：世界卫生组织（WHO）发布 2020 年最新全球癌症负担数据显示：2020 年中国胃癌新发病例 47.8 万，占全球新发病例 43.9%，死亡病例 37.3 万，占全球死亡病例 48.5%。已成为严重危害我国公民健康的疾病之一。进展期胃癌患者的 5 年总生存率仍然较低，肿瘤复发和转移是胃癌患者主要死亡原因，胆固醇代谢异常是恶性肿瘤的特征之一。胃癌作为一种异质性很高的恶性肿瘤。有研究表明，高胆固醇饮食会促进胃癌发病，另有研究表明胃癌患者血清中胆固醇水平低于正常人群，提示胃癌中的胆固醇代谢过程十分复杂。因此进一步明确胆固醇在胃癌中的作用及异常代谢机制，寻找相关预测和治疗靶点，从而建立个体化治疗方案，对改善胃癌患者预后至关重要。

方法：根据本中心 1058 例胃癌病人临床数据结果分析得出，胃癌患者血清胆固醇含量与肿瘤的不良病理特征负相关关系，并对胃癌组织癌和癌旁胆固醇含量进行检测并分析发现胃癌组织中胆固醇含量高于正常组织，提出科研假说：胃癌细胞需要摄取更多的血清胆固醇以满足肿瘤生长发展的需要，胃癌组织中胆固醇水平与胃癌恶性程度正相关，通过体内外功能实验探究胆固醇对胃癌细胞的作用及分子机制，上游探究胃癌细胞中胆固醇积累增高的原因。本课题研究内主要包括（1）分析胃癌患者血清/组织胆固醇与临床病理特征的相关性。（2）探索胆固醇对胃癌恶性行为的作用及机制（3）验证 LDLR 通过促进胆固醇摄取而发挥促癌作用。

结果：（1）通过本中心临床资料的分析，以及在细胞水平和组织水平检测肿瘤胆固醇含量证明了胆固醇的积累在胃癌恶性进展中具有重要作用并与胃癌患者肿瘤大小、T 分期相关。（2）明确胆固醇可以促进胃癌细胞增殖、侵袭和转移。（3）明确 LDLR 在胃癌中高表达 LDLR 在胃癌中高表达且其表达水平与胆固醇积累水平正相关。（4）敲低 LDLR 通过减少胃癌细胞中胆固醇水平从而抑制胃癌细胞增殖、侵袭等恶性行为。

结论：胃癌在发生发展过程中需要从血清中摄取大量的胆固醇。

关键字： 胃癌、胆固醇摄取、代谢重编程、低密度脂蛋白受体

343. Non-Invasive Urinary Untargeted Metabolomic Study for the Diagnostic Biomarkers Discovery of Colorectal Cancer (CRC) Using UPLC-MS Technology

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Background: Colorectal cancer (CRC) ranks as the third most prevalent malignancy globally, presenting a formidable early diagnostic challenge. An effective biomarker with high sensitivity and specificity can help diagnose CRC and improve the chances of successful treatment.

Methods:100 healthy controls and 95 CRC patients(25 Stage 0/I， 30 stage II and 40 stage III based on Clinical stages) were recruited. Subsequently, 195 urine samples were subjected to UPLC-MS analysis. Comparative analysis was employed to elucidate noteworthy metabolic variances, and pathway analysis was conducted to unveil perturbed metabolic functions. Ultimately, metabolic panels for CRC diagnosis were constructed.

Result:A total of 82 metabolites exhibited statistical significance between CRC patients and healthy controls. Moreover, pathway analysis revealed that they were associated with Steroid hormone biosynthesis, Nitrogen metabolism, and D-Glutamine and D-glutamate metabolism. A composite panel consisting of Retinol, L-β-aspartyl-L-glycine and 21-Deoxycortisol showed AUCs of 0.933/0.93 in the discovery/validation group. The panel also showed commendable

efficacy in indifferent CRC stages, with an AUC of 0.918 for stages 0/I, 0.862 for stage II, and 0.845 for stage III.

Conclusions: Urine metabolome could distinguish CRC from healthy control and reflect the changes in different stages of CRC. Potential biomarkers might be developed by targeted metabolomic analysis.

Feng Qi, Yulin Sun and Jiaqi Liu contributed equally to this work.Xin Qi,Xiaohang Zhao and Wei Sun were corresponding authors.

Key Words： Urine non-targeted metabolomics, Colorectal cancer, diagnostic biomarker

344. Cancer therapy with a CRISPR-assisted telomerase-activating gene expression system

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Background: Cancer is caused by a series of alterations in genome and epigenome and exists in multiple complex forms, making it difficult to be prevented and/or treated. Telomerase, an enzyme responsible for the maintenance of telomere, is silent in most normal somatic cells but activated in 90% of cancer cells, making it as an excellent target for cancer therapy. Therefore, various telomerase activity inhibitors have been developed to treat cancer but all failed due to side effects.

Methods: Here we acted oppositely to develop a cancer gene therapy named telomerase-activating gene expression (Tage) system by utilizing the telomerase activity in cancer cells. The Tage system consisted of an effector gene expression vector that carried a 3′ telomerase-recognizable stick end and an artificial transcription factor expression vector that could express dCas9-VP64 and a sgRNA targeting telomere repeat sequences.

Results: By using Cas9 as an effector gene, the Tage system effectively killed various cancer cells, including HepG2, HeLa, PANC-1, MDA-MB-453, A549, HT-29, SKOV-3, Hepa1-6, and RAW264.7, without affecting normal cells MRC-5, HL7702, and bone marrow mesenchymal stem cell (BMSC). More importantly, a 4-bases 3′ stick end produced by the homothallic switching endonuclease in cells could be recognized by telomerase, allowing the Tage system to effectively

kill cancer cells in vivo. The Tage system could effectively and safely realized its in vivo application by using adeno-associated virus (AAV) as gene vector.

Conclusions: The virus-loaded Tage system could significantly and specifically kill cancer cells in mice by intravenous drug administration without side effects or toxicity.

Key Words ： telomerase, CRISPR/Cas9, cancer therapy, AAV

345. Causal roles of immune cells in colorectal cancer: a two-sample Mendelian randomization (MR) study

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Background: Emerging evidence indicated that an imbalance in the tumor immune microenvironment could be a significant contributing factor to CRC. However, the distinct causal effect of immune cells on CRC remains unclear.

Methods: A two-sample Mendelian randomization study was performed to specify the correlation between immune cells and CRC based on the summary data from GWAS. Inverse variance weighted, MR-Egger, weighted median, weighted model and simple mode were used to examine the causal association between immune cell signatures and CRC. Sensitivity analyses were used to verify the robustness, heterogeneity, and horizontal pleiotropy of the results.

Results: Inverse variance weighted estimates suggested that increased lymphocyte %leukocyte had a significant causal effect on CRC (p =0.0004, PFDR= 0.1622). Then HLA DR on CD33br HLA DR+ CD14- of myeloid cell (p =0.0006, PFDR= 0.0235) and CD20- %lymphocyte of B cell (p =0.0065, PFDR= 0.1369) were found to have a causal effect on lymphocyte %leukocyte which were analyzed to be driven by CRC($p<0.05$). No significant heterogeneity of instrumental variables or horizontal pleiotropy was found.

Conclusions: This two-sample MR study found that lymphocyte %leukocyte were causally associated with CRC progress which would be promoted by later CRC drived HLA DR on CD33br HLA DR+ CD14- of myeloid cell and CD20- %lymphocyte of B cell. It may provide a

new avenue for researchers to explore the biological regulation of immune microenvironment on CRC which could lead to exploration of earlier intervention and treatment.

Key Words: Immune cell, Causal inference, CRC, MR analysis, Sensitivity

346. Simultaneous detection of methylation and genetic variations of BCR-ABL1 gene by nanopore Cas9-targeted sequencing

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Background: The structure variations (SVs) of BCR-ABL1 fusion gene are important companion diagnostic biomarkers for leukemia patient, and its kinase domain's single nucleotide variations (SNVs) and promoter aberrant methylations (5mC) are also associated with drug response. However, there is no technique that can detect these events simultaneously.

Methods: Based on nanopore Cas9-targeted sequencing (nCATS) protocol, we designed 4 crRNAs to target the interest of regions, including most breakpoints, ABL1 kinase domain and BCR promoter, of BCR-ABL1gene for library construction. The sequencing data was obtained from R9.4 flow cell with running on MinION sequencer, and analyzed by Cas9-nanopore pipeline.

Results: We found that coverages of the targeted regions were at 300×~500× and characterized a b3a2 subtype of BCR-ABL1 fusion gene. Furthermore, we evaluated Bcftools, Clair3 and Freebayes software for SNVs identification and Megalodon software for 5mC methylation. Our result showed that Bcftools had the best performance for SNVs detection in ABL1 kinase domain with 5 annotated SNPs identified. We also observed hypomethylated status in upstream half and hypermethylated status in the downstream half of the CpG island in BCR promoter region.

Additionally, we developed a pipeline, named as Cas9-nanopore, to simplify the analysis of SVs, SNVs, and 5mC for nCATS data and confirmed its performance with applications of the nCATS data of HTT gene from K562 cells.

Conclusions: This study established an nCATS technology specifically for detecting BCR-ABL1 fusion gene, its KD region mutations and promoter 5mC modification, providing a more comprehensive and efficient detection for hematological tumors with high incidence of BCR-ABL1 fusion gene, which has potential clinical application value and cutting-edge technological innovation.

Key Words ： BCR-ABL1 fusion gene; nanopore Cas9-targeted sequencing; genetic variation; BCR promotor methylation; companion diagnostics biomarker

347. 1 例 TP53 胚系突变相关 Li-Fraumeni 综合征

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李-佛美尼综合征（Li-Fraumeni syndrome,LFS）是一种罕见的常染色体显性遗传肿瘤易感综合征，既往对于该遗传综合征的识别主要依靠临床病史的收集，近年来随着高通量测序技术手段的发展，越来越多的患者在进行靶向药物靶点检测时意外发现携带有致病性胚系突变，临床尽早发现这些突变不仅可以帮助医生为患者制定全方位的诊疗方案，同时也可以为患者的亲属提供遗传咨询和预防监测。在本文，我们报道了一例 45 岁的 LFS 女性患者，她患有多原发恶性肿瘤，分析其临床病理特征、诊疗经过、基因检测结果及预后情况，以提升临床对遗传性肿瘤的认识，并指导临床诊疗。

关键字： 李-佛美尼综合征，TP53，胚系突变，遗传性肿瘤，高通量测序

348. Faecalibacterium mediates the effect of dairy preference on colorectal cancer susceptibility: evidence from large-scale GWASs

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Objective: We aimed to investigate the causal relationship between food preference, gut microbiota and colorectal cancer (CRC) susceptibility.

Methods: Using large-scale genome-wide association study (GWAS) datasets of gut microbes (18,340 individuals), food preference (161,625 individuals), and CRC (24,476 cases versus 23,073 controls), we conducted a two-step bidirectional Mendelian randomization analysis to assess the causal impact of 45 food preference on CRC susceptibility, as well as the evidence mediated by gut microbiota. The inverse variance weighted (IVW) method was primary to evaluate the causal associations, followed by multiple sensitivity analyses to ensure the validity.

Results: We found that F-fatty/salty food preference was suggestively associated with CRC susceptibility [IVW OR = 0.65, 95CI%: 0.43 to 0.98, P = 0.040], while no single food survived Bonferroni correction. Nine gut microbiota were found associated with CRC, and four food preference traits were associated with four gut bacterial taxa. Notably, we identified a significant causal association between genetically predicted preference for dairy intake and increased abundance of Faecalibacterium [IVW $\beta = 0.72$， 95% CI: 0.30-1.14, $P = 6.86\times10^{-4}$]. Additionally, the increment of *Faecalibacterium* could reduce the risk of CRC [IVW OR = 0.91, 95% CI: 0.85-0.97, P = 7.04×10^{-3}]. However, there was no evidence of an assocaition between dairy preference and CRC risk [IVW OR = 0.93, 95%CI: 0.34 to 2.57, P = 0.890]. Mediation analysis suggested that *Faecalibacterium* seemed to totally mediate the effect of dairy to CRC [indirect effect: -0.07, 95% CI: -0.14 to -0.01, P = 0.035]. According to subgroup analysis, the total mediation effect remained in late-onset CRC [indirect effect: -0.07, 95% CI: -0.15 to -0.02, P = 0.029] and female CRC [indirect effect: -0.07, 95% CI: -0.16 to -0.01, P = 0.049].

Conclusions: This study suggested the causal evidence of dairy-liking, gut *Faecalibacterium* level, and CRC risk using large-scale GWAS studies, providing additional insights into CRC etiology as well as prevention through dietary interventions.

Key Words ： causal pathway; food liking; gut microbiota; colorectal cancer risk; Mendelian randomization; mediation

349. The Causal Effect of Rheumatoid Arthritis on Skin Cancer and Its Subtypes: Discerning Genuine Associations Through Ancestry-Informative Markers

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Background

An increased risk of skin cancer was observed among rheumatoid arthritis (RA) patients, but it is unclear whether RA has a causal effect on skin cancer. We used Mendelian randomization (MR) analysis for causality inference of RA and skin cancers.

Methods

Based on genome-wide association studies from UK Biobank, FinnGen and IEU OpenGWAS project, single nucleotide polymorphisms (SNPs) strongly associated with RAs were selected as instrumental variables. Random-effect inverse-variance weighted (IVW) analysis was used as the primary method to assess the potential causal impact, along with weighted median and MR-Egger for sensitivity analysis. Heterogeneity was assessed by Cochran's Q test and leave-one-out analyses, and the horizontal pleiotropy was by the intercept test of MR-Egger regression for significant estimates.

Results

The results of IVW analysis showed genetic liability to RA was associated with decreased risks of overall skin cancer, non-melanoma skin cancer (NMSC) and basal cell carcinoma (BCC) in the European population (all odds ratios [ORs] < 1.000 with P values < 0.05). Stratifying by serostatus,

genetic liability to seropositive RA (sero+RA) was associated with a decreased risk of BCC (OR = 0.875, 95% CI 0.818-0.935, P < 0.001).

Conclusions

Genetic liability to overall RA and sero+RA in European ancestry was associated with a decreased risk of certain skin cancers and the finding warranted further confirmation. Despite possible tumor inhibition of RA, surveillance for skin cancers is still necessary for RA patients.

Key Words ： Rheumatoid arthritis, Skin cancer, Mendelian randomization, Causality

350. Diagnostic value of cerebrospinal fluid human epididymis protein 4 for leptomeningeal metastasis in lung adenocarcinoma

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Background: The diagnosis of lung adenocarcinoma (LUAD) leptomeningeal metastasis (LM) remains a clinical challenge. Human epididymis protein 4 (HE4) functions as a novel tumor biomarker for cancers. This study aimed to assess the diagnostic value of cerebrospinal fluid (CSF) HE4, and combined with CEACAM6, for LUAD LM.

Methods: The CSF HE4 protein level was measured in two independent cohorts by electrochemiluminescence. Test cohort included 58 LUAD LM patients, 22 LUAD patients without LM (Wiot-LM), and 68 normal controls. Validation cohort enrolled 50 LUAD LM patients and 40 normal controls, in parallel with Wiot-LM patients without brain metastases (19 Wiot-LM/BrM patients) or with BrM (26 BrM patients). The CSF level of CEA, CA125, CA153, CA199, CA724, NSE and ProGRP of these samples was measured by electrochemiluminescence, whereas the CSF CEACAM6 level was detected by enzyme-linked immunosorbent assay (ELISA). In addition, the serum level of these biomarkers was detected by same method as CSF.

Results: The level of HE4 or CEACAM6 in CSF samples from LUAD LM patients was significantly higher than those from normal controls and Wiot-LM patients. The HE4 level in CSF was higher than that in serum of LM patient. The CSF HE4 or CEACAM6 level for distinguished

LM from Wiot-LM showed good performance by receiver-operating characteristic analysis. The better discriminative power for LM was achieved when HE4 was combined with CEACAM6. In addition, the CSF HE4 and CEACAM6 level showed little or no difference between Wiot-LM/BrM and BrM patients, the BrM would not significantly influence the HE4 or CEACAM6 level in CSF. The diagnostic power of CSF CA125, CA153, CA199, CA724, NSE and ProGRP for LUAD LM were not ideal.

Conclusion: The combination with HE4 and CEACAM6 has the promising application for the diagnosis of LUAD LM.

关键字 ： cerebrospinal fluid, human epididymis protein 4, CEACAM6, lung adenocarcinoma, leptomeningeal metastasis

351. 直肠癌侧方淋巴结转移清扫术后的生存分析

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目的：回顾性分析腹腔镜直肠癌层面优先入路侧方淋巴结清扫患者侧方淋巴结及肠系膜淋巴结的转移特点及生存预后。

方法：收集 2017 年 5 月~2022 年 12 月天津市人民医院进行腹腔镜层面优先入路侧方淋巴结清扫的患者临床资料，对患者侧方淋巴结及肠系膜淋巴结的转移情况与生存预后进行分析，从而探讨侧方淋巴结转移应归属于局部转移还是远处转移。

结果：共纳入 111 例患者资料，通过 COX 比例风险模型对肠系膜-侧方+（n=20）和肠系膜+侧方+（n=58）患者的生存数据进行分析显示，肠系膜-侧方+（n=20）组 3 年生存率为 58%，肠系膜+侧方+（n=58）组 3 年生存率为 59.8%，与文献报道相比，两组生存曲线与直肠癌淋巴结转移分期的 N2 期生存曲线一致，3 年生存率与直肠癌 N2 期相近。

结论：直肠癌侧方淋巴结转移而直肠系膜淋巴结未转移的患者预后可能与直肠癌 N2 期的患者相似，优于IV期直肠癌患者，提示直肠癌侧方淋巴结转移应归属于区域淋巴结转移而非远处转移。

关键字： 直肠肿瘤；侧方淋巴结清扫术；腹腔镜；层面优先入路；生存曲线

352. Analysis of the Gene Expression Associated with Lymph Node Metastasis in Colorectal Cancer

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Objective: This study aimed to explore the genes regulating lymph node metastasis in colorectal cancer (CRC), and to clarify their relationship with tumor immune cell infiltration and patient prognoses.

Methods: The data sets of colorectal cancer patients were collected through the Cancer Gene Atlas (TCGA) database; the differentially expressed genes (DEGs) associated with CRC lymph node metastasis were screened; a protein-protein interaction (PPI) network was constructed; the top 20 hub genes were selected; the gene ontology (GO) functions and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were enriched and analyzed. The Lasso regression method was employed to further screen the characteristic genes associated with CRC lymph node metastasis in 20 hub genes, exploring the correlation between the characteristic genes and immune cell infiltration, conducting a univariate COX analysis on the characteristic genes, obtaining survival-related genes, constructing a risk score formula, conducting a Kaplan-Meier analysis based on the risk score formula, and performing a multivariate COX regression analysis on the clinical factors and risk scores.

Results: A total of 62 DEGs associated with CRC lymph node metastasis were obtained. Among the 20 hub genes identified via PPI, only CLCAI expression was down-regulated in lymph node metastasis, and the rest were up-regulated. A total of 9 characteristic genes associated with CRC lymph node metastasis (KIF1A, TMEM59L, CLCA1, COL9A3, GDF5, TUBB2B, STMN2, FOXN1, and SCN5A) were screened by means of the lasso regression method. The 9 characteristic genes were significantly related to different kinds of immune cell infiltration, from

which three survival-related genes (TMEM59L, CLCA1, and TUBB2B) were screened. A multi-factor COX regression showed that the risk scores obtained from TMEM59L, CLCA1 and TUBB2B were independent prognostic factors. Immunohistochemical validation was performed in tissue samples from patients with rectal and colon cancer.

Conclusion: TMEM59L, CLCA1 and TUBB2B were independent prognostic factors associated with lymphatic metastasis of CRC.

Key Words ： Colorectal Cancer, Lymphatic Metastasis, TMEM59L, CLCA1, TUBB2B

353. 七种肿瘤相关抗原自身抗体在非小细胞肺癌诊断中的应用

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目的：探讨七种肿瘤相关抗原自身抗体（p53、PGP9.5、SOX2、GAGE7、GBU4-5、MAGE A1 和 CAGE）在非小细胞肺癌（non-small cell lung cancer, NSCLC）辅助诊断中的临床价值。

方法：收集 2019 年 7 月至 2019 年 12 月在南京医科大学第一附属医院就诊的 188 例 NSCLC 初诊患者作为疾病组，同时选择 79 例肺部良性疾病患者（BLD）及 120 例健康体检者（HC）作为对照。采用 ELISA 法检测各组血清中七种肿瘤相关抗原自身抗体的水平，同时 ELICA 法检测癌胚抗原（CEA）、细胞角蛋白片段 19（CYFRA21-1）和神经元特异性烯醇化酶（NSE）水平，绘制 ROC 曲线分析并比较不同标志物对 NSCLC 的诊断效能。

结果：肺癌组 7 种自身抗体中有 6 项（p53、SOX2、GAGE7、GBU4-5 和 CAGE）的血清水平在 NSCLC 组均分别高于 BLD 组（p53：Z=-4.222，P=0.000；SOX2：Z=-4.627，P=0.000；GAGE7：Z=-4.495，P=0.000；GBU4-5：Z=-5.689，P=0.000；CAGE：Z=-5.432，P=0.000）和 HC 组（p53：Z=-5.785，P=0.000；SOX2：Z=-4.427，P=0.000；GAGE7：Z=-2.371，P=0.018；GBU4-5：Z=-5.433，P=0.000；CAGE：Z=-3.634，P=0.000），差异有统计学意义。MAGE A1 项在 NSCLC 组与 BLD 组间的差异有统计学意义（Z=-5.089，P=0.000）、与 HC 组无差异。七种肿瘤相关抗原自身抗体联合检测诊断 NSCLC 患者敏感性为 71.61%，特异性为 87.36%，AUC 为 0.795，其敏感性和 AUC 均高于传统肿瘤标志物（CEA：Sen=13.55%，AUC=0.510；

CYFRA21-1：Sen=19.35%，AUC=0.507；NSE：Sen=55.48%，AUC=0.629）。七种自身抗体联合检测在 NSCLC 组的阳性率明显高于 BLD 组($\chi 2 = 7.293$，P=0.007) 和 HC 组($\chi 2 = 8.411$，P=0.004)。

结论：七种肿瘤相关抗原自身抗体联合检测可作为 NSCLC 患者辅助诊断的指标，并且联合 CEA、NSE 和 CYFRA21-1 可以提高 NSCLC 患者的诊断敏感度。

关键字： 自身抗体；非小细胞肺癌；肿瘤标志物；辅助诊断

354. 外泌体 circ6853 促进胃癌血管形成和转移的作用与机制

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目的：胃癌（Gastric cancer,GC）是最常见的恶性肿瘤之一，其病因复杂、早期症状不明显、预后较差，寻找早期诊断标志物和治疗靶点是目前亟待解决的问题。外泌体（Exosomes）是近年来液体活检的主要成分之一，由于环状 RNA（circular RNA，circRNA）分布广泛、组织特异性强、具有比线性 RNA 更高的稳定性，因此外泌体 circRNA 具有作为标志物的巨大潜力和优势。本研究旨在探讨血浆外泌体来源的 circ6853 在胃癌中的诊断价值以及参与胃癌发生发展的作用和机制。

材料与方法：通过 ceRNA 芯片测序筛选胃癌、胃炎以及健康体检者血浆中差异表达的外泌体 circRNAs。使用液滴数字 PCR（ddPCR）建立外泌体 circRNAs 的检测方法以及分析胃癌患者的诊断效能。通过平板克隆、CCK8、transwell 迁移和侵袭实验研究外泌体 circ6853 在胃癌中的体外生物学功能。双荧光素酶报告基因实验、RNA 免疫共沉淀、RNA pulldown、染色质免疫共沉淀、功能回补等实验探讨外泌体 circ6853 参与胃癌进展的作用机制。最后，裸鼠荷瘤和转移瘤模型用于验证体内外泌体 circ6853 的生物学效应。

结果：circ6853 在胃炎和胃癌患者的血浆外泌体中高表达，且外泌体 cir6853 的水平随着胃癌的进展显著增加，术后水平下降，与胃肿瘤大小和远端转移相关。ddPCR 显著提高了血浆外泌体 circ6853 的检测灵敏度（检出限为 4.79copies/ul）和诊断效能（灵敏度=73.58%，特异度=89.66%，AUC=0.85），具有良好的精密度、特异度。过表达外泌体 circ6853（体外

和体内）促进胃癌细胞的增殖、迁移、侵袭和血管形成，而敲减 circ6853 则起到相反的作用。circ6853 通过吸附 miR-627-5p 增加 FLVCR1 的表达，促进血管形成和内皮细胞通透性。circ6853 与 HIF1A mRNA 竞争结合 FUS 蛋白，胃癌中上调的 circ6853 抑制 FUS 与 HIF1A mRNA 的结合，削弱了 FUS 蛋白对 HIF1A 的降解，导致 HIF1A/VEGFA 信号通路增强，血管形成增加。此外，外泌体 circ6853 可被 HUVEC 摄取，通过 miR-627-5p/FLVCR1 轴和 HIF1A/VEGFA 信号通路共同促进血管形成和内皮细胞通透性。

结论：我们的研究表明，血浆外泌体 circ6853 在胃癌诊断和监测肿瘤进展中极具标志物潜力，数字 PCR 在其检测方法学和诊断应用中具有重要价值，且肿瘤来源的外泌体 circ6853 通过促进血管生成和破坏内皮屏障进而增强胃癌细胞的转移能力。

关键字 ：胃癌；外泌体；circRNA；ddPCR；诊断

355. PIVKA-II 联合 AFP 在肝癌诊断中的应用价值研究

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目的：探讨血清肿瘤标志物异常凝血酶原（PIVKA-II）、甲胎蛋白 (AFP) 以及联合检测在肝癌诊断中的应用价值。

材料与方法：选取 2023 年 3 月至 2023 年 10 月北京大学肿瘤医院内蒙古医院收治的患者及健康体检人群，其中包含 56 例肝癌患者，412 例健康体检人员。采用电化学发光免疫分析仪（罗氏 cobas 8000 e801）及其配套试剂盒，严格按照标准操作流程对 AFP、PIVKA-II 血清水平进行检测，比较 2 组入组人群 PIVKA-II 与 AFP 的水平，并绘制受试者工作曲线（ROC），分析 PIVKA-II与 AFP 指标在肝癌诊断中的价值。

结果：肿瘤标志物 PIVKA-II 与 AFP 血清表达水平肝癌组明显高于对照组 (P＜0.05)，ROC 曲线结果显示，PIVKA-II与 AFP 指标检测的 AUC 分别为 0.833、0.718，PIVKA-II 检测对肝癌的诊断价值高于 AFP。

结论：肿瘤标志物 PIVKA-II 检测在肝癌诊断中具有较高的诊断价值，与 AFP 检查联合对肝癌患者具有较高的区分能力，有利于肝癌患者的早期诊断。

关键字： 异常凝血酶原(PIVKA-II). 甲胎蛋白（AFP） 肝癌

356. Prognostic role of tumor-infiltrating lymphocytes in gastric cancer: A systematic review and meta-analysis

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Background: Tumor-infiltrating lymphocytes (TILs) have been discussed to be associated with prognosis in gastric cancer (GC) patients. Limited studies have discussed prognosis based on subsets of TILs and their infiltration sites. This meta-analysis aimed to evaluate the potential values of main TILs subsets according to counting sites as prognosis predictors of GC.

Method: A total of 47 eligible articles were obtained through systematic retrieval and rigorous screening, collecting study information and extracting hazard ratio (HR), and 95% confidence interval (CI) for pooled analyses of disease-free survival (DFS) and overall survival (OS). Statistical software was used to calculate the pooled results and output relevant figures.

Results: Higher $CD4^+$ TILs were correlated with favorable OS (HR=0.79, 95%CI 0.66-0.94, *P*=0.009), the same applied to tumor center (HR=0.59, 95%CI 0.45-0.79, *P*=0.0004) and infiltration margin (HR=0.57, 95%CI 0.40-0.82, *P*=0.003). Higher $CD8^+$ TILs prolonged DFS (HR=0.69, 95%CI 0.51-0.95, *P*=0.02) and OS (HR=0.96, 95%CI 0.94-0.99, *P*=0.006), and in tumor center (HR=0.80, 95%CI 0.68-0.94, *P*=0.006), infiltration margin (HR=0.75, 95%CI 0.56-1.01, *P*=0.06) were also, for OS. The above results were affected by the analysis method, region, sample size and year of publication. Neither the overall analysis nor the subgroup analyses showed that the level of $FOXP3^+$ TILs was associated with prognosis (DFS: HR=0.89, 95%CI 0.66-1.19, *P*=0.42; OS: HR=0.98, 95%CI 0.85-1.13, *P*=0.75). Pooled results revealed that higher $CD3^+$ TILs were correlated with favorable DFS (HR=0.69, 95%CI 0.56-0.84, *P*=0.0003) but not OS (HR=1.00, 95%CI 0.99-1.01, *P*=0.48), while positive results were obtained in the infiltration margin and in the sample size ≥150 group (infiltration margin: HR=0.65, 95%CI 0.42-0.99, *P*=0.04; sample size ≥150: HR=0.74, 95%CI 0.63-0.88, *P*<0.001). Could not assume prolonged OS in high $CD45RO^+$ TILs group (HR=0.56, 95%CI 0.31-1.03, *P*=0.06) since only four studies were included.

Conclusion: High infiltrating $CD3^+$, $CD4^+$, $CD8^+$ T cells prolong survival, and $FOXP3^+$ subset is not related to prognosis in GC patients with surgery. For $CD4^+$ and $CD8^+$, such associations were also present in tumor center and infiltration margin groups. More relevant, large sample-sized clinical studies concerning some subsets and their infiltration sites are needed in the future to validate the prognostic effects.

Key Words： gastric cancer; tumor-infiltrating lymphocytes; prognosis; meta-analysis

357. Gut microbiome for predicting immune checkpoint blockade-associated adverse events

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Background

The impact of the gut microbiome on the initiation and intensity of immune-related adverse events (irAEs) prompted by immune checkpoint inhibitors (ICIs) is widely acknowledged. Nevertheless, there is inconsistency in the gut microbial associations with irAEs reported across various studies.

Methods

We performed a comprehensive analysis leveraging a dataset that included published microbiome data (n = 317) and in-house generated data from 16S rRNA and shotgun metagenome samples of irAEs (n = 115). We utilized a machine learning-based approach, specifically the Random Forest (RF) algorithm, to construct a microbiome-based classifier capable of distinguishing between non-irAEs and irAEs. Additionally, we conducted a comprehensive analysis, integrating transcriptome and metagenome profiling, to explore potential underlying mechanisms.

Results

We identified specific microbial species capable of distinguishing between patients experiencing irAEs and non-irAEs. The RF classifier, developed using 14 microbial features, demonstrated robust discriminatory power between non-irAEs and irAEs (AUC = 0.88). Moreover, the

predictive score from our classifier exhibited significant discriminative capability for identifying non-irAEs in two independent cohorts. Our functional analysis revealed that the altered microbiome in non-irAEs was characterized by an increased menaquinone biosynthesis, accompanied by elevated expression of rate-limiting enzymes menH and menC. Targeted metabolomics analysis further highlighted a notably higher abundance of menaquinone in the serum of patients who did not develop irAEs compared to the irAEs group.

Conclusions

Our study underscores the potential of microbial biomarkers for predicting the onset of irAEs and highlights menaquinone, a metabolite derived from the microbiome community, as a possible selective therapeutic agent for modulating the occurrence of irAEs.

Key Words： Immune-related adverse events, Gut microbiome, Immune checkpoint inhibitors, Programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1)

358. 血浆外泌体 hsa_circ_0006718 在胃癌进展及诊断中的作用机制

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目的：胃癌是全球常见的消化道肿瘤且预后较差，常用的诊断标志物缺乏灵敏度和特异度。本研究旨在找寻外泌体 circRNA 能否作为新型胃癌诊断标志物，探讨其胃癌进展中的作用与分子机制。

材料与方法：ceRNA 芯片筛选差异性表达的 circRNA，在胃癌患者血浆外泌体中分析其诊断效能。细胞增殖,Transwell 迁移检测细胞增殖和迁移功能。从新鲜胃癌组织中分离培养原代胃癌间充质干细胞（GC-MSC），检测癌症相关成纤维细胞（CAF）标志物和细胞因子水平。RIP、Co-Ip、chip、双荧光素酶报告基因、裸鼠体内荷瘤和转移瘤等实验体内外探究外泌体 hsa_circ_0006718 促进胃癌的作用机制。

结果：hsa_circ_0006718 在胃癌患者血浆外泌体中高表达，联合传统标志物诊断胃癌的 AUC 为 0.86。敲减其抑制胃癌的增殖和转移。生物信息学预测并验证其下游靶点

hsa-miR-561-3p 和 SAAL1，回补实验验证其调控功能。外泌体 hsa_circ_0006718 促进 SAAL1 与 PRRX1 的结合，增强 PRRX1 的转录活性，激活 TGFβ1/smad2/3 信号通路促进 GC-MSC 发生 CAF 样转化。

结论：血浆外泌体 hsa_circ_0006718 作为早期和鉴别诊断慢性萎缩性胃炎患者和胃癌患者标志物。胃癌细胞外泌体 hsa_circ_0006718 通过调控 hsa-miR-561-3p/SAAL1/PRRX1 激活 TGFβ1/smad2/3 信号通路促进胃癌进展以及 GC-MSC 发生 CAF 样转化，塑造利于肿瘤转移的微环境。

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关键字 ：外泌体 circRNA 胃癌 标志物 肿瘤微环境

359. Clinical Significance of Porphyromonas gingivalis Enriching Cancer Stem Cells by Inhibiting Programmed Cell Death Factor 4 in Esophageal Squamous Cell Carcinoma

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Purpose: Studies have confirmed that the colonization of *Porphyromonas gingivalis* (Pg) could promote the malignant evolution of esophageal squamous cell carcinoma (ESCC). Since pathogenic microorganisms can promote malignant tumour proliferation by inhibiting programmed cell death factor 4 (PDCD4) and the decrease of PDCD4 activity can enhance the stemness of cancer cells, we here investigate the functional mechanism by which Pg promotes ESCC chemoresistance and malignancy through inhibiting PDCD4 and enriching cancer stem cells (CSCs).

Materials and Methods: The effects of Pg and PDCD4 on CSCs, chemoresistance and malignancy of ESCC cells were evaluated by in vitro studies. The expression of Pg, PDCD4 and ALDH1 in ESCC tissues were detected by IHC, and the correlations between each index and postoperative survival of ESCC patients were analysed.

Results: The results showed that Pg could inhibit PDCD4 expression and lead to CSCs enrichment in ESCC cells. After eliminating Pg, the expression of PDCD4 was upregulated, the percentage of CSCs, chemoresistance and malignancy were decreased. And ESCC patients with Pg-positive, PDCD4-negative, and ALDH1-positive have a significant shorter survival.

Conclusion: This study proved that eliminating Pg and blocking CSCs enrichment caused by decreasing PDCD4 activity may provide a new strategy for ESCC treatment.

Key Words： cancer stem cells; esophageal squamous cell carcinoma; PDCD4; Porphyromonas gingivalis; tumor microenvironment

360. 流式细胞术检测外周血 PD-1+及 CD28+T 细胞对肺癌患者的临床意义

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目的：利用临床病例探讨外周血 T 淋巴细胞表面 PD-1 及 CD28 表达水平检测对于肿瘤患者的临床意义。

方法：利用流式细胞术，序贯检测肺癌患者外周血 T 淋巴细胞（CD45+CD3+）、辅助性 T 细胞（CD3+CD4+）及抑制性 T 细胞（CD3+CD8+）表面的 PD-1 及 CD28 表达状态，分享 5 个典型病例，探讨 PD-1/CD28 表达变化与肺癌患者临床表现之间的关系。

结果：通过 5 个典型病例的分析，第一，使用 PD-1 抗体进行治疗的患者，T 细胞表面的 PD-1 靶点被药物封闭，用于此项检测的流式抗体无法结合，因此检测结果中 PD-1 阳性的细胞数接近 0。第二，未使用 PD-1 抗体治疗的化疗患者中，PD-1 表达阳性 T 细胞比率升高与患者临床进展相关；第三、使用 PD-1 抗体治疗的患者中，CD28 表达阳性 T 细胞比率

升高与患者临床缓解相关；CD28 表达阳性 T 细胞比率降低与患者临床进展相关。我们的初步队列研究显示，肺癌患者基线 PD-1/CD28（比值）＞0.4，患者预后较差。

结论：外周血 PD-1/CD28 表达检测可以明确 PD-1 抗体对患者 PD-1 靶点的封闭效果。PD-1/CD28 检测可以用于评估患者预后。肺癌患者基线 PD-1/CD28（比值）＞0.4，患者预后较差（初步队列研究结果）。

关键字： 肺癌；T 淋巴细胞；流式细胞术；PD-1；CD28；

361. LncRNA MCF2L-AS1 promotes colorectal cancer progression by post-transcriptional activation of MCF2L

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Objective: To investigate the effect of long non-coding RNA (lncRNA) MCF2L-AS1 on the occurrence and development of colorectal cancer (CRC) by regulating the post-transcriptional activation of MCF2L, and to explore whether its mechanism of action is related to the interaction of heterogeneous nuclear ribonucleoprotein AUF1.

Methods: The expression of MCF2L-AS1 /MCF2L in CRC tissues and CRC cell lines was detected by qRT-PCR. The biological function of MCF2L-AS1 was investigated in vitro and in vivo (colony formation, CCK8, wound healing, Transwell invasion assays, and establishment of transplanted tumor model). Bioinformatic analysis, RNA fluorescence in situ hybridization, and RNA binding protein immunoprecipitation were used to investigate the mechanism.

Results: The expression level of MCF2L-AS1 in CRC tissues was significantly up-regulated compared with the matched paracancer tissues ($P<0.05$). Compared with NCM460, the expression level of MCF2L-AS1 in CRC cell lines (HCT116, HCT8, HT29, Caco2, SW620) was significantly up-regulated ($P<0.05$). Knocking down the expression of MCF2L-AS1 inhibited the viability and colony capacity of HCT116 and HCT8 cells ($P<0.05$), and the number of migratory and invasive cells was significantly reduced ($P<0.05$). Immunohistochemical results showed that the expression level of MCF2L was down-regulated in colorectal cancer cells with low expression of MCF2L-AS1. Western blot and functional assays confirmed that MCF2L-AS1 promoted the

proliferation, migration, and invasion of colorectal cancer cells by regulating the expression of MCF2L. Mechanism studies have shown that MCF2L-AS1 binds to the heterogeneous nuclear ribonucleoprotein AUF1, thereby activating the translation of MCF2L mRNA without affecting its mRNA levels.

Conclusions: The data from this study suggest that MCF2L-AS1 induces the proliferation, migration, and invasion of colorectal cancer cells through AUF1-mediated activation of MCF2L mRNA translation. MCF2L-AS1 may be an effective target for clinical intervention in advanced CRC.

Key Words： lncRNA, heterogenous nuclear ribonucleoprotein D0, Colorectal cancer

362. Multi-kingdom gut microbiota analyses define bacterial–fungal interplay and microbial markers of pan-cancer immunotherapy across cohorts

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The effect of gut bacteria on the response to immune checkpoint inhibitors (ICI) has been studied, but the relationship between fungi and ICI responses are not fully understood. Herein, 862 fecal metagenomes from 9 different cohorts were integrated for identification of differentially abundant fungi and subsequent construction of random forest (RF) models to predict ICI responses. Fungal markers demonstrate excellent performance with an average area under the curve (AUC) of 0.87, and improved performance reaching an average AUC of 0.89 when combined with bacterial markers. Higher enrichment of exhausted T cells are detected in responders as predicted by fungal markers. Multi-kingdom network and functional analysis reveal that the fungi Schizosaccharomyces octosporus may ferment starch into short-chain fatty acids in responders.

This study provides a fungal profile of the ICI response, and the identification of multi-kingdom microbial markers with good performance that may improve the overall applicability of ICI therapy.

Key Words： pan-cancer, immunotherapy, fungi, multi-kingdom, bacteria, metagenome

363. The E3 ligase PJA1 suppresses docetaxel-induced pyroptosis and antitumour immunity to facilitate chemoresistance in nasopharyngeal carcinoma

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Background: Nasopharyngeal carcinoma (NPC) is highly prevalent in South China. More than 70% of patients are diagnosed with locoregionally advanced NPC (LA-NPC) at initial presentation, and the addition of induction chemotherapy (IC) to concurrent chemoradiotherapy is recommended for these patients. However, the tumour response to TPF IC differs among patients, and a subgroup of patients who do not respond to TPF IC derive little benefit from IC and eventually experience recurrence or distant metastasis because of chemoresistance. Thus, there is an urgent need to learn more about mechanisms of NPC chemoresistance to identify effective prognostic biomarkers and therapeutic strategies for NPC.

Methods: A gene expression dataset and STRING database were used to identify core module and gene that are related to the efficacy of docetaxel-cisplatin-5-fluorouracil (TPF) IC in NPC patients. *In vitro* and *in vivo* functional experiments were used to test the effects of PJA1 on docetaxel chemoresistance of NPC cells. The flow cytometric analysis, western blot, lactate dehydrogenase (LDH) release assays，in vitro co-culture experiment，and ELISA were performed to determine the effects of PJA1 on GSDME-mediated cell pyroptosis and antitumor immune response. Co-immunoprecipitation, mass spectrometry, immunofluorescence staining, and ubiquitination assays were performed to explore the regulatory manners between PJA1 and PGAM5-DRP1 axis. in vitro and in vivo functional experiments and flow cytometric analysis were used to test the

effect of RTA402, a pharmacological inhibitor, on PJA1 dependent chemoresistance. Finally, Multiplex immunofluorescence, immunohistochemical staining and Kaplan-Meier survival analysis were used to evaluate the clinical relevance of PJA1 -PGAM5 axis in patients with NPC, and tested whether PJA1 can serve as an indicator for predicting induction chemotherapy efficacy in NPC patients.

Results: PJA1 was identified as a key E3 ligase of the top-ranked module ubiquitin-proteasome system dysregulation that involved in NPC chemoresistance, which was highly expressed in NPC patients with nonresponse to the TPF IC. PJA1 knockdown facilitated the chemotherapy sensitivity of NPC cells (including docetaxel-resistant SUNE1 cell line S-DR) to docetaxel through promoting the GSDME-mediated pyroptosis. Mechanistically, E3 ligase PJA1 interacted and co-located with the mitochondrial protein PGAM5 protein in mitochondrion and PJA1 promoted the degradation of PGAM5 protein by increasing its K48-linked ubiquitination at K88, further increasing the phosphorylation of DRP1 at S637 and reducing the mitochondrial reactive oxygen species (ROS) production, in turn resulting in a suppressive of GSDME-mediated pyroptosis and antitumor immune response. PGAM5 knockdown fully restored the docetaxel sensitization effect of PJA1 knockdown. Moreover, RTA402, a pharmacological inhibitor of PJA1, enhanced the docetaxel sensitivity of NPC cells *in vitro* and *in vivo*. Clinically, NPC patients with high PJA1 expression had worse disease-free survival (DFS), overall survival (OS), distant metastasis-free survival (DMFS). In addition, NPC patients with high PJA1 expression could not benefit from induced chemotherapy, while NPC patients with low expression of PJA1 have better DFS, OS and DMFS after receiving induction chemotherapy, indicating high PJA1 expression can serve as an indicator for predicting induction chemotherapy efficacy in NPC patients.

Conclusions: Our study emphasizes the essential role of E3 ligase PJA1 in regulating chemoresistance in NPC, provides a new indicator for predicting induction chemotherapy efficacy and new therapeutic strategies for NPC patients based on targeting the ubiquitin-proteasome system.

Key Words： Nasopharyngeal carcinoma, chemoresistance, ubiquitination, pyroptosis

364. DDX17-mediated upregulation of CXCL8 promotes hepatocellular carcinoma progression via co-activating β-catenin/NF-κB complex.

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Aims： Hepatocellular carcinoma (HCC) accounts for the fifth common malignancy and third-leading cause of cancer-related death worldwide. HCC is well known as an inflammation-related cancer. Chronic liver injury derived from hepatitis virus infection, alcohol intake, gut-derived microbial products, NAFLD or NASH, are responsible for liver inflammation and hepatocellular carcinogenesis, which results in the excessive secretion of a variety of cytokines and chemokines. Nevertheless, the molecular mechanism though which these pro-inflammatory signaling are activated and the therapeutic strategy targeting cytokines and chemokines to inhibit HCC progression remain poorly understood. Therefore, the purpose of this study was to explore the role and mechanism of inflammatory signals in promoting HCC progression

Methods： We investigated the effects of DDX17 overexpression on the proliferation, migration and invasion of HCC cells by in vivo and in vitro functional experiments. The IP experiment was used to verify the interaction between DDX17 and β-catenin and NF-κB/p65. Dual luciferase reporter gene assay was used to detect the function of DDX17/A/B in CXCL8 transcriptional activation.

Results: We found that DDX17 was highly expressed and presented as an independent prognostic factor in HCC. DDX17 overexpression promoted tumor proliferation and enhanced the migrative and invasive abilities of HCC cells. Mechanistically, DDX17 coupled with β-catenin/ NF-κB complex and promoted their nuclear translocation to activate the transcription of chemotactic gene, CXCL8. More importantly, CXCL8 augmented the interaction of NF-κB with DDX17/β-catenin

and enhanced its autocrine activation via phosphorylating NF-κB/p65. Inhibition of CXCR1/2, the transmembrane receptor of CXCL8, remarkably abrogated DDX17-mediated HCC growth and metastasis both in vitro and in vivo.

Conclusion: Our finding provided new insights into DDX17-mediated pro-inflammatory chemokine activation, which unveiled the association between DDX17 and β-catenin/ NF-κB complex in transactivating the expression of CXCL8. Usage of CXCR1/2 inhibitor to block DDX17-induced CXCL8 signaling activation might serve as a potential therapeutic approach for HCC treatment.

Key Words: Hepatocellular carcinoma, proliferation and metastasis, DDX17, CXCL8, β-catenin, p65, CXCR1/2 inhibitor

365. BRAFV600E 在细针穿刺细胞学良性甲状腺结节中的价值

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目的：细针穿刺细胞学（Fine-needle aspiration, FNA）的局限性包括标本无法诊断、细胞学结果不确定、假阴性及假阳性结果等。而 BRAFV600E 基因突变作为甲状腺乳头状癌（PTC）的特异性生物标志，在 FNA 良性的高危结节中诊断价值尚缺乏报道。该研究旨在探讨明确 FNA 良性甲状腺结节中 BRAFV600E 基因突变检测的附加诊断效果。

方法：吉林大学中日联谊医院甲状腺外科 2019 年 1 月-2022 年 9 月对 1560 名患者的 1725 个高风险甲状腺结节进行 FNA 及 BRAFV600E 基因突变检测。共有 549 名患者 668 个高危结节于我院行手术治疗并行术后石蜡病理学检查患者，根据纳入和排除标准，共 84 枚 FNA 良性结节纳入本研究。

结果：84 个 FNA 良性的甲状腺结节中，44 个结节 BRAFV600E 基因突变检测阳性，40 个结节 BRAFV600E 检测为阴性。在 44 个 BRAFV600E 检测阳性的结节中，患者平均年龄为 43.0±9.5 岁；结节平均大小为 0.54±0.32cm。其中 43 个结节术后石蜡病理学证实为恶性，1 个结节证实为良性。BRAFV600E 基因突变检测在 FNA 良性甲状腺结节中阳性预测值为

97.6%。术前 FNA 联合 BRAFV600E 基因突变检测将 FNA 良性结节 PTC 确诊率提高了 51.2%。43 例病理证实为 PTC 的结节中存在≥2 个可疑超声特征结节占 88.4%。40 个 BRAFV600E 基因突变阴性的结节中，患者平均年龄为 46.4±11.2 岁；结节平均大小为 0.83±0.67cm。20 个结节术后石蜡病理学证实为 PTC，余 20 个结节证实为良性。BRAFV600E 基因突变在 FNA 良性甲状腺结节中阴性预测值为 50.0%。结论：BRAFV600E 基因突变检测可较大程度降低 FNA 良性结节的漏诊率，存在＞2 个可疑超声特征的高危甲状腺结节应常规行 FNA 与 BRAFV600E 基因突变联合检测。

关键字 ：甲状腺乳头状癌，细针抽吸细胞学检查，BRAFV600E 基因检测

366. Lactate-induced dissociation of mitochondria-ER contacts promotes the progression of hepatocellar carcinoma

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Background & Aims: The dynamic interactions between mitochondria and endoplasmic reticulum (ER) is crucial for cellular homeostasis, and the disruption of this interaction has been implicated in the pathogenesis of various diseases. Nevertheless, the precise involvement of this interplay in the progression of cancer is far from clear. Thus, we focused on hepatocellular carcinoma (HCC), a type of liver cancer, and investigated the role of mitochondria-ER miscontacts in its development and progression.

Methods: We analyzed mitochondria-ER contacts in both human and murine models of HCC. To gain further insights, we overexprssed a specific spacer or linker to elucidate the direct consequences of miscontacts between mitochondria and ER on the initiation and progression of HCC.

Results: Mitochondria-ER contacts are significantly diminished in human HCC tissues, which correlates with unfavorable patient prognosis. The disruption of ER-mitochondria contacts accelerates hepatocarcinogenesis and the progression of HCC. Interestingly, our experimental manipulation to induce mitochondria-ER contacts successfully impedes the survival of HCC cells both in vitro and in vivo. Mechanistically, we unraveled a fascinating interaction between lactate, a byproduct of glycolysis, and a protein known as MFN1. This interaction causes a direct inhibition of MFN1's GTPase activity, which, in turn, triggers mitochondrial fragmentation and the subsequent dissociation of mitochondria-ER contacts. As a result, the decrease in mitochondria-ER contacts facilitates the survival of HCC cells by impeding the uptake of mitochondrial calcium, a crucial factor for mitochondrial oxidative phosphorylation and cell apoptosis.

Conclusions: We have unveiled the critical involvement of lactate in modulating mitochondria-ER contacts, thereby influencing the progression of HCC cells. These findings shed light on the potential of targeting mitochondria-ER contacts as a therapeutic approach for HCC.

Key Words ： mitochondria-ER contacts, lactate, Hepatocellular carcinoma (HCC), MFN1

367. Tubulin Carboxypeptidase VASH2 Promotes Aggression and Chemoresistance of Lung Squamous Cell Carcinoma by Enhancing KIF3C-dependent EGFR-endosomal Recycling

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Background: Lung squamous cell carcinoma (LUSC) is associated with high mortality and has few therapeutic strategies. Chemotherapy remains the main treatment for LUSC patients, especially for patients with low EGFR expression ($EGFR^{low}$) who have received few clinical benefits from EGFR-directed monoclonal antibodies. The effective therapeutic option for $EGFR^{low}$ LUSC patients is an urgent unmet need.

Methods: Differentially expressed gene analysis and pathway enrichment were performed to identify the key differential factors between low and high expression of EGFR in LUSC. EGFR internalization, recycling and degradation assays were performed to determine the role of vasohibin-2 (VASH2) in EGFR-endosomal trafficking. Xenograft tumor models were used to evaluate the treatment efficacy of paclitaxel in combination with tubulin carboxypeptidase (TCP) inhibitor.

Results: VASH2 expression and detyrosinated-tubulin levels were negatively correlated with LUSC patient prognosis. Inhibiting the detyrosination of α-tubulin attenuated the malignant biological behaviors of LUSC cells. The VASH2-induced increase in detyrosination of α-tubulin boosted the binding of KIF3C to microtubules and enhanced KIF3C-mediated endosomal recycling of EGFR, leading to prolonged activation of PI3K/Akt/mTOR pathway and chemotherapy resistance. Blocking the TCP activity of VASH2 inhibited xenograft tumor growth and increased paclitaxel sensitivity in vivo.

Conclusions: VASH2 is not only a prognostic biomarker but also a promising therapeutic target for $EGFR^{low}$ LUSC patients. VASH2 sustains PI3K/Akt/mTOR signaling activation and chemoresistance by its TCP activity, which offers a novel insight that combination of chemotherapy and the TCP inhibitor may be a promising treatment strategy for LUSC patients.

Key Words ： VASH2, Detyrosination of microtubule, EGFR-endosomal recycling, KIF3C, Lung squamous cell carcinoma, Chemoresistance

368. RAB22A 通过 PKM2-pSNAP23 促进外泌体分泌提高结直肠癌化疗耐药

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目的：化疗是肿瘤治疗的重要手段之一，尤其在结直肠癌(Colrectal cancer, CRC)治疗中发挥着举足轻重的作用，但化疗耐药现象的产生极大的阻碍了化疗的临床治疗效应，因此研究 CRC 化疗耐药具有重要的临床和理论价值。外泌体是一类参与细胞间通讯的微小囊泡。我们课题组前期研究发现小 G 蛋白 RAB22A 有促癌作用，并诱导 CRC 化疗耐药，但具体机

制不详。已知 RAB22A 所属的 Rab 家族是调控囊泡转运的关键因子。本研究旨在阐明 RAB22A 调控外泌体分泌诱导 CRC 化疗耐药的内在机制，为临床上逆转肿瘤耐药，改善患者预后提供理论依据。

材料与方法：利用生物信息学分析多个 TCGA 和 GEO 数据库，研究 RAB22A 表达水平和 CRC 化疗耐药和外泌体分泌水平的相关性。收集 CRC 患者血浆样本和 CRC 细胞系的培养上清样本，分别提取外泌体，分析耐药和敏感型样本中外泌体分泌量的差异。制作组织芯片，并诱导 CRC 耐药细胞株，通过免疫组化和 WB 分别检测大样本 CRC 组织标本和细胞样本中 RAB22A 表达。同时，RAB22A 表达水平与 CRC 患者的复发耐药综合分析，研究 RAB22A 高表达与预后、耐药的关系。将 RAB22A 过表达质粒 pRK7-FLAG-RAB22A 转染 293T 和 SW480 细胞，质谱分析初步筛选 RAB22A 潜在的互作分子，CO-IP 实验确定与 RAB22A 互作的蛋白分子 PKM2。利用免疫荧光实验分析 RAB22A 和 PKM2 的共定位情况；过表达和敲降 RAB22A，分析与 PKM2 蛋白的变化。利用放线菌酮和 MG132 处理 CRC 细胞，WB 检测 PKM2 表达变化，分析 RAB22A 调控 PKM2 表达的具体机制。利用 PKM2 和 RAB22A 的 siRNA 和过表达质粒转染，收集细胞蛋白和细胞培养上清，WB 检测 p-SNAP23 水平，Nanosight NS 300 检测外泌体分泌数量变化。在 HCT8-5FU 和 HCT116-LOHP 耐药细胞中检测 RAB22A 和 PKM2 表达，并通过功能回复实验，分析外泌体分泌水平、p-SNAP23 和细胞 IC50 的变化。进一步将耐药细胞 HCT8-5FU 和 HCT116-LOHP 的外泌体定量加入野生型 HCT8 和 HCT116 细胞，研究耐药细胞来源的外泌体能否通过传 RAB22A-PKM2、促进野生型细胞 SNAP23 磷酸化，进而提高其耐药能力。对裸鼠进行 HCT-8 细胞皮下植瘤，分别收集耐药株 HCT8-5FU 及其对照 HCT8 细胞上清外泌体并进行瘤内注射，对小鼠进行 5-FU 化疗治疗，通过肿瘤生长检测耐药株外泌体对肿瘤化疗敏感性的影响；收集小鼠肿瘤和外周血，IHC 和 WB 分析肿瘤组织中 RAB22A-PKM2-p-SNAP23 差异，Nanosight NS 300 检测小鼠外周血外泌体数量变化。构建 RAB22A 敲低质粒 pLK0.1-shRAB22A，并利用慢病毒技术构建 HCT8-5U-shRAB22A 稳转株；利用稳转株对裸鼠进行皮下植瘤，并对小鼠进行 5-FU 化疗治疗，监测肿瘤生长；收集小鼠肿瘤和外周血，IHC 和 WB 分析肿瘤组织中 RAB22A-PKM2-p-SNAP23 差异，Nanosight NS 300 检测小鼠外周血外泌体数量变化。

结果：（1）CRC 患者外泌体分泌增加与临床预后差密切相关。2）CRC 患者外泌体分泌和 RAB22A 的表达水平以及化疗耐药呈正相关。（3）RAB22A 促进化疗耐药和外泌体分泌。（4）RAB22A 通过抑制 PKM2 的蛋白泛素化降解发挥促进外泌体分泌的作用。（5）RAB22A-PKM2 通过促进 SNAP23 的第 95 位氨基酸磷酸化来增加 CRC 外泌体的分泌。（6）

CRC 耐药细胞会分泌更多富含 RAB22A-PKM2 的外泌体进入非耐药细胞，促进其 SNAP23 磷酸化并提高耐药水平。

结论：RAB22A 通过抑制 PKM2 降解，增加 SNAP23 磷酸化，从而促进外泌体分泌，提高 CRC 细胞化疗耐药。

关键字： 结直肠癌，化疗耐药，外泌体，RAB22A，PKM2

369. Analysis of the predictive value of TMB and HLA typing on the prognosis and outcome of lung cancer patients

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Objective: This study aims to investigate the predictive value of combined analysis of biomarkers based on tumor mutation load (TMB) and human leukocyte antigen (HLA) typing for the prognosis and efficacy of anti-tumor therapy in non-small cell lung cancer (NSCLC).

Methods: A total of 171 lung cancer patients who were diagnosed and received stage IIIB-IV target/immunotherapy at Peking University Cancer Hospital(Inner Mongolia Campus) from December 2020 to June 2023 were enrolled, and the gene mutation data, TMB and HLA typing were measured by high-throughput sequencing technology, and the case information of the patients was collected at the same time; according to certain criteria, the patients were classified by pathological type, clinical stage, treatment plan, TMB expression, and HLA typing were grouped; the relationship between TMB and HLA typing and clinicopathological features, as well as the prognostic impact on patients and molecular biological features were analyzed using the statistical software SPSS 27.0.

Results:(1) In a total of 171 samples, TMB expression level was correlated with pathological type, with or without history of radiotherapy, and treatment modality (all $P<0.05$), as well as with CEA, CA-125, and SCC (all $P<0.05$) among the tumor markers for lung cancer.HLA The presence or absence of LOH status was correlated with recent efficacy of treatment, and circulating DNA

concentration (P<0.05). In addition circulating DNA concentration was associated with gender (P=0.035) and BMI (P=0.034).

(2) In 78 patients who received targeted therapy, PFS was associated with TMB expression (P=0.019), and PFS was longer with low TMB expression.TMB expression was associated with TP53 mutation (P=0.012). Targeted therapy PFS was associated with EGFR being mutated (P=0.013), and targeted therapy was more effective in the EGFR mutation group than in the wild group. In the correlation analysis of gene co-expression and prognosis, EGFR+TP53 (71.43%) was co-mutated, and patients with EGFR and TP53 co-mutations had longer PFS compared to patients with single TP53 mutation (PFS 6.23m vs. 5.00m, P<0.05). In the unifactorial and multifactorial analyses of the efficacy of targeted therapies, TMB expression (P=0.039) was the main factor affecting the PFS of patients. the median PFS of the TMB low-expression-EGFR mutant group was significantly longer than that of the other groups (P=0.021), and the difference was statistically significant in all cases (P<0.05).

(3) In 93 patients who received immunotherapy, PFS was correlated with TMB expression (P=0.020) and HLA with or without LOH (P=0.045), and PFS was longer in the group with high TMB expression and the presence of LOH. Multifactorial analysis showed that TMB level (P=0.044) and number of LOH (P=0.012) were two independent prognostic factors affecting PF.S The percentage of PR (26.32%) was the highest in the TMB high group-HLA LOH group and PD (57.89%) was the lowest, which had the best efficacy of ICIs in this group.

Conclusion:(1) TMB expression level was correlated with pathological type, history of radiotherapy or not, treatment modality, and CEA, CA-125, and SCC among lung cancer tumor markers.HLA with or without LOH status was correlated with recent efficacy and circulating DNA concentration. (2) It has the following predictive value for the efficacy of targeted therapy in lung cancer: those with low expression of TMB have relatively better efficacy than those with high expression of TMB; patients with co-mutation of EGFR and TP53 have longer PFS than those with single TP53 mutation, and have better prognosis when receiving targeted therapy. (3) The predictive value of the efficacy of immunotherapy in lung cancer is as follows: the efficacy of immunotherapy is better in patients with high TMB expression and HLA LOH, and the prognosis of efficacy of immunotherapy is better in the high TMB-HLA LOH group.

Key Words： Tumor mutation load; Human leukocyte antigen typing; Predictive value

370. Metal-organic frameworks-enhanced CRISPR-Cas12a biosensor for ultrasensitive detection of circulating tumor DNA

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Herein, we propose an improved electrochemical CRISPR biosensor for efficient detection of circulating tumor DNA (ctDNA) based on our finding that metal-organic frameworks (MOFs) can boost the trans-cleavage activity of CRISPR-Cas12a. In this design, customized enzyme activators (manganese ions) are co-assembled with Cas12a/crRNA duplex to form enzyme-MOF composites. The MOFs-induced proximity effect can continuously provide manganese ions to sufficiently interact with Cas12a during the release process, boosting the trans-cleavage activity of Cas12a/crRNA available for biosensor construction. We demonstrate that the developed biosensor can achieve ultrasensitive detection of PIK3CA point mutation (H1047R) with a low detection limit of 0.33 fM without pre-amplification, possessing a higher signal to noise ratio than previous reports. Furthermore, our biosensor has been successfully used to detect the targets spiked in serum samples, requiring low-dose samples and a short time. We believe that this strategy sheds new light on the applications of cancer diagnosis, treatment and surveillance.

Key Words ：circulating tumor DNA (ctDNA); biosensor; CRISPR-Cas12a; Metal-organic frameworks.

371. 新型双靶标肿瘤外泌体生物传感器的开发

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研究目的：外泌体（exosomes）是由细胞内多囊泡体（MVE）与细胞膜融合释放到胞外具有脂质双分子层，直径分布在 30 到 150 nm 不等的囊泡。其携带着来自供体细胞许多重要生物分子，如蛋白质、核酸及脂质等，可作为细胞间通讯的重要载体，同时也可作为多数

疾病无创性液体活检的重要标志物，如肿瘤。本研究旨在开发一种新型双靶标肿瘤外泌体生物传感器，实现对肿瘤外泌体便捷、精准检测，为精准医疗及肿瘤诊断的液体活检提供参考。本报告聚焦于传感器开发中的关键元素——二苯乙烯分子的构建。

材料与方法：传感器研究的总体路线为：同时联合外泌体特异性标志物适配体（AptESM）及肿瘤特异性标志物适配体（AptTSM），并结合二苯乙烯类化合物（Stilbenes, ST）构建基于荧光衰减的双靶标肿瘤外泌体生物传感器。本报告聚焦于二苯乙烯分子的构建，拟首先通过 HECK 等反应合成两端具有偶联活性基团的 ST；另一方面，通过差速离心法提取肿瘤细胞外泌体；研究结果为构建基于荧光衰减信号的双靶标肿瘤外泌体传感器提供重要基础。

结果：通过对外泌体的多维度表征，结果显示成功提取肿瘤外泌体；另一方面，质谱及核磁共振等数据表明成功合成两端具有偶联活性基团的 ST。

结论：本研究合成了两端具有偶联活性基团的 ST，为构建基于荧光衰减信号的适配体传感器、用于双靶标肿瘤外泌体定性定量分析提供重要基础。

关键字： 肿瘤标志物，肿瘤外泌体，荧光检测，二苯乙烯分子

372. 伴 ALK 融合突变的晚期肺大细胞神经内分泌癌经靶向治疗后耐药一例

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目的：肺大细胞神经内分泌癌 (LCNEC) 是一种具有高度转移潜能和不良预后的类型。间变性淋巴瘤激酶(ALK) 重排患者可从 ALK 酪氨酸激酶抑制剂（ALK-TKI）中获益。而 ALK 重排在肺 LCNEC 中十分罕见，且其对相关 ALK-TKI 的响应尚不清楚。鉴于此，我们特报道一例经二代测序（NGS）确认 ALK 融合突变的晚期 LCNEC 患者，在尝试一线使用阿来替尼后达到部分缓解(PR)，随后 ALK 基因发生新突变，最终导致阿来替尼耐药并产生新进展的患者，旨在为晚期肺 LCNEC 的靶向治疗提供新的参考。

方法：组织标本均经 10%中性福尔马林固定，石蜡包埋，常规切片，HE 染色；免疫组织化学染色采用全自动免疫组织化学系统进行；使用石蜡组织及血浆样本进行核酸提取、纯化、探针捕获及构建目标文库；使用 Illumina 上机试剂盒及高通量测序仪进行测序；下机数

据使用南京世和基因自动分析系统进行质控、初步分析并进行人工审核；根据 RECIST 标准评估病情进展。

结果：患者肺穿刺组织病理示神经内分泌肿瘤伴多灶凝固性坏死，核分裂象 4/10HPF，大细胞神经内分泌癌不能除外。NGS 检出患者血浆及原发组织中均发生 EML4-ALK 融合突变；TP53、RB1、STK11、KEAP1 等具有潜在分子分型意义的相关基因未检出突变；微卫星稳定（MSS），低肿瘤突变负荷(TMB)。随后患者择口服阿来替尼行靶向治疗，治疗后一月余评估病情为 PR，后续间断性复查病灶无明显变化，直至七月后复查增强 CT 示肝内新发病灶，疑似肝转移。行肝穿刺后病理考虑转移性肺 LCNEC。对肝穿刺组织再行 NGS 检测，除原有 EML4-ALK 融合突变外，ALK 第 23 外显子发生复合错义突变：p.G1202R、p.L1196Q，提示为患者对阿来替尼耐药并进展原因。

结论：使用阿来替尼一线治疗伴 ALK 突变晚期肺 LCNEC 患者的国内外报道不足 10 例。本例患者已发生脑转移，相比克唑替尼，阿来替尼具有更好的通过血脑屏障的能力，因此首选使用。晚期肺 LCNEC 的一线治疗目前多借鉴小细胞肺癌和非小细胞肺癌的治疗方案。相比以上治疗方案，本例患者经靶向治疗后表现出了较好的 PFS。但随即发生的耐药和进展也凸显了晚期肺 LCNEC 的治疗难度，后续方案可考虑三代 ALK-TKI 如劳拉替尼行进一步治疗。综上，对于晚期不可手术肺 LCNEC 患者，可尽早明确其驱动基因情况进而为靶向治疗提供有力依据。

关键字： 肺大细胞神经内分泌癌，ALK 融合突变，靶向治疗，二代测序

373. 结直肠癌来源的细胞外小囊泡通过上调肿瘤相关巨噬细胞 PD-L1 的表达促进肿瘤免疫逃避

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目的：肿瘤的发生进展与其所处的微环境密切相关。巨噬细胞是肿瘤微环境中的主要免疫细胞之一，因其具有对环境敏感及可塑性强等特点，常被肿瘤细胞“驯化”，进而促进肿瘤细胞生存。然而，结直肠癌（CRC）浸润的巨噬细胞（TAMs）如何被 CRC 细胞调控，以及

其在 CRC 进展中发挥的作用尚不十分清楚。本研究从外泌体角度阐明 CRC 细胞如何驯化巨噬细胞使其帮助肿瘤细胞实现免疫逃逸的分子机制，拟为 CRC 进展提供新的理论依据，并为 CRC 免疫治疗提供新的策略和思路。

材料与方法：（1）利用单细胞测序数据绘制 CRC 的 TAM 图谱，揭示 TAM 的异质性分子特征。转录组数据生存分析结合组织芯片免疫组化（IHC），评估 CD206+PD-L1+巨噬细胞与 CRC 患者预后的关系。(2)流式检测与 CRC 细胞共培养后的巨噬细胞是否对 CD8+T 细胞具有抑制作用。组织芯片 IHC 实验研究 CRC 组织中 CD206+PD-L1+巨噬细胞与 CD8+T 细胞浸润的相关性。（3）WB 和 qRT-PCR 检测与 CRC 细胞共培养后的巨噬细胞中 PD-L1 表达水平的变化，流式检测其对 CD8+T 细胞的抑制作用。PKH67 标记的外泌体尾静脉注射小鼠，免疫荧光、WB 和 qRT-PCR 检测腹腔巨噬细胞摄取外泌体后 PD-L1 水平变化。（4）差异分析筛选 CRC 外泌体中含量丰富的 miRNAs，在巨噬细胞中过表达候选 miRNA，进一步筛选调控巨噬细胞 PD-L1 的外泌体 miRNAs。将过表达 miRNA-21-5p 和 miRNA-200a 的外泌体分别或同时与巨噬细胞共培养，或利用“RNA 海绵”技术在 CRC 细胞中分别或同时敲除 miRNA-21-5p 和 miRNA-200a 后收集外泌体与巨噬细胞共培养，检测巨噬细胞 PD-L1 的表达变化，以及其对 CD8+T 细胞的抑制。(5)生物信息学筛选 miRNA-21-5p 和 miRNA-200a 调控巨噬细胞 PD-L1 表达的靶基因；双荧光素酶报告基因实验明确 miRNA 与靶基因的调控关系；WB 研究外泌体 miRNA-21-5p 和 miRNA-200a 通过 PTEN/AKT 和 SOCS1/STAT1 途径上调巨噬细胞 PD-L1 表达。（6）动物实验验证以上结论。

结果：（1）CD206+PD-L1+巨噬细胞浸润水平提示患者预后不良。（2）与 CRC 细胞共培养促进巨噬细胞对 CD8+ T 细胞的抑制，且 CRC 组织中浸润的 CD206+PD-L1+巨噬细胞与 CD8+T 细胞显著负相关。（3）CRC 外泌体能被巨噬细胞高效摄取，显著上调巨噬细胞 PD-L1 的表达，进而促进其对 CD8+T 细胞的抑制。（4）外泌体中的 miRNA-21-5p 和 miR-200a 上调巨噬细胞 PD-L1 的表达，并且促进其抑制 CD8+T 细胞。(5)PTEN 和 SOCS1 是外泌体 miRNA-21-5p 和 miR-200a 调控巨噬细胞 PD-L1 表达的靶基因，外泌体 miRNA-21-5p 和 miR-200a 通过 PTEN/AKT 和 SOCS1/STAT1 途径发挥调控 PD-L1 表达的功能。（7）动物实验证明，小鼠肿瘤组织中巨噬细胞 PD-L1 表达水平也和 CD8+T 细胞浸润负相关；CRC 外泌体 miRNA-21-5p 和 miRNA-200a 通过促进巨噬细胞 PD-L1 的表达而抑制 CD8+T 细胞对肿瘤的杀伤作用，进而促进 CRC 进展。

结论：CRC 外泌体 miRNA-21-5p 和 miR-200a 可通过 PTEN/AKT 和 SCOC1/STAT1 信号途径诱导巨噬细胞高表达 PD-L1，促进其抑制 CD8+T 细胞，帮助 CRC 细胞实现免疫逃逸。

关键字： 结直肠癌，肿瘤相关巨噬细胞，外泌体，miRNA，免疫逃逸

374. Tumor cell-derived LC3B+extracellular vesicles is a novel prognostic biomarker and a potential target for immunotherapy in hepatocellular carcinoma

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Background: Inflammatory factors are being recognized as critical modulators of host antitumor immunity in liver cancer. We have previously shown that tumor cell-released LC3B positive extracellular vesicles (LC3B+ EVs) are responsible for malignant progression by dampening antitumor immunity. However, the relationship between LC3B+ EVs and inflammatory factors in the regulation of the liver cancer microenvironment remains unclear.

Methods: Flow cytometry analyses were performed to examine the panel of 12 cytokines, the main source of positive cytokines, and plasma LC3B+ EVs carrying HSP90α in peripheral blood of liver cancer patients. We correlated the levels of plasma IL-6, IL-8 with LC3B+ EVs carrying HSP90α and with prognosis. In vitro culture of healthy donor leukocytes with liver cancer-derived LC3B+ EVs was performed to evaluate the potential effect of blocking HSP90α, IL-6 or IL-8 alone or in combination with PD-1 inhibitor on CD8+ T cell function. We also investigated the potential associations of MAP1LC3B, HSP90AA1, IL6 or IL8 with immunotherapy efficacy using the TCGA databases.

Results: In liver cancer patients, plasma IL-6 and IL-8 levels were significantly higher than in healthy controls and associated with poor clinical outcome. In peripheral blood, levels of plasma LC3B+ EVs carrying HSP90α were significantly elevated in HCC patients and positively associated with IL-6 and IL-8 levels, which are predominantly secreted by monocytes and neutrophils. Moreover, LC3B+ EVs from human liver cancer cells promoted the secretion of IL-6 and IL-8 by leukocytes through HSP90α. Besides, we show that the cytokines IL-6 and IL-8 secreted by LC3B+ EVs-induced leukocytes were involved in the inhibition of CD8+ T-cell function, while blockade of the HSP90α on the LC3B+ EVs, IL-6, or IL-8 could enhance

anti-PD-1-induced T cell reinvigoration. Finally, patients who received anti-PD-1/PD-L1 immunotherapy with high MAP1LC3B, HSP90AA1, IL6, or IL8 expression had a lower immunotherapy efficacy.

Conclusions: Our data suggest that liver cancer-derived LC3B+ EVs promote a pro-oncogenic inflammatory microenvironment by carrying membrane-bound HSP90α. Targeting HSP90α on the LC3B+ EVs, IL-6, or IL-8 may synergize with anti-PD-1 treatment to enhance the CD8+ T-cell functions, which may provide novel combination strategies in the clinic for the treatment of liver cancer.

Key Words： Extracellular vesicles; Liver cancer; Heat shock protein 90α; IL-8; IL-6; Immunotherapy

375. Pan-cancer analysis of Sp1 with a focus on prognostic and immunological roles in gastric cancer

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Objective： Transcription factor Specificity Protein 1 (Sp1) plays a pivotal role in tumorigenesis and tumor development. However, comprehensive pan-cancer analyses of the functional, prognostic and predictive implications of this gene is still unclear. Here, we investigated the potential oncogenic roles of Sp1 across 33 tumors using public datasets and verification of its immunological role in gastric cancer cohort of our hospital.

Methods： Gene mapping and protein structure analysis were based on the UCSC genome browser on human and the "HomoloGene" function of the NCBI. The SP1 expression level was studied in TCGA and GTEx database with online tool of HPA, GEPIA 2.0, HEPIA 2.0 and TIMER 2.0. The phosphoprotein level of Sp1 was investigated via the UALCAN portal. The potential value of SP1 as a diagnostic and prognostic biomarker in pan-cancer was evaluated with the TCGA database and GEPIA. The Sp1 gene alteration characteristics were analyzed using the cBioPortal database. The online tool Sangerbox was used to investigate the correlations between tumor mutational

burden (TMB), microsatellite instability (MSI) and Sp1 in all types of cancers in TCGA and also the correlations between the Sp1 expression and four classical DNA methyltransferase. The TIMER, CIBERSORT, CIBERSORT-ABS, QUANTISEQ, XCELL, MCPCOUNTER and EPIC algorithms were applied for immune infiltration estimations. We used iPTMnet database to analyze the predicted phosphorylation features of Sp1. The STRING online tool was applied to investigate the top 50 experimentally determined Sp1-binding proteins. GO analysis and KEGG analysis of SP1 related genes were combined and submitted to DAVID. Immunohistochemistry was used to evaluate the Sp1 expression of our gastric cancer cohort. The immunostaining signals were evaluated by two researchers and the final score was the sum of the intensity and the percentage. Multiplex Immunofluorescence staining was used to validate the correlations between Sp1 expression and several types of immune cells.

Results： Sp1 exhibits high expression levels in numerous cancers including breast cancer, esophageal cancer, and cholangiocarcinoma; these associations may be linked to clinical stage, prognosis, tumor mutational burden (TMB), and microsatellite instability (MSI) status among patients with tumors. Furthermore, our findings indicate that classical DNA methyltransferase levels of Sp1 are correlated with specific cancer prognoses. Additionally, phosphorylation levels at multiple phosphorylation sites of Sp1 are significantly elevated in several tumors. In our gastric cancer cohort, the Sp1 expression was positively correlated with CD8+ cytotoxic T cells in cancerous tissues ($r=0.591$, $P<0.01$). We also found that patients achieving partial response (PR) had higher level of Sp1 in tumor tissues than those achieving stable disease (SD) or progressive disease (PD) ($P<0.01$). Patients with high expression of Sp1 had better overall survival (OS) than those with low expression of Sp1 (10.9 vs. 8.5 months, $P<0.05$). The univariate analysis and multivariate Cox regression identified ECOG PS at ICI initiation, Sp1 level as potential and independent prognostic factors in patients with STAD treated by ICIs.

Conclusions: Our first pan-cancer analysis provides a comprehensive understanding of the role of Sp1 in tumorigenesis and highlights its potential function as a new target for cancer immunological therapy.

Key Words ： Sp1, pan-cancer analysis, prognosis, immunotherapy response

376. MSIsensor-RNA: Microsatellite Instability Detection for Bulk and Single-cell Gene Expression Data

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Microsatellite instability (MSI) is an indispensable biomarker in cancer immunotherapy. Currently, MSI scoring methods by high-throughput omics methods have gained popularity and demonstrated better performance than the gold standard method for MSI detection. However, the MSI detection method on expression data, especially single-cell expression data, is still lacking, limiting the scope of clinical application and prohibiting the investigation of MSI at a single-cell level. Herein, we developed MSIsensor-RNA, an accurate, robust, adaptable, and standalone software to detect MSI status based on expression values of MSI-associated genes. We demonstrated the favorable performance and promise of MSIsensor-RNA in both bulk and single-cell gene expression data in multiplatform technologies including RNA sequencing (RNA-seq), microarray, and single-cell RNA-seq. MSIsensor-RNA is a versatile, efficient, and robust method for MSI status detection from both bulk and single-cell gene expression data in clinical studies and applications. MSIsensor-RNA is available at https://github.com/xjtu-omics/msisensor-rna.

Key Words ： Microsatellite instability, Gene expression, Single-cell RNA-seq, RNA-seq, Microarray

377. Comprehensive analysis of cuprotosis-related genes in hepatocellular carcinoma identifying DLAT as a potential target

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Background: Hepatocellular carcinoma is a major global healthcare problem. There is evidence to prove that there is a close relationship between liver cancer and immune cells, especially T cells. Recently, due to the application of Immune–checkpoint inhibitors (ICI) in treatment, hepatocellular carcinoma patients' prognosis has been tremendously improved. However, the treatment effect varies from patient to patient. Cuproptosis, a novel form of copper-mediated regulated cell death, participates in tumor progression. In this study, we aim to construct and validate a risk model related to Cuproptosis to improve prognosis in liver cancer and explore the relationship between immune infiltration and related copper death genes.

Methods: We downloaded data from the TCGA database and analyzed it from three aspects. Firstly, we conducted differential gene screening and analysis of them to explore the biological characteristics of liver cancer patients. Secondly, we conducted Cox regression analysis, PCA analysis, and cuprotosisScore to discuss the correlation between differential genes and copper death, Finally, we attempt to explore the relationship between copper death-related genes and immune infiltration.

Results: We downloaded data from the TCGA database and analyzed it from three aspects. Firstly, we conducted differential gene screening and analysis of cancer and adjacent tissues to explore the biological characteristics of liver cancer patients. Secondly, we used cuprotosisScore to discuss the correlation between differential genes and copper death, Finally, we attempt to explore the relationship between copper death-related genes and immune infiltration.

Conclusion: We found a significant correlation between the copper death-related gene DLAT and the prognosis of liver cancer, and identified some potential targets and pathways through

comparison between cancer and adjacent tissues. At the same time, we speculate that immune infiltration is related to DLAT.

Key Words： cuprotosis-related genes, biomarker,pathways,DLAT

378. Platelet clumps in peripheral blood occur frequently in patients with digestive system cancer and are associated with chemotherapy drugs

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Objective. This study aimed to calculate the frequency of platelet clumps in patients with different tumors of malignancies and receiving various chemotherapy drugs.

Methods. The patients with platelet clump interpretive program (PCIP) messages and significant pseudothrombocytopenia (PTCP) detected by the hematology analyzer were collected at the First Affiliated Hospital of Nanjing Medical University from August 2013 to December 2019. The frequency of PCIP messages in classification of solid tumors and the utilization rate of various chemotherapy drugs were analyzed.

Results. Among the 1235 patients with PCIP messages, 70.4% were found to have malignancies, of which 64.6% were digestive system cancer. In the 70 patients with malignancies and PTCP, the most common type of cancer was gastrointestinal cancer (34.3%, 24/70). The platelet clumps were not associated with the tumor stage and metastasis. PTCP occurred after chemotherapy in 50% of the 70 patients (35/70).

Conclusion. Platelet clumps in peripheral blood occur frequently in patients with digestive system cancer. Moreover, these clumps may occur in the chemotherapy process. Thus, the phenomenon of platelet clumps may be a sensitive indicator of cancer development and chemotherapy effect.

Key Words： Platelet clumps, Platelet activation, Malignant, Chemotherapy

379. 妥协性亚肺叶切除治疗 I 期非小细胞肺癌术后胸腔引流液 SHOX2 和 RASSF1A 甲基化检测的临床价值初探

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背景及研究目的：NCCN 非小细胞肺癌治疗指南提出，对于肺功能较差（FEV1<60%）不能耐受肺叶切除的 I 期非小细胞肺癌患者，可以考虑行妥协性亚肺叶切除。其优势是既能完整的切除肿瘤，又能明确肿瘤的病理分期，缺点是术后局部复发率较高。多项研究显示，对于恶性胸水以及早期非小细胞肺癌肺泡灌洗液中，联合 SHOX2 、RASSF1A 基因甲基化检测有助于肺癌的早期诊断。本研究重点探讨妥协性亚肺叶切除治疗 I 期非小细胞肺癌术后胸腔引流液 SHOX2 、RASSF1A 基因甲基化检测的临床价值。

方法： 2021 年 05 月至 2022 年 12 月，93 例肺功能较差不能耐受肺叶切除的 I 期非小细胞肺癌患者接受了妥协性亚肺叶切除手术，同期 106 例行肺叶切除的 I 期 NSCLC 患者作为对照。收集术中开胸后但未进行肿瘤切除前的胸腔冲洗液以及术后不同时间段（术后 1h,24h,48h,72h）胸腔引流液，分别行细胞学检测，同时采用定量甲基化特异性 PCR (quantitative methylation specific PCR, QMSP) 法行 SHOX2、RASSF1A 基因甲基化检测。根据检测结果绘制 ROC 曲线，确定两种基因甲基化的阳性截断值。单因素和多因素分析与胸腔引流液中 SHOX2、RASSF1A 基因甲基化阳性表达的独立相关因素。对引流液阳性表达的患者进行独立队列分析，探讨甲基化阳性检测的最佳窗口期。术后随访 14-32 月，按照术后引流液 SHOX2、RASSF1A 基因甲基化情况对妥协性亚肺叶切除组进行亚分组，制作 Kaplan-Meier 生存曲线，主要研究终点是 RFS。

结果：共 199 例 NSCLC 患者入组，包括肺叶切除 106 例，亚肺叶切除 93 例。所有患者无论是开胸后但未进行肿瘤切除前的胸腔冲洗液还是术后引流液，细胞学检测均未见癌细胞。

1. 胸腔引流液 SHOX2 和 RASSF1A 基因甲基化阳性判断标准设定：建立 ROC 曲线，SHOX2 和 RASSF1A 基因单独甲基化检测的 AUC 分别为 0.634 和 0.727，而 SHOX2,RASSF1A 联合检测的 AUC 为 0.738 优于 SHOX2 和 RASSF1A 单基因检测。SHOX2 和 RASSF1A 截断值分别为 11.94 和 7.29。

2. 术中未进行肿瘤切除前的冲洗液 SHOX2、RASSF1A 基因甲基化联合检测均为阴性。术后引流液中 SHOX2、RASSF1A 基因联合甲基化检测阳性，亚肺叶切除 19 例（19/93），肺叶切除 1 例（1/106，可能与术中优先楔形切除取病理且肿瘤累及胸膜有关）。

3. 多因素分析肿瘤大小（OR 3.27, 95%CI 3.02-3.54, P<0.001），切缘（OR 0.39, 95%CI 0.35-0.43, P<0.001），手术方式（OR 6.59, 95%CI 5.93-7.33, P<0.001）是 SHOX2、RASSF1A 基因联合甲基化检测阳性的独立预后因素。

4. 术后 1h、24h、48h，72h 四次收集患者胸腔引流液，其中 RASSF1A 基因甲基化阳性分别为 1 例、1 例、0 例、0 例，SHOX2 基因甲基化阳性为 15 例、6 例、3 例、0 例。根据甲基化检测的ΔCt 值绘制小提琴图行差异性比较：RASSF1A 甲基化四个时间点无明显统计学差异(1h vs 24h p=0.69, 1h vs 72h p=0.59, 24h vs 48h p=0.33, 48h vs 72h p=0.33)。SHOX2 甲基化四个时间点比较：术后 1h 较术后 24h、48h、72h 更易检出甲基化阳性结果(1h vs 24h p=0.03, 1h vs 48h p=0.02，1h vs 72h p=0.02)，而 24h、48h、72h 则无明显统计学差异(24h vs 48h vs 72h p=0.48)。

5. 术后随访截至 2023 年 12 月，平均 14-32 月，结果显示 19 例 SHOX2、RASSF1A 基因联合甲基化检测阳性组中死亡 2 例，复发或转移 7 例，存活 10 例。引流液 SHOX2、RASSF1A 联合甲基化阳性与阴性患者无病生存期无明显差异（P=0.624）。

结论：妥协性亚肺叶切除治疗 I 期非小细胞肺癌术后胸腔引流液 SHOX2 、RASSF1A 基因甲基化阳性与肿瘤的大小、手术切缘高度相关。术后 24h 检测为阳性最佳窗口期。对术后局部复发预测需要更多的数据支持。

关键字 ：甲基化、非小细胞肺癌、早期肺癌、亚肺叶切除、胸腔引流液

380. The implication of integrative multiple RNA modification-based subtypes in gastric cancer immunotherapy and prognosis

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Previous studies have focused on the impact of individual RNA modifications on tumor development. This study comprehensively investigated the effects of multiple RNA modifications, including m6A, alternative polyadenylation, pseudouridine, adenosine-to-inosine editing, and uridylation, on gastric cancer (GC). By analyzing 1,946 GC samples from eleven independent cohorts, we identified distinct clusters of RNA modification genes with varying survival rates and immunological characteristics. We assessed the chromatin activity of these RNA modification clusters through regulon enrichment analysis. A prognostic model was developed using Stepwise Regression and Random Survival Forest algorithms and validated in ten independent datasets. Notably, the low-risk group showed a more favorable prognosis and positive response to immune checkpoint blockade therapy. Single-cell RNA sequencing confirmed the abundant expression of signature genes in B cells and plasma cells. Overall, our findings shed light on the potential significance of multiple RNA modifications in GC prognosis, stemness development, and chemotherapy resistance.

Key Words： RNA modification, gastric cancer subtype, m6A methylation, prognosis signature, immune infiltration, stemness

381. Differential association between organ-specific immune-related adverse events and survival in non-small cell lung cancer patients treated with programmed death-1 inhibitors-based combination therapy

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Background: The profile of immune-related adverse events (irAEs) due to PD-1 inhibitors-based combination therapy and its relationship with survival in non-small cell lung cancer (NSCLC) patients has not been fully described.

Method: This retrospective study included patients with advanced NSCLC treated with PD-1 inhibitors at Jiangsu Cancer Hospital. Designed to capture the spectrum of irAEs and explore the association between irAEs and survival using landmark analysis and time-dependent Cox regression. The subgroup analyses investigated the impacts of organ-specific irAE, irAE grade, and steroid dose used to treat irAE.

Results: This study included 301 patients, 199 of whom received PD-1 inhibitors plus chemotherapy. The most common irAEs were skin toxicity (19.3%), endocrinopathy (21.3%) and pneumonitis (17.6%). In the entire cohort, the median progression-free survival (PFS) for patients developing and not developing irAE was 12.3 months and 10.7 months ($P < .001$), and the median overall survival (OS) was 23.5 months and 20.1 months ($P = .137$), respectively. Subgroup analyses indicated that grade ≥3 irAE, high steroid dose and pneumonitis was detrimental to OS, while skin toxicity was beneficial to survival. These findings were further corroborated by landmark analyses and Cox regression models conducted over four time points (1-month, 3-month, 6-month and 12-month).

Conclusion: Skin toxicity is associated with a better prognosis, while pneumonitis, grade ≥3 irAE and high steroid dose compromises survival in NSCLC patients receiving PD-1 inhibitor-based

combination therapy. Clinicians should remain cognizant of the organ-specific manifestations of irAE and take proactive measures to mitigate the progression of irAE.

Key Words： Immune-related adverse event,Organ-specific,Non-small cell lung cancer,PD-1 inhibitors,Time bias

382. Distribution and clinical significance of tumor-infiltrating γδ T cells in non-small cell lung cancer patients

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Objective: To investigate the role of tumor-infiltrating γδ T cells and its clinical significance in non-small cell lung cancer (NSCLC) patients.

Methods: The percentages of γδ T cells and its subset derived from 15 paired NSCLC and paracancerous specimens, as well as peripheral blood were analyzed by flow cytometry. The cytokines levels of IFN-γ and IL-17A secreted by γδ T cells were detected by flow cytometry.

Results: The percentages of tumor-infiltrating γδ T cells (P＜0.05) and Vδ1 T cells (P＜0.05) were significantly increased in patients with NSCLC, which γδ T cells and Vδ1 T cells were positively related to lymph node metastasis (P＜0.05). While there were no significant difference in γδ T cells and its subset of peripheral blood between NSCLC patients and healthy controls (P ＞ 0.05), but Vδ2 T cells was significantly lower than healthy controls (P ＜ 0.001). Meanwhile, IFN-γ is decreased and IL-17A is increased secreted by γδ T cells both in peripheral blood and in tumor tissues.

Conclusions: These findings suggest that γδ T cells and its subsets may be involved in the progression of NSCLC.

Key Words ： Non-small cell lung cancer (NSCLC); γδ T cells; Vδ1 T cells; IL-17A; lymph node metastasis.

383. 基于 TCGA 数据库肺腺癌 mRNA 预后风险模型的建立与分析

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目的：寻找肺腺癌中失调表达的基因，筛选出与肺腺癌病人预后存在显著关联的基因，构建基于 mRNA 表达谱的预测肺腺癌病人预后的风险模型。

方法：从 TCGA 官方网站下载肺腺癌原始 RNA 测序数据和病人的临床资料，使用 R 3.6.0 软件的 edgeR 包筛选肺腺癌中差异表达的基因，使用单因素 cox 回归分析这些差异的基因中与生存显著相关的 mRNA，进一步使用多因素 cox 回归分析筛选，建立风险预测模型。使用 ROC 曲线和 C-index 指数评价建立的模型的准确性。

结果：多因素 Cox 回归分析纳入了 18 个 mRNA 并建立风险预测模型。Risk score = 0.11 * KRT6AEXP + 0.09 * IGF2BP1EXP+ 0.20 * MELTFEXP+ 0.13 * RTL1EXP+ 0.09 * DKK1EXP+ 0.36 * HMMREXP - 0.15 * CREG2EXP+ 0.31 * ERO1AEXP+ 0.13 * FETUBEXP+ 0.08 * NTSR1EXP+ 0.07 * IGFBP1EXP+ 0.26 * KIF14EXP - 0.35 * PRC1EXP- 0.24 * CDKN3EXP- 0.11 * GJB3EXP- 0.09 * GRIA1EXP- 0.15 *ARNTL2EXP- 0.14 *SLC2A1EXP。模型中高风险组的病人总生存率显著低于低风险组，ROC 曲线下面积数值（AUC = 0.743）和 C-index 数值（C-index = 0.752）显示模型具有良好的灵敏度和特异度。

结论：成功构建了肺腺癌 mRNA 风险预后模型，这 18 个 mRNA 是肺腺癌的关键基因。

关键字： TCGA；肺腺癌；mRNA；预后，风险模型

384. Clinical value of serum DJ-1 in lung adenocarcinoma

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Objective.

DJ-1 is an oncoprotein secreted by cancer cells. However, the physiological and pathological significance of DJ-1 secretion is not clearly understood. This study investigated the clinical value of serum DJ-1 in lung adenocarcinoma (LUAD).

Methods.

The study involved 224 LUAD patients, 110 patients with benign pulmonary disease and 100 healthy controls from the First Affiliated Hospital of Nanjing Medical University. We detected the expression of DJ-1 in lung cell lines in vitro. Meanwhile, serum concentrations of DJ-1, carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and cytokeratin 19 fragment (CYFRA21-1) were measured. The diagnostic performance of LUAD was obtained using receiver operating characteristic (ROC) curves. Kaplan–Meier, univariate and multivariate Cox regression analyses were performed for progression-free survival (PFS).

Results.

DJ-1was highly expressed in LUAD cell lines. Serum DJ-1 levels were significantly higher in the LUAD group compared to the benign pulmonary disease group (5.04 vs. 3.66 ng/mL, P<0.001) and healthy controls (5.04 vs. 3.51 ng/mL, P<0.001). DJ-1 levels were associated with gender (P=0.002), smoking history (P=0.042) and lymph node metastasis (P=0.040). ROC curve analysis of DJ-1 revealed an area under the curve (AUC) of 0.758 (95% CI 0.714-0.803, P<0.001) with a sensitivity of 63.8% and specificity of 78.6% at a cutoff value of 4.62 ng/mL for the detection of LUAD. Univariate and multivariate analyses confirmed that the preoperative serum DJ-1 level, tumor stage and smoking history were independent prognostic factors of PFS.

Conclusion.

Our study is the first to explore the clinical value of serum DJ-1 in LUAD comprehensively. Serum DJ-1 could be a potential diagnostic and prognostic biomarker for LUAD.

Key Words ： DJ-1, lung adenocarcinoma, clinical value, ROC curve, AUC

385. 2 型糖尿病患者血糖水平对肿瘤标志物 CEA、CA199、CA724 的影响

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目的：探讨 2 型糖尿病患者血糖水平对肿瘤标志物 CEA、CA199、CA724 的影响。

方法：收集 2021 年 1 月至 2021 年 6 月在江苏省人民医院内分泌科就诊的 2 型糖尿病患者 96 例，及同期在体检中心进行健康体检者 51 例，两组均排除肿瘤、肝炎以及贫血等疾病。使用罗氏 Cobas e 602 电化学发光分析仪检测 CEA、CA199 及 CA724 水平，使用奥林巴斯 AU2700 全自动生化分析仪检测空腹血糖水平，使用全自动糖化血红蛋白分析仪 HLC-723G11 检测 HbA1c 水平。分析两组人群 CEA、CA199 及 CA724 水平的差异，以及血糖、HbA1c 与 CEA、CA199、CA724 的相关性。

结果：糖尿病组 CEA、CA199 的水平显著高于健康体检组，差异有统计学意义（P<0.001），CA724 亦随血糖水平的增高而呈上升趋势，Spearman 相关性分析显示，FBG 与 CEA、CA199 呈正相关（P<0.001）、HbA1c 与 CEA、CA199 呈正相关（P<0.001）。FBG、HbA1c 与 CA724 呈弱相关（P<0.05）。

结论：2 型糖尿病患者 CEA、CA199 及 CA724 水平较健康体者显著升高，且与 FBG、HbA1c 有相关性，推测其肿瘤标志物升高与血糖控制不佳密切相关。

关键字 ：2 型糖尿病、血糖、CEA、CA199、CA724

386. The role and metabolic adaptations of neutrophils in premetastatic niches

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It has been found that tumor cells create microenvironments in distant organs that promote their survival and growth in advance of their arrival. These predetermined microenvironments are referred to as "pre-metastatic niches". Increasing attention is being paid to neutrophils' role in forming the pre-metastatic niche. As major components of the pre-metastatic niche, tumor-associated neutrophils (TANs) play an important role in the formation of the pre-metastatic niche through communication with multiple growth factors, chemokines, inflammatory factors, and other immune cells, which together create a pre-metastatic niche well suited for tumor cell seeding and growth. However, how TANs modulate their metabolism to survive and exert their functions in the process of metastasis remains largely to be discovered. Accordingly, the objective of this review is to assess the role that neutrophils play in the

formation of pre-metastatic niche and to explore the metabolism alteration of neutrophils in cancer metastasis. A better understanding of the role of TANs in pre-metastatic niche will help us discover new mechanisms of metastasis and develop new therapies targeting TANs.

Key Words ： Cancer; Metabolism; Metastasis; Neutrophil; Pre-metastatic niches

387. Tobacco exposure primes the secretion of CCL21 positively associated with tertiary lymphoid structure and response to immunotherapy

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Background

Smoking history has been reported to be associated with favorable responses for non-small cell lung cancer (NSCLC) patients treated with immunotherapy. The positive correlation between tertiary lymphoid structures (TLSs) and treatment with immune checkpoint inhibitors (ICIs) among NSCLC patients has been established. Nonetheless, the association between tobacco exposure and TLSs is not fully comprehended.

Methods

The lung adenocarcinoma (LUAD) patients' cohort and the orthotopical transplanted mouse model were utilized to explore the correlation between smoking status and tertiary lymphoid structure (TLS) and chemokine CCL21, respectively. Cell adhesion and co-immunoprecipitation assays were performed to explore the interaction between CD4+ T cells and CD20+ B cells under tobacco exposure. Chromatin immunoprecipitation (ChIP)-PCR was used to dissect the mechanism of up-regulated CCL21 secretion in tobacco treatment. Serum CCL21 level was recorded in LUAD patients treated with immunotherapy.

Results

Here we observed that individuals with a smoking history exhibit an increased quantity and maturation level of TLS compared to non-smokers, along with higher levels of CCL21 secretion.

Tobacco exposure promoted CCL21 expression in an epithelial cell-intrinsic manner, of which BaP, the main component of tobacco, facilitated the nuclear retention of the aryl hydrocarbon receptor that occupied the promoter of CCL21. Additionally, the activated CCL21/CCR7 axis increased the CD11a expression of CD4+ T cells, boosting the interaction with CD20+ B cells dependent on ICAM1, which potentially induced the TLSs formation. Patients with elevated serum levels of CCL21 benefited more from immunotherapy.

Conclusions

Patients with a smoking history exhibited higher levels of TLS via the CCL21-dependent mechanism, serum CCL21 was identified as a reliable biomarker for predicting the efficacy of immunotherapy.Our study provided potential mechanism for patients with smoking history benefit from the immunotherapy. Furthermore, we suggest that serum CCL21 levels can serve as a valuable non-invasive biomarker to assess the presence of TLSs in advanced NSCLC patients undergoing immunotherapy, as biopsy may not be possible.

Key Words ： Tobacco exposure, tertiary lymphoid structure, CCL21, immunotherapy

388. miR-1229-3p 抑制结直肠癌恶性进展及作为潜在生物标志物的研究

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目的：探讨微小 RNA（microRNA, miRNA）在结直肠癌（colorectal cancer, CRC）恶性进展中的作用。

方法：基于 TCGA 数据库，筛选分析人类结肠癌及癌旁组织的转录组差异表达的 miRNA-1229-3p 作为研究对象。在 GEO 数据库与 Starbase 数据库中验证其表达水平。采用生物信息学方法对 miR-1229-3p 的生物功能特征进行分析，构建 miR-1229-3p 过表达细胞系及 miR-1229-3p 敲降细胞系，通过 CCK-8 实验、克隆形成实验、EdU 实验、transwell 实验、流式细胞术实验在体外探究 miR-1229-3p 对 CRC 细胞增殖、转移、凋亡的影响，并通过裸

鼠移植瘤试验探究 miR-1229-3p 对 CRC 细胞体内增殖的影响。通过 DIANA 、TargetScan、miRDB 数据库筛选 miR-1229-3p 的靶基因并通过 KEGG 富集分析、GO 分析靶基因的生物学功能。检测 60 例 CRC 患者及 60 例健康体检者血浆外泌体中的 miR-1229-3p 含量，采用受试者工作特征曲线（receiver operating characteristic curve, ROC）分析其对 CRC 患者的诊断效能。

结果：数据分析显示，miR-1229-3p 在 CRC 细胞和组织中表达下调。生物信息学方法预测 miR-1229-3p 与肿瘤的进展途径如上皮间质转化、血管形成等呈显著的负相关（R<0，P<0.05）。体内外研究表明，过表达 miR-1229-3p 后 CRC 细胞增殖受到抑制，且可抑制 CRC 细胞的迁移和侵袭能力，且其潜在靶基因 SETD7 在细胞中的表达下调；而敲低 miR-1229-3p 后可抑制 CRC 细胞的凋亡。CRC 患者血浆外泌体中的 miR-1229-3p 含量较健康体检者降低，ROC 曲线分析显示，miR-1229-3p 诊断 CRC 的最佳临界值为 0.5868，曲线下面积为 0.8632（P<0.01）。

结论： miR-1229-3p 在 CRC 中表达下调，SETD7 是其潜在的靶基因，miR-1229-3p 可抑制 CRC 细胞增殖、迁移与侵袭受到抑制，促进 CRC 细胞凋亡；miR-1229-3p 可作为诊断 CRC 的潜在生物标志物。

关键字 ：结直肠癌；miR-1229-3p；SETD7；外泌体 ；生物标志物

389. cIGF1R 编码的 C-IGF1R 作为分子开关抑制非小细胞肺癌中耐药持续性肿瘤细胞的线粒体自噬

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目的：EGFR-TKI（酪氨酸激酶抑制剂）是晚期 EGFR 突变的 NSCLC（非小细胞肺癌）患者的一线治疗方案。然而，获得性耐药是不可避免的，这极大地限制了 EGFR-TKI 的临床应用。为了进一步提高疗效，以 EGFR-TKI 为基础的联合治疗已成为更好的选择。我们假设在 EGFR 初始治疗下恢复失调的 circRNA 能够增强其有效性。因此，我们旨在找出与 EGFR-TKI 协同增效的 circRNA 分子，并探究其分子机制以及临床应用前景。

材料和方法：通过 circRNA 测序找出在 EGFR-TKI 初始用药后表达失调的 circRNA 分子；通过高通量体内筛选出可以有效协同 EGFR-TKI 的 circRNA - cIGF1R；通过体外和体内功能实验验证 cIGF1R 本身的功能以及其与 EGFR-TKI 的协同效果；通过 WB，PCR 等实验验证其对亲本基因 IGF1R 的表达的影响；通过 RNA 下拉实验，银染，质谱检测，免疫荧光和计算机分子对接模拟等实验寻找并验证与 cIGF1R 相互作用的剪切因子 RHA；通过荧光素酶报告基因实验，RIP 和公共数据库验证等验证 cIGF1R 以及 RHA 对于 IGF1R 可变剪切的影响；通过短期和长期的平板培养，3-D 培养以及体内实验等比较 cIGF1R 或 IGF1Ri 与 EGFR-TKI 联用的短期和长期疗效差别；通过 RNA 测序、细胞周期、细胞凋亡、细胞衰老和细胞自噬等检测探究 cIGF1R 或 IGF1Ri 与 EGFR-TKI 联用差异的分子机制；通过 CRISPR-cas9 构建 IGF1R 敲除细胞系探索 cIGF1R 协同 EGFR-TKI 的其他机制；通过核糖体离心、质谱检测以及构建特异性抗体、线粒体自噬相关实验等检测 C-IGF1R 的表达并探索其分子机制；最后通过构建 TET - ON 的 cIGF1R 过表达载体并进行皮下和肺原位种植的小鼠模型探索 cIGF1R 的临床应用。

结果：CircRNA - cIGF1R 在经过 EGFR-TKI 初始治疗后显著低表达。同时过表达 cIGF1R 在体外和体内均可以有效的协同 EGFR-TKI，增加其疗效。cIGF1R 与 RHA 相互作用，竞争性抑制 IGF1R mRNA 剪接，负向调节亲本基因 IGF1R 信号通路。这种调控与 IGF1Ri 相似，诱导肿瘤细胞的 DTP 状态，同时激活线粒体自噬。cIGF1R 还编码一种蛋白 C-IGF1R，C-IGF1R 可减少 Parkin 介导的 VDAC1 泛素化，抑制 DTP 细胞的线粒体自噬，作为促进 DTP 向凋亡转变的分子开关。联合 cIGF1R 的治疗方案可以显著提高小鼠生存，具有一定的临床应用前景。

结论：我们的研究结果表明，cIGF1R 联合用药可显著提高 EGFR-TKIs 体外和体内的疗效。这些数据支持探索 EGFR-TKI 联合 cIGF1R 作为提高 EGFR 突变 NSCLC 患者初始缓解率和扩大获益的策略。

关键字 ：EGFR-TKI，环状 RNA，肺腺癌，药物耐受持久状态，线粒体自噬。

390. SIRT5-mediated ME2 desuccinylation promotes cancer growth by enhancing mitochondrial respiration

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Objective: Mitochondrial malic enzyme 2 (ME2), which catalyzes the conversion of malate to pyruvate, is frequently upregulated during tumorigenesis and a potential target for cancer therapy. However, the regulatory mechanism underlying ME2 activity is largely unknown. Here we focused on exploring the function and molecular mechanism of ME2 in the progression of colorectal cancer (CRC).

Methods: First, bioinformatics analysis and Western blotting (WB) were performed to examine the ME2 level in CRC cells. Immunohistochemistry (IHC) staining was used to detect the ME2 expression in CRC clinical tissue samples. The impact of ME2 on the prognosis of CRC patients was analyzed by Kaplan-Meier method, and its correlation with clinical pathological parameters was analyzed by Cox regression model analyses. CCK-8 assay was adopted to examine the proliferation capabilities of ME2 knockdown cells. Protein immunoprecipitation (IP) and mass spectrometry analysis were performed to screen ME2 binding proteins and potential modification sites, and immunofluorescence (IF) and WB were used to further validate the target protein interacting with ME2, the key modification site and the related molecular mechanism. The effect of succinylation on ME2 enzyme activity was detected using in vitro enzyme activity assay and further explained by the crystal structure analysis of ME2 protein. The relevant metabolite detection kits were used to examine the effect of ME2 succinylation on CRC cell metabolism. CCK-8, clone formation and xenograft model in nude mice were performed to investigate the effect of ME2 succinylation on tumor proliferation. IHC staining of CRC tissue microarrays was performed to analyze the relevance between the ME2-interacting protein and ME2 succinylation.

Results: ME2 is highly expressed in human CRC tissues, and ME2 knockdown inhibits the proliferation of CRC cells. Mechanically, ME2 is succinylated and Sirtuins 5 (SIRT5) is identified as an ME2 desuccinylase. Glutamine deprivation directly enhances the interaction of SIRT5 with ME2 and thus promotes SIRT5-mediated desuccinylation of ME2 at lysine 346, enhancing ME2 enzymatic activity. Activated ME2 significantly enhances mitochondrial respiration, thereby counteracting the effects of glutamine deprivation and supporting cell proliferation and tumorigenesis. Additionally, the levels of succinylated ME2 at K346 and SIRT5 in CRC tissues, which are negatively correlated, are associated with patient prognosis.

Conclusion: Our study demonstrates that the mechanism of SIRT5-mediated ME2 K346 desuccinylation in CRC metabolism and proliferation. SIRT5-catalyzed ME2 desuccinylation is a key signaling event through which cancer cells maintain mitochondrial respiration and promote CRC progression under glutamine deficiency conditions, offering the possibility of targeting SIRT5-mediated ME2 desuccinylation for CRC treatment.

Key Words ： Succinylation; Malic enzyme; Colorectal cancer; SIRT5; Mitochondrial metabolism

391. Constructing a prognostic model for colon cancer patients based on coagulation genes enriched in cancer-associated fibroblasts to guide personalized immunotherapy

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Background: Colon cancer is a prevalent global health challenge characterized by late-stage diagnosis and heightened recurrence and metastasis risks. Emerging evidence implicates the coagulation cascade in shaping the tumor microenvironment and influencing patient outcomes. This study aims to construct a prognostic model that can personalize the guidance of immunotherapy in colon cancer patients.

Methods: The transcriptomic and clinical data were harnessed from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases, coupled with coagulation-related genes from KEGG and MsigDB resources. The univariate Cox analyses were used to identify coagulation-related prognostic genes which were subsequently integrated into a Least Absolute Shrinkage and Selection Operator (LASSO) algorithm for constructing a prognostic model. The predictive potential of coagulation-related risk score (CRRS) in prognosis and immunotherapy outcomes was rigorously assessed. Furthermore, a nomogram was devised to facilitate clinical use of risk scores. Finally, single-cell RNA-seq data were used to explore the cellular origin of genes in the coagulation-related prognostic model.

Result: Our findings showed our developed CRRS model effectively stratified patients into high risk group and low risk group. High-risk patients exhibited worse overall survival (OS). Multivariate regression analysis affirmed the independence of the coagulation-related risk score model in predicting OS. A nomogram was subsequently devised, enabling quantitative survival prediction by incorporating risk score, age, sex, and TNM stage. Moreover, the CRRS model predicted the extent of cancer-associated fibroblasts (CAFs) infiltration. Analysis further indicated diminished immune responsiveness in high-risk patients, and single-cell data analysis pinpointed TIMP1+CAFs as a potential contributor to cancer progression.

Conclusion: In conclusion, the CRRS model can be used as a prognostic tool for colon cancer patients and guide clinical immunotherapy decisions, that is, low-risk patients are more suitable for treatment with immune checkpoint inhibitors.

Key Words ： colon cancer, coagulation, risk score, cancer-associated fibroblast, immunotherapy

392. Peripheral blood PD-1 predicts the efficacy of immunotherapy for advanced non-small cell lung cancer and implications for clinical application

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Abstract: Objective Programmed cell death protein 1 (PD-1) is an important immunosuppressive molecule on the surface of T cells, and has an important role in inhibiting T cell activation. In this study, we investigated the clinical significance of peripheral blood PD-1 in advanced non-small cell lung cancer, and analyzed the dynamic changes of peripheral blood PD-1 for the prediction of the efficacy and prognosis of immunotherapy.

Materials and methods The clinical data of 119 patients with advanced non-small cell lung cancer attending Jiangsu Provincial Cancer Hospital from April 2020 to August 2023 were retrospectively collected, and blood was collected before, 2 cycles, 4 cycles and 6 cycles of immunosuppressant use. The correlation between peripheral blood PD-1 expression and gender, age, histological type, ECOG score, lymph node metastasis, and distant metastasis was analyzed using the chi-square test, trajectory analysis was used to describe the dynamic changes of peripheral blood PD-1, and survival analysis was performed by the Kaplan-Meier method and Log rank test.

Results In 119 patients with advanced non-small cell lung cancer, the PD-1 expression levels of total T lymphocytes, helper T lymphocytes, and cytotoxic T lymphocytes had no significant correlation with gender, age, histologic type, ECOG score, lymph node metastasis, and distant metastasis. The analysis showed a statistically significant difference between the dynamic decrease in PD-1 expression levels in total T lymphocytes associated with good PFS, and helper T lymphocytes as well as cytotoxic T lymphocytes associated with better OS.

Conclusion PD-1/PD-L1 immune checkpoint inhibitor-based immunotherapy has made a breakthrough in advanced lung cancer and has an important role in the prediction of the efficacy and prognosis of immunotherapy, and the study showed that a dynamic decrease in peripheral

blood PD-1 was associated with a good prognosis, which may provide a direction to screen for optimal immunosuppressant beneficiaries in the clinic.

Key Words： non-small cell lung cancer; peripheral blood; PD-1; immunotherapy

393. 一种基于细胞衰老的新型预后模型揭示结直肠癌中细胞与微环境相互作用和耐药性产生

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背景：在中国结直肠癌（CRC）的发病率逐年上升。目前主要的难题是肿瘤异质性和耐药性的产生。本研究深入探讨了 CRC 中的细胞衰老，旨在设计一个预后模型并找出影响药物抗性的机制。

方法：利用孟德尔随机化（MR）分析 CRC 与细胞衰老之间的关联。癌症基因组图谱（TCGA）-CRC 数据作为训练集，GSE38832 和 GSE39582 作为验证集。采用了各种生物信息学方法来构建和验证风险模型。并且根据免疫细胞浸润分析以及衰老相关基因与 SASP 因子的相关性分析，所以使用 CRISPR-Cas9 技术生成了 NADPH 氧化酶 4（NOX4）敲除的 CRC 细胞。蛋白质印迹和集落形成试验阐明了 NOX4 在 CRC 细胞衰老和药物抗性中的作用。

结果：本研究利用 MR 分析探索了 CRC 和细胞衰老之间的关系。结果显示，与端粒长度相关的 SNPs 与 CRC 的发病和进展存在显著的因果关系。基于 15 个基因的 mRNA 表达水平构建了一个预后风险模型，通过单因素和多因素 COX 回归分析，证明了风险评分是一个独立的预后因素。ROC 曲线评估了 TCGA-CRC 患者的 1 年、3 年和 5 年 OS 概率，其中 5 年生存的 AUC 最高，为 0.727。风险模型与肿瘤分级、T 分期、N 分期和 M 分期显著相关。我们还构建了一个用于预测 1 年、2 年和 3 年 OS 概率的标尺，提高了预后准确性。此外，基于该模型的 1 年 AUC 为 0.817，证明其具有优于基于临床风险因素的传统模型的区分能力。这些结果进一步确认了我们的风险评分模型在预测 CRC 患者预后方面的有效性和可靠性。发现在 CRC 中衰老相关基因 NOX4 与部分免疫细胞具有显著相关性，且发现与 NOX4 高度相关的 SASP 因子 VEGFC 可能会引起肿瘤细胞耐药性的产生。总的来说，风险评分模型为 CRC 的预后分析提供了一个强大的工具。从数据集分析中得出的预后模型揭示

了高风险组与癌症进展之间的联系。在风险组之间观察到肿瘤微环境的显著差异。最后，发现 NOX4 与 CRC 中的细胞衰老及药物耐药性产生有关。

结论：研究提供了对细胞衰老与结直肠癌（CRC）之间复杂关系的全面分析。它引入了一个创新的风险模型，用于预测 CRC 患者的预后和药物反应。我们在 CRC 中确定了与衰老相关的基因 NOX4，作为 CRC 药物抗性的潜在关键因素。这些发现对于增强 CRC 患者的治疗策略，以及应对药物抗性这一持久挑战，具有重大的前景。

关键字： 结直肠癌（CRC）、细胞衰老、肿瘤微环境（TME）、NOX4、耐药性

394. Biochemical, Enzymatic, and Computational Characterization of Recurrent Somatic Mutations of the Human Protein Tyrosine Phosphatase PTP1B in Primary Mediastinal B Cell Lymphoma

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Human protein tyrosine phosphatase 1B (PTP1B) is a ubiquitous non-receptor tyrosinephosphatase that serves as a major negative regulator of tyrosine phosphorylation cascades ofmetabolic and oncogenic importance such as the insulin, epidermal growth factor receptor (EGFR),and JAK/STAT pathways. Increasing evidence point to a key role of PTP1B-dependent signalingin cancer. Interestingly, genetic defects in PTP1B have been found in different human malignancies.Notably, recurrent somatic mutations and splice variants of PTP1B were identified in human B celland Hodgkin lymphomas. In this work, we analyzed the molecular and functional levels of threePTP1B mutations identified in primary mediastinal B cell lymphoma (PMBCL) patients and locatedin the WPD-loop (V184D), P-loop (R221G), and Q-loop (G259V). Using biochemical, enzymatic, andmolecular dynamics approaches, we show that these mutations lead to PTP1B mutants with extremelylow intrinsic tyrosine phosphatase activity that display alterations in overall protein stability andin the flexibility of the active site loops of the enzyme. This is in agreement with the key role of theactive site loop regions, which are preorganized to interact with

the substrate and to enable catalysis.Our study provides molecular and enzymatic evidence for the loss of protein tyrosine phosphataseactivity of PTP1B active-site loop mutants identified in human lymphoma.

Key Words ： lymphoma; protein tyrosine phosphatase; PTP1B; oncogenic mutations; enzyme activity

395. The Diagnostic and Prognostic Value of miR-155 in Cancers: An Updated Meta-analysis

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Background： MicroRNA-155 has been discussed as a biomarker in cancer diagnosis and prognosis. Although relevant studies have been published, the role of microRNA-155 remains uncertain because of insufficient data.

Methods： We conducted a literature search in PubMed, Embase, and Web of Science databases to obtain relevant articles and extract data to evaluate the role of microRNA-155 in cancer diagnosis and prognosis.

Results： The pooled results showed that microRNA-155 presented a remarkable diagnostic value in cancers (area under the curve = 0.90, 95% confidence interval (CI) 0.87–0.92; sensitivity = 0.83, 95% CI 0.79–0.87; specificity = 0.83, 95% CI 0.80–0.86), which was maintained in the subgroups stratified by ethnicity (Asian and Caucasian), cancer types (breast cancer, lung cancer, hepatocellular carcinoma, leukemia, and pancreatic ductal adenocarcinoma), sample types (plasma, serum, tissue), and sample size (n >100 and n <100). In prognosis, a combined hazard ratio (HR) showed that microRNA-155 was significantly associated with poor overall survival (HR = 1.38, 95% CI 1.25–1.54) and recurrence-free survival (HR = 2.13, 95% CI 1.65–2.76), and was boundary significant with poor progression-free survival (HR = 1.20, 95% CI 1.00–1.44), but not significant with disease-free survival (HR = 1.14, 95% CI 0.70–1.85). Subgroup analyses in overall survival showed that microRNA-155 was associated with poor overall survival in the subgroups stratified by ethnicity and sample size. However, the significant association was

maintained in cancer types subgroups of leukemia, lung cancer, and oral squamous cell carcinoma, but not in colorectal cancer, hepatocellular carcinoma, and breast cancer, and was maintained in sample types subgroups of bone marrow and tissue, but not in plasma and serum.

Conclusions： Results from this meta-analysis demonstrated that microRNA-155 was a valuable biomarker in cancer diagnosis and prognosis.

Key Words ： microRNA-155, biomarker, cancer, diagnosis and prognosis

396. Plasma proteomic biomarkers predict therapeutic responses in advanced biliary tract cancer patients receiving Camrelizumab plus the GEMOX treatment

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Background

Biliary tract cancer (BTC), known as one of highly lethal malignancies, has influenced people's lives for many years. Nowadays, immunotherapy represents a promising breakthrough and proteomics is one of powerful technologies in biomarker research.

Methods

Plasma and tissue samples were isolated from 37 Chinese patients with advanced BTC and treated with immune checkpoint blockade (ICB) and camrelizumab plus gemcitabine and oxaliplatin (GEMOX) at baseline (T1), 6 weeks (T2) and 6 months (T3). 92 proteins were analyzed by proximity extension assay (PEA) and related differentially expressed proteins (DEPs) were sought through a series of enrichment analysis. Linear-mixed effect models and correlation scatterplots helped to analyze DEPs from three angles including response-effect, time-effect and

interaction-effect. Ultimately, characteristics of genes and proteins were compared using cox proportional-hazards models.

Results

Compared to partial response (PR) group, 8 proteins, IL7, ANGPT2, IL15, HO-1, CXCL1, CXCL5, IL33 and VEGFA, exhibited significantly higher expression in stable disease and progressive disease (SD_PD) group in response-effect analysis. It was also revealed that a subset of proteins increased over time, including PDCD1, TNFRSF4, DCN, CRTAM, VEGFR-2 and ADA in PR group and PDCD1, IL10, ADA, CD28 and PTN in SD_PD group. Among them, the abundance of programmed cell death 1 (PDCD1) increased most dramatically in both groups. In interaction-effect analysis, HO-1, ANGPT2, IL15 were three significant DEPs and were all higher in SD_PD group compared with PR group at T1, T2, T3, and the trend of alteration became different as time goes. Receiver operating characteristic (ROC) analysis further demonstrated that HO-1, ANGPT2, IL15 showed high accuracy in patients with ICB treatment plus chemotherapy (AUC=0.74). In addition, based on the obtained plasma and tissue samples, two nomogram models were constructed for predicting the prognosis of BTC by genome combined with proteomics.

Conclusion

Proteomics has higher sensitivity and is conducive to predict the biomarker of immunotherapy's efficacy of BTC. The combination marker consisting of HO-1, ANGPT2, IL15 might function as a desirable predictive biomarker for BTC immunotherapy response.

Key Words： proteomics ，biliary tract cancer， immunotherapy

397. 失巢凋亡相关基因的胃癌预后模型构建与单细胞测序

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目的：利用生物信息学方法，基于失巢凋亡相关基因(anoikis-related genes, ARGs)构建胃癌(Stomach adenocarcinoma,STAD)的预后模型，同时进行药物敏感性分析，为精准临床诊疗提供潜在作用；通过单细胞数据分析，明确预后模型构建基因差异水平。

方法：STAD 相关的转录组数据与临床数据从癌症基因组图谱(The Cancer Genome Atlas, TCGA)数据库中获得，通过 GeneCards 数据库、Harmonizome 数据库筛选 ARGs，在高通量基因表达（Gene Expression Omnibus,GEO）数据库（平台号：GSE84437）中下载 STAD 生存相关的平台和矩阵文件并进行数据注释。然后将 TCGA-STAD 的表达输入文件与 ARGs 合并，以|logFC|＞1 且 fdr＜0.05 为过滤标准筛选显著差异基因，同时数据合并后进行批次校正，提取差异基因的表达量。对 ARGs 进行生存分析，从 UCSC Xena 平台获取 STAD 拷贝数数据后，提取 ARGs 拷贝数并计算拷贝数变异频率，同时将其与基因注释文件合并。通过 ARGs 的表达水平对样本进行分型，采用生存分析、主成分分析(Principal Component Analysis,PCA)对分型结果验证，使用差异分析鉴定 ARGs 与免疫细胞在不同分型中的表达水平。为发现通路在不同分型中是否具有差异，我们进行 GSVA 分析。同时利用 GSEA 分析可视化功能或通路在分型中的活跃程度。通过随机分组将样本分为实验组和验证组，通过 lasso 回归、多因素 cox 分析对实验组完成预后模型构建，将预后模型公式得到风险评分作为中位值区分高低风险样本。利用生存分析、ROC 曲线验证模型准确性，独立预后分析、决策曲线、列线图与校准曲线评估模型效用。同时还利用风险差异分析、免疫细胞差异分析、肿瘤微环境(Tumor microenvironment,TME)差异分析、药物敏感性差异分析判断患者风险得分、免疫细胞、TME 打分、药物敏感性在不同分型或分组的差异性；最后，使用 tisch2 数据库、STAD-GSE167297 数据集进行单细胞数据分析，观察模型基因在不同细胞中的差异程度。

结果：以 Relevance score>0.4 为阈值，对 GeneCards 数据库的检索结果进行过滤，获得 501 个 ARGs，结合 Harmonizome 数据库中的 139 个 ARGs，最终获得 640 个 ARGs,通过差异分析筛选出 161 个差异表达的 ARGs，根据其表达量不同，分为两个亚型，生存分析和 PCA 验证分型可靠。从 46 个与预后相关的 ARGs 中确定 10 个基因构建预后模型并计算风

险评分。生存分析结果显示高低风险组患者生存具有显著差异(p<0.001)；ROC 曲线表明该模型预测结果良好(曲线下面积(Area Under Curve,AUC)1 年:0.664，3 年:0.690，5 年:0.682);独立预后分析表明所构建模型可以作为独立预后因子(p<0.001);TME 差异分析表明高低风险组具有显著差异(p<0.001)。单细胞分析显示 MUC4 在上皮细胞中高表达。

结论：基于 10 个 ARGs 构建 STAD 相关的预后模型，能够较好的预测患者生存期、免疫细胞相关性、药物敏感性。该模型未来将对 STAD 治疗起到一定指导作用。

关键字： 胃癌；失巢凋亡；预后模型；肿瘤微环境

398. 妇科癌阴道微生物组共性与差异性分析

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目的：探讨妇科癌症女性阴道微生物组特征构建妇科癌症风险筛查模型。探究三种妇科癌症（宫颈癌、卵巢癌、子宫内膜癌）阴道微生物特征差异及标志物的潜在诊断价值。

方法：我们对 529 个来自女性阴道 16S rRNA 数据样本进行研究。数据分为妇科癌症组（n=348）和对照组（n=181）。妇科癌症组进一步分为宫颈癌组（n=161）、卵巢癌组（n=71）及子宫内膜癌组（n=100）。我们使用 VSEARCH 对原始数据进行处理，使用 Chao1、Shannon 和 Simpson 指数评估组间α多样性，加权 Unifrac 距离的主成分分析(PCA)检验β多样性。利用 LEfSe 线性判别方法分析组间物种差异。基于 Spearman 相关性分析，建立组间的细菌共丰度网络。基于属水平构建妇科癌风险随机森林模型并验证，测试模型诊断效果。

结果：与对照组相比，妇科癌症患者阴道α多样性升高，β多样性显著分离。绝经状态对阴道菌群影响不显著。在物种构成方面，妇科癌女性阴道 Firmicutes 及 Lactobacillus 丰度下降，而 Bacteroidetes、Proteobacteria，Prevotella、Streptococcus、Anaerococcus 等富集。基于属水平得到的 56 个生物标志物构建的随机森林模型在妇科癌症风险预测中实现了高精度（AUC=84.59%）。此外，共丰度分析表明，妇科癌症患者与对照人群阴道菌群网络复杂性存在变化。

结论：妇科癌女性具有独特的阴道菌群结构，微生物可能参与妇科癌症发生过程。基于特征属建立的妇科癌风险预测模型有良好的诊断价值。

关键字： 妇科癌症；16S rRNA；微生物；阴道；随机森林

399. Novel oleanolic acid derivative ZQL-4c targets SCD to modulate lipid metabolism reprogramming to overcome trastuzumab resistance in HER2 positive breast cancer

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Approximately 15% to 20% of patients with breast cancer are characterized as Human epidermal growth factor2 (HER2) positive with a high recurrence rate. With the application of anti-HER2 drugs such as trastuzumab, the prognosis of patients with HER2-positive breast cancer has improved significantly. However, more than 30% of patients experience recurrence, and distant metastasis due to drug resistance. It is important to develop new drugs to overcome trastuzumab resistance. Therefore, in collaboration with a research group at Dalian University of Technology, we synthesized ZQL-4c, a novel oleanolic acid (OA) derivative, which was found to target the lipid metabolism reprogramming function of stearoyl-CoA desaturase (SCD), inducing lipotoxicity-mediated apoptosis. This provides an attractive future direction for the treatment of HER2-positive trastuzumab-resistant breast cancer.

Key Words： Trastuzumab; Drug-resistance; Oleanolic acid; Stearoyl-CoA desaturase; Lipid metabolism

400. Highly specific vaginal microbiome signature for gynecological cancers

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Objective: To explore the vaginal microbiota signature of gynecologic cancer patients and assess its value as potential diagnostic biomarkers.

Methods: We included vaginal 16S rRNA-seq data from 529 women and processed the raw data using VSEARCH. Alpha diversity was assessed using Chao1, Shannon and Simpson indices, and beta diversity was assessed by principal component analysis (PCA) using weighted Unifrac distances. Linear discriminant analysis effect size (LEfSe) was used to assess species differences between groups. A bacterial co-abundance network was established based on Spearman correlation analysis. A random forest model of gynecologic tumor risk based on genus was constructed and validated to test its diagnostic efficacy.

Results: Vaginal α-diversity was elevated and β-diversity was significantly separated in gynecologic cancer patients compared to controls, with no significant correlation with whether the subject women were menopausal or not. In terms of species composition, vaginal Firmicutes and Lactobacillus were decreased and Bacteroidetes, Proteobacteria, Prevotella, Streptococcus, and Anaerococcus were enriched in women with gynecological cancer. A random forest model constructed based on 56 genus achieved high accuracy (Area Under the Curve, AUC=84.96%) in gynecological cancer risk prediction. In addition, the co-abundance networks showed variations in the community complexity in gynecologic cancer patients versus the controls.

Conclusion: Women with gynecologic cancer have a unique vaginal flora structure and microorganisms may be involved in the gynecologic carcinogenesis process. A gynecological cancer risk prediction model based on characteristic genera has good diagnostic value.

Key Words： gynecological cancer; 16S rRNA-seq; microbiome; vagina; random forest

401. 宫颈癌女性阴道、肠道菌群特征及微生物组作为宫颈癌诊断工具的临床潜力

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目的：探讨宫颈癌发生过程中阴道菌群的动态变化及宫颈癌相关阴道、肠道生物标志物的辅助诊断价值。

方法：我们对 416 个来自女性阴道 16S rRNA 基因数据集及 116 个来自女性肠道 16S rRNA 公共数据样本进行研究。其中阴道组按严重程度分为正常组（Normal）（n=180）、宫颈上皮内瘤变（CINs）组（n=152）及宫颈癌（Cervical cancer）组（n=84）。肠道组分为正常（Normal）组（n=51）、宫颈癌（Cervical cancer）组（n=65）。使用 Vsearch 对 reads 进行处理，Alpha 多样性通过 Chao1、Shannon 和 Simpson 指数检验，Beta 多样性通过加权 Unifrac 距离的主坐标分析(PCoA)检验，并基于 Bray-curtis 距离进行 PERMANOV A 分析。利用 LEfSe 线性判别方法进行组间物种差异分析。基于 Spearman 相关性分析，建立了每个组的细菌共丰度网络。基于物种构成和多样性分析结果，结合临床数据，构建随机森林模型，并对模型进行验证，测试模型诊断效果。不仅如此，我们通过京都基因和基因组百科全书 (KEGG) 和直系同源组 (COG) 注释研究宫颈癌与非癌菌群主要的代谢途径差异。

结果：与非癌人群相比，宫颈癌患者阴道、肠道两生态位都有独特的微生物群落特征。受试女性阴道微生物多样性及丰度的增加与疾病严重程度呈正相关，并伴随着乳酸菌属等共生菌群减少和加德纳菌属等致病菌丰度增高。宫颈癌患者肠道菌群多样性及丰度降低，物种构成也有显著改变，包括拟杆菌属、普氏菌属等的富集及粪杆菌属、罗氏菌属等丰度的降低。总的来说，宫颈癌的发生导致两生态位微生物变化，与非癌人群有显著差异。此外，共丰度分析表明，不同病理特征女性，菌群网络复杂性存在变化。为了确定用于无创诊断目的的最佳微生物群特征，我们在两生态位基于属水平得到的生物标志物的预测模型在宫颈癌诊断中实现了高精度（阴道模型 AUC = 91.58%；肠道模型 AUC=99.95%）。基于 KEGG 数据库的潜在功能路径分析表明，正常妇女微生物组和宫颈癌妇女微生物组之间的预测功能谱存在显著差异。

结论：宫颈癌患者阴道、肠道微生物与非癌人群相比有显著差异，在阴道中还存在微生物随疾病严重程度改变发生的动态变化现象，菌群参与宫颈癌的发生发展。在两生态位基于属水平构建的预测模型均对宫颈癌有良好的诊断价值。

关键字 ：子宫颈癌；16S rRNA；阴道微生物；肠道微生物；诊断

402. Specific vaginal and gut microbiome and the anti-tumor effect of butyrate in cervical cancer women

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Objective: To investigate the vaginal and gut microbes changes during the carcinogenesis of cervical and the auxiliary diagnostic value of microbial markers. To investigate the effect of microbiome-specific metabolites butyric on cervical cancer cells.

Methods: We studied 416 vaginal 16S rRNA sequencing data and 116 gut data. Reads were processed using VSEARCH. We used Shannon index, Chao1 index, Simpson diversity index, Beta diversity index, LEfSe analysis, co-abundance network analysis and KEGG enrichment analysis to explore microbiome differences between groups. We constructed random forest models based on genus and validated the models to test their diagnostic effectiveness. Finally, we used the cell counting kit-8 (CCK-8) method to detect cell proliferation capacity and flow cytometry to detect apoptosis and induction of cell cycle progression.

Results: Compared to the non-cancerous population, patients with cervical cancer had unique microbial community characteristics in both vaginal and gut ecological niches. Our predictive model based on genus in two ecological regions achieved high accuracy in the diagnosis of cervical cancer (vaginal model AUC=91.58%; gut model AUC=99.95%). Potential functional pathways analysis indicated significant differences between the normal women microbiomes and cervical cancer women microbiomes. Butyric inhibited cervical cancer cell proliferation in a concentration-dependent manner and promoted apoptosis of cancer cells.

Conclusion: Significant differences were found in vaginal and gut microbes in patients with cervical cancer compared to the non-cancerous population, and the microflora is involved in cervical carcinogenesis. The prediction models constructed at the genus level in both ecological sites have good diagnostic value for cervical cancer. Microorganisms may be involved in cervical cancer progression in a metabolite-dependent way, and targeting butyric may provide therapeutic options for cervical cancer.

Key Words： cervical cancer; 16S rRNA; vaginal; gut; butyrate; ROC

403. Association of XRCC gene family and CDH1 gene polymorphisms with gastric cancer risk in a Chinese population

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Background: Gastric carcinogenesis is associated with defects in DNA damage repair pathways, in which the XRCC gene family plays an important role in DNA repair. It is also well known that the CDH1 gene, as a tumor suppressor, is related to the development of gastric cancer. Here, we investigated the association between the XRCC gene family (XRCC1, XRCC5, and XRCC6) and CDH1 gene polymorphisms and gastric cancer risk and patients' survival.

Methods: We recruited 484 gastric cancer patients and 471 healthy controls. DNA was extracted and purified using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit and samples were genotyped using the Sequenom Mass-ARRAY platform. Helicobacter pylori immunogold detection kit was used to detect Helicobacter pylori.

Results: No differences in genotype distribution were observed between gastric cancer cases and healthy controls. Stratified analysis revealed that XRCC1 rs25487 TC/TT was associated with an increased gastric cancer risk in the following four subgroups of males (adjusted OR = 1.40, 95% CI: 1.04-1.90, P = 0.031), positive Helicobacter pylori (adjusted OR = 1.58, 95% CI: 1.09-2.28, P = 0.015), tumor stage III-IV (adjusted OR = 1.42, 95% CI: 1.06-1.89, P = 0.017), and non-gastric cardiac adenocarcinoma (adjusted OR = 1.36, 95% CI: 1.02-1.82, P = 0.034). Additionally,

survival analysis indicates that XRCC1 rs25487 TC/TT genotype (HR = 1.35, 95% CI: 1.08-1.69, P = 0.010) is associated with unfavorable survival in gastric cancer patients.

Conclusion: XRCC1 rs25487 CC genotype decreased the risk of gastric cancer, and predicted a favorable survival prognosis.

Key Words: XRCC, CDH1, polymorphisms, gastric cancer

404. Potential Targets And Mechanisms Of Bitter Almond-Licorice For COVID-19 Treatment Based On Network Pharmacology And Molecular Docking

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Background: The outbreak of Corona Virus Disease 2019 (COVID-19) has resulted in millions of infections and raised global attention. Bitter almonds and licorice are both Traditional Chinese Medicines (TCM), often used in combination to treat lung diseases. Several prescriptions in the guidelines for the diagnosis and treatment of coronavirus disease 2019 (trial version ninth) contained bitter almond-licorice, which were effective in the treatment of COVID-19. However, the active ingredients, drug targets and therapeutic mechanisms of bitter almonds-licorice for the treatment of COVID-19 remained to be elucidated.

Methods: The active ingredients and targets were derived from the Traditional Chinese Medicine Systems Pharmacology (TCMSP). Meanwhile, targets associated with COVID-19 were obtained from the GeneCards database, PharmGkb database and DrugBank database. Then, the potential targets of bitter almond-licorice against COVID-19 were screened out. Protein-protein interaction (PPI) networks and core targets were analyzed through the String database and Cytoscape software. In addition, gene ontology (GO), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed based on potential targets using R statistical software. Finally, molecular docking was used to validate the binding of the active ingredients to the core targets.

Result: The results of the TCMSP database showed that the bitter almond-licorice had 89 active components against COVID-19, involving 102 targets. PPI network and core target analysis indicated that IL-6, TNF, MAPK1, and IL1B were the key targets against COVID-19. In addition, GO and KEGG enrichment analysis showed that the bitter almond-licorice were involved in various biological processes through inflammation-related pathways such as TNF signaling pathway, and IL-17 signaling pathway. Finally, molecular docking approaches confirmed the affinity between the active components of the bitter almond-licorice and the therapeutic targets.

Conclusion: The bitter almond-licorice could be used to treat COVID-19 through inhibiting inflammatory responses and regulating cellular stress. This work based on data mining and molecular docking, and the finding need to be interpreted with caution.

Key Words： Bitter almond; Licorice; COVID-19; network pharmacology; molecular docking; Traditional Chinese Medicine

405. Expression of cancer-testis antigens MAGE-A1, MAGE-A4, NY-ESO-1 and PRAME in bone and soft tissue sarcomas: the experience from a single center in China

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Objective: Sarcomas are a heterogenous group of malignancies, low disease-control levels and the limited durability of responses have motivated the exploration of various novel immunotherapeutic approaches. To preliminarily explore the feasibility of cancer vaccines based on cancer testis antigen in the immunotherapy of sarcomas. We investigate the expression of

Cancer/Testis Antigens (CTA) MAGE-A4, PRAME, MAGE-A1, KK-LC-1 and NY-ESO-1 in bone and soft tissue sarcomas.

Methods and results: We investigated MAGE-A4, PRAME, MAGE-A1, KK-LC-1 and NY-ESO-1 expression by immunohistochemistry and multiplex immunostaining chip (MI chip) in sarcoma specimens which consisted of 21 undifferentiated pleomorphic sarcoma (UPS), 26 leiomyosarcomas, 28 liposarcomas, 40 osteosarcomas(OS) and 13 chondrosarcomas. Among these tumors, MAGE-A4 was detected in 40.00% of osteosarcomas, 33.33% of UPS, 17.85% of liposarcomas, 11.54% of leiomyosarcomas. PRAME expression was found in 47.62% UPS, 26.92% of leiomyosarcomas, 15.00% of osteosarcomas, 14.28% of liposarcomas, 7.69% of chondrosarcomas. MAGE-A1 expressed 32.50% of osteosarcomas, 28.57% UPS, 15.38% of leiomyosarcomas, 10.71% of liposarcomas. NY-ESO-1 was detected in only 10.71% of liposarcomas, 9.52% of malignant fiber histiocytomas, 2.50% of osteosarcomas. None of these sarcomas express KK-LC-1.

Conclusions: The expression of CTA in bone and soft tissue sarcomas depends on the type of CTA and the subtype of sarcoma. With the development of CTA-based cancer vaccines, this study will provide more evidence for the application of these vaccines in sarcomas, especially in UPS and OS, which have a high probability of expressing CTAs.

Key Words： sarcoma, cancer testis antigen (CTA), immunotherapy, MAGE-A4, NY-ESO-1.

406. HR+/HER2-乳腺癌中 CDK4/6 抑制剂耐药机制研究进展

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细胞周期蛋白依赖性激酶 4/6（Cyclin-dependent kinase 4 and 6,CDK4/6）抑制剂是一种靶向治疗药物，通过阻断细胞周期抑制肿瘤细胞增殖。目前 CDK4/6 抑制剂已被批准联合内分泌治疗用于治疗激素受体（Hormone receptor，HR）阳性/人表皮生长因子受体-2（Human epidermal growth factor receptor，HER2）阴性的乳腺癌患者，但其原发或继发耐药性仍不可避免地影响患者的治疗疗效和预后。CDK4/6 抑制剂的耐药机制主要分为细胞周期特异性机

制、细胞周期非特异性机制等。深入了解耐药机制有助于寻找能够克服或延缓耐药性的创新策略，解决耐药后治疗策略有限的难题，改善患者的预后。本文对 CDK4/6 抑制剂耐药性机制的相关进展展开综述。

关键字： CDK4/6 抑制剂；耐药性；乳腺癌

407. Intratumoral and fecal microbiota reveals microbial markers associated with gastric carcinogenesis

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Study Objectives: The relationship between dysbiosis of the gastrointestinal microbiota and gastric cancer (GC) has been extensively studied. However, microbiota alterations in GC patients vary widely across studies, and there are still no diagnostic biomarkers for early GC that can be replicated in multiple populations. Therefore, this study aimed to characterize the gastrointestinal microbial communities associated with gastric carcinogenesis and identify microbial markers for non-invasive early screening of GC based on open datasets.

Materials and Methods: We reanalyzed 16s rRNA sequencing data from 1,642 gastric biopsy samples and 394 stool samples from 11 studies. Changes in the gastrointestinal microbiota composition, microbial interactions, and potential functions were analyzed. The random forest model was constructed and validated to differentiate between GC patients and healthy individuals. Furthermore, we classified the gastric tissue samples into Helicobacter pylori (HP)-negative and HP-positive groups to analyze the role of non-HP.

Results: Meta-analysis showed altered intratumoral and fecal microbiota in GC patients. We found that intratumoral, gut-specific and co-differentiated Lactobacillus and Streptococcus could well differentiate GC patients from healthy individuals (area under the curve (AUC) = 0.7949) and demonstrated their generalizability and reproducibility by LODO (mean AUC = 0.81) and external validation (AUC = 0.7712). The positive correlation between GC-enriched bacteria increased, and the positive correlation between GC-depleted bacteria decreased compared to healthy individuals. Pathways associated with inhibition of ferroptosis were significantly enriched in GC. Also, we reported that Lactobacillus, Streptococcus, Peptostreptococcus, and Ochrobactrum may contribute to developing HP-positive GC along with HP. Arthrobacter, Geobacillus, Lactococcus, and Fusobacterium independently contribute to developing HP-negative GC.

Conclusions: This study reveals the characteristics of the intratumoral and fecal microbiota of GC patients and demonstrates that GC-specific microbial markers of fecal origin can be used for the early non-invasive diagnosis of GC.

Key Words： Gastric cancer, Intratumoral microbiota, Fecal microbiota, Microbial marker, Non-invasive prediction

408. LAMC2 acts as a novel and potential biomarker in CRC and shapes the immune-suppressive tumor microenvironment

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Background: Colorectal cancer(CRC) is one of the most threatening cancers which seriously endangers human life and health. LAMC2 expression has been correlated with the development, growth, and progression of multiple cancer types. However, the biological role of LAMC2 has not been investigated in patients with CRC (CRC). Here, we performed a comprehensive

bioinformatics analysis of the CRC dataset to determine the mechanisms underlying the regulation of tumorigenesis by LAMC2.

Methods: We used the R language to construct ROC (Receiver-Operating Characteristic) curves, KM (Kaplan–Meier) curves and nomograms based on databases such as the TCGA and GEO to analyze the diagnostic and prognostic value of LAMC2 in CRC patients. Enrichment analysis, immune scoring, GSVA (Gene Set Variation Analysis) were used to investigate the potential biological functions and the impact on the immune microenvironment of LAMC2. Finally, the effect of LAMC2 on CRC cell proliferation and invasion was determined in vitro .

Result: We found A higher expression of LAMC2 was linked to a shorter overall survival (OS) and a worse pathological stage, while LAMC2 expression was associated with immune cell infiltration and immune-related markers in the CRC tumor microenvironment. CRC with high LAMC2 expression tends to be a cold tumor. Furthermore, GO and KEGG enrichment analysis indicated that LAMC2-related genes were enriched in the cell adhesion and immune signaling pathways of LAMC2. Furthermore, cellular assays verified that LAMC2 promotes the proliferation, migration and invasion of HCT116 cell.

Conclusion: Our findings revealed that LAMC2 is overexpressed in CRC and is linked to a poor prognosis. Our study demonstrates the potential of LAMC2 as an immunotherapeutic and predictive biomarker in CRC.

Key Words： Colorectal cancer，LAMC2，Biomarker，Immune infiltrates，Prognosis

409. 小分子药物纳米制剂在宫颈癌治疗中的应用前景

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宫颈癌是女性中较高发的一类恶性肿瘤，晚期疗效较差且容易发生转移，常规治疗方法疗效有限。小分子药物虽在宫颈癌治疗中不断探索，并且取得了一定疗效，但由于副作用较大，难溶于水，无法靶向肿瘤局部等，尚不能让人信服。随着纳米技术的发展，金属有机骨架材料（MOFs）以其可通过靶向输送、缓释给药、改变体内分布以及提高生物利用度等方

面的优点逐渐成为肿瘤领域的研究热点。ZIF-8 是由 2-甲基咪唑和锌离子构建的具有生物相容性的 MOFs，是进行吸附、催化、载药的理想纳米载药系统，本文就小分子纳米制剂在宫颈癌治疗中的应用及 ZIF-8 作为载药系统的研究进展进行综述，为 ZIF-8 协载小分子药物在宫颈癌治疗中的应用研究提供参考。

关键字： 宫颈癌　小分子药物　纳米制剂　MOFs　ZIF-8

410. CD2AP Is a Potential Prognostic Biomarker of Renal Clear Cell Carcinoma

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Background: CD2-associated protein (CD2AP) is a podocyte-associated gene and its reduced expression is associated with the development of proteinuria and glomerulosclerosis. However, few studies have focused on the correlation between the expression and prognosis of CD2AP in renal clear cell carcinoma (ccRCC). Therefore, we aimed to assess the regulation of CD2AP expression and prognostic value in ccRCC.

Methods: Multiple databases were employed to examine the expression of CD2AP in ccRCC. RT-qPCR, Western Blot and immunohistochemistry were used to validate CD2AP expression in different cell lines and tissue samples. Kaplan-Meier analysis and ROC curve analysis were performed on the predictive prognostic performance of CD2AP. COX regression was used to construct CD2AP-related prognostic models. The TIMER and TISIDB databases were used to analyze the correlation of tumor-infiltrating immune cells with gene expression, mutations, somatic copy number variation, and immune molecules. Mass spectrometry was used to detect methylation status of the promoter CpG site of CD2AP in multiple cells.

Results: We found that CD2AP expression was downregulated in ccRCC and its lower expression level was correlation with worse patient prognosis, higher tumor stage and grade and distant metastasis through analysis of databases, ccRCC cell lines and clinical tissue samples. Moreover, database and mass spectrometry techniques identified and validated cg12968598

hypermethylation as one of the key reasons for the downregulation of CD2AP expression. CD2AP expression was also associated with macrophage and neutrophil infiltration.

Conclusions: Taken together, our results suggest that CD2AP can be used as a diagnostic and prognostic biomarker in ccRCC patients and that DNA hypermethylation plays an important role in reducing CD2AP expression.

Key Words ： CD2AP, ccRCC, DNA methylation, risk model

411. 一种独特的循环 microRNA 对标记可作为泛癌早期诊断的工具

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Abstract: Background: Cancer remains a major burden globally and the critical role of early diagnosis is self-evident. Although various miRNA-based signatures have been developed in past decades, clinical utilization is limited due to a lack of precise cutoff value. Here, we innovatively developed a signature based on pairwise expression of miRNAs (miRPs) for pan-cancer diagnosis using machine learning approach.

Method: We analyzed miRNA spectrum of 15832 patients, who were divided into training, validation, test, and external test sets, with 13 different cancers from 10 cohorts. Five different machine-learning (ML) algorithms (XGBoost, SVM, RandomForest, LASSO, and Logistic) were adopted for signature construction. The best ML algorithm and the optimal number of miRPs included were identified using area under the curve (AUC) and youden index in validation set. The AUC of the best model was compared to previously published 25 signatures.

Result: Overall, Random Forest approach including 31 miRPs (31-miRP) was developed, proving highly efficient in cancer diagnosis across different datasets and cancer types (AUC range: 0.980-1.000). Regarding diagnosis of cancers at early stage, 31-miRP also exhibited high capacities, with AUC ranging from 0.961-0.998. Moreover, 31-miRP exhibited advantages in differentiating cancers from normal tissues (AUC range: 0.976-0.998) as well as differentiating

cancers from corresponding benign lesions. Encouragingly, comparing to previously published 25 different signatures, 31-miRP also demonstrated clear advantages.

Conclusion: In conclusion, 31-miRP acts as a powerful model for cancer diagnosis, characterized by high specificity and sensitivity as well as a clear cutoff value, thereby holding potential as a reliable tool for cancer diagnosis at early stage.

关键字： microRNA pair, liquid biopsy, pan-cancer, cancer detection, machine learning algorithm

412. Genetically Predicted Metabolites Mediate the Association between Immune Cells and Pancreatic Cancer: A Mendelian Randomization Study

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Objective: Pancreatic cancer is characterized by metabolic dysregulation and unique immunological profiles. Nevertheless, the comprehensive understanding of immune and metabolic microenvironment of pancreatic cancer remains unclear. In this study, we aim to investigate the causal relationship of immune cells and pancreatic cancer and identify the metabolites as potential mediators.

Methods: The exposure and outcome GWAS data used in this study were obtained from an open-access database (https://gwas.mrcieu.ac.uk/). This study used 731 immune cell features, 1400 types of metabolites, and pancreatic cancer from GWAS. We then performed bidirectional MR analyses to explore the causal relationships between the immune cells and pancreatic cancer, and two-step MR to discover potential mediating metabolites in this process. All statistical analyses were performed in R software. The STROBE-MR checklist for the reporting of MR studies was used in this study.

Results: MR analysis identified seven types of immune cells were causally associated with pancreatic cancer. And there was no strong evidence that genetically predicted pancreatic cancer

had an effect on these seven types of immune cells. Further two-step MR analysis found 10 types of metabolites were causally associated with pancreatic cancer and the associations between CD39+CD8+ T cells and pancreatic cancer were mediated by orotates with proportions of 5.18% (P= 0.016).

Conclusions: In conclusion, our study provides evidence supporting the causal relationships between various immune cells, especially CD39+CD8+ T cells, and pancreatic cancer, with a potential effect mediated by orotates. Further research is needed on additional risk factors as potential mediators and establish a comprehensive immunity-metabolism network in pancreatic cancer.

Key Words： Mendelian randomization, immune cells, metabolites, orotate levels, CD39+CD8+ T cells, pancreatic cancer

413. 肿瘤标志物 CA125 在心力衰竭患者中的应用价值研究

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目的：CA125 是一种临床上常用的肿瘤标志物，已经在临床实践中被常规使用了超过 30 年，主要用于诊断和监测卵巢癌患者。心力衰竭(心衰)是因心脏结构或功能异常所致心室充盈或射血能力受损的一组复杂临床综合征，是目前最重要的心血管病之一。研究发现，在心力衰竭人群中 CA125 的阳性率显著偏高，本文对其原因进行了研究分析。

方法：调研知网、PubMed 等数据库的文献，研究 CA125 与心脏疾病相关疾病之间存在的关系，分析心力衰竭人群 CA125 偏高的原因。

结果： CA125 主要由心包、胸膜或腹膜中的间皮细胞合成。虽然其生物学作用尚不清楚，但它似乎参与了多种途径，包括细胞介导的免疫反应。1999 年，Nagele 等首次描述了 71 例心衰患者的 CA125 水平较高。在过去的 20 年里，大量的研究重新评估并证实了 CA125 在心衰中的预后作用。CA125 最吸引人的特性之一是监测心衰失代偿后的临床病程的潜力。CA125 显示与不良临床结果呈正相关，特别是在急性心力衰竭（AHF）的情况下。另外，CA125 和利钠肽不同但互补，互补使用这两种标记物来评估每个心脏侧参与的程度，其中 CA125 和利钠肽分别反映了右侧和左侧的心力衰竭（HF）。CA125 在大多数临床实验室的

广泛可用性，以及其标准化测量和成本的降低，使该标记物对失代偿性心衰的常规使用具有吸引力。未来需要进一步的研究以更好地了解 CA125 自身的生物学作用作为指导心衰减充血治疗的工具之一。

结论：当临床上遇到慢性心衰人群 CA125 升高时，给予相应合理的解释，可以避免患者对肿瘤的怀疑与恐惧，减少不必要的检查。CA125 不是心脏特异性的标志物，其上调也可能发生在一些良性和肿瘤性疾病中。因此，需要特别注意，在没有 HF 诊断的情况下，CA125 值的升高可能表明存在广泛和异质性的情况，需要进行全面的临床评估。卵巢和转移性恶性肿瘤中 CA125 水平通常远高于急性和稳定心衰的水平。CA125 提供的信息应考虑到症状、体征、超声心动图参数和其他生物标志物的状态。

关键字： CA125；心衰；利钠肽；

414. 扶正减毒汤对大肠癌放化疗抵抗动物模型增效减毒的疗效观察及其机制研究

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【目　的】

1．探索扶正减毒汤对大肠癌放化疗抵抗动物模型的增效减毒作用。

2．筛选扶正减毒汤放化疗增效作用的关键基因并分析其可能的调控机制。

【方　法】

1. 将放化疗抵抗细胞株 HCT116CRR 注射到裸鼠右前肢背部皮下建立皮下移植瘤模型，待移植瘤体积长至 100mm^3 左右，分为 4 组：对照组；放化疗组；扶正减毒汤+放化疗组；扶正减毒汤组。

2．治疗期间观察扶正减毒汤对裸鼠体重、肿瘤体积的影响以及各组治疗前后血常规和肝肾功的对比，治疗结束剥取皮下移植瘤，称瘤重，计算各组肿瘤抑制率。

3．运用全基因组表达谱芯片方法鉴定 b 组和 c 组的差异表达基因，进一步 GO 富集分析、KEGG 通路富集分析。构建 lncRNA-mRNA 的共表达网络。

4．通过 RT-qPCR 实验检测上调基因表达情况，检测其是否差异表达，与芯片分析结果是否一致。

5．采用 SPSS25.0、GraphPad prism8.0 和 Cytoscape 软件，对实验数据进行统计分析和作图，满足正态分布的定量资料用均数±标准差(±s)的形式描述，组间比较使用 t 检验；统计检验为双侧，P<0.05 为有统计学意义。

【结　果】

1.与 b 组相比，c 组的裸鼠体重增加、肿瘤体积缩小、瘤重降低、肿瘤抑制率高（P<0.05）；血常规和肝肾功的检测结果表明扶正减毒汤对大肠癌放化疗抵抗动物模型具有增效减毒作用。

2．全基因组表达谱芯片方法鉴定 b 组和 c 组的差异表达基因，得到 31 个差异 mRNA（10 个表达上调，21 个表达下调）和 166 个差异 lncRNA（97 个表达上调，69 个表达下调）。

3．差异 mRNA 的 GO 富集分析，差异基因主要分布在分子功能的珠蛋白结合、有机酸结合和过氧化物酶活性以及细胞组分的血红蛋白和血红蛋白复合体；差异 mRNA 的 KEGG 富集分析，差异基因主要富集的前 5 条通路为精氨酸生物合成、非洲锥虫病、疟疾、氨基酸生物合成和糖胺聚糖生物合成。

4．差异 lncRNA 的 GO 富集分析，差异基因主要分布在生物学过程的尿素循环和氧气运输、细胞组分的血红蛋白复合体以及分子功能的鸟氨酸氨基甲酰转移酶活性和氧转运体活性；差异 lncRNA 的 KEGG 富集分析，差异基因主要富集的 5 条通路为泛酸和辅酶 A 生物合成、糖胺聚糖生物合成-硫酸角蛋白、精氨酸和脯氨酸代谢、氨基酸生物合成和非洲锥虫病。

5.通过 Cytoscape 软件得到网络中心基因：lncRNA（lnc-ZNF680-41、ENSG00000236434.2、NONHSAG095545.2、NONHSAG058752.1）和 mRNA（TEX38、OR4C6、ARG1、IL1RL1、SCAND1、KLRD1）。

【结　论】

1．扶正减毒汤对大肠癌放化疗抵抗动物模型具有增效减毒作用。

2．差异 lncRNA 和 mRNA 可能通过调节正常生理代谢产生作用。

3．经验证表达上调的基因在肿瘤组织中存在明显差异，且与芯片结果一致。

关键字： 肠癌；放化疗抵抗；扶正减毒汤；lncRNA；mRNA

415. 芳香疗法在癌症患者焦虑抑郁情绪中的应用进展

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目前，我国恶性肿瘤发病率持续上升，由于疾病本身或治疗等因素，在癌症患者的整个病程中伴随着生理、心理、精神等各方面症状，特别是出现焦虑抑郁症状，严重影响患者的生活质量。芳香疗法最初用于美容行业，现已广泛应用于医疗保健领域，可作为一种补充照护手段，具有减轻疼痛、改善睡眠、缓解焦虑抑郁、防止皮肤干燥等作用。本文阐述焦虑抑郁情绪对癌症患者的影响和相关治疗、芳香疗法的起源、作用途径和机制及其在焦虑抑郁癌症患者中的应用现状，以为芳香疗法更好的应用于癌症焦虑抑郁患者提供参考。

416. The research progress of opioid-based cancer pain management and patient prognosis

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Pain is a common symptom in cancer diagnosis. While substantial progress and associated improvements have been made in chronic cancer pain management over the past few years, poor pain control remains a major concern for many cancer patients. Opioids are regarded as the mainstay of pain management. However, the dependence, abuse, and misuse of opioids by patients due to their side effects prompted a reassessment of the safety of opioids for the treatment of pain (acute pain, chronic non-cancer pain, and cancer pain). Recent studies have found that in addition to some common side effects, the use of opioids also have an impact on the patient's immune function and endocrine function. This article discusses the management of cancer pain and some problems found in the current application of opioids.

Key Words ： Opioids; Breast cancer; Cancer pain

417. Oncogenic KRAS effector USP13 promotes metastasis in non-small cell lung cancer through deubiquitinating β-catenin

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Objective： Lung cancer is the leading cause of cancer incidence and mortality worldwide, of which non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases. Oncogenic driver mutations in genes such as EGFR, RAS, PIK3CA, MET, and translocated anaplastic lymphoma kinase (ALK) play critical roles in NSCLC initiation and progression. Of these, 15%-30% of non-small cell lung cancers have KRAS mutations. Aberrant activation of KRAS is a key driver of malignant proliferation and metastasis of non-small cell lung cancer. Although covalent KRASG12C inhibitors have been developed to treat KRASG12C-mutant cancers, effective treatments are still lacking for other KRAS-mutant NSCLCs. Therefore, identifying the key node molecules of KRAS mutation promoting NSCLC process and expounding its molecular mechanism are still of great significance for the accurate treatment and targeting strategy of KRAS-driven cancers.

Materials and Methods： In this study, we used methods such as The Cancer Genome Atlas (TCGA) database, Cell culture and transfection, Transwell cell invasion assays, Immunohistochemistry (IHC) staining analysis, Mass spectrometry analysis of K63-linked ubiquitination sites in β-catenin, Deubiquitination assay, Colony formation assay, Generation of knockout (KO) or knockdown(KD) cells, Quantitative PCR assays, Cytoplasmic and nuclear fractionation assay, Luciferase reporter assay, Chromatin immunoprecipitation (ChIP) assay, Immunofluorescence analysis and related materials to explore relevant mechanisms and validate phenotypes in different cells. We also identified USP13 inhibitor through a natural compound library, and further characterized protein and small-molecule interactions with Microscale thermophoresis (MST) binding assay. For in vivo experiments, we constructed Lung metastasis

model, KrasG12D-driven mouse spontaneous NSCLC to further validate relevant phenotypes and physiological significance.

Results： This study found that KRAS drives expression of deubiquitinase USP13 through Ras-responsive element-binding protein 1 (RREB1). Elevated USP13 promotes KRAS-mutant NSCLC invasion and metastasis, which is associated with poor prognosis in NSCLC patients. Mechanistically, we performed mass spectrometry (MS) analysis of the immunoprecipitation complex of Flag-USP13, and immunoprecipitation experiments showed that USP13 can interact with β-Catenin. Although we failed to detect obvious change in β-Catenin protein level as well as its effector TCF4 protein level in USP13-KO cells, cell fractionation analysis confirmed the reduction of nuclear β-Catenin in USP13-KO cells. Then, through IP assay, we found that USP13 promotes β-catenin/TCF4 association and stimulates the expression of β-catenin target genes such as vimentin. Furthermore, through a series of ubiquitin analysis in vivo and in vitro, we found that USP13 directly removes the polyubiquitin modification of the K63 connection of the β-Catenin K508 site. Using structural simulation, we found that the K508 site of β-Catenin is located at the interface between β-Catenin/TCF4 and transcription factor TCF4. The removal of polyubiquitin at this site by USP13 can significantly enhance β-Catenin/TCF4 interaction and promote the transcription of downstream target genes. At last, we identified 2-methoxyestradiol as an effective inhibitor for USP13 from a drug library of natural products. In cell and animal experiments, it was confirmed that 2-methoxyestradiol could significantly inhibit the metastasis of KRAS mutant non-small cell lung cancer.

Conclusion： Thus, this study reveals that USP13 is a potential drug target for the treatment of metastatic KRAS mutant tumors. At the same time, screening found that a natural small molecular drug 2-Methoxyestradiol can directly inhibit the activity of USP13, which provides a lead compound for targeted USP13 treatment of KRAS mutant tumor metastasis, and this compound has the potential for clinical translation. This will provide a new scientific basis for the accurate treatment of KRAS mutant tumors.

Key Words： USP13；β-catenin；deubiquitination；NSCLC；metastasis

418. Plasma anti-PRTN3 IgG and IgM autoantibodies as novel diagnosis biomarkers for lung adenocarcinoma

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Purpose: Lung cancer is the leading cause of cancer death worldwide, especially because most patients are only diagnosed at an advanced and noncurable stage. Lung adenocarcinoma (LUAD) is the most common subtype. At present, most patients can be preliminarily diagnosed with pulmonary nodules by low-dose CT (LDCT). However, LDCT has its limitations in distinguishing between benign and malignant nodules, leading to a high rate of false-positive results and excessive treatments. The levels of IgG and IgM autoantibodies in plasma of cancer patients have been proposed as early diagnostic biomarkers because they appear early in the cancer, are sensitive, readily available, and noninvasive. The association of PRTN3 with malignant tumors has received increasing attention. The purpose of this study is to evaluate the feasibility of plasma autoantibodies to PRTN3 in diagnosis of LUAD.

Methods: The PRTN3 protein levels in 61 LUAD tissues, 5 para-carcinoma tissues and 10 normal tissues were detected by immunohistochemistry. The plasma levels of anti-PRTN3 IgG and IgM autoantibodies were detected by enzyme-linked immunosorbent assay (ELISA) in the training set and validation set. The training set contained 95 plasma samples from LUAD patients and 98 plasma samples from age-and sex-matched normal control (NC). The validation set included another 275 LUAD, 275 NC and 223 benign pulmonary nodules (BPN) plasma samples. Western blotting and immunofluorescence were performed to further confirm the results of ELISA.

Results: PRTN3 was highly expressed in LUAD tissues compared with para-carcinoma and normal tissues. In two different sets, the levels of anti-PRTN3 IgG and IgM autoantibodies were significantly higher in LUAD than that in BPN and NC ($p<0.0001$). Meanwhile, both anti-PRTN3 IgG and IgM autoantibodies can distinguish LUAD from BPN and NC. In the training set, the area under the curve (AUC) for anti-PRTN3 IgG and IgM autoantibodies to distinguish LUAD from NC were 0.717 (95%CI: 0.644-0.789) and 0.640 (95%CI: 0.563-0.718), respectively. In the

validation set, the AUC of anti-PRTN3 IgG autoantibody in distinguishing LUAD from NC was 0.696 (95%CI: 0.653-0.739) and that in distinguishing LUAD from BPN was 0.697 (95%CI: 0.651-0.743). The AUC for anti-PRTN3 IgM autoantibody distinguishing LUAD from NC, BPN were 0.688 (95%CI: 0.644-0.731), 0.651(95%CI: 0.604-0.699) respectively. Importantly, the AUC of combined anti-PRTN3 IgG and IgM autoantibodies were 0.770 (95%CI: 0.730-0.809) for distinguishing LUAD from NC and 0.750 (95%CI: 0.707-0.792) for distinguishing LUAD from BPN. The results of western blotting confirmed the existence of plasma immune response to PRTN3. Furthermore, immunofluorescence staining validated the immunoreactivity of LUAD plasma to PRTN3 in LUAD cells.

Conclusion: Our study indicated that anti-PRTN3 IgG and IgM autoantibodies can distinguish LUAD from NC and BPN. Anti-PRTN3 autoantibodies are potential biomarkers for diagnosis of LUAD.

Key Words ： lung adenocarcinoma; autoantibodies; diagnosis; biomarker

419. HER2 阳性乳腺癌靶向治疗：耐药机制及耐药后新策略

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HER2 的发现对乳腺癌的治疗是一重大突破,HER2 阳性乳腺癌约占所有乳腺癌的 20%，同时 HER2 还是一种高度敏感的治疗靶点。随着抗 HER2 治疗的发展，显著改善了 HER2 阳性乳腺癌患者的预后，但部分患者因耐药性导致疾病进展或复发。在这篇综述中，我们讨论了传统 HER2 靶向治疗的耐药机制。我们还讨论了耐药后 HER2 靶向治疗的新策略，其中主要讨论了新型 HER2 靶向治疗药物 ADC 的作用机制及它独有的耐药机制。

关键字： HER 2 阳性乳腺癌　HER 2 耐药

420. Prevotella copri exhausts intrinsic indole-3-pyruvic acid in the host to promote breast cancer progression: Inactivation of AMPK via UHRF1-mediated negative regulation

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Objects: Emerging evidence has revealed the novel role of gut microbiota in the development of cancer. The characteristics of function and composition in the gut microbiota of patients with breast cancer patients has been reported, however the detailed causation between gut microbiota and breast cancer remains uncertain.

Materials and methods: 16S rRNA sequencing was employed to analyzed difference between the gut microbiota of breast cancer patients and that of their counterparts. The cancer promotion activity of *Prevotella corpi* was confirmed in the 4T1 breast cancer-bearing model with specific pathogen-free (SPF) mice and germ-free (GF) mice following by quantitative proteomics and bisulfite sequencing. Targeted metabolomics analysis was used to revealed the consumption of indol-3-pyruvid acid (IPyA) by *P. corpi* in vivo and in vitro. Molecular mechanism of cytotoxicity of IPyA on breast cancer cells were explored by western blotting, relative quantitative PCR (qPCR), methylation specific quantitative PCR (MS qPCR), and ATP production analysis.

Results: 16S rRNA sequencing revealed that *Prevotella*, particularly the dominant species *Prevotella copri*, is significantly enriched and prevalent in gut microbiota of breast cancer patients. Prior-oral administration of *P. copri* could promote breast cancer growth in specific pathogen-free mice and germ-free mice, accompanied with sharp reduction of indole-3-pyruvic acid (IPyA). Mechanistically, the present of excessive *P. copri* consumed a large amount of tryptophan (Trp),

thus hampering the physiological accumulation of IPyA in the host. Our results revealed that IPyA is an intrinsic anti-cancer reagent in the host at physiological level. Briefly, IPyA directly suppressed the transcription of UHRF1, following by the declined UHRF1 and PP2A C in nucleus, thus inhibiting the phosphorylation of AMPK, which is just opposite to the cancer promoting effect of P. copri. Therefore, the exhaustion of IPyA by excessive *P. copri* strengthens the UHRF1-mediated negative control to inactivated the energy-controlling AMPK signaling pathway to promote tumor growth, which was indicated by the alternation in pattern of protein expression and DNA methylation.

Conclusions: Our findings, for the first time, highlighted *P. copri* as a risk factor for the progression of breast cancer.

Key Words： Breast cancer; Prevotella copri; Indole-3-pyruvic acid; UHRF1; AMPK

421. CONUT 评分在晚期乳腺癌中的预后预测价值分析

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目的：晚期乳腺癌预后不理想，目前有关晚期乳腺癌预后和预测因子的报道较少。近年来，控制营养状态（Controlling nutritional status, CONUT）评分在肿瘤中的预后价值受到越来越多关注。目前尚无关于 CONUT 评分在晚期乳腺癌中临床价值的研究，本研究旨在讨论 CONUT 评分在晚期乳腺癌中的预后应用，并进一步分析晚期乳腺癌转移部位的相关因素。

研究方法：收集 2010 年 1 月至 2023 年 12 月期间就诊于辽宁省肿瘤医院乳腺内科一病区 170 例乳腺癌患者的临床资料和化验结果。以 CONUT 评分 2 分为界值将总体人群分成 2 组：高 COUNT 组（≥2 分，79 例）和低 COUNT 组（＜2 分，91 例），单因素分析患者疾病进展的危险因素，并进一步纳入多因素 logistic 回归分析晚期乳腺癌疾病进展的独立危险因素。PFS 定义为从确诊晚期乳腺癌到进展/随访截点的时间间隔。

结果：高、低 CONUT 组相应的 PFS 中位数分别为 319 天、495 天，高、低 CONUT 分组的 PFS 差异无统计学意义（P＝0.271）。进一步分析提示，高、低 CONUT 组在晚期乳腺癌 1 年内发生进展事件差异有统计学意义（P＝0.034）。对晚期乳腺癌 1 年内发生进展事件进行单因素分析，结果发现 CONUT 评分（P=0.034）、ER 状态（P=0.016）、Ki-67 状态（P=0.005）、

晚期基线转移部位是否含内脏（P=0.017）和晚期一线化疗方案是否含铂类（P=0.022）与晚期乳腺癌接受一线化疗 1 年内发生进展事件有关，将以上因素纳入多因素 logistic 回归分析，最终得到 3 个影响因素，CONUT 评分（P=0.018）、Ki-67 状态（P=0.012）、晚期基线转移部位是否含内脏（P=0.003）是晚期乳腺癌接受一线化疗 1 年内发生进展事件的独立危险因素。构建晚期乳腺癌 1 年内进展风险的 nomogram 预测模型，校正曲线、决策曲线均提示模型预测能力良好。对高、低 CONUT 的晚期乳腺癌转移部位进行比较，结果发现高 CONUT 组肝转移率更高。对晚期乳腺癌发生肝转移进行单因素分析，结果发现 CONUT 评分（P=0.033）、HER2 状态（P=0.030）与晚期乳腺癌发生肝转移事件有关，将以上因素纳入多因素 logistic 回归分析，最终得到 2 个影响因素，CONUT 评分（P=0.027）、HER2 状态（P=0.025）是晚期乳腺癌发生肝转移事件的独立危险因素。对肝转移晚期乳腺癌患者进行亚组分析，发现 CONUT 在发生肝转移的 HER2 阳性晚期乳腺癌人群中预后能力较好，在不同 HR 亚组及 HER2 阴性人群中预后能力差。

结论：CONUT 评分、Ki-67 和内脏转移是接受一线化疗的晚期乳腺癌 1 年疾病进展的独立预后因子，列线图能够方便准确地预测患者 1 年进展风险。高 CONUT 评分和 HER2 阳性与乳腺癌患者发生肝转移相关。CONUT 评分在发生肝转移的 HER2 阳性晚期乳腺癌人群中预后能力较好，在不同 HR 亚组及 HER2 阴性人群中预后能力差。

关键字： 晚期乳腺癌；控制营养状态评分；预后；预测；肝转移；

422. PIVKA-II 联合甲胎蛋白在肝癌诊断中的应用价值研究

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目的：探讨血清肿瘤标志物异常凝血酶原（PIVKA-II）、甲胎蛋白 (AFP) 以及联合检测在肝癌诊断中的应用价值。

材料与方法：选取 2023 年 3 月至 2023 年 10 月北京大学肿瘤医院内蒙古医院收治的患者及健康体检人群，其中包含 56 例肝癌患者，412 例健康体检人员。采用电化学发光免疫分析仪（罗氏 cobas 8000 e801）及其配套试剂盒，严格按照标准操作流程对 AFP、PIVKA-II

血清水平进行检测，比较 2 组入组人群 PIVKA-II 与 AFP 的水平，并绘制受试者工作曲线（ROC），分析 PIVKA-II与 AFP 指标在肝癌诊断中的价值。

结果：肿瘤标志物 PIVKA-II 与 AFP 血清表达水平肝癌组明显高于对照组 (P＜0.05），ROC 曲线结果显示，PIVKA-II与 AFP 指标检测的 AUC 分别为 0.833、0.718，PIVKA-II 检测对肝癌的诊断价值高于 AFP。

结论：肿瘤标志物 PIVKA-II 检测在肝癌诊断中具有较高的诊断价值，与 AFP 检查联合对肝癌患者具有较高的区分能力，有利于肝癌患者的早期诊断。

关键词：异常凝血酶原（PIVKA-II）甲胎蛋白（AFP）肝癌

关键字： 异常凝血酶原（PIVKA-II）甲胎蛋白（AFP）肝癌

423. LINC00638 促进结直肠癌生长和转移的机制研究

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目的：本课题主要目的在于研究长链非编码 RNA（longnon-codingRNAs）—LINC00638 对结直肠癌（colorectalcancer，CRC）细胞的影响，并对其生长和转移进行初步探讨。

方法：首先通过荧光定量逆转录 PCR（quantitativereversetranscriptionPCR，RT-qPCR）来检测 CRC 组织和细胞中 LINC00638 的表达情况，采用 Kaplan-Meier 法分析 LINC00638 表达对 CRC 患者预后的影响，Cox 回归模型分析其与临床病理参数的相关性。接着用 CCK-8 和平板克隆形成，流式细胞术实验检测 LINC00638 对 CRC 细胞体外增殖和克隆形成能力的影响；利用 Transwell 实验观察 LINC00638 对 CRC 细胞迁移和侵袭的影响；通过裸鼠皮下成瘤模型和原位成瘤肝转移模型来研究 LINC00638 对肿瘤细胞体内生长和转移的影响。机制方面，采用 RNApulldown、蛋白质谱分析筛选 LINC00638 在 CRC 细胞中的结合蛋白，并用 RNA 免疫沉淀（RIP）和 WesternBlot（WB）等技术进一步验证与 LINC00638 互作的靶蛋白及其下游作用机制；免疫组化实验进一步验证靶蛋白在 CRC 组织中的表达；最后通过功能回复实验再次验证 LINC00638 和靶蛋白之间的相互作用。

结果：LINC00638 在 CRC 组织中的表达水平明显升高（P<0.01），且 LINC00638 的高表达与 CRC 患者不良预后相关（P=0.0058）。功能实验结果表明，过表达 LINC00638 显著促进 CRC 细胞增殖、迁移和侵袭能力；敲降 LINC00638 表达后，CRC 细胞增殖、迁移和

侵袭能力受到抑制；动物实验结果证明，过表达 LINC00638 能够促进肿瘤体内生长和转移，而敲降 LINC00638 抑制肿瘤体内生长和转移。机制上，通过 RNApulldown 实验结合质谱分析，确定 LINC00638 结合的靶蛋白为核转运蛋白α2（KPNA2），且 LINC00638 与 KPNA2 相互作用抑制其泛素化降解，促进 KPNA2 表达，进而激活 PI3K/AKT 信号通路。功能回复实验证明敲降 KPNA2 可恢复 LINC00638 对 CRC 细胞增殖、迁移的促进作用。

结论：LINC00638 在 CRC 中发挥促癌基因的作用；LINC00638 能够促进 CRC 细胞的增殖，迁移和侵袭；LINC00638 通过抑制 KPNA2 的泛素化降解，激活 PI3K 信号通路，促进结直肠细胞增殖、侵袭和迁移；以上结论提示 LINC00638 有望成为 CRC 的一个新的肿瘤标志物及候选治疗靶点。

关键字 ：结直肠癌；长链非编码 RNA；LINC00638；KPNA2

424. 外泌体 circ12172 在胃癌进展中的作用与机制

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目的：胃癌是一种发病率和死亡率均较高的消化道恶性肿瘤，其诊断和治疗仍具有一定的局限性。本研究旨在探究血浆外泌体来源的 circRNA 在胃癌进展中的临床价值和作用机制。

方法：提取健康人、胃炎患者以及胃癌患者的血浆外泌体，通过 ceRNA 芯片测序筛选出差异表达的 circRNA 分子。RNaseR 实验和 Sanger 测序验证其稳定性。采用 NTA、TEM 以及蛋白表征鉴定血浆及细胞来源外泌体。运用 qRT-PCR 检测 circ12172 在胃黏膜正常上皮细胞（GES-1）/胃癌细胞以及健康人/胃炎患者/胃癌患者血浆外泌体中的表达，ROC 曲线评估其诊断效能。利用 FISH 实验和核质分离实验确定 circ12172 在胃癌细胞中的定位。运用 CCK8、克隆形成、迁移侵袭以及 Western Blot 探究过表达和敲减 circ12172 在胃癌细胞中的生物学功能。利用生物信息学预测、RIP 实验、qRT-PCR 以及双荧光素酶报告基因实验探究 circ12172 在胃癌进展中的机制。收集过表达 circ12172 的细胞上清，采用超速离心法提取外泌体后与胃癌细胞共培养，通过细胞功能学实验探究外泌体中 circ12172 的生物学作用。

结果：Circ12172 在胃炎患者、及胃癌患者血浆外泌体中均较健康人下调，胃癌患者术后有所上调，在胃癌中的诊断效能为 0.7133，临床相关性分析与患者年龄（p=0.032）、侵

袭深度（p=0.047）相关。Circ12172 在胃癌细胞及其外泌体中显著低表达。Circ12172 在细胞核与细胞质中均有定位，能够耐受 RNaseR 的消化。过表达 circ12172 能够抑制胃癌细胞的增殖与迁移侵袭，敲减后则反之。RIP 实验证明 circ12172 能够与 AGO2 结合，生物信息学和双荧光素酶报告基因实验预测并验证 miR-6799-3p 能够与 circ12172 结合，回补实验可以验证其调控功能。MXI1 作为 miR-6799-3p 的下游靶标，可以抑制胃癌的进展，进一步影响 C-myc、CyclinD1 的表达。此外，过表达 circ12172 的外泌体可以抑制胃癌细胞的增殖、迁移与侵袭，参与细胞间通讯。

结论：Circ12172 在胃癌细胞、胃炎患者及胃癌患者血浆外泌体中显著下调，可以通过 miR-6799-3p/MXI1/C-myc/CyclinD1 轴发挥抑癌作用，并通过外泌体途径介导细胞间通讯，有望成为胃癌进展中的新型诊断标志物和治疗新靶点。

关键字： 胃癌；外泌体；circRNA；诊断

425. 机器学习模型揭示结直肠癌可变剪切事件与预后模型研究

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目的： 本研究旨在探究结直肠癌（CRC）可变剪切（AS）能否用于 CRC 诊断，以及其对患者预后的影响。

方法： 首先，我们在 TCGA SpliceSeq 数据库中对 49 例 CRC 患者的可变剪切 PSI 值进行了差异分析，鉴定出 1674 个具有差异的基因 AS。随后，我们构建了剪切因子的进化树，并对 TCGA-CRC 公共数据库中的 50 例配对样本进行了剪切因子表达量的差异分析，鉴定出了 35 个差异表达的剪切因子。为了获得与诊断相关的基因 AS，我们使用 Lasso 筛选出了 16 个特征 AS，同时使用 SVM 筛选出了 9 个特征 AS。Lasso 和 SVM 的筛选结果中有 5 个 AS 事件是交集事件。接着，我们进行了单因素 COX 回归分析，筛选出了 191 种与预后相关的 AS 事件，其中包括了涵盖 29 种不同 AS 事件的多个基因。通过多种机器学习方法，我们最终筛选出 21 种关键 AS 事件用于构建最终的预后模型。同时，我们将数据集中的患者分成了低风险组和高风险组，并进行了 Kaplan-Meier 分析，结果显示高风险组的患者生存时间显著短于低风险组。

结果： 我们成功成功发现可由于诊断的 5 中 AS 事件，并构建了一个机器学习模型，利用 21 种关键 AS 事件准确预测了结直肠癌患者的预后。高风险组患者的生存时间明显短于低风险组，模型的预测效果显著。

讨论： 本研究揭示了 AS 在结直肠癌的发展和预后中的重要作用。我们发现 HNF4A|59461|AP 和 HNF4A|59462|AP 可能作为结直肠癌的诊断标志物，并发现 PRMT5 对 PCBP1 对 OBSCN 的不同可变剪切调控具有影响，从而影响了结直肠癌患者的预后。这些结果为进一步理解结直肠癌的发展和提供治疗策略提供了重要线索。

关键字： 结直肠癌；机器学习；可变剪切；肿瘤标志物

426. HSP110 通过抑制 Claudin 7 的表达而增强结直肠癌细胞上皮-间质转化

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目的：上皮-间质转化过程（EMT）可加速结直肠癌的侵袭、迁移等恶性表型，并在肿瘤复发中占据重要地位。HSP110 蛋白可促进结直肠癌细胞的 EMT，并且可通过抑制β-catenin 的降解而激活 Wnt/β-catenin 信号通路。本研究利用我们之前自主研发合成的新型 HSP110 抑制剂 H-007，探讨 HSP110 增强结直肠癌细胞 EMT 的分子机制，阐明 HSP110 可通过激活 Wnt/β-catenin 信号通路后，抑制细胞紧密连接蛋白 Claudin 7 的表达，而促进结直肠癌细胞的 EMT。

材料与方法： H-007 作用 HCT116 细胞 48h 后 RNA-seq 二代测序技术筛选具有表达差异的基因。在 SW480 和 HCT116 细胞中，以 H-007 作用以及使用 siRNA 敲降 HSP110 表达后，通过 Western Blot 和 qPCR 检测 Claudin 7 在蛋白水平和 mRNA 水平的表达。siRNA 敲降 Claudin 7 表达后，以 H-007 作用细胞，通过 Western Blot、划痕实验和 Transwell 小室实验，分别检测细胞的 EMT 相关蛋白 E-cadherin、N-cadherin 和 Snail 的表达，以及细胞的迁

移、侵袭能力。H-007 和 siHSP110 作用细胞后，通过 qPCR 检测 Wnt 信号通路下游靶基因 c-myc、Survivin 和 cyclin D1 的表达，Western-blot 检测β-catenin 和磷酸化β-catenin 蛋白的表达。将蛋白酶体抑制剂 MG132、细胞内蛋白合成抑制剂 CHX 与 H-007 共同作用细胞后，通过 Western-blot 检测β-catenin 和磷酸化β-catenin 的表达。H-007 和 siHSP110 作用细胞后，转染ΔN-catenin 表达载体，通过 qPCR 和 Western-blot 检测 Claudin 7 在 mRNA 和蛋白水平的表达。

结果：结直肠癌细胞中 HSP110 的表达被抑制后，Claudin 7 的表达上调，且 HSP110 发挥促进结直肠癌细胞 EMT 的作用依赖于下调 Claudin 7 的表达。H-007 和 siHSP110 作用细胞后，细胞中 c-myc、Survivin 和 cyclin D1 基因的转录水平下调，β-catenin 减少而磷酸化β-catenin 积聚，这说明 H-007 可抑制 Wnt/β-catenin 信号通路，相较于单纯 H-007 作用组，MG132 和 H-007 共同作用组中磷酸化和非磷酸化的均β-catenin 积聚增加，CHX 和 H-007 共同作用组中β-catenin 逐渐减少，说明 H-007 影响了β-catenin 的降解。相较于单纯 H-007 对照作用组和 siHSP110 作用组，同时过转染ΔN-catenin 表达载体组细胞中 Claudin 7 的表达降低。

结论：我们首次揭示了 HSP110 通过增强 Wnt/β-catenin 信号通路，进而抑制 Claudin 7 的表达而促进结直肠癌 EMT 的分子机制，阐明了新型 HSP110 抑制剂 H-007 可通过调控为 HSP110/β-catenin/Claudin 7 轴而发挥抑制结直肠癌 EMT 的药理学机制，为未来抗结直肠癌治疗新的干预手段的开发提供了理论基础及实验依据。

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关键字： 结直肠癌，上皮-间质转化，HSP110，Claudin 7

427. Gold Nanoclusters-Based Nano Capture-Detection System for Early Lung Cancer Diagnosis

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Background

Autoantibodies appear early in the blood and are stable for a long time. Our previous study has reported that the expression level of anti-PDL1 autoantibody (AAb) in lung cancer (LC) patients

was significantly higher than that of normal controls (NC), which could be served as a potential marker of LC. The detection of autoantibody (AAb) is critical for the diagnosis of early lung cancer (LC). However, the specificity and sensitivity are often limited by the characteristics of the antigens and the detection systems such as enzyme-linked immunosorbent assay (ELISA). Here, a highly sensitive gold nanoclusters-based nano capture-detection system is developed to detect anti-PDL1 AAb as the biomarker of LC.

Methods

1. Design of PDL1 polypeptide

In this study, the corresponding amino acid sequence of PDL1 protein (NP_054862.1) was downloaded through NCBI, and it contained 290 amino acids. The linear epitopes of the PDL1 protein were predicted online by IEDB and ABCpred, and two polypeptide sequences were finally determined, and synthesized by Shanghai Gill Polypeptide Co., LTD., named peptide1 and peptide2. The optimal polypeptide sequences for subsequent methods were screened by ELISA.

2. Preparation of Gold Nanoclusters Coated with HRP

HAuCl4 (10 mM, 1 mL) and HRP (100 mg mL-1, 1 mL) solutions were mixed and gently stirred at 37 °C for 10 minutes. NaOH (1 M) was used to adjust the pH of the mixture to 11 and gently stirred for 24 hours at a water bath of 37 °C. The reaction mixture was dialyzed overnight at 4 °C, and then the dialyzed product was mixed with an equal volume of isopropanol, centrifuged at 8000 rpm for 30 min, and repeated three times. The precipitate was collected and suspended with the same amount of pure distilled water to obtain a blackish-green solution as gold nanoclusters coated with HRP (HRP-AuNCs) and the concentration was determined by the BCA method.

3. Goat Anti-human IgG Immobilization Procedure

HRP-AuNCs were conjugated with goat anti-human IgG by the sodium periodate (NaIO4) method. NaIO4 (20 mg mL-1, 45 μL) solution was added into HRP-AuNCs (5 mg mL-1, 500 μL), thoroughly mixed, and dark at room temperature for 20 minutes. Then add ethylene glycol (40 μL), and leave for 30 minutes, and above liquid was dialyzed in carbonate buffer（CBS, 50 mM）at 4°C overnight. The oxidized HRP-AuNCs were mixed with goat anti-human IgG (5 mg mL-1, 500 μL) at room temperature for dialysis for 2.5 hours. The cross-linked product was taken out of the dialysis bag and placed in a light-resistant vessel, and NaBH4 (80 μL) was added for a reaction of 2 hours at 4°C and the reduction solution was placed in PBS buffer (10 mM, PH 7.2) at 4°C for

overnight dialysis, during which the solution was changed 3-4 times, which was the final synthetic material anti-IgG-HRP-AuNCs.

4. Nano Capture-Detection System

Firstly, the commercial streptavidin magnetic beads (Av-MB) are combined with synthetic biotinylated peptide (MB-peptide) as the immunocapture part, 50 μL of MB-peptide was incubated with 50 μL diluted anti-PDL1 AAb plasma at 37 °C for 30 minutes. The MB-peptide captures the anti-PDL1 AAb from the test samples to form the MB-peptide/anti-PDL1 AAb immunocomplex. The microtiter wells are washed with PBST to remove the unbound anti-PDL1 AAb, 100 μL anti-IgG-HRP-AuNCs with signal amplification as detection probes are added to each well and incubated for 30 minutes at 37 °C. The color development was achieved by adding 100 μL of the TMB substrate solution into each well. The reaction was incubated for 10 minutes, and 50 μL of the termination solution H2SO4 (10.9 %) is added. The absorbance is measured at 450 nm after the addition of the termination solution.

5. Study Sample

ELISA was used to detect the best peptides in 305 LC, 305 BPN and 305 NC samples. Blood samples from 79 LC patients and 79 Ncs were collected.

79 LC patients and 79 Nc as a sample to evaluate the nanoscale detection system.

Results

The nano capture-detection system assay time is 50 minutes, which is more quickly than conventional ELISA detection. Anti-PDL1 AAb are examined in 79 LC patients and 79 healthy controls (NCs) using the nano capture-detection system. The nano capture-detection system area under the curve (AUC) is highly enhanced to 0.884 (0.819-0.949) compared with the 0.746 (0.651-0.841) of traditional ELISA in the early stages of LC. The results indicate that the nano capture-detection system is an effective detection platform and provide a more sensitive detection system for the diagnosis of early LC.

Key Words ： peptide, lung cancer, gold nanoclusters, nanomagnetic capture-detection System, anti-PDL1 autoantibody

428. RNA 甲基化阅读器蛋白YBX1在人类肿瘤中的表达预后分析

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研究背景和研究目的：YBX1 是一种多功能癌蛋白，其参与癌症相关的细胞增殖与存活，染色体失稳及耐药性等相关广泛基因的调节。YBX1 作为多种基因的转录因子，参与多种 DNA/RNA 依赖性事件，包括 DNA 修复，前体 mRNA 剪接，mRNA 转录，mRNA 包装，mRNA 稳定性以及翻译的调节，在细胞水平，YBX1 的活性表现为参与细胞的增殖和分化，细胞凋亡，应激反应和恶性细胞转化等过程。研究与正常细胞相比，癌细胞中 Y-盒结合蛋白-1（YBX1）的表达，并研究其在癌症组织中的调节途径。

研究方法：通过从癌症基因组（TCGA）获得的数据，比较 YBX1 在泛癌及其正常组织中的表达水平。使用 UCSC 数据库的基因模块 TCGA+GTEx 进行了基因表达差异和免疫细胞相关性分析。

研究结果：与相应的正常组织相比，大多数肿瘤中 YBX1 的表达明显更高，在嗜铬细胞瘤和副神经节瘤、肾嫌色细胞癌、睾丸癌中 YBX1 的表达低于相应的正常组织。结果表明，在许多癌症中，YBX1 的表达高于正常细胞，特别是在胃癌中，在不同分期的患者中，YBX1 的表达均高于正常细胞，即 YBX1 与肿瘤发生相关。在许多癌症中，YBX1 表达的个体发病风险有显著提高。胃癌患者的发病风险与 YBX1 的表达没有明显相关性。使用 UCSC 数据库的基因模块 TCGA+GTEx 分析肿瘤中基因表达和免疫浸润之间的相关性。YBX1 的表达与大多数肿瘤的免疫浸润呈现显著负相关。在胃癌中，YBX1 的表达与肿瘤的免疫浸润呈负相关。使用 Timer 进行免疫细胞分析， 浸润肿瘤的免疫细胞类型与癌症复发的风险相关。YBX1 与大多数肿瘤中的免疫细胞浸润呈正相关，但在 KIRC,THYM 中免疫细胞浸润的相关性表现最显著。在八种肿瘤（KIRC、KIPAN、PRAD、GBMLGG、PCPG、LIHC）中，在 B 细胞、CD4 T 细胞、CD8 T 细胞、中性粒细胞、巨噬细胞和树突状细胞 （DC）中观察到 YBX1 的高表达。但上述免疫细胞与 STAD 中 YBX1 的表达无统计学相关性。我们分析了 YBX1 表达与 24 个免疫抑制因子以及 36 个免疫激活因子免疫检查点途径相关性。在 DLBC、TGCT、UCS、CESC、LUSC、NB、ALL、GBM、COAD、COADREAD、THYM、LAML、ESCA、LUAD、STAD、STES、HNSC、SKCM 等基因中 YBX1 免疫检查点多数基

因显著负相关，在 ACC、LIHC、OV、UVM、KICH、PAAD、KIPAN、KIRC 登基因中 YBX1 则与免疫检查点多数基因显著正相关。

结论：YBX1 的表达水平在大多数肿瘤中显著升高，YBX1 表达高的个体发病风险显著提高。YBX1 的表达与大多数肿瘤的免疫浸润呈显著负相关，与大多数肿瘤的免疫细胞浸润呈正相关，可能在肿瘤免疫调节中发挥重要作用。YBX1 在不同癌症中对于免疫检查点的调控存在差异，YBX1 与刺激性免疫检查点和抑制性免疫检查点在多种癌症中有显著相关性。探索 YBX1 在肿瘤组织中的调节机制可能会为肿瘤治疗提供更多方向。

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关键字：YBX1;泛癌分析；TCGA；预后

429. Plasma autoantibody IgG to PDGFRα as a potential novel biomarker in detection of non-small cell lung cancer

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Background: Platelet-derived growth factor receptor α (PDGFRα) is a member of the receptor tyrosine kinase superfamily that plays a crucial role in early hematopoiesis, angiogenesis, and organ development. Dysregulation of PDGF receptor signaling in pathological conditions has been implicated in cancer, vascular disease, and fibrotic disease. Our previous research found that in 154 human recombinant customized protein chips based on 138 cancer driver genes, the expression level of anti-PDGFRα autoantibody was significantly higher in the serum of lung cancer patients than in normal control serum, but whether anti-PDGFRα autoantibody can be used as a biomarker for lung cancer diagnosis has not been verified. This study aimed to determine the detection of anti-PDGFRα autoantibody levels from NSCLC, BPN patients and NC plasma to provide a rationale for its use as a blood biomarker for the diagnosis of lung cancer patients.

Methods： The expression level of anti-PDGFRα IgG was detected in plasma of 421 NSCLC, 328 BPN and 421 NC by indirect enzyme-linked immune sorbent assay (ELISA). Western blotting and

indirect immunofluorescence (IIF) were used to verify the ELISA results. The Multivariate Regression analysis was used to evaluate the odds ratio (OR) of NSCLC.

Results: The frequency of anti-PDGFRα IgG was significantly higher in NSCLC patients than that in NC and BPN in both test (n=186) and validation (n=656) cohorts. The area under the curves (AUCs) of anti-PDGFRα IgG for discriminating NSCLC from NC were 0.600 in test cohort and 0.735 in validation cohort, and the AUC of anti-PDGFRα IgG for discriminating NSCLC from BPN was 0.714 in validation set. In validation cohort, Between the different clinical features of NSCLC, Plasma anti-PDGFRα IgG expression was higher in females than males (P <0.001), and also higher in older age groups (P <0.001), moreover, the AUC value of anti-PDGFRα IgG for discriminating NSCLC from NC was significantly higher than that of clinical traditional tumor biomarkers CEA and CA125.

Conclusion: Our results indicate that anti-PDGFRα IgG can be used as a potential novel biomarker for the early diagnosis of NSCLC.

Key Words ： PDGFRα, Autoantibody, Lung cancer, Biomarker, Detection

430. Y01 通过靶向 IKBKE 影响 Hippo 信号通路抑制三阴性乳腺癌增殖和侵袭

韩兆雪

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乳腺癌是女性中最常见的癌症，也是全球第二大癌症相关死亡原因。TNBC 约占所有乳腺癌的 15% 至 20%。与 HR 阳性乳腺癌相比，TNBC 的预后更差，超过 50%的患者在诊断后 3 至 5 年内复发，基于当前疗法的中位总生存期（OS）为 10.2 个月。由于缺乏相关的受体标记物，TNBC 患者不会受益于内分泌或 HER2 靶向药物。因此，非手术 TNBC 的治疗标准仍然是非特异性化疗。TNBC 靶向药物治疗药物目前有 PARP 抑制剂，如奥拉帕尼等；VEGF 和 VEGFR 抑制剂，如贝伐单抗；EGFR 抑制剂，西妥昔单抗等；AR 拮抗剂，比卡鲁胺等；Trop-2 抗体偶联药物等，部分已上市，部分仍处于临床试验阶段，虽然部分患者对这些疗法有一定敏感性，但仍有研究证实 I 期 TNBC 患者 5 年存活率为

77%，II 期降至 50%，大部分患者最初 5 年中复发或发展为致命的转移性疾病的概率仍很大，5 年存活率仅 14%，因此，研发新型的抗 TNBC 药物至关重要。本项目前期与大连理工大学合作，合成上百种齐墩果酸衍生物，通过体外胞培养模型，体内异种移植瘤模型，转录组学联合生信分析，采用分子结构学技术，以 CETSA 技术检测结合效率，DARTS 技术，SPR 技术，共结晶技术，细胞及动物模型，IKBKE 融除的功能缺失模型及挽救实验，检测细胞的增殖及侵袭，细胞周亡增殖及周期阻滞铁死亡等死亡模式，Westem Blot,RT-PCR,免疫荧光，挽救实验，异种移植瘤模型等，筛选出 Y01 具有最佳的抗 TNBC 活性，体外研究结果显示 Y01 可有效抑制三阴性乳腺癌的增殖和侵袭，可能成为 TNBC 治疗的新型靶向药物，IC 50 为：0.63 μmol/L，提示 Y01 药效显著，具有较强的药物开发潜能。

关键字： TNBC，HIPPO 通路，肿瘤侵袭

431. Correlation between SHOX2 and RASSF1A methylation levels and the pathological evolution of early lung adenocarcinoma

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Background: The methylation of SHOX2 and RASSF1A shows promise as a potential biomarker for the early screening of lung cancer, offering a solution to remedy the limitations of morphological diagnosis. The aim of this study is to measure the methylation levels of SHOX2 and RASSF1A in lung adenocarcinomat issue before and after invasion, in order to obtain more accurate molecule staging。

Methods: The methylation levels of SHOX2 and RASSF1A were quantified using a LungMe® test kit through methylation-specific PCR (MS-PCR). The diagnostic efficacy of SHOX2 and RASSF1A and the cutoff values were validated using ROC curve analysis. The hazardous factors

influencing the T stage and pathological grading of lung adenocarcinoma were calculated using multiple regression.

Results: The cutoff values of SHOX2 and RASSF1A were 8.3 and 12.0, respectively. The sensitivities of LungMe® in IA, MIA and AIS patients were 71.3% (122/171), 41.7% (15/36), and 16.1% (5/31) under the specificity of 94.1% (32/34) for benign lesions which can effectively identify the pathological evolution of early lung adenocarcinoma . Additionally, in IA group, the methylation level of SHOX2, RASSF1A and LungMe® correlated with the high invasive clinicopathological feature ,such as tumor size (p=0.003) T stage (P<0.001), pleural invasion (P<0.001) and STAS (p=0.044). The age (HR=0.025, 95% CI 0.000-0.050, P=0.048), tumor size (HR 0.598 ,95% CI 0.324-0.872, p ＜ 0.001), CTR values (HR=0.582, 95% CI -0.067,1.231, p=0.039) and LungMe® methylation levels (HR=2.447, 95% CI 1.868,3.027 ,p=0.001) were identified as independent hazardous factors influencing the T stage and pathological grading of lung adenocarcinoma.

Conclusion: SHOX2 and RASSF1A combined methylation can be used as an early detection indicator of lung adenocarcinoma before and after invasion .The SHOX2 and age, RASSF1A methylation levels, tumor size and CTR values could predict the T stage and pathological grading of the tumor, thereby providing accurate molecule staging.

Key Words： lung adenocarcinoma; SHOX2; RASSF1A; methylation; invasiveness

432. Amplification-Free Analysis of Bladder Cancer MicroRNAs on Wrinkled Silica Nanoparticles with DNA-Functionalized Quantum Dots

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Bladder cancer (BC) occurrence and progression are accompanied by alterations in microRNAs (miRNAs) expression levels. Simultaneous detection of multiple miRNAs contributes to the accuracy and reliability of BC diagnosis. In this work, wrinkled silica nanoparticles (WSNs) were

applied as the microreactor for the multiplex miRNAs analysis without enzymes or nucleic acid amplification. Conjugated on the surface of WSNs, the S9.6 antibody was adopted as the universal module for binding DNA/miRNA duplexes regardless of their sequence. Furthermore, single-strand DNA (ssDNA) was labeled with quantum dots (QDs) for identifying a given miRNA to form QDs-ssDNA/miRNA, which enabled the specific capture of the corresponding QDs onto the wrinkled surface of WSNs. Based on the detection of fluorescence signals that were ultimately focused on WSNs, target miRNAs could be sensitively identified to a femtomolar level (5 fM) with a wide dynamic range of up to six orders of magnitude. The proposed strategy achieved high specificity to obviously distinguish single base mutation sequences and possessed multiplex assay capability. Moreover, the assay exhibited excellent practicability in the multiplex detection of miRNAs in clinical serum specimens.

Key Words： Bladder cancer；miRNAs；Wrinkled silica nanoparticles；Quantum dots；Multiplex assay

433. MAP3K14 在肝细胞癌中的潜在作用:基于综合生物信息学分析的研究

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目的: 据报道，*MAP3K14* 作为一种致癌基因，在多种类型的肿瘤细胞中均存在异常表达，其异常表达与多种癌症的发生和进展有关。其在 HCC 中的表达及预后价值尚不明确。基于一系列公共数据库的数据挖掘，我们评估了 *MAP3K14* 在 HCC 中的潜在作用。

方法: 基于 TCGA、GEO、TIMER、cBioportal、Kaplan-Meier plotter、MethSurv、ENCORI、CellMiner 等数据库进行生物信息学分析，研究 MAP3K14 在结直肠癌中的表达、预后价值和功能。免疫组化法检测肝癌组织中 *MAP3K14* 蛋白的表达。

结果: 肿瘤组织中 *MAP3K14* mRNA 和蛋白表达水平均高于正常组织(P< 0.05)。*MAP3K14* 的表达与病理 T 分期(*P*=0.026)、病理分期(*P*=0.032)、肿瘤状态(*P*=0.024)、AFP (*P*=0.002)相关。*MAP3K14* 高表达的 HCC 患者总生存期(OS)、无进展生存期(PFS)和无复发

生存期(RFS)较差。多因素 Cox 回归分析显示，病理分期(P<0.001)和 *MAP3K14* 表达水平(P<0.05)是影响肝癌患者生存的独立预后因素。GO/KEGG 分析提示关键生物学过程(PI3K-Akt 信号通路)可能是促进 HCC 发展的机制。此外，*MAP3K14* 与 B 细胞、CD8+T 细胞、CD4+T 细胞、巨噬细胞、中性粒细胞和树突状细胞的浸润水平显著相关(P<0.05)。

结论: *MAP3K14* 在 HCC 中表达上调，与 HCC 患者预后密切相关。*MAP3K14* 可能作为 HCC 预后不良的潜在生物标志物。

关键字： 肝细胞癌;MAP3K14;预后

434. MethMarkerDB: a comprehensive cancer DNA methylation biomarker database

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Aims

DNA methylation alterations emerge as an early and widespread event across various cancers. There has been considerable interest in translating DNA methylation alterations into clinical biomarker applications. An important prerequisite for the clinical translation of DNA methylation biomarkers is accurate genomic location information. Determining the precise location of clinically relevant DMRs (Differentially Methylated Regions) is a critical step in the development of DNA methylation biomarkers. However, there is currently a lack of dedicated platforms or resources specifically designed for the identification of DMRs as cancer biomarkers using WGBS data. Therefore, it is necessary to establish a cancer DNA methylation biomarker database based on WGBS data, which offers biomarkers with accurate genomic information. This will help advance the clinical application of cancer DNA methylation research.

Materials and Methods

Firstly, we collected cancer-related WGBS data from the GEO and SRA databases, methylation 450K BeadChip data from TCGA, and the reported DNA methylation biomarker genes from PubMed. Using the WGBS data, we identified DMRs in various cancer. We curated a diverse range of genomic regulatory elements to annotate these DMRs. Building upon these results, we

established the MethMarkerDB (https://methmarkerdb.hzau.edu.cn/) database. MySQL (version 5.7.26) was utilized to organize the database, while Ngnix and Django were employed for web interface development. ECharts was utilized for data visualization. MethMarkerDB integrates the JBrowse (version 1.16.6) genome browser, enabling the display of DMR regions and single-base DNA methylation levels. It includes multiple search functions, and offers analysis functions to facilitate the exploration of DNA methylation biomarkers.

Results

MethMarkerDB integrated 658 WGBS datasets, incorporating 724 curated DNA methylation biomarker genes from 1425 PubMed published articles. Based on WGBS data, we documented 5.4 million DMRs from 13 common types of cancer as candidate DNA methylation biomarkers. We provided search and annotation functions for these DMRs with different resources, such as enhancers and SNPs, and developed diagnostic and prognostic models for further biomarker evaluation. With the database, we not only identified known DNA methylation biomarkers, but also identified 781 hypermethylated and 5245 hypomethylated pan-cancer DMRs, corresponding to 693 and 2172 genes, respectively. These novel potential pan-cancer DNA methylation biomarkers hold significant clinical translational value.

Conclusions

In MethMarkerDB, we offer a vast collection of DNA methylation biomarkers with precise genomic information, facilitating their clinical utilization. The database integrates search, analysis, visualization and download functions to assist the identification and evaluation of cancer DNA methylation biomarkers. Furthermore, the ‘Pan-cancer DMR’ module within MethMarkerDB is specifically designed to aid in the identification of pan-cancer DNA methylation biomarkers. In summary, MethMarkerDB serves as a comprehensive cancer DNA methylation biomarker database, capable of identifying DNA methylation biomarker genes/DMRs in different cancers and promoting their clinical application.

References

Zhixian Zhu, Qiangwei Zhou, Yuanhui Sun, Fuming Lai, Zhenji Wang, Zhigang Hao, Guoliang Li, MethMarkerDB: a comprehensive cancer DNA methylation biomarker database, Nucleic Acids Research, Volume 52, Issue D1, 5 January 2024, Pages D1380–D1392, https://doi.org/10.1093/nar/gkad923

Key Words： DNA methylation; Biomarker; WGBS; Cancer; Pan-cancer

435. Anti-FDX1 Autoantibody as a Potential Biomarker for Non-Small Cell Lung Carcinoma Detection

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Background: Non-Small Cell Lung Carcinoma (NSCLC) represents the predominant subtype of lung cancer and ranks among the most prevalent malignancies globally, characterized by a significant mortality rate. Autoantibodies can be readily identified and diagnosed prior to biopsy, serving as valuable biomarkers for disease detection. Cuproptosis is a hot topic in current research. It is currently thought to be a novel mode of cell death that is dependent on copper. It is evident that cuproptosis is involved in the development of different cancers. It has been discovered that cuproptosis-related genes (CRGs), which are associated with carcinogenesis and immune infiltration, are aberrantly expressed in a variety of cancer types, including pancreatic cancer, breast cancer, and lung cancer. Ferredoxin 1 (FDX1) is one of the main regulators in the process of Cuproptosis. FDX1 can regulate the thiooctanoylation of proteins and reduce Cu2+ to the more toxic Cu+. Moreover, FDX1 can inhibit the synthesis of the Fe-S proteins, which leads to cell death. FDX1 was found to impact the prognosis of lung cancer. In this study, we investigated whether anti-FDX1 autoantibody can serve as a novel biomarker in detection of NSCLC.

Methods: 1155 plasma samples were divided into discovery group and validation group. Discovery group containing 87 serum samples from NSCLC patients and 87 serum samples from normal controls (NC) were used to detect the levels of anti-FDX1 autoantibody by enzyme-linked immunosorbent assay (ELISA). Validation group containing 327 NSCLC, 327 benign pulmonary nodule patients (BPN) and 327 NC serum samples were tested to confirm the levels of autoantibody to FDX1. Western blotting and immunofluorescence were performed to further confirm the results of ELISA.

Results: ELISA results showed that the level of serum anti-FDX1 autoantibody was significantly increased in NSCLC compared to that in NC in both discovery and validation groups. Anti-FDX1 autoantibody could discriminate NSCLC patients from NC with the area under curve (AUC) values of 0.921 and 0.806 in discovery and validation group, respectively. Anti-FDX1 autoantibody could distinguish NSCLC patients from BPN in validation group, with an AUC value of 0.627. The results of ELISA were confirmed by western blotting and immunofluorescence. The AUC value of anti-FDX1 autoantibody combined with traditional tumor marker carcino-embryonic antigen (CEA) was increased to 0.884, which was much higher than that of these two markers alone to discriminate NSCLC from NC .

Conclusion: Our study indicated the potential significance of anti-FDX1 autoantibody as a novel biomarker for detection of NSCLC.

Key Words： FDX1, Tumor-associated antigen, Autoantibody, Detection, Non-Small Cell Lung Carcinoma

436. Plasma anti-COPT1 autoantibodies as potential biomarkers for detection of non-small cell lung cancer

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Purpose： Protein encoded by cuproptosis-related genes COPT1 is a high affinity copper transporter found in cell membrane. It was found that COPT1 is a tumor-associated antigen, which is abnormally expressed in patients with non-small cell lung cancer (NSCLC) and a potential biomarker for clinical diagnosis. This study aims to investigate whether plasma anti-COPT1 autoantibodies can serve as biomarkers for detecting NSCLC.

Methods: The mRNA and protein expression levels of COPT1 in NSCLC and normal tissues were analyzed on HPA online database. The discovery group included 89 cases of NSCLC and 89 cases of negative control（NC）, and the verification group included 321 cases of NSCLC, 321 cases of

BPN (Benign pulmonary nodules) and 321 cases of NC. Enzyme-linked immunosorbent assay (ELISA) was used to detect the expression level of anti-COPT1 autoantibodies in plasma of different patients. Subsequently, the results of ELISA were further verified by western blot and indirect immunofluorescence experiment. The anti-COPT1 autoantibody was combined with the traditional tumor marker carcino-embryonic antigen (CEA) to evaluate its diagnostic efficacy.

Results: On HPA online database, COPT1 was significantly higher in NSCLC tissues compared with normal tissues. The results of ELISA showed that the expression level of anti-COPT1 autoantibodies in NSCLC patients was significantly higher than that in BPN and NC. In the discovery group, the AUC value of anti-COPT1 autoantibodies used to distinguish NSCLC from NC were 0.885. In the verification group, the AUC value of anti-COPT1 autoantibodies to distinguish NSCLC from NC were 0.733. The AUC value used to distinguish NSCLC from BPN are 0.648. The combination of anti-COPT1 and CEA can improve the diagnostic efficiency when distinguishing NSCLC from NC, and the AUC value is 0.742. When distinguishing NSCLC from BPN, the combination of anti-COPT1 and CEA can improve the diagnostic efficiency, and the AUC value is 0.67. The results of Western blot and indirect immunofluorescence aligned with ELISA findings.

Conclusion： Anti-COPT1 autoantibodies show promise as biomarkers for detecting NSCLC.

Key Words： Autoantibody;COPT1;Non-small cell lung cancer;Biomarkers

437. 弥漫性大 B 细胞淋巴瘤微环境中的免疫细胞促肿瘤作用研究进展

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弥漫性大 B 细胞淋巴瘤（DLBCL）是成人非霍奇金淋巴瘤最常见的类型，由于个体差异较大，传统的 R-CHOP 标准疗法，可以使 70%的患者治愈，但仍有 30%患者出现耐药，因此寻找新的治疗方法成为临床实践中亟待解决的难点之一。肿瘤微环境通过调节免疫细胞组成及功能,促进微血管的生成等方式影响肿瘤的发生发展及耐药。免疫细胞的抗肿瘤作用已被熟知，但近期研究表明，DLBCL 中肿瘤细胞积极调控其复杂的肿瘤微环境，吸引各类

免疫细胞亚群进入组织，借以支持它们自身的生存和增殖，并创造一个免疫抑制微环境，逃避抗肿瘤免疫监视。因此研究微环境中各类免疫细胞对 DLBCL 的促肿瘤机制有助于深入了解该疾病并寻找新的治疗靶点。在 DLBCL 中，CXCR5+ CD4+ T 细胞，即滤泡辅助 T 细胞通过增加 IL-10 的分泌促进恶性 B 细胞增殖并抑制其凋亡。部分患者肿瘤细胞上过度表达 PD-L1，通过与肿瘤浸润 T 细胞上的 PD-1 结合，抑制了 T 细胞的活性，造成"T 细胞衰竭"。同时 Treg 细胞在 DLBCL 中主要起负调控免疫应答作用，抑制 Th1 介导的淋巴细胞增殖。大量研究表明 M2 型巨噬细胞通过过表达豆荚蛋白、基质金属蛋白酶 9、血管内皮生长因子等促进 ECM 降解和血管生成，加速 DLBCL 进展。高 M2 型巨噬细胞浸润患者与低浸润患者相比，R-CHOP 治疗的 CR 更低，OS 更短，与患者严重的临床表现密切相关。目前针对 T 细胞和巨噬细胞的靶向治疗在临床试验中被证实有效，相关的药物研发也有望让更多耐药患者受益。

关键字： 弥漫大 B 细胞淋巴瘤；肿瘤微环境；靶向治疗

438. 基于生物信息学分析 VTA1 在泛癌诊断和预后中的应用价值

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目的：肿瘤是目前导致人类死亡的主要原因，是阻碍人类预期寿命提高的巨大的屏障。由于肿瘤细胞的自我更新、高增殖及转移能力，肿瘤治疗中药物耐药频繁发生，导致肿瘤患者的生存率仍然不高。因此，我们有必要探索新的临床诊断标志物及靶标，以拓宽肿瘤预测和治疗的选择。内吞体运输必需分选复合物（endosomal sorting complex required for transport, ESCRT）功能异常与肿瘤发生发展密切相关，VTA1 是其重要的辅助因子，对于 ESCRT 系统功能的维持至关重要，本研究利用生物信息学手段综合分析 VTA1 在肿瘤中的潜在作用，以期为肿瘤诊断和治疗提供新的分子靶标。

方法：本研究主要下载 TCGA 和 GTEx 数据库中的基因表达数据，利用 R 语言分析 VTA1 在肿瘤组织和正常组织中的基因表达差异、诊断和预后能力、免疫相关特征及在肿瘤发生发展过程中的潜在作用。

结果：基因表达分析发现 VTA1 在大多数肿瘤中的表达上调，ROC 曲线分析发现 VTA1 在许多肿瘤（包括 CHOL，KICH，LGG，LUSC，ESCA，LAML，GBM，PAAD，READ 及 STAD）中表现出良好的诊断能力（AUC 值>0.9），单因素 Cox 回归分析及 KM 生存曲线分析发现，VTA1 高表达与 ACC (HR=2.232, p = 0.038)，BRCA (HR=1.444, p = 0.026)，KICH (HR=9.985, p = 0.005)，MESO (HR=1.824, p = 0.015)，SARC (HR=1.750, p = 0.006)，UCEC (HR=1.516, p = 0.045) 和 OV (HR=1.332, p = 0.029)患者较差的 OS 相关，而与 GBM (HR=0.673, p = 0.023)，READ (HR=0.368, p = 0.014) 和 KIRC (HR=0.683, p = 0.013)患者较好的 OS 相关。相关性分析发现，VTA1 的表达与 ACC（R=0.279，p=0.013），BRCA（R=0.152，p<0.0001），LUAD（R=0.177，p<0.0001），SKCM（R=0.174，p=0.00016），STAD（R=0.38，p<0.0001）及 THCA（R=-0.236，p<0.0001）患者的肿瘤突变负荷（TMB）相关，而与 COAD（R=0.116，p=0.016），READ（R=0.319，p<0.0001）, STAD（R=0.247，p<0.0001）,UCEC（R=0.171，p<0.0001）, DLBC（R=-0.394，p=0.005）, LUAD（R=-0.145，p<0.0001）及 PRAD（R=-0.145，p<0.0001）患者的微卫星不稳定性（MSI）相关。VTA1 表达与免疫细胞浸润的相关性分析发现 VTA1 的表达与多种免疫细胞浸润相关，其中在 GBM, LUSC, PAAD, SKCM, TGCT, THYM 及 UCEC 中，VTA1 的表达与免疫细胞浸润的相关性最广泛。此外，通过分析 VTA1 的表达与免疫相关基因（包括趋化因子，趋化因子受体，MHC 基因，免疫激活及免疫抑制基因）相关性分析发现，VTA1 与多种免疫相关基因的表达具有显著相关性。最后，通过 GSEA 富集分析发现在多数肿瘤中 VTA1 可能通过参与细胞周期及免疫相关通路影响肿瘤发生发展。

结论：VTA1 在多数肿瘤中能够作为潜在的诊断和预后标志物，其在肿瘤免疫治疗中能够作为一个良好的有前景的治疗靶标。

关键字： 内吞体运输必需分选复合物；VTA1；泛癌；肿瘤免疫

439. LncRNA BCCE4 genetically enhances the PD-L1/PD-1 interaction in smoking-related bladder cancer by modulating miR-328-3p-USP18 signaling

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Identification of cancer-associated variants, especially those in functional regions of long noncoding RNAs (lncRNAs), has become an essential task in tumor etiology. However, the genetic function of lncRNA variants involved in bladder cancer susceptibility remains poorly understood. Herein, we identified that the rs62483508 G > A variant in microRNA response elements (MREs) of lncRNA Bladder cancer Cell Cytoplasm-Enriched abundant transcript 4 (*BCCE4*) was significantly associated with decreased bladder cancer risk (odds ratio = 0.84, $P = 7.33 \times 10^{-8}$) in the Chinese population (3,603 cases and 4,986 controls) but not in the European population. The protective genetic effect of rs62483508 A allele was found on smokers or cigarette smoke-related carcinogen 4-aminobiphenyl (4-ABP) exposure. Subsequent biological experiments revealed that A allele of rs62483508 disrupted the binding affinity of miR-328-3p to facilitate USP18 from miRNA-mediated degradation and thus specifically attenuated the downstream PD-L1/PD-1 interaction. LncRNA *BCCE4* was also enriched in exosomes from bladder cancer plasma, tissues and cells. This comprehensive study clarifies the genetic mechanism of lncRNA *BCCE4* in bladder cancer susceptibility and its role in the regulation of the immune response in tumorigenesis. Our findings provide a valuable predictor of bladder cancer risk that could facilitate diagnosis and prevention.

Key Words ： Bladder cancer, cigarette smoking, PD-L1/PD-1 interaction, lncRNA, variant

440. CDK1 巴豆酰化修饰抑制结直肠癌细胞增殖及其机制的研究

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目的：结直肠癌（CRC）是一种常见的恶性肿瘤，CRC 的转移和复发导致治疗失败，这都与蛋白质组密切相关。然而，对于 CRC 中的翻译后修饰（PTMs），特别是最近发现的赖氨酸巴豆酰化修饰（Kcr）在其中的作用尚不明确。CDK1（Cyclin-Dependent Kinase 1）是一种重要的蛋白激酶，在细胞周期调控中扮演着关键的角色。本研究的目的是探究 CDK1 赖氨酸巴豆酰化修饰对结直肠癌进程的影响

材料与方法：我们首先利用 TCGA 数据库分析 CDK1 在多种肿瘤中的表达情况。然后，收集了结直肠癌患者的组织样本，将肿瘤组织和癌旁组织的蛋白进行质谱分析。此外，我们将 CDK1 野生型（CDK1-WT）和第九位赖氨酸突变为精氨酸的突变体（CDK1-K9R）的 cDNA 克隆到 pCDNA3,1 载体上得到野生型和突变型的质粒，利用脂质体将质粒转染进结直肠癌细胞系 MC38 中进行 CCK8、EDU、克隆形成和 Transwell 实验，检测 CDK1 巴豆酰化修饰对细胞增殖、迁移能力的影响。为了进一步确认 CDK1 巴豆酰化修饰调控结直肠癌进程的机制，我们运用了流式细胞术、Western blot 等实验方法，明确 CDK1 巴豆酰化修饰影响结直肠癌进展的分子机制。

结果：质谱分析结果显示，结直肠癌组织标本中 CDK1 第九位赖氨酸残基的巴豆酰化修饰水平明显增加。细胞功能实验结果显示 CDK1-K9 巴豆酰化修饰明显抑制 MC38 细胞的增殖和迁移功能。流式细胞术结果表明 CDK1-K9 巴豆酰化修饰是通过阻滞细胞周期停滞在 G2/M 期抑制细胞增殖。WB 结果结果表明 CDK1-K9 巴豆酰化修饰可通过促进细胞凋亡和降低 CDK1 激酶活性进而抑制细胞增殖。

结论：本研究揭示了 CDK1 第九位赖氨酸巴豆酰化修饰在结直肠癌进程中的重要作用。CDK1 巴豆酰化修饰可能参与了多个信号通路的调控，影响细胞的增殖、凋亡和转移。这些发现表明巴豆酰化修饰在结直肠癌的转移和复发中扮演着关键角色，进一步研究巴豆酰化修饰与结直肠癌的相关机制，有望为该疾病的治疗和预防提供新的靶点和策略。

关键字： CDK1，巴豆酰化修饰，PTMs，结直肠癌

441. ID3 调控下的肝脏巨噬细胞：开启肿瘤免疫治疗的新篇章

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近年来，免疫疗法在癌症治疗领域取得了显著的突破，其中巨噬细胞作为免疫系统的重要组成部分，对于抗肿瘤免疫反应的调节起着关键作用。本综述回顾了巨噬细胞在肝脏抗肿瘤免疫中的关键作用，特别是其在清除异常细胞和促进免疫应答中的功能。随后，深入探讨 DNA 结合抑制剂 3（Inhibitor of DNA binding 3, ID3）在这一过程中的调控机制。ID3 作为一种转录抑制因子，其在调控免疫细胞分化和功能中的作用逐渐引起了研究者的关注。通过调控 ID3 的表达水平，可以显著增强巨噬细胞的抗肿瘤活性，从而提高肝脏抗肿瘤免疫的效果。针对 ID3 作为潜在治疗靶点的发现，我们总结了相关的治疗策略和可能的临床应用前景。对 ID3 的精准调控有望成为肝脏癌症免疫治疗的新途径，为患者提供更有效的治疗选择。总体而言，本综述系统性地介绍了巨噬细胞在肝脏抗肿瘤免疫中的角色，并突出了 ID3 作为潜在的治疗靶点的重要性。这一发现不仅深化了研究人员对肝脏免疫调节机制的理解，也为开发新型的癌症免疫治疗策略提供了有力的支持。

关键字： 免疫疗法；巨噬细胞；ID3；转录抑制因子；新型治疗策略

442. PD-L1 as a biomarker for immunochemotherapy in advanced triple-negative breast cancer: A meta-analysis of randomized clinical trials

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Background: Triple-negative breast cancer (TNBC) presents as a heterogeneous disease characterized by diverse immune cell compositions, resulting in differential sensitivity to immunochemotherapy (ICT). While various biomarkers, including tumor mutation burden and tumor-infiltrating lymphocytes, have been linked to improved treatment response, there exists a necessity to discern patients poised for a favorable response to ICT. In this pursuit, we conducted a meta-analysis utilizing data gleaned from randomized clinical trials (RCTs) to evaluate the significance of PD-L1 status as a potential biomarker for gauging ICT efficacy in the treatment of advanced TNBC (aTNBC).

Methods: A comprehensive literature search encompassing PubMed, Embase, and Web of Science databases was conducted up to February 15, 2024. Subsequently, meta-analyses were executed to aggregate hazard ratios (HRs) alongside their respective 95% confidence intervals (CIs) for overall survival (OS) and progression-free survival (PFS), as well as odds ratios (ORs) with their corresponding 95% CIs for objective response rate (ORR).

Results: Six RCTs (IMpassion130, KEYNOTE-355, IMpassion131, ALICE, TBCRC 043, TORCHLIGHT) involving 3,105 patients met the inclusion criteria. In comparison with chemotherapy (CT), ICT demonstrated statistically significant improvements in OS (HR, 0.75; 95%CI, 0.64-0.87), PFS (HR, 0.67; 95%CI, 0.58-0.77), and ORR (OR, 1.47; 95%CI, 1.16-1.84) within the PD-L1 positive population. However, there were no statistically significant differences observed in the PD-L1 negative population.

Conclusion: ICT demonstrates superior efficacy in the treatment of aTNBC within PD-L1 positive population. PD-L1 status may serve as a valuable biomarker in discerning aTNBC patients who are particularly predisposed to derive benefit from ICT.

Key Words： Biomarker, immunochemotherapy, triple-negative breast cancer, efficacy, meta-analysis

443. Microbial-specific metabolites in tumor progression, tumorenvironment immunity and predictive for therapy

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Several studies have indicated that the gut microbiome and tumor microbiome may affect tumors. Recent metabolomics studies suggest that it is essential to investigate the differences in microbial metabolite composition between cancer patients and healthy individuals. Microbial metabolites can affect tumour progression and immunity through mechanisms such as modulating the patient's immune system, cancer or immune-related signalling pathways, epigenetic modification of proteins, and DNA damage. They can also alleviate side effects and drug resistance during chemotherapy and immunotherapy, while effectively activating the immune system to exert tumour immunotherapy. However, some microbial metabolites exhibit a bidirectional effect. Microbial metabolites can both promote and enhance tumor immunity, with their effects potentially related to the concentration of metabolites or the type of cancer. This article summaries the roles of various microbial metabolites in different solid tumors, as well as their impact on tumor immunity and treatment. Additionally, clinical trials evaluating the therapeutic effects of microbial metabolites or related microbiome on cancer patients are listed. As a key node between the microbiome and tumors, research on microbial metabolites might result in the discovery of novel adjuvant therapies for cancer treatment, thereby enhancing the efficacy of cancer treatment and improving patient prognosis.

Key Words： cancer, microbial metabolites, gut microbiome, tumor microbiome, tumor microenvironment, immunotherapy, chemotherapy

444. Tumor-related fungi and its crosstalk with gut fungi in canccinogenesis and tumor microenvironment

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Abstract

Most studies describing the human gut microbiome in health and disease have emphasized the bacterial component, but mycoomics has been less studied and lags behind our understanding of the bacterial microbiome.In recent years, with the development of detection technology, the research on fungi has also grown from scratch. Symbiotic fungi are increasingly influential in health and disease and regulate various physiological functions in the host body. Fungi cause high morbidity and mortality in immunocompromised patients, and can even be life-threatening. In addition to bacterial dysbiosis, alterations in fungal communities are also important and have been linked to many diseases, including inflammatory bowel disease, asthma, mental illness, and various cancers. When studying cancer, fungi, like viruses and bacteria, should be taken into account. In this review, we profile the role of intestinal fungi and peri-tumor fungi in tumorigenesis, development, and drug therapy. We provide evidence that specific members of the fungal biota are involved in intestinal diseases, including inflammatory bowel disease, colorectal

and pancreatic cancer, and parenteral diseases such as lung and liver cancer； In addition, we also discussed the mechanism of fungal action in the tumor microenvironment.We also explored the effects of fungus-bacteria interactions on tumorigenesis and development, with potential applications in cancer diagnosis and treatment.

Key Words ： cancer,fungi,gut microbiome

445. Intratumoral and gut microbiome enrichment and impact on carcinogenesis, and its role of anti-tumor therapy and prognosis in liver cancer

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Liver cancer is an aggressive malignancy with a poor prognosis. There is a special relationship between the gut and the liver, called the gut-liver axis. The pathogenesis of liver cancer is not only related to the enrichment of the gut microbiome but also closely related to the enrichment of microorganisms in the tumor. Recent studies have shown general changes in gut and intratumoral microbiota in patients with liver cancer, suggesting the potential contribution of these two microbiota to liver cancer development. At the same time, from the perspective of the gut microbiome, relevant treatment strategies for liver cancer can be explored. In addition, different microbiome compositions were observed in patients who responded differently to radiation and chemotherapy, suggesting a role for the gut microbiome and the tumor in regulating treatment outcomes. In this review, we examine the gut microbiome and intratumoral microbiome of normal healthy individuals and those with chronic liver disease or liver cancer and then explore the

cancer-promoting effects of intestinal pathogens easily located in the liver and the effects of B virus infection on liver cancer. In addition, we also proposed relevant HCC therapeutic strategies targeting gut microbiota. Finally, to understand the impact of gut microbiome and intratumoral microbiome on the prognosis of liver cancer, and ultimately bring better results for patients.

Key Words ： liver cancer； microbiome； carcinogenesis； treatment strategies； prognosis

446. Prognostic role of miR-99 family in cancers: a meta-analysis

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Background: The microRNA-99 family is one of the evolutionary most ancient microRNA families including three members “miR-99a, miR-99b, and miR-100”[1]. Studies have shown that the miR-99 family can promote cell proliferation and metastasis and act as a key regulator of stem cell self-renewal in various tumors[2]. However, contradictory results were reported about the prognostic value of miR-99 family in cancers[3]. To better understand the connection between the expression of these miR-99 family members (miR-99a, miR-99b and miR-100) and the outcome of patients with cancers, this study conducted a comprehensive search of the relevant researches evaluating the prognostic role of miR-99 family members in cancers.

Methods: We conducted a comprehensive search via the online databases PubMed and Web of Science. The terms “miR-99a OR miR-99b OR miR-100 OR miR-99 family OR miR-99 cluster OR microRNA-99a OR microRNA-99b OR microRNA-100 OR microRNA-99 family OR microRNA-99 cluster” and “survival OR prognosis OR prognostic OR Prognoses” and “cancer OR tumor OR tumor OR neoplasm OR neoplasma OR neoplasia OR carcinoma OR malignancy” were used to identify the relevant studies. We calculated the pooled hazard ratios (HRs) and 95% confifidence intervals (CIs) for the associations between levels of miR-99 family expression and overall survival (OS) or disease-free survival (DFS) in patients with cancers. In addition, the publication bias was tested and a sensitivity analysis of each study was performed to evaluate the stability of the pooled result.

Results: This study enrolled 18 articles involved in 2202 patients, and half of studies have the sample size more than 120, and a total of 15 studies were conducted with tumor tissue, 3 articles were conducted based on serum or blood. Besides, the study involved different kinds of cancer: hepatocellular carcinoma, bladder cancer, colorectal cancer, lung cancer, squamous cell carcinoma, osteosarcoma, endometrioid endometrial carcinoma, renal cell carcinoma, acute myeloid leukemia, glioblastoma and breast cancer, respectively. The quantitative real-time polymerase chain reaction (qRT-PCR) was performed in all articles to evaluate the expression levels of miR-99 family. The pooled results revealed that higher expression of miR-99 family predicted unfavorable prognosis of patients with cancers (HR =2.42; 95% CI:1.75-3.35). In the subgroup analysis, higher expression of miR-99 family was associated with unfavorable survival of OS (HR=2.66; 95%Cl:1.89-3.74), as well as in tissues (HR =2.26; 95% CI:1.59-3.21) and blood-/serum (HR =3.92; 95% CI:2.38-6.46). The elevated expression of miR-99 family was found to be associated with poor patients' survival in the subgroup of sample size (>120: HR=2.03; 95% CI =1.30-3.16; ≤120: HR=3.06; 95% CI =2.08-4.51), publication year (before 2017 year: HR=2.52, 95% Cl: 1.58-4.03, after 2017 year: HR=2.35, 95%Cl: 1.45-3.82). In addition, the result revealed that no single study deletion changed the significance of the pooled result and we found that there was no significant publication bias in the included literatures (Begg's: p =0.108; Egger's: p=0.206).

Conclusion: The study revealed that the miR-99 family can be served as prognostic biomarkers for cancers. Nevertheless, this article still has some limitations. First, only a few articles are eligible for a specific cancer leading to the relative shortage in subgroup analysis. Secondly, after data integration and subgroup analysis, some data still lack statistical significance. Third, the results of this meta-analysis lack experiments to confirm, which should be further identified by future study.

Key Words： miR-99 family; cancer; prognostic; biomarkers; meta-analysis

447. 肝癌中瘤内和肠道菌群的富集和对癌变的影响，及其在抗肿瘤治疗和预后中的作用

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肝癌是一种侵袭性恶性肿瘤，预后较差。肠道与肝脏之间存在特殊的关系，这种关系被称为肠-肝轴。肝癌的发病机制不仅与肠道微生物组的富集有关，同时也与瘤内微生物的富集存在密切联系。最近研究显示，在肝癌患者中，肠道微生物群和瘤内微生物群的普遍变化，从而提示了这两种微生物群对肝癌发展的潜在贡献。同时，从肠道微生物组的角度能够挖掘出肝癌的相关治疗策略。此外，在对放疗和化疗反应不同的患者中观察到不同的微生物组组成，这表明肠道微生物组和瘤内在调节治疗结果中的作用。在这篇综述中，我们研究了正常健康个体和慢性肝病或肝癌的肠道微生物组与瘤内微生物组，接着探讨了肠道致病菌易位于肝脏的促癌作用和乙型病毒感染对肝癌的影响。此外，我们还针对肠道微生物群提出了相关的肝癌治疗策略。最后，了解肠道微生物组和瘤内微生物组对肝癌预后的影响，最终为患者带来更好的结果。

关键字： 肝癌；微生物组；致癌作用；治疗策略；预后

448. 双靶向工程化牛奶外泌体药物递送体系重编程肿瘤相关巨噬细胞

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研究目的：建立牛奶外泌体（mExo）的纳米抗体和 M2pep 多肽的工程化修饰方法，从而实现基于工程化 mExo 的 TME 特异性靶向递送的通用技术体系；并以高表达 EGFR 的恶性肿瘤为测试模型，EGFR 纳米抗体为代表修饰分子，以 siPD-L1 作为模型治疗分子，通过

体内外水平的研究，验证该技术体系的有效性、安全性和可靠性，并进一步评估其与 ICB 联用的可行性和价值，最终建立具有临床推广和应用价值的基于 TAM 的肿瘤靶向免疫治疗新方法，推进肿瘤的个体化治疗水平。

材料与方法：在本研究中，我们利用 Sortase-A (SrtA)介导的酶连接方法，构建了含有 7D12 和 M2pep 的 mExo 系统(7D12-mExo-M2pep-siPDL1)，以特异地将 siPDL1 递送到 M2 TAMs 中。纳米抗体 7d12 修饰的 mExos 能够在 EGFR+肿瘤组织中积极聚集，M2pep 修饰进一步促进了 mexo 包裹的 siPDL1 被 M2 TAMs 摄取，从而使 TAM 有效地从 M2 复极化到 M1, TME 重塑，从而发挥良好的抗癌作用。

研究结果：我们成果构建了一种修饰 M2pep 和 EGFR 纳米抗体的 mExo 系统。并通过体内外验证发现设计的 mExo 系统专门将 siPDL1 输送到 M2 TAMs 中，使 PDL1 有望成为基于 TAM 的肿瘤免疫治疗的新靶点，同时 mExo 系统对 EGFR 阳性肿瘤显示出有效的抗肿瘤活性。我们目前的数据结果提示，固有和适应性免疫系统都可能介导工程 mExos 的抗癌作用，从而产生强大和持久的抗肿瘤免疫。

研究结论：本研究开发了一种纳米药物(7D12-mExo-M2pep-siPDL1)，该药物可以特异性靶向 M2 型 TAMs 上的 PDL1，使其复极化为抗肿瘤 M1 型巨噬细胞。该系统具有以下优势:(1)对 EGFR 阳性肿瘤的 M2 型 TAMs 具有较高的靶向性。(2)负载 sipdl1 的工程 mExos 能有效抑制 M2 TAM 中 PDL1 的表达，诱导 M2 TAM 重编程，从而逆转抑制性 TME。mExos 具有低系统免疫原性、高可用性、高生物相容性和良好的安全性，显示出良好的应用潜力。因此，7D12-mExo-M2pep-siPDL1 治疗触发了 TME 的有效重塑，使其达到抗肿瘤状态，并显示出强大的单药抗癌活性，这使这种新型癌症免疫疗法有别于其他巨噬细胞靶向疗法。

关键字： 肿瘤免疫治疗；牛奶外泌体；纳米抗体；PDL1；肿瘤微环境；肿瘤相关巨噬细胞

449. 小分子肽 ANXA114-26 抑制卵巢癌细胞增殖和逆转顺铂耐药性

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背景及目的：卵巢癌耐药是目前影响卵巢癌治疗和愈后的一大障碍。因此，寻找与卵巢癌耐药相关的因素，可能有利于逆转卵巢癌耐药性。我们利用 iTRAQ 技术，发现了一种以 ANXA1 为前体蛋白的小分子肽在卵巢癌耐药患者血清中低表达，在卵巢癌敏感患者血清中高表达。之前已有文献显示 ANXA1 及其相关肽段与肿瘤耐药存在相关性。我们将新发现的肽段命名为 ANXA114-26，探究其与卵巢癌耐药的关系及其作用机制。

方法：应用 iTRAQ 技术对卵巢癌顺铂耐药/敏感血清进行了差异多肽鉴定。以卵巢癌耐药细胞系（SKOV3/DDP）和亲本细胞系（SKOV3）作为研究对象。利用 CCK-8 检测 SKOV3 和 SKOV3/DDP 的 IC50，利用 qRT-PCR 和 Western blot 检测 MRP1 和 ANXA1 的表达差异。采用 CCK-8 和 EdU 检测 ANXA114-26 或者 ANXA114-26 联合 DDP 对细胞增殖的影响；采用 qRT-PCR 和 Western blot 检测 ANXA114-26 或者 ANXA114-26 联合 DDP 对 BAX、Bcl-2 和 MRP1 表达量的影响。

结果：ANXA114-26 在对化疗敏感的卵巢癌患者血清中高表达。ANXA114-26 促进卵巢癌细胞凋亡，增加卵巢癌细胞对顺铂的敏感性。

结论：我们在卵巢癌患者血清中发现了一种 ANXA1 模拟肽 ANXA114-26。ANXA114-26 促进卵巢癌细胞凋亡和降低 MRP1 表达。

关键字： ANXA114-26

450. Long non-coding RNA SREBF2-AS1 promotes cell progression by increasing SREBF2 expression in Hepatocellular carcinoma

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Objective: Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Long non-coding RNAs (lncRNAs) are emerging as one of important regulators that may be involved in the progression of cancers in humans.

Methods: Comprehensive analysis of the lncRNA expression profile of HCC was performed by using TCGA and Gene Expression Omnibus (GEO) database to screen the target lncRNA(s). LncRNA of SREBF2-AS1 was selected and its expression level in a cohort of 15 pairs of HCC tissues was verified by quantitative real-time PCR (qRT-PCR). Loss-of-function and gain-of-function assays were carried out to investigate the role of SREBF2-AS1 in HCC progression in vitro. Tumor formation assay was performed to verity the role of SREBF2-AS1 in HCC progression in vivo.

Results: Database analysis showed that the expression of SREBF2-AS1 was upregulated in HCC, which was correlated with neoplasm grade and over survival time. The expression of SREBF2-AS1 was verified in a cohort of 15 pairs of HCC tissues. SREBF2-AS1 knockdown mitigated HCC cell growth and promoted apoptosis in vitro and in vivo. Whereas, SREBF2-AS1 overexpression promoted tumor cell growth. Furthermore, our investigation demonstrated that the oncogenic activity of SREBF2-AS1 is partially attributable to the regulation of sterol regulatory element-binding protein 2 (SREBF2) expression.

Conclusions: Our study highlights the regulatory role of SREBF2-AS1 in promoting HCC progression, suggesting that SREBF2-AS1 might be a potent therapeutic target by regulating the expression of SREBF2 for patients with HCC.

Key Words: Hepatocellular carcinoma, lncRNAs, SREBF2-AS1, sterol regulatory element-binding protein 2 (SREBF2)

451. 肠道菌群与前列腺癌的因果作用:双样本孟德尔随机化研究

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目的：通过双样本孟德尔随机化(Mendelian randomization,MR)分析的方法研究肠道菌群与前列腺癌(Prostate Cancer,PCa)之间的因果关系。

方法：将公共数据库 MiBioGen（https://mibiogen.gcc.rug.nl/）所包含的肠道菌群 Gwas 数据视为暴露因素。欧洲全基因组关联研究(Genome-wide association study, Gwas)数据库中的 PCa 的遗传数据(数据集编号：ukb-b-7773)视为结局因素。通过关联性分析挑选与肠道菌群丰度具有强相关的单核苷酸多态性（single nucleotide polymorphism,SNP)作为工具变量，筛选标准为 p<1e-05，为确保 SNP 独立，使用 R 包 TwoSampleMR 中的 clump.data()方法限制连锁不平衡条件(kb=10000，R2=0.001)，计算每个 SNP 的 F 检验值筛选与肠道菌群具有强相关的遗传变异作为工具变量。主要采用逆方差加权法(inverse-variance weighted,IVW)、MR-Egger 回归、加权中位数法、简单众数法和加权众数法通过效应指标优势比以及置信区间对结果进行评价，同时通过留一法分析、Cochran's Q 检验、MR 多效性残差和和离群值分析对结果进行质控。

结果：肠道菌群 Gwas 数据中包括来自欧洲、北美和东亚血统共 18340 名个体，以菌属水平作为研究工具，PCa 遗传数据包括正常组样本 368725 例，PCa 患者 30945 例。样本均为欧洲人。SNP 数目 9851867 个。去除弱工具变量后确定 1097 个强相关 SNP 进行 MR 分析。通过 IVW 方法共检测到 3 个肠道微生物群与 PCa 产生关联，毛螺菌属 LachnospiraceaeUCG008（OR：0.9949，95% CI = 0.991−0.999，pFDR = 0.0149）的丰度增加有助于 COPD 发病风险的降低。而厌氧细杆菌属 anaerofilum（OR：1.0044，95% CI = 1.001−1.002，pFDR = 0.0153）、毛螺菌属 LachnospiraceaeNK4A136group（OR：1.0062，95% CI = 1.001−1.011，pFDR = 0.0111）起到相反作用。同时各类质控分析显示结果稳定。

结论：双样本 MR 分析显示 LachnospiraceaeUCG008 与 PCa 呈负向因果效应，anaerofilum、LachnospiraceaeNK4A136group 为 PCa 的刺激因素。提示肠道菌群在 PCa 发生过程中可能发挥一定作用，该结果对后续因果关系研究具有参考价值。

关键字： 肠道菌群；前列腺癌；孟德尔随机化；因果关系

452. 瘤内和粪便微生物群揭示了与胃癌发生相关的微生物标记物

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研究目的：胃肠道微生物菌群失调与胃癌之间的关系已被广泛研究。然而，不同研究中胃癌患者的微生物群变化差异很大，而且仍没有可在多人群中复制的早期胃癌诊断生物标志物。因此，本研究旨在基于多个已发表的数据集，描述与胃癌发生相关的胃肠道微生物群落的特征并确定用于胃癌早期无创筛查的微生物标志物。

材料与方法：我们重新分析了来自 11 项独立研究的 1642 份胃组织样本和 394 份粪便样本的 16s rRNA 测序数据。分析了胃肠道微生物群组成的变化、微生物之间的相互作用和潜在功能。我们构建并验证了用以区分胃癌患者和健康人的随机森林模型。此外，我们还将胃组织样本分为幽门螺旋杆菌阴性组和幽门螺旋杆菌阳性组，以分析非幽门螺旋杆菌在幽门螺旋杆菌阴性胃癌和幽门螺旋杆菌阳性胃癌中的作用。

结果：荟萃分析表明，胃癌患者的瘤内和粪便微生物群发生了改变。我们发现瘤内和肠道特异性和共分化的乳酸菌和链球菌能很好地将胃癌患者与健康人区分开来（曲线下面积(AUC) = 0.7949），并通过 LODO 验证（平均 AUC = 0.81）和外部验证（AUC = 0.7712）证明了其在多人群中适用。与健康人相比，在胃癌中富集的细菌之间的正相关性增加，而在胃癌中耗竭的细菌之间的正相关性降低。功能分析显示抑制铁死亡的相关通路在胃癌中明显富集。此外，我们还报道了乳酸菌、链球菌、消化链球菌和苍白杆菌可能与幽门螺杆菌一同导致幽门螺杆菌阳性胃癌的发生，而节杆菌、芽孢杆菌、乳球菌和梭杆菌则可能单独导致幽门螺杆菌阴性胃癌的发生。

结论：这项研究揭示了胃癌患者瘤内和粪便微生物群的特征，并证明粪便来源的 胃癌特异性微生物标记物可用于胃癌的早期无创筛查。

关键字： 胃癌，肿瘤内微生物群，粪便微生物群，微生物标记物，无创筛查

453. Study on the mechanism of galectin-14 enhancing HSPGs level on liver cancer cells through hexosamine biosynthetic pathway to trigger T cell exhaustion

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Background and objective: Liver cancer ranks fifth in the incidence rate and second in the mortality rate of cancer in China. It is difficult to make early diagnosis, the tumor progresses quickly and is easy to resist drugs. The liver is an important organ for the metabolism and synthesis of carbohydrates in the body. The extension, degradation, and transport of sugar chains in liver cells lead to abnormal changes in glycosylation modifications, mediating the occurrence of various diseases such as liver cancer. The abnormal glycosylation modification of tumor cells promotes the occurrence and development of liver cancer, affects tumor immune suppression, but the regulatory mechanism behind it remains unclear currently. The specific mechanism by which abnormal glycosylation modifications affect the occurrence and development of liver cancer needs to be elucidated.

Methods: We explored the correlation between PAS glycogen staining and various glycosylation modification key enzymes with the survival of liver cancer patients by analyzing the tissue chips of liver cancer patients. The key factor galectin-14 regulating the expression of HSPGs in liver cancer cells had been screened. And the expression of galectin-14 in tumor and normal tissues of liver cancer patients in the TCGA database was explored. Through subcutaneous transplant tumor model, we studied the effects of galectin-14 on liver cancer tumor growth and HSPGs level. With the help of differential gene KEGG enrichment analysis and metabolic flux experiments, the impact of galectin-14 on glycol-metabolism pathways was explored. Meanwhile, we detected the expression changes of immune exhaustion molecules on T cells and CAR-T cells after co-cultured

with galectin-14 knockdown liver cancer cells through FACS. Moreover, the impact of galectin-14 mediated HCC cells on the immune killing effect of CAR-T cells was evaluated *in vitro* and *in vivo*.

Results: The results show that the levels of HSPGs in liver cancer are positively correlated with poor prognosis in patients. Galactin-14, as a key factor in regulating HSPGs levels, upregulates surface HSPGs modification in liver cancer cells through the hexosamine synthesis pathway (HBP), promotes T cell exhaustion, and antagonizes CAR-T cell immunotherapy effects.

Conclusion: This study demonstrates that galectin-14 is an important regulatory factor in regulating glycosylation modifications in HCC cells. It can reshape tumor cell metabolism, promote immune exhaustion, and promote malignant progression of HCC by regulating the level of HSPGs in HCC cells. The research work provides new theoretical basis for understanding the molecular mechanisms by which glycosylation modifications affect the malignant progression of liver cancer, and also provides new candidate targets for developing feasible strategies for the diagnosis and treatment of liver cancer.

Key Words： liver cancer; galectin-14; HSPGs; glycosylation modification; hexosamine biosynthetic pathway; T cell exhaustion

454. Somatic mutations in 4 novel genes contribute to homologous recombination deficiency in breast cancer: a real-world clinical tumor sequencing study

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Breast cancers involving mutations in homologous recombination (HR) genes, most commonly BRCA1 and BRCA2 (BRCA1/2), respond well to PARP inhibitors and platinum-based chemotherapy. However, except for these specific HR genes, it is not clear which other mutations contribute to homologous recombination defects (HRD). Here, we performed next-generation sequencing (NGS) of tumor tissues and matched blood samples from 119 breast cancer patients using the OncoScreen Plus panel. Genomic mutation characteristics and HRD scores were analyzed. In the HR genes, we found that BRCA1/2 and PLAB2 mutation was related to HRD. HRD was also detected in a subset of patients without germline or somatic mutations in BRCA1/2, PLAB2, or other HR-related genes. Notably, LRP1B, NOTCH3, GATA2, and CARD11 (abbreviated as LNGC) mutations were associated with high HRD scores in breast cancer patients. Furthermore, functional experiments demonstrated that silencing CARD11 and GATA2 impairs HR repair efficiency and enhances the sensitivity of tumor cells to Olaparib treatment. In summary, in the absence of mutations in the HR genes, the sensitivity of tumor cells to PARP inhibitors and platinum-based chemotherapy may be enhanced in a subset of breast cancer patients with LNGC somatic mutations.

Key Words： Homologous recombination, Next-generation sequencing, Breast cancer.

455. 游离脂肪酸对乳腺癌化疗疗效的预测价值分析

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目的：乳腺癌发病率逐年升高，进一步开发疗效预测标志物是一项紧迫问题。游离脂肪酸在肿瘤发生发展中的价值受到越来越多关注，本研究旨在评估游离脂肪酸对乳腺癌化疗疗效的预测价值。

方法：收集 2020 年 6 月至 2023 年 12 月就诊于辽宁省肿瘤医院诊断为乳腺癌的女性患者，晚期乳腺癌患者 306 例，术前新辅助化疗患者 182 例。采用串联质谱法检测患者化疗前血清中 20 种游离脂肪酸水平，并收集临床病理资料进行回顾性分析。根据化疗疗效将晚期以及新辅助两个治疗阶段的乳腺癌患者各自分为两组，将晚期疗效为 CR、PR、SD 以及新辅助疗效为 G4-G5 定义为疗效较佳组；将晚期疗效为 PD 以及新辅助疗效为 G1-G3 定义为疗效不佳组。利用$\chi 2$ 检验和非参数检验分别分析临床特征和 FFA 与化疗疗效之间的相关性，绘制基于 FFA 结合临床参数预测化疗疗效的列线图并验证。

结果：晚期乳腺癌患者中，单因素分析表明，疗效较佳组患者的月桂酸、棕榈酸、二十二碳五烯酸、神经酸、棕榈油酸、花生四烯酸、花生酸的水平均高于疗效不佳组（P<0.05）。多因素分析结果显示，患者的月桂酸、神经酸、化疗线数是晚期乳腺癌患者化疗疗效的独立预测因子（P<0.05），联合诊断效能良好（AUC=0.711），二线及以上化疗人群的预测能力较高。新辅助化疗患者中，单因素分析显示，疗效较佳组患者的肉豆蔻酸、二十碳二烯酸、棕榈油酸、肉豆蔻油酸水平均高于疗效不佳组（P<0.05）。二十碳五烯酸、二十二碳六烯酸在疗效较佳组有增高趋势（P<0.1），癸酸水平在疗效较佳组相较于疗效不佳组有减少的趋势（P<0.1）。多因素分析表明，患者的肉豆蔻酸、棕榈油酸、癸酸、二十碳二烯酸以及 ER、HER2、Ki67、月经状态均可以独立预测新辅助化疗患者的化疗疗效（P<0.05），联合诊断效能 AUC=0.837，Ki67 高表达人群的预测能力较好。验证以上两个模型的校准曲线、临床决策曲线（DCA）显示，该预测模型具有良好的临床预测价值。

结论：

1、月桂酸、神经酸是预测晚期乳腺癌患者化疗疗效的潜在预测指标，尤其是二线及以上人群的预测效能更佳；

2、肉豆蔻酸、棕榈油酸、癸酸、二十碳二烯酸是预测新辅助化疗阶段乳腺癌患者化疗疗效的潜在预测指标，在 Ki67 高表达人群中预测效能更佳；

3、不同游离脂肪酸联合临床参数开发的列线图能够准确地分别对乳腺癌晚期化疗和新辅助化疗疗效进行预测，经过验证后具有可靠性。

关键字： 乳腺癌，游离脂肪酸，月桂酸，化疗，新辅助化疗

456. Targeting human telomere protective protein TPP1 with Elbasvir induces autophagy and suppresses esophageal cancer tumorigenesis

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To investigate the role of human telomere protective protein TPP1 in the occurrence and development of esophageal cancer, and to screen the target drug Elbasvir using TPP1 as a target, and reveal the potential molecular mechanism of Elbasvir in the treatment of esophageal cancer.

The expression of TPP1 protein in 54 patients with clinical esophageal cancer was analyzed by immunohistochemical staining. Cell Counting Kit-8 (CCK8) and colony formation assay were used to evaluate the proliferation of esophageal cancer cell lines (KYSE150 and TE1) after silencing TPP1 or treatment with Elbasvir at specified concentrations. The migration ability was measured by Transwell and scratch methods. The number of autophagosomes produced was observed by fluorescence microscopy. The fluorescence intensity of autophagy (LC3 and P62) of esophageal cancer cells after TPP1 siltation was detected by flow cytometry, and the apoptosis and cell cycle changes of esophageal cancer cells treated with Elbasvir were detected. Western blot analysis was performed to detect the changes of TPP1, AKT-mTOR signaling pathway, autophagy, apoptosis and other related proteins in esophageal cancer cells treated with Elbasvir, and to evaluate the anti-cancer effect of Elbasvir in nude mice bearing tumor.

In immunohistochemical staining, the expression of telomere protective protein TPP1 was significantly upregulated in esophageal squamous cell carcinoma tissues compared with adjacent tissues 3-5cm away from esophageal carcinoma tissues. Silencing TPP1 significantly inhibited the proliferation and migration of esophageal cancer cells in vitro, and induced autophagy through the AKT-mTOR signal axis. This proved that TPP1 protein plays a carcinogenic role in esophageal cancer. Elbasvir, a small molecule inhibitor targeting TPP1 protein, was screened through a

high-throughput drug screening platform. Fortunately, we found that Elbasvir could significantly inhibit the proliferation and metastasis of esophageal cancer cell lines KYSE150 and TE1 in vitro. The expression of TPP1 protein was significantly down-regulated at the protein level in a time - and dose-dependent manner. Further studies showed that Elbasvir can also inhibit autophagy induced by AKT-mTOR signaling axis after down-regulation of TPP1 protein. Interestingly, rescue experiments showed that 3-MA can enhance the inhibitory effect of silenced TPP1 or Elbasvir on the proliferation and migration of KYSE150 and TE1 cells, so inhibition of autophagy can enhance the sensitivity of esophageal cancer cells to Elbasvir or silenced TPP1 cells. Elbasvir significantly inhibited tumor growth and the expression of TPP1 protein was significantly down-regulated in tumor tissues in nude mice with tumor, while HE staining showed no side effects in heart, liver, spleen, lung tissue, and kidney.

TPP1 has a carcinogenic effect in esophageal cancer, and autophagy is induced by the AKT-mTOR signaling axis. Elbasvir can target telomere protective protein TPP1 to play an anti-cancer activity in esophageal cancer, and inhibition of autophagy can enhance the sensitivity of esophageal cancer cells to Elbasvir or silence TPP1 cells.

Key Words Elbasvir, Esophageal cancer, Telomere protective protein, AKT-mTOR, Autophagy

457. Machine Learning-Based Models for the Prediction of Breast Cancer Recurrence Risk

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Breast cancer is the most common malignancy diagnosed in women worldwide. The prevalence and incidence of breast cancer is increasing every year; therefore, early diagnosis along with suitable relapse detection is an important strategy for prognosis improvement. This study aimed to compare different machine algorithms to select the best model for predicting breast cancer recurrence. The prediction model was developed by using eleven different machine learning (ML) algorithms, including logistic regression (LR), random forest (RF), support vector classification (SVC), extreme gradient boosting (XGBoost), gradient boosting decision tree (GBDT), decision

tree, multilayer perceptron (MLP), linear discriminant analysis (LDA), adaptive boosting (AdaBoost), Gaussian naive Bayes (GaussianNB), and light gradient boosting machine (LightGBM), to predict breast cancer recurrence. The area under the curve (AUC), accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and F1 score were used to evaluate the performance of the prognostic model. Based on performance, the optimal ML was selected, and feature importance was ranked by Shapley Additive Explanation (SHAP) values. Compared to the other 10 algorithms, the results showed that the AdaBoost algorithm had the best prediction performance for successfully predicting breast cancer recurrence and was adopted in the establishment of the prediction model. Moreover, CA125, CEA, Fbg, and tumor diameter were found to be the most important features in our dataset to predict breast cancer recurrence. More importantly, our study is the first to use the SHAP method to improve the interpretability of clinicians to predict the recurrence model of breast cancer based on the AdaBoost algorithm. The AdaBoost algorithm offers a clinical decision support model and successfully identifies the recurrence of breast cancer.

Key Words breast cancer, machine learning, artificial intelligence, disease recurrence, prediction model

458. MFSD2A 介导脂质代谢抑制肝细胞癌进展

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目的：肝细胞癌(hepatocellular carcinoma, HCC)是我国第二大癌症死亡原因，尽管手术切除和肝移植仍是 HCC 患者最有效的治疗方法，但其预后很差。在同一临床阶段的 HCC 患者中存在显著的预后差异，而分子分型的确定为个性化精准治疗提供了可行性。

材料与方法：本研究对 62 例具有完整随访信息的 HCC 组织标本进行转录组测序，通过非负矩阵因式分解（non-negative matrix factorization, NMF）将这 62 例样本分为 3 个亚型，

并进行了生存分析。接着我们分析了 3 个亚型中代谢相关通路的激活情况。最后我们验证了 MFSD2A 在 HCC 中的功能。

结果：通过 NMF 聚类，将 HCC 患者分为 Cluster 1，Cluster 2 以及 Cluster 3 三种亚型，其中 Cluster 1 预后最好，Cluster 2 次之，Cluster 3 预后最差。这三种亚型具有不同的临床和分子特征。与其他两种亚型相比，预后最差的 Cluster 3 中 HCC 患者血清中甲胎蛋白（alpha-fetoprotein, AFP）水平最高，微血管侵犯(microvascular invasion, MVI）阳性患者所占比例更多。相关性分析显示，用于构建这三种亚型的 62 个关键基因与代谢高度相关，脂质代谢相关基因主要促进因子超家族成员 2a（Major Facilitator Superfamily Domain Containing 2A, MFSD2A）在 Cluster 3 中显著下调。通过单样本基因集富集分析（single-sample gene set enrichment analysis, ssGSEA）分析京都基因与基因组百科全书（Kyoto Encyclopedia of Genes and Genomes, KEGG）数据库中的 55 条代谢通路，发现 Cluster 3 中脂质代谢通路（类固醇生物合成（Steroid biosynthesis），甘油脂代谢（Glycerolipid metabolism），不饱和脂肪酸的生物合成（Biosynthesis of unsaturated fatty acids））显著激活，这提示 MFSD2A 可能通过介导脂质代谢通路抑制 HCC 进展。油红染色显示，MFSD2A 过表达的 Huh7 细胞中的脂滴含量降低，而 MFSD2A 敲除后脂滴含量上升，甘油三酯的定量实验也证实了这一点。最后，我们确定了敲低 MFSD2A 基因的表达促进了 Huh7 的增殖和抑制了 Huh7 的凋亡。

结论：通过对 62 例 HCC 患者的转录组数据进行分析，我们成功将其分为三个亚型，并发现这些亚型在临床和分子特征上存在显著差异。进一步的分析表明，与脂质代谢相关的基因 MFSD2A 在 Cluster 3 中显著下调，而该亚型的脂质代谢通路则显著激活。实验结果进一步证实了 MFSD2A 在调节 HCC 代谢以及增殖和凋亡方面的重要作用。MFSD2A 可能成为 HCC 治疗的潜在靶点。

关键字： 肝细胞癌(hepatocellular carcinoma, HCC)；主要促进因子超家族成员 2a（Major Facilitator Superfamily Domain Containing 2A, MFSD2A）；脂质代谢；非负矩阵因式分解（non-negative matrix factorization, NMF）

459. Molecular characterization of FGFR fusion in a large real-world population and clinical utility of bidirectional fusion

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Fibroblast growth factor receptor (FGFR) gene fusions are rare oncogenic drivers and targets of TRK inhibitors in solid tumors. Little is known about FGFR fusion in Chinese patients with pan-cancer. Our study investigated the prevalence and genomic features of FGFR1/2/3/4 fusions in 17810 Chinese patients with pan-cancer using next-generation sequencing (NGS) data to guide TRK inhibitor treatment. The prevalence of FGFR fusion in the pan-cancer population was 1.19%, with 92 unique FGFR-fusion partner pairs, of which 79 were not previously reported. In pan-cancer or biliary tract cancers (BTC), bidirectional fusion was associated with a significant decrease in tumor mutation burden (TMB) score. Further analysis showed that BTC patients had the highest probability of bidirectional fusion (32.86%), followed by gastric cancer (GC). However, GC is more likely to develop bidirectional fusion discordance than other cancers (p=0.0454). In one patient with FGFR2 bidirectional fusion BTC, pemigatinib was treated for 7 cycles with the best assessment of partial response and progression-free survival of 6.5 months, the overall survival was 8.5 months. Our study revealed previously unreported FGFR fusion partners, the associations of FGFR fusion with TMB, and the molecular characterization and prognosis of bidirectional fusion.

Key Words： FGFR, bidirectional fusion, tumor mutational burden, pemigatinib

460. 基于干扰素响应基因的结直肠癌预后评分模型

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研究目的：干扰素在抗肿瘤免疫中扮演着至关重要的角色。特别是在肿瘤微环境中，干扰素能够通过激活免疫细胞、增强抗原呈递及促进细胞毒性作用等多种机制，发挥抗肿瘤功能。我们希望提出一种新的评分方法，即利用与干扰素应答相关的基因来预测结直肠癌患者的临床预后，对患者进行更为精确的风险分层，进而为每位患者提供个性化的治疗建议。此外，通过比较不同预后患者群体的干扰素应答特征，我们可以深入理解影响结直肠癌患者预后的分子机制，这不仅对于病人的精准治疗具有重要意义，同时也为发展新的治疗方法提供了科学依据。

材料与方法：从 MSigDB 数据库提取关于肿瘤免疫反应的两个关键 HALLMARK 基因集“HALLMARK_INTERFERON_GAMMA_RESPONSE”和“HALLMARK_INTERFERON_ALPHA_RESPONSE”，共 224 个基因。应用单因素 Cox 回归分析在数据集 TCGA_COAD 和 GSE39582 中识别与患者预后显著相关的基因（$P < 0.05$）。选定的基因被用于构建多因素 Cox 回归模型：IFN_Score。基于这一评分患者被分为两组，评分高组和评分低组。为了评估 IFN_Score 对患者预后的预测价值，使用 Kaplan-Meier 生存曲线分析两组患者的生存情况，并利用 log-rank 检验评估生存率的差异。利用 Cibersort 算法，对比两组患者免疫微环境的差异，以揭示不同免疫细胞类型的分布和相对丰度。基于先前研究中建立的三级淋巴结构（TLS）评分，我们使用 ssGSEA 算法评估两组患者间 TLS 生成的可能性。通过分析 TCGA 数据库中提供的 HE 染色切片，我们定义包含超过 50 个细胞的免疫细胞聚集体为 TLS，并比较了不同患者组中 TLS 数量的差异。

结果：在 224 个基因中，同时在 TCGA_COAD 与 GSE39582 中与生存相关的基因共 3 个，分别为 DHX58、CASP3 及 PROCR。在训练集 TCGA_COAD 中，通过多因素 COX 建立预后评分 IFN_Score。该评分在训练集及验证集中，均能够有效地区分高低风险患者，其中评分高组患者展现更好的生存预后，而评分低组患者则相反。通过对两组患者的免疫微环境进行比较，我们发现，预后较好的患者具有更加活跃的抗肿瘤免疫，肿瘤中浸润更多的 M1 巨噬细胞，Tfh 细胞及活化的 CD4+T 细胞。而预后差的患者肿瘤中抑制性的 Treg 细胞增多。活跃的免疫微环境常伴随着 TLS 的出现。使用我们在前期研究中建立的 TLS 评分，我们发现预后好的患者中 TLS 形成评分也增高。我们还利用 TCGA 数据库中的病理切片信

息进行了验证，进一步支持了预后较好的患者群体在肿瘤侵袭前缘有更多 TLS 形成的观察结果。

结论： 本研究成功建立了基于干扰素应答基因的结直肠癌预后评分模型——IFN_Score，该模型能够准确区分具有不同预后风险的患者群体。两组患者在抗肿瘤免疫反应中存在显著差异，与良好预后相关的患者显示出更加活跃的免疫微环境及更多的 TLS 形成。综上所述，IFN_Score 不仅为结直肠癌患者的风险分层提供了一个有效的工具，而且还增进了我们对肿瘤免疫微环境在肿瘤发展中作用的理解，为未来开发针对免疫微环境的治疗策略提供了科学依据。

关键字： 干扰素；结直肠癌；预后；免疫

461. 微生物代谢物在肿瘤进展、免疫和治疗中的作用及其机制研究进展

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先前的研究已经发现，肠道微生物和肿瘤微生物会对肿瘤产生影响。越来越多的代谢组学研究表明，探究肿瘤组织（癌症人群肠道）和良性组织（健康人群肠道）之间微生物代谢物组成差异是十分重要的。微生物代谢物能够通过调控患者免疫系统、癌症或免疫相关信号通路、蛋白质的表观遗传修饰、DNA 损伤等机制影响肿瘤进展和免疫。微生物代谢物减轻了化疗和免疫治疗过程中的副作用和耐药性，同时还能有效地激活免疫系统发挥肿瘤免疫效应。但是，某些微生物代谢物却表现出双向作用。它们既能促进肿瘤进展，又能促进肿瘤免疫。这可能与微生物代谢物的浓度或不同癌症类型有关。本文综述了多种微生物代谢物在各种实体瘤中的作用。还讨论了微生物代谢物对肿瘤免疫和治疗的影响。此外，我们还列举了评估微生物代谢物或相关微生物对癌症患者治疗作用的临床试验。微生物代谢物作为微生物组和肿瘤之间的一个关键节点，对微生物代谢物的研究可能会为癌症治疗找到新辅助治疗药物，这将提高癌症治疗的疗效并改善患者的预后。

关键字： 癌症、肠道微生物、瘤内微生物、微生物代谢物、肿瘤微环境、化学治疗、免疫治疗

462. Dual Inhibiting DNA Damage Repair Sensitized Photodynamic Therapy for Triple Negative Breast Cancer

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Photodynamic therapy (PDT) has emerged as an ideal candidate among reactive oxygen species (ROS)-mediated tumor therapies. However, the self-repairable mechanism of DNA damage induced by excessive intracellular ROS is one of the leading causes of PDT resistance. Polyadenosine diphosphate ribose polymerase (PARP), which plays a key role in DNA damage detection and repair, has drawn extensive attention. Likewise, p38-mitogen-activated protein kinase (MAPK) pathway is also activated by PDT for protection in cancer. Capitalizing on this feature, we constructed a therapeutic system, Ce6@MSN-ZOP-HA, to achieve the active targeting of tumors and prevent the DNA repair process. The therapeutic system can target the tumor site accurately through the surface modification of hyaluronic acid (HA), which can specifically bind to CD44 (highly expressed in breast cancer cells). The efficient codelivery of photosensitizer (Ce6), p38 inhibitor (p38i, SB203580) as well as PARP inhibitor (Olaparib, ola) increased the expression of DNA damage related molecule γH2AX, and dually reduced the resistance of cells to PDT treatment. Meanwhile, the active targeting reduced the accumulation of drugs in liver and spleen. The as-prepared active targeting and pH-responsive nanoparticle Ce6@MSN-ZOP-HA provided a new thought for the development of PDT synergistic nanodrugs with low biotoxicity and high anti-tumor efficiency.

Key Words： Photodynamic therapy, DNA damage repair, Reducing resistance, pH response, Triple negative breast cancer

463. Camrelizumab combined with gemcitabine and apatinib in treating advanced PD-L1-Positive biliary tract cancers:A single-arm, exploratory clinical trial（Cognition Study）

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Background

Previous studies have demonstrated the efficacy of combining chemotherapy and immunotherapy in patients with biliary tract cancer. The aim of this study is to assess the efficacy and safety of camrelizumab in combination with gemcitabine and apatinib as first-line or second-line treatment for PD-L1-positive advanced biliary tract cancer.

Methods

This prospective, single-arm and exploratory clinical trial aimed at recruiting 20 PD-L1-positive patients (TPS≥1% or CPS≥1) who met the inclusion criteria. Patients received camrelizumab (200mg) in combination with gemcitabine (800mg/m2) and apatinib (250mg). The primary endpoint was the objective response rate (ORR), the secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety.

Results

Between September 2, 2020, and December 15, 2022, a total of 14 patients were enrolled in the study. At the data cutoff on August 16, 2023, the median follow-up time was 11.4 months (IQR 4.5-15.4), with one patient still undergoing treatment. Among the enrolled patients, six achieved a partial response, and four had stable disease. The ORR was 42.9% (95% CI 17.7-71.1), and the DCR was 71.4% (95% CI 41.9-91.6). The median PFS was 5.4 months (95% CI 2.8-not reached),

and the median OS was 13.5 months (95% CI 5.7-not reached). The most frequent grade 3 or 4 treatment-related adverse events were neutropenia (four [29%] patients).

Conclusions

The combination of camrelizumab with gemcitabine and apatinib shows promising efficacy and acceptable safety for advanced PD-L1-positive cholangiocarcinoma patients.

Key Words： Advanced biliary tract cancer, PD-L1-positive, Camrelizumab combined with gemcitabine and apatinib

464. 肿瘤相关三级淋巴结构异质性在肾透明细胞癌精准免疫治疗中的效应与机制研究

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Tertiary lymphoid structures (TLS) are organized aggregates of immune cells that form under pathological conditions. However, the predictive value of TLS in clear cell renal cell carcinoma (ccRCC) for immunotherapies remain unclear. We comprehensively assessed the implications for prognosis and immunological responses of the TLS spatial and maturation heterogeneity in 655 ccRCC patients. Immunohistochemistry, multispectral fluorescent and spatial transcriptomics were used to evaluate the TLS heterogeneity along with TME cell-infiltrating characterizations. Totally, TLS typically comprises B-cell follicles with germinal centers and are surrounded by T-cell zones and dendritic cells. TLS infiltrates were identified in 34.2% of the ccRCC samples. A higher proportion of early TLS was found in peritumoral TLS, while intratumoral TLS mainly comprised secondary follicle-like TLS (SFL-TLS), indicating markedly better survival. Notably, presence of TLS, especially intratumoral TLS and SFL-TLS significantly correlated with better survival and objective reflection rate for ccRCC patients receiving anti-PD-1/PD-L1 immunotherapies. In peritumoral TLS cluster, primary follicle-like TLS, the proportion of tumor-associated macrophages and Treg infiltration in the peritumoral regions increased prominently, suggesting an immunosuppressive tumor microenvironment. Interestingly, spatial transcriptome annotation and multispectral fluorescent showed that an abundance of

mature plasma cells within mature TLS has the capacity to produce IgA and IgG, which demonstrate significantly higher objective response rates and superior prognosis for ccRCC patients subjected to immunotherapy. In conclusion, this study revealed the implications of TLS spatial and maturation heterogeneity on the immunological status and clinical responses, allowing the improvement of precise immunotherapies of ccRCC.

Key Words： clear cell renal cell carcinoma (ccRCC), tertiary lymphoid structures (TLS), tumor microenvironment (TME), tumor heterogeneity, immune checkpoint inhibitors (ICIs)

465. 非小细胞肺癌相关特征基因筛选及人工神经网络模型建立

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目的：基于生物信息学方法，通过随机森林和人工神经网络建立非小细胞肺癌诊断模型。

方法：以 GEO 数据库获得的芯片数据集 GSE33532、GSE62113 作为建模组，GSE27262 作为验证组，筛选差异表达基因，对差异表达基因进行 GO 功能和 KEGG 通路富集分析，通过随机森林算法从差异表达基因中筛选出特征基因，利用人工神经网络建立非小细胞肺癌诊断模型并采用 ROC 曲线评价模型性能。

结果：共筛选出差异表达基因 321 个，其中上调基因 96 个，下调基因 225 个。差异表达基因主要参与细胞间粘附、细胞分裂和血管生成等生物学过程以及与 ECM-受体相互作用、细胞周期、蛋白质消化和吸收、白细胞经内皮细胞迁移和 PPAR 信号通路密切相关。随机森林算法共筛选出 10 个特征基因用于建立人工神经网络诊断模型，建模组 AUC 为 0.997，验证组 AUC 为 0.982，均表明所构建的模型具有良好的诊断效能。

结论：人工神经网络诊断模型有助于非小细胞肺癌患者的早期评估预测，为患者后续治疗提供帮助指导。

关键字： 生物信息学；非小细胞肺癌；随机森林；人工神经网络；诊断模型

466. Tumor-informed deep sequencing of ctDNA detects minimal residual disease and predicts relapse in sarcoma

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Background: Tumor relapse is the main cause of poor outcome in sarcoma patients, but current surveillance modalities exhibit limited sensitivity and specificity. Although circulating tumor DNA (ctDNA) has been established as a biomarker of minimal residual disease (MRD) in many solid tumors, a sensitive ctDNA detection technique has not been thoroughly explored for longitudinal MRD detection in sarcomas.

Methods: 98 sarcoma patients were evaluated in this study. Tumor-informed MRD panels were developed through whole exome sequencing (WES) of tumor tissues. Longitudinal blood samples were collected during treatment and subjected to multiplex PCR-based next-generation sequencing (NGS).

Results: WES analysis of 171 patients revealed substantial heterogeneity in somatic variants among sarcomas, with non-recurrent variants accounting for 45.0%.

Tumor-informed MRD panels were successfully obtained for 80.7% of patients (138/171). Among 98 patients with successful MRD panel customization and available blood samples, patients with negative post-operative ctDNA had better progression-free survival (PFS) compared to those with positive ctDNA, at 1-6 months after surgery, after adjuvant chemotherapy, and more than 6 months after surgery ($p < 0.001$, $p < 0.001$ and $p = 0.001$, respectively). In both univariate and multivariate Cox regression analysis, ctDNA results emerged as a significant predictor of PFS ($p < 0.001$ and $p = 0.010$, respectively). The incorporation of post-operative ctDNA into the prognostic model comprising clinicopathological factors showed greater predictive performance compared to clinicopathological features alone. ctDNA detection preceded positive imaging in 14 patients

(14.3%), with an average lead time of 75.3 days. Stage III and stage IV patients had higher percentages of positive ctDNA after surgery than stage I/II patients ($p < 0.001$).

Conclusion: Our study underscores the applicability of tumor-informed deep sequencing of ctDNA in sarcoma MRD surveillance and, to our knowledge, represents the largest cohort to date. ctDNA detection is a significant prognostic factor, enabling the early identification of tumor relapse and progression compared to standard imaging, thus offering valuable insights in guiding sarcoma patient management.

Key Words ： Sarcoma relapse, Circulating Tumor DNA (ctDNA), Minimal Residual Disease (MRD), Next-Generation Sequencing (NGS), Tumor-informed MRD Panel.

467. High ALDH2 expression is associated with better prognosis in patients with gastric cancer

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The relationship among alcohol, acetaldehyde, and gastric cancer (GC) is a very interesting research direction. Although many studies have focused on the correlation between ALDH2 polymorphism and GC, ALDH2 expression in GC and its relationship with the prognosis of GC patients remain to be fully understood. To explore these, 455 GC cases were included in this study. The relationships of ALDH2 expression with patients' survival and clinicopathological characteristics were assessed. The immune infiltration characteristics of ALDH2 in GC were also analyzed. Furthermore, the gene regulatory network and functional pathways of ALDH2 in GC were investigated. We found that high expression of ALDH2 was associated with better prognosis in GC patients. GC patients with high ALDH2 expression had a lower degree of pathological malignancy, consistent with our hypothesis that ALDH2 may play as a tumor suppressor role in GC. Mechanistically, ALDH2 may cooperate with genes such as C5orf32, TSPAN8 and RILP to inhibit GC progression via regulating multiple signaling pathways and chemical carcinogenesis. Therefore, our study suggested that ALDH2, an important variant gene in Asians, might serve as a prognostic marker and a potential therapeutic target for patients with GC.

Key Words： Gastric cancer, ALDH2, Prognosis, Targeted therapy, Immune infiltration

468. Personalized neoantigen vaccine enhances the therapeutic efficacy of bevacizumab and anti PD-1 antibody in advanced non-small cell lung cancer

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Clinically, a considerable number of non-small cell lung cancer (NSCLC) patients are unable to receive or resist chemotherapy, and the efficacy of non-chemotherapy treatment strategies based on anti-angiogenic agents combined with immune checkpoint blockade is still unsatisfactory. Neoantigen vaccine, based on personalized tumor DNA mutations, could elicit tumor specific T cell infiltration into the tumor site, exerting potent anti-tumor efficacy. Here, we evaluated the feasibility and safety of a new antitumor strategy by adding neoantigen vaccine to the regimen of bevacizumab and anti-PD-1 antibody. Firstly, 7 novel immunogenic neoantigen peptides were identified and developed for neoantigen vaccine (LLCvac), which can elicit strong antitumor immune response in vivo. Then, in orthotopic lung cancer model, LLCvac further combining with bevacizumab and anti PD-1 antibody exerted a stronger antitumor effect exhibiting significant decrease of tumor volume without obvious toxicity. Furthermore, tumor immune microenvironment assessment also showed that the proportion of neoantigen-specific T cells in blood could be induced dramatically by the combined therapy. And a large amount of neoantigen-specific Ki67-positive CD8+ T cells were found in tumor tissues, which infiltrated tumor tissues effectively to kill tumor cells expressing identified neoantigens. Overall, these results suggested that this combined therapy could safely induce robust antitumor efficacy, serving as an effective chemotherapy-free strategy for NSCLC treatment.

Key Words： Non-small cell lung cancer, neoantigen vaccine, chemotherapy-free treatment, Ki67-CD8+ T cells

469. 血清中 miRNA1290 在胃癌发生发展中的诊断价值与临床意义

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目的：研究分析非编码 miRNA 1290 在胃癌组织及病患者血清中的表达及其作为肿瘤标志物的诊断与临床治疗监测意义。

方法：收集 2018 年 5 月至 2021 年 6 月就诊于常熟市第二人民医院的 40 例胃癌患者的胃癌、癌旁组织与血清标本，同时收集年龄与性别相匹配的健康体检血清 40 例作为对照。提取组织与血清中的 RNA，经逆转录后以 RT-PCR 荧光定量法检测组织 miRNA1290 表达量；以数字 PCR 绝对定量法检测血清中 miRNA1290 的表达量。统计分析组织与血清中 miRNA1290 表达量之间，以及与胃癌病理特征之间的相关性；绘制受试者工作曲线评估 miRNA1290 作为胃癌肿瘤标志物的诊断与临床意义。

结果：胃癌组织中的 miRNA 1290 表达水平显著高于配对癌旁正常组织（3.32±3.36 vs 2.03±1.34, P<0.05），胃癌患者血清中 miRNA 1290 量（68.4±20.6 copies/ml）显著高于健康体检组（16.533±5.784 copies/ml）（P<0.05）。与临床病理特征参数分析显示 miRNA1290 的量与患者年龄性别等无关，与淋巴结远端转移、分化程度及胃癌 TNM 分期显著相关。ROC 曲线分析显示其 AUC 线下面积达到了 0.9545，最优诊断敏感度与特异性分别达到了 81.82% 和 97.06%。结论 miRNA 1290 在胃癌组织及患者血清中高表达，与胃癌的恶性程度正相关，有望作为胃癌诊断与治疗监测的新型肿瘤标志物。

关键字： miRNA 1290；胃癌；血清；诊断；数字 PCR

470. Evaluation of microsatellite instability with somatic mutation in colorectal cancer

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Background: In recent years, immunotherapy has become a very promising treatment option for colorectal cancer (CRC). Evaluation of deficient DNA mismatch repair/high-grade microsatellite instability (dMMR/MSI-H) is currently recommended for all patients with CRC. The most widely used techniques for MSI detection are polymerase chain reaction (PCR) and next-generation sequencing (NGS), both of which require non-tumor controls, which makes the process laborious and time-consuming. Thus, we aim to discover a new method to detect MSI using tumor tissue sample only.

Method: We review NGS data of 144 Chinese CRC patients whose tumor tissue and peripheral blood were collected and conducted target-sequencing of 700 pan-cancer genes. Grouped these patients as MSS and MSI-H according to 3 software programs that use NGS data to determine MSI status (MSIsensor、mSINGS and MANTIS). Analyse the somatic mutations of MSI-H group and selected the overlapped mutations as novel MSI-H biomarker.

Result: By analyzing the somatic mutations of 22 MSI-H samples, we summarized 4 overlapped mutations as biomarker panel of MSI-H CRC. Overall agreement was found in the Kingmed and MSKCC databases to be 97.92% and 97.89%, respectively.

Conclusion: We discovered a novel somatic marker set capable of detecting MSI with acceptable accuracy, which make it possible to detect MSI with tumor tissue sample only.

Key Words ： Colorectal cancer; dMMR; MSI-H; Somatic mutations; NGS

471. ASB3 E3 泛素连接酶通过介导 DR5 泛素化促进肝细胞癌的进展和调控 TRAIL 耐药

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研究目的：原发性肝癌（HCC）是全球第八大常见癌症和第三大癌症死因，严重损害患者生命质量。泛素-蛋白酶体系统是细胞内蛋白选择性降解的重要途径，其中的 E3 泛素连接酶负责特异性识别大量靶蛋白。最近有研究表明，E3 连接酶失调参与了 HCC 的发展、化疗耐药和不良临床预后 ，而靶向 E3 泛素连接酶可能是治疗 HCC 的一种有前景的策略。

研究材料与方法：通过高内涵技术在肝癌细胞针对 600 个 E3 泛素连接酶 RNAi 文库进行筛选；利用肝癌公共数据库以及肝癌组织芯片进行病理相关性分析；通过构建肝特异性敲除的转基因小鼠以及原位肝癌模型进行体内相关验证；通过 RNAseq、RNAi 技术以及泛素化实验进行体外机制研究。

研究结果：1）通过高内涵筛选，发现 ASB3 E3 泛素连接酶的高表达与 HCC 患者的不良预后相关；2）发现敲除 ASB3 可减少 DEN 药物诱导肝癌模型和 LM3 异种移植的肝癌模型的发生比率和增殖速率；3）揭示沉默 ASB3 可通过死亡受体 DR5 介导的途径诱导细胞凋亡；3）阐明 DR5，特别是 DR5L 通过外源性和线粒体内源性途径介导沉默 ASB3 诱导细胞凋亡；4）体外泛素化实验显示 ASB3 与 DR5 存在互作，ASB3 可以调控 DR5 的泛素化，提示 DR5 可能是 ASB3 的潜在底物；5）体内外实验进一步阐明沉默 ASB3 显著增强 HCC 对 TRAIL 的敏感性。

研究结论：我们的研究揭示了 ASB3 E3 泛素连接酶如何调控 HCC 生长和存活的机制，同时也为靶向 ASB3 提高肝癌（尤其是 TRAIL 耐药癌）的 TRAIL 治疗敏感性提供了临床前证据。

关键字 ：ASB3 E3 泛素连接酶，肝癌，DR5，TRAIL，DR5L

472. Hypomethylation of UHRF1 and its high expression mediate Keap1/Nrf2 to up-regulate JAG1 promoting angiogenesis and vascular mimicry in breast cancer

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Breast cancer (BC) is the most common cancer in women. With the development of society, its incidence is increasing year by year. Surgery, chemotherapy, radiotherapy, endocrine therapy and targeted therapy are the traditional methods for breast cancer treatment. Although the treatment of breast cancer has developed, the prognosis of breast cancer patients is still unsatisfactory because of its characteristics of metastasis and recurrence. Therefore, the pathogenesis of breast cancer still needs further exploration.

Epigenetics is an inheritable molecular mechanism to regulate gene expression without changing the actual sequence of deoxyribonucleic acid (DNA), and its pre-transcriptional or post-transcriptional regulation of gene expression is very important for the occurrence and development of breast cancer. DNA methylation is the most widely studied epigenetic modification in human beings. Under the catalysis of DNA methyltransferase (DNMTs), the fifth position of cytosine in cytosine-phosphate-guanine (CpG) dinucleotide is added with methyl to form 5- methylcytosine. Methylation of gene promoter region directly inhibits gene transcription by blocking the binding site of transcription factors or recruiting methyl CpG binding proteins. The specific hypomethylation of specific genes is one of the abnormal DNA methylations. Abnormal methylation of DNA is involved in the regulation of tumor progress, and abnormal hypomethylation of oncogene DNA promoter mediates the up-regulation of gene expression, which promotes the occurrence and development of tumor.

Tumor growth and spread depend on angiogenesis. Tumor cells also get nutrition and oxygen through the non-angiogenic mechanism of vascular mimicry (VM) formation. DNA methylation mediates the imbalance between pro-angiogenic and anti-angiogenic molecules to regulate angiogenesis in breast cancer. The expression of antiangiogenic genes is down-regulated by hypermethylation of promoters, while the hypomethylation of promoters of antiangiogenic genes

leads to the increase of their expression in tumor microenvironment. The hypoxia microenvironment caused by anti-angiogenesis therapy will induce VM formation. Therefore, it is necessary to screen genes involved in angiogenesis and VM formation while DNA methylation is regulated, so as to develop potential targets for breast cancer angiogenesis and vascular mimicry.

In this study, genes with high expression and low methylation in breast cancer were screened based on GEO database, and it was further identified that the ubiquitin-like genes related to angiogenesis and vascular mimicry contain PDH and ring finger domain 1 (UHRF1), which are important epigenetic regulatory factors for maintaining DNA methylation in cells and are highly expressed in many cancers. UHRF1 plays a key role in biological behaviors including cell proliferation, cell cycle and apoptosis due to its special domain. This study further explored the role of abnormal hypomethylation-mediated UHRF1 expression in angiogenesis and vasomimicry formation of breast cancer, and analyzed its mechanism, providing a theoretical basis for the development of drugs targeting angiogenesis and vasomimicry formation of breast cancer.

Methods: 1. The differentially expressed genes in GSE22820 and GSE42568 data sets and the differentially methylated genes in GSE73808 and GSE22249 data sets were screened based on GEO database. The correlation between UHRF1 expression and overall survival (OS) and progression-free interval (PFI) of breast cancer patients was analyzed based on the sample patient information downloaded from TCGA database.

2. T47D cells were selected to establish breast cancer cells with stable UHRF1 knockdown, and the expression of UHRF1 in the cells was detected by RT-QCPR and Western blot to verify the transfection efficiency. CCK-8 method, flow cytometry and Transwell experiment were used to detect the proliferation activity, apoptosis rate, migration and invasion ability of T47D cells in turn.

3. Methylation-specific PCR was used to detect the methylation level of UHRF1 DNA in normal breast epithelial cell line MCF10A, breast cancer T47D cells with relatively high expression of UHRF1 and breast cancer MCF7 cells with relatively low expression of UHRF1.

4. HUVEC cells were cultured in T47D conditioned medium with UHRF1 knocked out, and the tube-forming ability of the cells was tested by tube-forming experiment. The tube-forming experiment also tested the tube-forming ability of T47D cells with UHRF1 knocked down. Screening differentially expressed genes in GSE135424 and GSE181519 data sets based on GEO

database. Wayne analysis further screened the differentially expressed genes related to angiogenesis and vascular mimicry.

Results: 1. UHRF1 is a highly expressed and hypomethylated gene related to angiogenesis and vascular mimicry in breast cancer screened based on GEO database.

2. UHRF1 is up-regulated in breast cancer tissues, and its DNA methylation level is down-regulated in breast cancer tissues.

3. High expression of UHRF1 is related to lower OS, PFI, DMFS and RFS in patients with breast cancer.

4. The expression of UHRF1 in breast cancer cells was higher than that in normal breast epithelial cells, and the expression of UHRF1 in T47D cells was the highest, while that in MCF7 cells was the lowest.

Conclusion:1. Knockout UHRF1 inhibits the proliferation, migration, invasion and tumor growth of breast cancer cells in vivo, reduces the expression of matrix-related proteins in breast cancer cells and induces apoptosis.

2. Knocking down UHRF1 reduces DNA methylation of Keap1 promoter and up-regulates its expression, thus down-regulating Nrf2 expression, inhibiting its binding to JAG1 promoter and promoting its transcription.

Key Words： Breast cancer; DNA methylation; UHRF1; Angiogenesis; Vasculogenic mimicry; Keap1/Nrf2 signal path; JAG1

473. Lactate Dehydrogenase C4 Regulates Ovarian Cancer Progression via Modulating Histone H4K13 Lactylation

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Background: Lactate dehydrogenase C4 (LDHC4), a cancer testis antigen, has been implicated in the energy metabolism of tumors. However, its specific role in the energy metabolism of ovarian cancer (OV) remains to be elucidated.

Methods: We comprehensively profiled lactylproteome in ovarian cancer cell lines exhibiting increased LDHC4 expression. Based on the analysis findings, a specialized primary antibody against the H4 domain site 13 (H4K13) was generated to investigate the association between alterations in lactylation at the H4K13 site in OV cancer tissues and the clinicopathological characteristics, as well as overall survival prognosis of patients. Experiments involving lactylation induction, delactylation, LDHC4 knockdown, and energy metabolism were designed to examine the impact of LDHC4 on the biological function of OV cells by modulating histone lactylation.

Results: The positive rate of lactylation at the H4K13 site in OV patients was 49.315% (72/146). The overall survival time for patients with positive lactylation at the H4K13 site was superior to that of patients with negative lactylation at the H4K13 site (HR=0.260, 95% CI: 0.117- 0.578, P=0.001). The lactylation level of histone H4K13 site in A2780 OV cells of the empty vector group was considerably higher than that in the LDHC4 overexpression group. The expression of LDHC4 in A2780 OV cells was inversely correlated with the H4K13 lactylation level. Upon lactylation induction, the growth, proliferation, invasion, metastasis, and metabolic levels of A2780 OV cells declined significantly, while the opposite results were observed after delactylation. The H4K13 site mutation experiment showed that lactylation alteration at this site influenced the energy metabolism and biological function of CHO cells.

Conclusions: Lactylation at the H4K13 site may serve as a prognostic indicator for OV. LDHC4 regulates the lactylation level of histone H4K13, subsequently affecting the growth, proliferation, invasion, and metastasis of OV cells.

Key Words： Lactylation; LDHC4; ovarian cancer; H4K13

474. LDHC4 Enhances Breast Cancer Progression via Modulating SUCLA2/SDHA/FH Protein Lysine Residues Lactylation

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Background: Lactate dehydrogenase C4 (LDHC4) serves as a crucial enzyme in the regulation of tumor energy metabolism. However, its role in breast cancer (BC) energy metabolism remains elusive.

Methods: We characterized the lactylproteome expression signature in LDHC4-overexpressed BC cell lines and subcutaneous tumorigenic tumors in nude mice, aiming to identify differential lactylation sites. The precision of the identified sites was corroborated by co-immunoprecipitation (Co-IP) and immunoblotting, based on lactate-modified pan-antibody IgG binding. Wild-type and mutant protein expression systems were established. Additional experiments, such as lactylation induction, delactylation, and fumaric acid (FA) induction, were employed to investigate the regulation of the lactylation of lysine at a single site of these three enzyme protein subunits within the tricarboxylic acid (TCA) cycle.

Results: The protein subunits of key regulatory enzymes in the TCA cycle, such as succinyl-CoA synthetase (SUCLA2), succinate dehydrogenase (SDHA), and fumaric acid hydratase (FH) in LDHC4-overexpressed MDA-MB-231 cell line and nude mouse tumorigenic tumors, underwent single-site lysine lactylation (situated at 143 K, 480 K, and 170 K, respectively). The lactylation of SUCLA2, SDHA, and FH unit lysine exerts a positive regulatory effect on the activity of the corresponding enzyme protein, thereby influencing the energy metabolism, invasion, and metastasis of MDA-MB-231 cells. This forms a lactic acid SUCLA2-SDHA-FH biological axis, which plays a positive regulatory role, thereby the content of metabolite FA increases, ultimately promoting the invasion and metastasis of BC cells.

Conclusions:LDHC4 potentially modulates the protease subunits (SUCLA2, SDHA, FH) in the TCA cycle, leading to lactylation of non-histone lysine at the unit point in BC. This study may

open an avenue for the exploration of the regulatory roles of SUCLA2-SDHA-FH axis in TCA cycle mediated by protein lactylation.

Key Words： lactylation; TCA cycle; breast cancer

475. ACAA2-mediated lipid metabolism regulates renal cancer cell proliferation, migration, and invasion through autophagy-related protein signaling

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Background: Renal cell carcinoma (RCC) is a prevalent malignancy of the urinary system, with kidney renal clear cell carcinoma (KIRC) being the most common type, followed by kidney renal papillary cell carcinoma (KIRP) and kidney chromophobe (KICH). Acetyl coenzyme A acyltransferase (ACAA2), a crucial metabolic enzyme involved in fatty acid β-oxidation, plays a pivotal role in various cancers. This study aimed to evaluate the significance of ACAA2 in KIRC and KIRP.

Methods: RCC and paracancerous transcriptional data was sourced from The Cancer Genome Atlas database. The predictive value and clinicopathologic relevance of ACAA2 in patients with RCC were assessed using Kaplan-Meier, Cox regression analysis, Wilcoxon rank sum test, and logistics regression. Gene Ontology (GO), Gene Set Enrichment Analysis (GSEA), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were conducted to explore the biological function and potential role of ACAA2. Additionally, we evaluated the impact of ACAA2 on proliferation, migration, invasive ability, and apoptosis in two renal cancer cell lines, Caki-1 and Caki-2 cells, using the Cell Counting Kit-8, scratch, Transwell, plate cloning, and apoptosis assays. Real-time quantitative polymerase chain reaction and immunohistochemistry were used to detect the expression levels of ACAA2 while immunoblotting was used for gaining insights into its potential mechanisms. Further detection and localization of autophagy proteins and lipid droplet formation were conducted using cellular immunofluorescence, and cellular autophagosomes were observed through projection electron microscopy.

Results: Low ACAA2 expression in two RCC types was associated with a poor prognosis, with ACAA2 being identified as an independent prognostic factor in RCC in both univariate and multivariate Cox regression studies. GSEA and KEGG enrichment analyses suggest that ACAA2 might be involved in fatty acid metabolism, apoptosis, and cellular autophagy.Immune infiltration analysis indicated that ACAA2 was negatively correlated with activated memory CD4+ T cells. Its overexpression significantly inhibited the proliferation, migration, and invasion of Caki-1 and Caki-2 cells, promoting apoptosis and autophagic p62 protein degradation. This accelerated the conversion of LC3I to LC3II, promoting early-stage autophagy and autophagosome formation. ACAA2 also participates in fatty acid metabolism, inhibiting FFA deposition. Subsequently, it impacts RCC cell growth. Exogenous FFA induction alleviated the inhibitory effect of ACAA2 on cancer cell proliferation.

Conclusions: ACAA2 functions as a tumor suppressor in RCC and may be a predictive biomarker in this pathology.

Key Words: Acetyl coenzyme A acyltransferase, renal cell carcinoma, prognosis, biomarker

476. The Role of Wnt/β-Catenin Signaling Pathway in Hepatocellular Carcinoma: Insights into Expression Patterns

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Background and Objective: The Wnt/β-Catenin signaling pathway is a crucial cellular signaling mechanism regulating cell proliferation, differentiation, and survival under normal conditions. In hepatocellular carcinoma (HCC), this pathway is often aberrantly activated, primarily through genetic mutations, leading to increased stability of β-Catenin protein and subsequent upregulation of tumor-related genes, including those promoting cell proliferation and inhibiting apoptosis. This dysregulated activation is closely associated with the malignant characteristics of HCC, including cell proliferation, infiltration, metastasis, and drug resistance. Therefore, understanding the mechanisms of action of the Wnt/β-Catenin signaling pathway in HCC, along with therapeutic

strategies targeting this pathway, holds significant importance for the treatment and prevention of HCC. This study aims to explore the expression levels of Wnt/β-Catenin signaling pathway-related molecules in HCC and their association with patient prognosis.

Materials and Methods: The study utilized data from TCGA, GeneCards, CST, and UALCAN databases to analyze the expression levels of WNT pathway molecules in HCC tissues and their correlation with immune checkpoint molecules. Additionally, TARGET follow-up data were obtained from the UCSC Cancer Browser as a supplement. Samples with follow-up times shorter than 30 days were excluded, and log2(x+0.001) transformation was performed on each expression value to analyze the relationship between the expression levels of relevant molecules and patient survival prognosis.

Results: The results show that the expression levels of GSK3B, AXIN1, CTNNB1, KIF2C, TLE1, GLUL, TBX3, OAT, and SP5 genes in Wnt/β-Catenin signal transduction in liver cancer tissues are significantly different compared with normal tissues. R software (version 3.6.4) calculated the expression difference between normal samples and tumor samples in each tumor. Unpaired Wilcoxon Rank Sum and Signed Rank Tests were used to analyze the significance of the difference. It was found that the expression of TBX3 and OAT was significantly down-regulated in liver cancer tissues, and GSK3B , AXIN1, CTNNB1, KIF2C, TLE1, GLUL, and SP5 expression were significantly up-regulated. The prognosis of liver cancer patients with high expression of four genes, GSK3B, AXIN1, CTNNB1, and KIF2C, is poor, while the high expression of five genes, TLE1, GLUL, SP5, TBX3, and OAT, has no significant correlation with the prognosis of liver cancer.

From immune checkpoint analysis, we found that Wnt/β-Catenin pathway genes are significantly related to immune checkpoints related to liver cancer. Among them, the stimulatory immune checkpoints of GSK3B, CTNNB1, AXIN1, and KIF2C in liver cancer include CD40, CD80, CD28, CXCL9, CXCL10, TNF, CD70, CD27, CCL5, etc.; while the inhibitory immune checkpoints of GSK3B, CTNNB1, AXIN1, and KIF2C in liver cancer are The immune checkpoints include C10orf54, CD274, CD276, VEFA, IL-4, IL-10, VEGFB, etc. The balance and regulation of these immune checkpoints are critical to maintaining the normal function of the immune system, and their imbalance may lead to the occurrence of immune-related diseases.

Conclusion: The Wnt/β-Catenin signaling pathway plays a crucial role in HCC, with its aberrant activation closely linked to the occurrence, progression, and prognosis of HCC. Furthermore, the Wnt/β-Catenin signaling pathway may modulate the immune response in HCC by influencing the expression of immune checkpoint molecules, providing new theoretical foundations and potential targets for the treatment and prognosis assessment of HCC.

Key Words ： Wnt/β-Catenin signaling pathway, Hepatocellular carcinoma,Expression levels, Data analysis

477. ARA55 participates in TGFβ1-induced epithelial-mesenchymal transition in CNE2 nasopharyngeal carcinoma cells

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Objective: ARA55 (androgen receptor coactivator 55kDa protein) was first identified as a TGFβ1-inducible protein and function as a molecular scaffold in coordinating protein-protein interactions. Herein, we focused on validating the functional role of ARA55 in TGFβ1-induced epithelial-mesenchymal transition (EMT) in human CNE2 nasopharyngeal carcinoma cells.

Methods: Expression of ARA55 in the CNE2 cells was stimulated by TGFβ1 (5ng/ml), and a commercial RNA interference plasmid (siRNA-ARA55) was utilized to silence ARA55 expression in response to TGFβ1 induction.

Results: Our results manifested that forced expression of ARA55 enhances growth as well as migration and invasion of the CEN2 cells. In contrast, cells depleted of ARA55 resulted in suppressed cell proliferation and metastasis capability, along with a down-regulation of N-cadherin and up-regulation of Claudin-1. Further co-immunoprecipitation analysis exhibited that induced ARA55 yields a direct physical interaction with Smad7 in TGFβ1 signaling.

Conclusions: Our data demonstrate that ARA55 exerts a causative role and functions as a critical regulator in TGFβ1-mediated EMT in CNE2 nasopharyngeal carcinoma cells through binding with Smad7.

Key Words ： ARA55; nasopharyngeal carcinoma; CNE2; Smad7

478. ARA55 基因在 CNE2 鼻咽癌细胞中的功能研究

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目的：研究 ARA55 过表达对 CNE2 鼻咽癌细胞生物学特性的影响，明确 ARA55 在 TGFβ1 介导的 CNE2 细胞上皮间质转化及侵袭、迁移中的作用。

方法：构建 pCMV-ARA55-EGFP 真核表达载体，经 ZLip2000 转染至 CNE2 鼻咽癌细胞，荧光显微镜和免疫印迹检测 ARA55-EGFP 融合蛋白的表达；通过 CCK-8 比色、划痕修复实验、Transwell 小室、Annexin V-PE/7-AAD 双荧光染色、DNA 梯状电泳等实验，探讨 ARA55 过表达对 CNE2 鼻咽癌细胞生物学特性的影响。一定浓度的 TGFβ1 诱导 CNE2 细胞株中 ARA55 的表达，免疫印迹检测 ARA55 蛋白及 EMT 相关标志物 N-cadherin、Claudin-1 等的表达变化；采用 ARA55 的 siRNA 质粒，经 X-treme GENE siRNA 转染至 CNE2 细胞株；通过 CCK-8 比色、划痕修复、Transwell 侵袭迁移等实验，研究 TGFβ1 介导的 ARA55 表达上调及沉默以 ARA55 表达对 CNE2 鼻咽癌细胞 EMT 及侵袭迁移的影响。

结果： DNA 测序及双酶切分析显示 pCMV-ARA55-EGFP 重组载体构建成功。pCMV-ARA55-EGFP 组细胞生长增殖、侵袭迁移能力明显低于 pCMV-C-EGFP 空载体组和/或空白对照组（P＜0.05 或 0.01）；Annexin V-PE/7-AAD 双荧光染色及 DNA 梯状电泳结果可见，pCMV-ARA55-EGFP 组细胞产生凋亡，且凋亡率明显高于 pCMV-C-EGFP 空载体组（P＜0.05）；免疫印迹显示 pCMV-ARA55-EGFP 组细胞 Bcl-2 表达下调，Cytochrome C 表达上调，同时伴有 Caspase-9 和 Caspase-3 的激活。TGFβ1 诱导后，免疫印迹显示 ARA55 在 CNE2 细胞中的表达上调；ARA55 诱导组细胞发生间质样改变，N-cadherin 的表达上升，Claudin-1 表达下降，同时细胞的生长增殖及侵袭迁移能力明显高于对照组（P＜0.05 或 0.01）；诱导表达的 ARA55 通过 siRNA 下调后，siRNA-ARA55 组细胞生长增殖及侵袭迁移能力下降（P＜0.05 或 0.01）。

结论：成功构建 pCMV-ARA55-EGFP 重组载体； ARA55 过表达可抑制 CNE2 鼻咽癌细胞生长增殖，诱导凋亡；3. ARA55 参与了 TGFβ1 介导的 CNE2 细胞 EMT 及侵袭迁移过程。

关键字： 鼻咽癌；ARA55；TGFβ1；上皮间质转化；CNE2

479. 生物信息学分析 BATF2 在头颈部肿瘤的表达及其预后价值

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目的：通过 TCGA 和 GEPIA 数据库分析 BATF2(basic leucine zipper transcription factor, ATF-like 2)在头颈部鳞状细胞癌(head and neck squamous cell carcinoma，HNSCC)中的表达和预后价值。

方法：利用 TCGA 数据库、GEPIA 数据库分析 BATF2 在不同癌症组织中的表达进行对比；在 TCGA 数据的基础上，通过 R 语言进行 BATF2 与基因的共表达及相关性分析，分析这些基因与 BATF2 可能存在的相互作用通路。通过 UALCAN 数据库分析 BATF2 的表达情况与 HNSCC 生存期的关系，评估预后价值，得到预后风险比（HR）森林图。

结果：BATF2 在 HNSCC 中的表达处于中等水平，WARS、GBP5、GBP1 与 BATF2 相关性最强，呈正相关；BATF2 表达与丝氨酸蛋白酶抑制剂因子 Serpin B3 呈正相关（r=0.13,P=0.0025）。BATF2 的表达在 HNSCC 患者预后评估中不具有统计学意义。

结论：BATF2 在 HNSCC 中呈中低水平表达，对 HNSCC 中所有癌种的生存期评估尚无统计学差异。

关键字： BATF2；生物信息学；HNSCC；预后

480. Transcription factor E2F8 is a therapeutic target in the basal-like subtype of breast cancer

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Introduction: Tumorigenesis in breast cancers usually accompanied by the dysregulation of transcription factors (TFs). Abnormal amplification of TFs leads aberrant expression of its downstream target genes. However, breast cancers are heterogeneous disease with different subtypes that have distinguished clinical behaviours, and the identification of prognostic TFs may enable to provide diagnosis and treatment of breast cancer based on subtypes, especially in Basallike breast cancer.

Methods: The RNA-sequencing was performed to screen differential TFs in breast cancer subtypes. The GEPIA dataset analysis was used to analyze the genes expression in invasive breast carcinoma. The expression of MYBL2, HOXC13, and E2F8 was verified by qRT-PCR assay in breast cancers. The depiction analysis of co-expressed proteins was revealed using the STRING datasets. The cellular infiltration level analysis by the TISIDB and TIMER databases. The transwell assay was performed to analyze cellular migration and invasion. CCK-8 assay was used to evaluate cellular drug susceptibility for docetaxel treatment. Predicted targeted drugs in breast cancers by GSCA Lite database online.

Results: Kaplan-Meier plotter suggested that high expression of both E2F8 and MYBL2 in Basal-like subtype had a poor relapse-free survival. Functional enrichment results identified that apoptosis, cell cycle, and hormone ER pathway were represented the crucial regulation pathways by both E2F8 and MYBL2. In the meantime, database analysis indicated that high expression of E2F8 responded to chemotherapy, while those patients of high expression of MYBL2 responded to endocrinotherapy, and a positive correlation between the expression of E2F8 and PD-L1/CTLA4. Our cell line experiments confirmed the importance of E2F8 and MYBL2 in proliferation and chemotherapy sensitivity, possibly, the relationship with PD-L1. Additionally, we also observed that the up-regulation of E2F8 was accompanied with higher enrichments of CD4+ T cells and CD8+ T cells in breast cancers.

Conclusion: Taken together, our findings elucidated a prospective target in Basallike breast cancer, providing underlying molecular biomarkers for the development of breast cancer treatment.

Key Words： breast cancer, transcription factors, E2F8, biomarker, immune checkpoint molecules

481. Comprehensive analysis of the prognostic implications and biological function of HDACs in hepatocellular carcinoma

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Background: The prognostic value and biological functions of the histone deacetylases (HDACs) in liver hepatocellular carcinoma (LIHC) remain unexplored. Here, we report the prognostic value and biological functions of the HDACs family of genes in LIHC.

Methods: A risk score prognostic model of LIHC based on HDAC genes was established using least absolute shrinkage and selection operator (LASSO) regression. The effects of CKD-581, a specific inhibitor of the expression of endogenous HDACs, on cell growth, cell proliferation, invasion, and migration, in LIHC cell lines were evaluated in vitro and in vivo.

Results: The prognostic model based on six HDACs (HDAC1, HDAC4, HDAC5, HDAC11, SIRT6, and SIRT7) showed that overall survival was lower in patients with high-risk scores than

in those with low-risk scores. Immunohistochemistry and RT-PCR results showed that all five HDACs except HDAC5 were up-regulated in LIHC, and HDAC1 was found to be a core gene associated with poor prognosis in LIHC patients. The inhibition of endogenous HDAC expression results in the inhibition of the proliferation, invasion and migration, and promoted apoptosis of LIHC cells. In vivo experiments showed that HDAC expression inhibits the growth of tumorigenic tumors in mice. Subsequent mechanistic investigations revealed that HDACs expression inhibition upregulates the protein expression of P21 and P27 and downregulates the protein expression of cyclins A2, B1, and D1.

Conclusions: The risk score prognostic model based on HDAC genes may serve as an effective prognostic biomarker for LIHC. CKD-581 may serve as a potential drug for the clinical treatment of LIHC.

Key Words： Histone deacetylases (HDACs), CKD-581, liver hepatocellular carcinoma, prognostic model

482. Endogenous SARI induced cell apoptosis in nasopharyngeal carcinoma by targeting the intrinsic apoptotic pathway

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The SARI (suppressor of AP-1, regulated by IFN) gene, also named as BATF2, is associated with the risk of several kinds of cancers, and loss of SARI expression is frequently detected in aggressive and metastatic cancer. Nevertheless, the functional of SARI in nasopharyngeal carcinoma (NPC) remains exclusive. In this study, we discovered that knock-down of SARI expression suppressed cell growth and colony formation, inhibited invasion, promoted apoptosis, and induced G0/G1 and G2/M arrest in human CNE2 nasopharyngeal carcinoma cells. Of note, SARI restoration could trigger the mitochondrial pathway in CNE2 cells. Our data provide evidence that SARI exerts a role as a tumor suppressor gene in leukemia, possibly by inhibiting proliferation and promoting apoptosis via the mitochondrial pathway.

Key Words： suppressor of AP-1, regulated by IFN; SARI; CNE2; nasopharyngeal carcinoma

483. G 试验在肿瘤患者侵袭性念珠菌感染中的临床价值

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目的 讨论 G 试验在恶性肿瘤患者侵袭性念珠菌(invasive candidiasis, IC) 感染中的临床早期诊断价值及其临床特征之间的关系。

方法 选取福建省肿瘤医院 2019 年 1 月至 2020 年 12 月期间 64 例侵袭性念珠菌感染(invasive candidiasis, IC)患者、58 例念珠菌粘膜定植者，采用免疫比浊法分别检测两组 G 试验与 pct 浓度，分析 G 试验早期诊断恶性肿瘤患者 IC 的灵敏度、特异度、阳性预测值、阳性预测值等指标，以受试者工作特征（ROC）曲线评估 G 试验在恶性肿瘤患者 IC 早期诊断中的价值，并比较 G 试验阳性率与患者临床特征之间的关系，以及与 PCT 联合检测对肿瘤患者 IC 的诊断价值。结果用 SPSS 26.0 分析。

结果 IC 组 G 试验浓度与粘膜定植组相比显著增高；64 例 IC 组患者中，白色念珠菌比例高于非白色念珠菌；G 试验诊断总体灵敏度为 56.25%，特异度为 87.9%，阳性预测值为 85.71%，阴性预测值为 67.1%，阳性似然比为 4.648，阴性似然比为 0.498，约登指数为 0.44；G 试验 ROC 曲线下面积 AUC 为 0.628；IC 患者 G 试验阳性率与病原菌、粒细胞、体温、合并感染的情况、治疗方法等临床特征无关；G 试验与 PCT 联合检测的灵敏度及特异度（分别为 75%、65.31%）高于二者单独检测（P＜0.05），但阴阳预测值并未明显改变。

结论 G 试验对于恶性肿瘤患者 IC 的早期诊断具有一定临床可用性，能区分定植和感染，但其在恶性肿瘤的患者临床应用价值准确性一般，实验室应优化检测方法，临床连续检测 G 试验以减少假阳性和假阴性的发生，提高 IC 诊断的准备性。

关键字 ：(1,3)-β-D-葡聚糖；PCT；侵袭性念珠菌病；肿瘤患者

484. Lactate Dehydrogenase C4 is associated with breast cancer prognosis and affects cancer cell proliferation and invasion

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Objective: Human lactate dehydrogenase C4 (LDH-C4) is a known cancer/testis antigen (CTA). Nevertheless, its clinical effects and molecular role remains unclear in breast cancer (BC).

Methods: Expression of LDH-C4 in BC tissue, paired adjacent normal tissue, and cell lines were quantified by qRT-PCR, western blotting and immunohistochemistry. Additionally, we assessed the clinical and prognostic significance of LDH-C4 in BC by Kaplan-Meier method. Cell proliferation, migration and invasion, and cell apoptosis were measured by means of a cell counting kit-8, clone forming, Transwell assay, and TUMMEL, respectively. Invio an

Results: Expression levels of LDH-C4 were markedly upregualted in BC cells and tumor tissues but not expressed in normal BC tissue. Furthermore, survival showed that high LDH-C4 expression conferred reduced survival rates ($P < 0.05$). Functional analyses revealed that LDH-C4 overexpression and down-regulation attenuated cell proliferation, invasion, and migration as well as energy metabolism in BC cells. LDH-C4 could affect mTOR activity.

Conclusions: Expression of LDH-C4 in BC may serve as a potential indicator for poor prognosis. LDH-C4 displays tumor suppressive behavior, warranting future investigations into its therapeutic potential in the treatment of BC.

Key Words ： lactate dehydrogenase C4；breast cancer；invasion；migration；mechanism

485. Lactylproteome analysis indicates histone H4K12 lactylation as a novel biomarker in triple-negative breast cancer

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Background: Posttranslational modifications of histone or non-histone lysine (K) have intrinsic connections with cell metabolism and participate in the carcinogenesis of various cancers. However, the expression signature of protein lactylation and the clinical role of lactylated proteins in triple-negative breast cancer (TNBC) have rarely been investigated.

Methods: We comprehensively profiled the lactylproteome in eight pairs of TNBC samples and matched adjacent tissues by combining 4-Dimensional label-free quantitative proteomics with lactylation analysis (4D-LFQP-LA). Immunoblotting and immunohistochemistry (IHC) with specific primary antibodies were used to detect the expression of identified lactylated proteins in TNBC, and the clinicopathological and prognostic significance was assessed.

Results: We identified 58 lactylation sites on 48 proteins and mapped the protein lactylation alteration signatures of TNBC. Bioinformatic and functional analyses revealed that lactylated proteins are involved in the regulation of important biological processes in TNBC. Lactylproteome expression analysis revealed that the histone H4 domain was upregulated in the lactylation of lysine at position 12 (H4K12lac) in TNBC. Further investigations showed that H4K12lac expression was elevated in TNBC, and yielded a positive rate of 93.19% (137/147) and 92.29% (92/99) in TNBC tissue chip and validation cohorts, respectively. H4K12lac expression was positively correlated with Ki-67 (antigen identified by monoclonal antibody Ki 67) expression. Survival analysis showed that H4K12lac expression was negatively correlated with the overall survival (OS) time of TNBC (HR [hazard ration] =2.813, 95%CI [credibility interval]: 1.242-6.371, P=0.0164), and that H4K12lac was an independent prognostic factor of prognosis in patients with TNBC.

Conclusions: Lactylation is an all-protein post-translational modification occurring in TNBC. H4K12lac is a promising biomarker for TNBC.

Key Words： triple negative breast cancer; histone H4; lactylation; biomarker; prognosis

486. New understanding of the application of procalcitonin as an infection biomarker in Non-Hodgkin's Lymphoma

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Background: This study aimed to examine the diagnostic significance of procalcitonin (PCT) in Non-Hodgkin's lymphoma (NHL) and identify the influencing factors that affect its diagnostic accuracy. Additionally, the study sought to explore its rational application in the clinic.

Methods: Through a retrospective analysis of clinical data, serum PCT levels were measured using an automatic immunoassay, and a receiver operating characteristic (ROC) curve was constructed.

Results: The determined cut-off value for serum PCT in diagnosing infection was found to be 0.120 ng/mL. Serum PCT level was significantly higher in the group with bloodstream infections compared to the group with local infections. Bloodstream infections caused by Gram-negative bacilli exhibited higher PCT levels compared to those caused by Gram-positive cocci, and coagulase-negative staphylococci in the bloodstream infection group had higher PCT levels compared to the contamination group. The presence of various factors exerts an influence, leading to the emergence of tumor metastasis and tumor progression as distinct risk factors associated with elevated serum PCT levels in patients with NHL.

Conclusions: Serum PCT levels are elevated in patients with NHL, and these levels are influenced by tumor stage and progression. The diagnostic utility of a single PCT test is constrained to diagnose infections. It is advisable to admit NHL patients to the hospital for the purpose of establishing a baseline serum PCT level, which can serve as a control measure in the diagnosis of infections.

Key Words ： Procalcitonin; Infection; Non-Hodgkin lymphoma; application.

487. Validation of serological models for detection and prognostication of AFP-negative hepatocellular carcinoma

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Objective: A considerable proportion, 20%-40% of individuals with hepatocellular carcinoma (HCC) do not manifest heightened Alpha-fetoprotein (AFP) levels. This study aimed to investigate the utility of serum glypican-3 (GPC3) and protein induced by vitamin K absence or antagonist II (PIVKA-II) in an AFP-negative HCC (HCC-N) population, and to develop a nomogram prognostic scoring model.

Methods: Serum GPC3 and PIVKA-II levels were measured in this case-control study, subsequently leading to establish a receiver operating characteristic (ROC) curve , restricted cubic spline(RCS) and Kaplan-Meier survival curve . Additionally, a nomogram prognostic scoring model was constructed using LASSO regression.

Results: Serum GPC3 and PIVKA-II expression levels were significantly elevated in untreated patients with HCC-N compared to the control group. PIVKA-II demonstrated the largest area under the ROC curve (AUC) value of 0.925 and GPC3 + PIVKA-II exhibited the highest sensitivity for stage I (94.60%) and small HCCs (93.10%). Moreover, the cut-off points for GPC3 (0.124 mAU/mL) and PIVKA-II (274 mAU/mL) expression levels by RCS significantly correlated with the survival time and rate of the patients.Finally,the utilization of GPC3, albumin (ALB), portal venous thrombosis (PVT), and surgical treatment as parameters in the nomogram prognostic scoring model effectively differentiated between the high- and low-risk prognostic patients with HCC-N with relatively high accuracy.

Conclusions: Serological models demonstrates clinical significance in the timely detection and prognosis assessment of HCC-N. The utilization of a nomogram prognostic scoring model could serve as an essential adjunctive instrument for predicting the prognosis of HCC-N.

Key Words ： glypican-3; protein induced by vitamin K absence or antagonist II; hepatocellular carcinoma; diagnosis; nomogram; prognosis

488. A Nomogram Based on Autoantibodies for Noninvasive Detection of AFP-negative Hepatocellular Carcinoma: a multicenter study

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Background

The diagnosis of AFP-negative hepatocellular carcinoma (HCC) poses a significant challenge. Autoantibodies to tumor-associated antigens have been extensively investigated as early serum biomarkers.

Methods

In this study, we employed serological proteome analysis and protein microarray to identify potential autoantibodies for HCC, followed by a two-center and two-independent-phase validation and evaluation study using enzyme-linked immunosorbent assay in AFP-negative HCC (ANHCC) patients. To address multicollinearity issues among biomarkers, LASSO regression was performed. Four machine-learning methods were applied to develop diagnostic models for ANHCC. Receiver operator characteristic curve (ROC) analysis and various evaluation indicators were used to assess the performance of the biomarkers.

Results

As a result, eight autoantibodies out of sixteen candidates, including Survivin, NPM1, GNAS, SRSF2, GNA11, PTCH1, GAPDH, and HSP90, were validated as superior biomarkers. The Logistic regression model was considered the optimal model for ANHCC with an area under ROC (AUC) of 0.883 in the training dataset, and AUC of 0.840 in the validation dataset. When tested on the whole HCC patients, including those with ANHCC accounting for 37.5%, the AUC reached 0.825, with sensitivity of 66.4%, and specificity of 84.2%. Combining this model with AFP showed substantial enhancement efficacy, with an AUC of 0.945, and an integrated discrimination improvement (IDI) of 23.1%, and a net reclassification improvement (NRI) of 21.1% compared to using AFP alone.

Conclusion

In summary, these findings indicated that the Logistic regression model demonstrates superior diagnostic performance for ANHCC patients. Furthermore, the integration of this model with AFP reveals an enhanced diagnostic efficacy for the whole HCC population.

Key Words ： AFP-negative HCC, autoantibody, diagnostic, nomogram, machine learning

489. NT-proBNP and cTnT are Effective Biomarkers for Predicting Occurrence and Prognosis of Symptomatic Cardiovascular Toxicities Caused by Anthracycline Chemotherapy in Non-Hodgkin's Lymphoma

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Objective: We aimed to investigated the role of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin T (cTnT) in predicting the occurrence and prognosis of symptomatic cardiovascular toxicities (CVTs) in patients with Non-Hodgkin's lymphoma (NHL) receiving anthracyclines (ATCs).

Methods: We performed a retrospective analysis of the changes in serum NT-proBNP and cTnT levels in 182 NHL patients treated with anthracyclines. We calculated the post-treatment elevation ratio (ER) of NT-proBNP (NT-proBNP-ER), and the receiver operating characteristic curves (ROCs) were plotted.

Results: The area under the curves (AUCs) of NT-proBNP-ER, cTnT, and a combination for diagnosing symptomatic CVTs were 0.903, 0.811, and 0.9807, respectively. Serum NT-proBNP-ER≥2.56 and cTnT≥11.68 pg/ml positively correlated with the occurrence of symptomatic CVTs. Median progression-free survival (PFS) and overall survival (OS) were both shorter in patients with a post-treatment NT-proBNP-ER≥2.56 than in patients with an NT-proBNP-ER <2.56. The median PFS and OS of patients with post-treatment cTnT≥11.68 pg/ml were markedly shorter than those in patients with cTnT <11.68 pg/ml.

Conclusion: Single NT-proBNP-ER≥2.56 or cTnT≥11.68 pg/ml, or a combination are significant predictors of symptomatic CVTs. Exceeding these thresholds suggests a poor prognosis in NHL patients treated with anthracyclines.

Key Words： Non-Hodgkin's lymphoma; cardiovascular toxicities; N-terminal pro-B-type natriuretic peptide/NT-proBNP; cardiac troponin T /cTnT; prognosis

490. 肿瘤睾丸相关抗原 LDH-C4 在鼻咽癌中的表达及其功能研究

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目的：研究乳酸脱氢酶 C4（LDH-C4）蛋白在鼻咽癌癌组织中的表达情况以及在临床诊疗过程中的价值。明确 LDHC 基因过表达在 CNE2 鼻咽癌细胞的生物学作用，并初步探讨相关分子机制。

方法：通过免疫组化染色方法检测高通量鼻咽癌组织芯片中 LDH-C4 蛋白的表达量，根据染色的结果进行评分，分析鼻咽癌患者的临床和病理分期、转移、复发及预后等临床病理特征和 LDH-C4 蛋白表达的高低的相关性。通过慢病毒载体将外源性 LDHC 基因导入 CNE2 鼻咽癌细胞，并采用稀释法结合绿荧光表达情况筛选出单克隆化且 LDH-C4 表达阳性的细胞系。通过 CCK-8 比色、平板克隆形成、划痕修复实验、Transwell 小室等实验，研究 LDH-C4 表达上调后，CNE2 鼻咽癌细胞在体外增殖能力、迁移和侵袭能力的改变；通过 Western blot 检测 AKT/mTOR 信号转导通路相关蛋白的表达改变。

结果： 129 例高通量鼻咽癌组织标本结果显示：LDH-C4 主要表达于鼻咽癌细胞的细胞质中，阳性率为 88.4%（114/129）；Spearman 相关性分析结果表明，鼻咽癌的临床分期、颈部淋巴结转移均与 LDH-C4 的表达水平呈正相关（$P<0.05$）；Kaplan-Meier 生存分析表明，LDH-C4 低水平患者预后明显优于高水平患者（$P<0.05$）。CCK-8 比色实验、克隆形成、划痕实验、基质胶 Transwell 小室等一系列实验，证明 LDH-C4 过表达可增强 CNE2 鼻咽癌细胞的生长增殖、克隆形成以及侵袭和迁移能力；Western blot 结果证实，LDH-C4 在 CNE2 细胞中过表达可上调 AKT、mTOR 等蛋白的表达。

结论： LDH-C4 蛋白在鼻咽癌癌组织中的表达量明显增高，并与患者的临床分期、颈部淋巴结转移呈现正相关关系；LDH-C4 可作为鼻咽癌预后监测的一项重要指标，其高表达提示患者临床预后不良。上调 LDH-C4 可明显增强 CNE2 细胞体外增殖、侵袭及迁移能力，可能通过激活 AKT/mTOR 信号通路起作用。

关键字： 鼻咽癌，LDH-C4，CNE2，侵袭转移，机制

491. 应用四项新型凝血指标评估妇科肿瘤手术患者的凝血功能

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目的 检测妇科肿瘤患者手术前、后凝血及纤溶分子标志物的变化及探讨其临床意义。

方法 以 55 例健康体检者为对照组，92 例妇科肿瘤患者为研究组（良性肿瘤组 38 例、恶性肿瘤 54 例）。研究组于术前、术后 1d、3 d、5 d、7 d 分别采血，采用高敏化学发光免疫分析方法检测上述标本中凝血酶-抗凝血酶复合物（TAT）、纤溶酶-α2-抗纤溶酶复合物（PIC）、组织型纤溶酶原激活剂及其抑制剂-1 复合物（tPAI·C）、血栓调节蛋白（TM）的表达水平。

结果：恶性肿瘤组术前的四项指标水平均较健康对照组及良性肿瘤组升高（P<0.05），良性肿瘤组术前仅 TAT 及 TM 水平高于健康对照组（P<0.05）；恶性肿瘤组术后 1d、3d、5d 的 PIC 及 TAT 水平均高于术前（P<0.05），tPAI·C 仅在术后第 1d 较术前高（P<0.05），但 TM 水平术前术后无差异（P>0.05），但均高于正常组；良性肿瘤组术后四项指标仅在术后第一天短暂性的升高，术后 3d 即恢复至术前水平或者正常水平。除了术后第一天的 TM，恶性肿瘤组 tPAI·C、TM、TAT、PIC 表达均明显高于同一时期的良性肿瘤组。

结论 妇科恶性肿瘤患者机体内存在着明显的凝血与纤溶系统功能的异常，TAT、PIC、tPAI·C、TM 等指标的动态检测和分析有利予血栓前状态的判断，对预警血栓形成具有重要意义。

关键字： 妇科肿瘤；凝血及纤溶系统标志物 凝血酶-抗凝血酶复合物/TAT、纤溶酶-抗纤溶酶复合物/PIC；组织型纤溶酶原激活抑制复合物/tPAI·C；血栓调节蛋白/TM

492. 血清 miRNA-223 在非小细胞肺癌化疗疗效监测中应用

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目的：探讨 microRNA-223（miRNA-223,miR-223）作为非小细胞肺癌（NSCLC）晚期（III-IV期）患者化疗疗效评价指标的可行性。

方法：收集 14 例非小细胞肺癌晚期患者化疗前及化疗第一周期后血清，提取总 RNA 后采用实时荧光定量 PCR 方法检测血清 miRNA-223 水平变化，计算各个患者化疗第一周期后相对化疗前的变化量，并依据临床对患者疗效进行的化疗疗效评估（RECIST），将 14 例样本分为疾病进展（PD, progressive disease）组、疾病稳定(SD, stable disease) 组、部分缓解(PR, partial response)组，比较三组患者化疗第一周期后血清 miR-223 变化量，探讨不同组别血清 miR-223 作为 NSCLC 患者化疗疗效评估指标的可行性。

结果：数据统计显示，miRNA-223 在 PR 组中化疗后表达水平低于化疗前的水平，其相对表达含量为 0.70±0.32，在 SD 组中化疗后相对表达含量为 1.18±0.34，在 PD 组中化疗前后相对表达含量最高，为 2.84±0.87。化疗后 miR-223 相对化疗前的表达水平与患者年龄(u=23.00,P=0.848)、性别(u=10.00,P=0.157)、TNM 分期（u=20.00,P=1.000）差异无统计学意义。PR、SD、PD 组间 miR-223 化疗后水平呈趋势性变化，差异具有统计学意义（$\chi 2$=8.9,P=0.012）。

结论：血清 miR-223 在化疗一个周期后的变化水平能较好预示 NSCLC 患者的化疗疗效，提示血清 miR-223 可作为 NSCLC 患者化疗疗效评价指标之一，对于实现肺癌个性化治疗有着重要的临床意义。

关键字： 微小核糖核酸 223；非小细胞肺癌；早期疗效监测；实时定量聚合酶链反应

493. 白细胞介素 6 在结直肠癌患者中的表达及与肿瘤疗效关系

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目的：探讨人白细胞介素 6（Interleukin-6，IL-6）在结直肠癌患者中的表达及意义。

方法：收集 132 例首诊结直肠癌患者（CRC）、34 例肠道良性疾病患者(CBD)及 84 例表观健康体检者(HC)血清,采用电化学发光双抗体夹心免疫分析法（ECLIA）检测血清中白细胞介素 6（IL-6）及癌胚抗原（CEA）含量，分析 IL-6 水平与结直肠癌患者临床病理特征的相关性；应用受试者工作特性曲线（ROC）和二元 Logistic 法回归分析 IL-6 和 CEA 两指标对结直肠癌的诊断价值；对随访资料完整的 120 例结直肠癌患者动态观察治疗前后血清 IL-6 和 CEA 水平，分析两指标与肿瘤疗效的关系。

结果：结直肠癌患者血清 IL-6 水平显著高于肠道良性疾病组(P<0.01)和健康对照组(P<0.01)，结直肠癌患者血清 CEA 水平显著高于肠道良性疾病组(P<0.05)和健康对照组(P<0.01),差异均有统计学意义。CRC 患者血清 IL-6 水平与肿瘤直径、分化程度、组织类型、淋巴结转移、远处转移、TNM 分期均显著相关(P<0.05)，而与年龄、性别及肿瘤发生部位无明显相关。IL-6 诊断结直肠癌的灵敏度（72.7%）和准确性（78.6%）均高于 CEA(分别为 68.2%和 77.9%，特异性（85.2%）低于 CEA（88.9%），两指标联合检测能够提高灵敏度（97.2%）和准确性（85.6%）。结直肠癌肿瘤控制组(CR+PR+SD)治疗后两指标均较治疗前有显著下降(P<0.05)，差异有统计学意义，而肿瘤进展组(PD)治疗后两指标均未显著下降(P>0.05)。

结论：IL-6 和 CEA 两指标联合检测有助于结直肠癌的诊断和疗效观察。

关键字： 结直肠癌、白细胞介素 6、癌胚抗原

494. SARI 蛋白在乳腺癌中的表达及其临床意义

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目的：探讨 SARI 蛋白在乳腺癌中的表达及其临床意义。

方法：采用免疫组化技术检测 SARI 蛋白在乳腺癌及其癌旁组织中的表达，探讨 SARI 蛋白表达水平与乳腺癌的临床病理特征及预后的关系。

结果：基于高通量的乳腺癌组织芯片免疫组化分析显示，在 87 例乳腺癌石蜡标本中，93.1%（81/87）的组织中 SARI 蛋白低呈现低表达或不表达，其中 80 例（98.8%）SARI 无表达，1 例（1.2%）SARI 蛋白低表达，6 例(6.9%)BATF2 高表达。SARI 蛋白在乳腺癌组织及旁组织表达差异无相关性（P=0.950）。SARI 的表达水平与乳腺癌的临床病理分级密切相关（P=0.000），患者年龄是影响乳腺癌预后的独立因素（P=0.027）。

结论：SARI 蛋白在乳腺癌中存在低表达，可能发挥肿瘤抑癌因子的作用，其临床意义有待于进一步被证实。

关键字： 乳腺癌；SARI；临床病理特征

495. 孟德尔随机化算法在胃癌风险因素评估中的应用

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目的：胃癌(GC)是第五大最常见的癌症，也是癌症相关死亡的第三大常见原因,由于早期疾病的微妙症状和定期筛查的低比率，大多数病人在晚期被诊断出来，从而限制了治疗的选择。使用孟德尔随机化分析（MR）来评估肠道微生物是否为胃癌的危险因素。

材料与方法：研究采用两样本 MR，以单核苷酸多聚体（SNP）作为工具变量（Instrumental variable,IV），分析肠道菌群与胃癌之间潜在的因果关系。从 MiBioGen 联盟（https://mibiogen.gcc.rug.nl/）数据库中筛选肠道菌群的遗传变异样本。从全基因组关联研究中筛选胃癌的遗传位点作为工具变量。结局数据来源于英国生物样本数据库（https://gwas.mrcieu.ac.uk/）发布的胃癌 GWAS（bbj-a-119）。首先，以阈值 P＜1×10-5 来筛选 IV，我们利用关联性分析来识别与暴露因素紧密相关的 SNP，并将其视为潜在的 IV。其次，为了保障每个 SNP 的独立性，我们根据连锁不平衡（Linkage disequilibrium, LD）的条件（r2=0.001，kb=10000）来筛选符合条件的 SNP。随后，从胃癌 GWAS（bbj-a-119）汇总数据中提取与上述肠道菌群相关的 SNP 信息，并剔除缺失的数据和弱工具变量。随后使用逆方差加权法、加权中位数法、MR-Egger 回归分析法等评估肠道菌群与胃癌的因果关系，评估肠道菌群中是否存在胃癌发生的风险因素。为了评估潜在的异质性和多效性是否对结果有显著影响，进行了敏感性分析。Cochran's Q 检验被用于评估工具变量的异质性（P＞0.05）。使用 MR-Egger 回归、多效性残差和离群值（MR pleiotropy residual sum and outlier, MR-PRESSO）检验来评估水平多效性（P＞0.05）。所有 MR 分析均使用 R 软件（版本 4.3）通过“Two Sample MR ”进行，结果均以 OR 及 95% CI 表示，P＜0.05 为差异有统计学意义。

结果：IVW 分析结果表明 LachnospiraceaeNC2004group（OR=0.817，95% CI 0.699−0.957，P=0.012）、Clostridiumsensustricto1（OR=0.462，95% CI 0.247−0.864，P=0.016）、Prevotella7（OR=0.883，95% CI 0.802−0.972，P=0.011）、Anaerostipes（OR=1.265，95% CI 1.012−1.582，

P=0.039）与胃癌相关。敏感性分析显示可以剔除异质性和水平多效性对因果效应产生的影响。

结论：肠道菌群与胃癌之间存在因果关系。MR 分析显示 LachnospiraceaeNC2004group、Clostridiumsensustricto1、Prevotella7 与胃癌呈负向因果效应，是保护因素，Anaerostipes 与胃癌呈正向因果效应，是危险因素。

关键字 ：孟德尔随机化、胃癌、肠道菌群

496. SARI 过表达对 CNE2 鼻咽癌细胞生物学活性的影响及其机制研究

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目的：构建 SARI 基因过表达真核表达载体并完成鉴定。研究 SARI 基因过表达对 CNE2 鼻咽癌细胞的生物学特性的影响并初步探讨相关分子机制。

方法：钓取并克隆 SARI 基因的全长 cDNA 序列，纯化后用 Bgl II 和 Xba I 进行双酶切消化，经 T4 DNA 连接酶作用，连接至 pDsRed2-C-RFP 真核表达载体，连接产物经转化、挑取克隆、扩增培养后，提取小量质粒，进行 DNA 测序鉴定，并用 Bgl II 和 Xba I 内切酶消化酶消化连接产物，琼脂糖凝胶电泳鉴定。重组质粒转染 SARI 阴性表达的 CNE2 细胞，荧光显微镜观察 SARI-RFP 融合蛋白的表达。Western blot 检测转染后 SARI-RFP 融合蛋白的表达。pDsRed2-SARI-RFP 真核表达载体转染至 CNE2 细胞，通过 CCK-8 比色绘制生长曲线、Transwell 小室侵袭实验、划痕修复实验、Caspase-3 活性检测、DNA 片段电泳检测等实验，探讨 SARI 过表达对 CNE2 鼻咽癌细胞生长增殖、凋亡等生物学特性的影响。Western blot 检测内源性线粒体凋亡途径相关蛋白的表达变化，探讨 SARI 过表达对 CNE2 细胞增殖、凋亡影响的分子机制。

结果：DNA 测序结果表明，SARI 全长 cDNA 序列已正确连接至 pDsRed2-C-RFP 载体。双酶切鉴定结果显示，pDsRed2-SARI-RFP 真核表达载体的构建成功。重组质粒转染至 CNE2 细胞后可表达 SARI-RFP 融合蛋白。CCK-8 比色、Transwell 小室侵袭、划痕修复实验结果显示 SARI 过表达组细胞生长增殖、侵袭迁移能力显著低于空载体对照组和空白对照组（$P<0.05$）；Caspase-3 活性及 DNA 梯状电泳结果显示，SARI 过表达诱导 CNE2 细胞产生凋

亡，明显高于空载体对照组和空白对照组（P＜0.05）。Western blot 检测显示 SARI 过表达组 CNE2 细胞较空载体对照组和空白对照组 Bcl-2 表达下调，Bax、Cytochrome C 表达上调，同时伴有凋亡途径相关蛋白 Caspase-3 和 Caspase-9 剪接激活以及 PARP 的表达上调。

结论：成功构建 pDsRed2-SARI-RFP 真核表达载体； SARI 过表达可明显抑制鼻咽癌 CNE2 细胞增殖和侵袭迁移能力，诱导细胞凋亡； SARI 可能通过激活线粒体内源性凋亡途径诱导 CNE2 鼻咽癌细胞凋亡，发挥抑癌作用。

关键字： 鼻咽癌；CNE2；SARI；过表达；凋亡；分子机制

497. 降钙素原在非霍奇金淋巴瘤患者伴感染中的诊断价值

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目的：分析降钙素原(Procalcitonin，PCT)在非霍奇金淋巴瘤（NHL）患者中的影响因素、评估感染诊断价值，探讨其在临床中的合理应用。

方法：收集 2017 年 1 月 1 日至 2020 年 12 月 31 日入住福建省肿瘤医院 736 例 NHL 患者病例，根据临床特点划分感染组与非感染组，并对两组患者的血清 PCT 水平进行比较；分析 NHL 非感染组基础血清 PCT 水平与肿瘤病理分型、肿瘤分期、肿瘤进程以及中性粒细胞数等影响因素，并进行多因素及独立影响因素分析；分析 80 例 NHL 患者在基础状态、感染状态、有效抗感染治疗后的三个阶段血清 PCT 检测值；分析感染组血清 PCT 水平与感染部位和致病菌类型之间关系。

结果：血清 PCT 水平在组织病理学类型、IPI 评分（0-2 与 3-4 分）、肿瘤分期、肿瘤进展和性别等方面有明显差异（P<0.05），与患者年龄无显著性差异（P>0.05），肿瘤转移和肿瘤进展是非感染 NHL 患者血清 PCT 水平升高的独立影响因素。I-III 与 IV 期比较，血清 PCT 诊断肿瘤 IV 期转移的 ROC 曲线下面积为 0.6532，最佳临界值为 0.065ng/mL，敏感度、特异性分别为 61.1%、59.9%，阳性预测值、阴性预测值分别为 56.3%、64.6%。血清 PCT 诊断感染 ROC 曲线下面积为 0.7885，最佳临界值为 0.120ng/mL，敏感度、特异性分别为 54.9%、89%，阳性预测值、阴性预测值分别为 65.6%、83.8%；在 80 例 NHL 患者中，其基础值、抗感染有效治疗后与感染阶段比较，血清 PCT 水平统计学均具有显著差异（P<0.001）。血清 PCT 水平在血流感染和局部感染之间统计学有显著差异（P<0.001）；

在血流感染中血清 PCT 水平在 G+和 G-之间统计学存在差异（P=0.012，<0.05），凝固酶阴性葡萄球菌（coagulase-negative staphylococcus，CNS）血流感染组与污染组的血清 PCT 水平差异具有统计学意义（P=0.007，<0.05），诊断 CNS 感染的 ROC 曲线下面积为 0.7143，最佳临界值为 0.165ng/mL，患者 PCT 诊断指标敏感度、特异性、阳性预测值、阴性预测值分别为 60%、85.71%、75%、60%。

结论：血清 PCT 水平有望作为诊断 NHL 患者是否转移的参考指标；可作为 NHL 伴感染诊断和抗感染治疗监测指标，诊断感染 cut-off 值为 0.12ng/mL；同时对区分 NHL 患者血流感染与局部感染、区分血流感染 G+与 G-菌、血浆 CNS 血流感染与污染具有一定价值；建议 NHL 患者入院进行常规 PCT 检查，建立患者的 PCT 基础值，作为后续感染诊断对照。

关键字： 降钙素原；非霍奇金淋巴瘤；影响因素；感染

498. 鼻咽癌患者血浆外泌体 miR-BART 水平与临床转移之间的关系

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目的：检测鼻咽癌患者血浆外泌体中 miR-BART 的含量，分析和鼻咽癌 miR-BART 的表达和患者临床病理参数之间的相关性，探讨它在 NPC 侵袭转移过程中的作用。

方法：收集 24 对鼻咽癌患者的配对血浆（治疗前和发生转移时总共 48 份血浆）和 12 名健康人的血浆，通过 exoRNeasy 血清/血浆 Maxi 试剂盒对鼻咽癌患者血浆中外泌体和外泌体中总 RNA 的提取。再通过 TaqMan MicroRNA 逆转录试剂盒进行多重 RT-PCR 完成 60 份标本的 miR-BART3、miR-BART7 和 miR-BART13 的检测。用 SPASS13.0 进行数据分析，探讨鼻咽癌患者血浆外泌体中 miR-BART 的表达水平与鼻咽癌临床病理参数(年龄、远处转移和临床分期)之间和复发转移的关系。

结果：血浆外泌体中的 miR-BART3 和 miR-BART7 对鼻咽癌有诊断意义，诊断的准确率为 0.794 和 0.817（95%置信区间分别为：0.641-0.946 和 0.671-0.964）；血浆外泌体中的 miR-BART13 在 NPC 组合健康对照组间不存在相关性。不同性别血浆外泌体中的 miR-BART3、miR-BART7、miR-BART13 表达量无差别；血浆外泌体中的 BART7、BART13 表达水平与年龄不存在相关性，但年龄大于 50 岁患者血浆外泌体中的 BART3 呈现高表达；

BART7 与 T 分期、N 分期、临床分期均无相关性；而 BART13 与 T 分期、N 分期及临床分期都存在相关性，但由于其表达量很低，因此无意义；BART3 则与 N 分期存在较强相关性，但是随着 N 分期越晚，miR-BART3 表达量增加。

结论：miR-BART3 和 miR-BART7 对鼻咽癌有诊断意义，诊断的准确率分别为 0.794 和 0.817；转移前后的 miR-BART3 表达量有较大差别，但二者在统计学上的差异并不十分显著；miR-BART3 在 50 岁以上的鼻咽癌患者中高表达，且二者存在相关性；miR-BART3 则与 N 分期存在较强相关性，随着 N 分期越晚，miR-BART3 表达量增加。

关键字： 鼻咽癌；血浆外泌体；miR-BART；转移

499. 乳酸脱氢酶 C4 在肺腺癌中的表达及意义

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目的 探讨 LDH-C4（lactate dehydrogenase C4）在肺腺癌中的表达及其与患者预后的关系。

方法 基于高通量肺腺癌组织芯片 HLugA180Su05，通过免疫组化技术检测 92 例肺腺癌患者癌组织及对应癌旁组织中 LDH-C4 蛋白的表达水平，分析 LDH-C4 蛋白在肺腺癌中的表达量及其与临床病理特征和预后的关系。

结果 LDH-C4 在癌组织中阳性表达率为 96.7%（89/92），明显高于癌旁组织 22.6%（19/84）（P<0.001），癌组织中 LDH-C4 阳性表达与患者年龄、性别、肿瘤大小、淋巴结转移、临床分期、表皮生长因子受体基因（EGFR）突变无关（均 P>0.05）。LDH-C4 高表达组患者中位生存时间（OS）为（35 个月），显著低于低表达组（62 个月）（P<0.05）；LDH-C4 高表达组患者 5 年生存率为（24.0%）显著低于低表达组（53.3%），进一步 COX 多因素回归分析显示 LDH-C4 高表达是肺腺癌患者总 OS 的独立因素，LDH-C4 高表达是低表达患者死亡风险的 3.619 倍。

结论 LDH-C4 在肺腺癌中的表达水平升高，LDH-C4 高表达肺腺患者的预后负相关，可成为肺腺患者潜在的治疗靶点。

关键字： 肺腺癌；LDH-C4；预后

500. 乳腺癌合并甲状腺癌患者的临床病理特征分析

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福建省肿瘤医院

目的：通过分析乳腺癌合并甲状腺癌的临床病理特征，探讨甲状腺癌、甲状腺激素功能及甲状腺相关抗原抗体在乳腺癌发生发展的作用。

方法：回顾性分析福建省肿瘤医院 2001 年 1 月-2017 年 12 月期间收治的乳腺癌合并甲状腺癌患者 76 例（合并癌组），并随机收集同期收治的单纯乳腺癌患者（对照组）116 例，同时收集患者治疗前甲状腺激素（T3、T4、FT3、FT4、TSH）、甲状腺自身抗原和抗体（TG 、TPOAb、TGAb)、临床病理（TNM 分期、临床分期、淋巴转移、原发结节大小）和乳腺癌免疫组化指标（ER、PR、HER-2、Ki-67）等；通过 SPSS 25.0 软件统计分析合并癌组和对照组各临床病理和免疫组化指标，进一步探讨甲状腺癌在乳腺癌发生发展中的作用。

结果：合并癌组的淋巴受累率高于对照组（60.9% VS 37.7%），具有统计学差异（p＜0.05）；甲状腺的功能状态：合并癌组与对照组 T3（1.74 VS 1.68）和 TSH（2.19 VS 10.27）具有统计学差异（p＜0.05）；甲状腺相关抗原抗体：合并癌组与对照组 TPOAb（3.693 VS 12.3)和 TG（10.71 VS 2.77）的表达水平具有统计学差异（p＜0.05）；其它病理特征：合并癌组与对照组在 ER、PR、HER-2、Ki-67 和 TNM 分期等免疫组化和病理特征上不具有统计学意义（p＞0.05）。

结论：乳腺癌合并甲状腺癌组的淋巴受累率明显高于对照组（60.9% VS 37.7%）；同时发现乳腺癌合并甲状腺癌组 T3 和 TG 表达水平高于对照组，TSH 和 TPOAb 表达水平低于对照组，提示甲状腺癌在乳腺癌的发生发展中起作用，其机制可能与 T3 和 TG 的升高和 TSH 和 TPOAb 降低有关。

关键词：乳腺癌；甲状腺癌；甲状腺激素

501. 乳酸脱氢酶 C4 在肝癌中的表达及其生物学功能研究

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目的：通过分析乳酸脱氢酶 C4(LDH-C4)在(HCC)中的表达及其与 HCC 患者的临床病理特征及其预后的关系,明确 LDH-C4 过表达对 HCC 细胞 Bel-7402 的细胞生物学行为能力的影响，并探讨相关分子机制。

方法：基于高通量肝癌组织芯片，采用免疫组化染色技术检测 HCC 癌组织中 LDH-C4 蛋白的表达水平，分析 LDH-C4 表达情况与肝癌患者临床病理特征的关系。荧光显微镜观察 GV492-LDHC 病毒感染后的 Bel-7402HCC 细胞中 EGFP 表达情况，筛选 LDH-C4 表达呈阳性的细胞系。通过 RT-qPCR 鉴定 LDH-C4 mRNA 过表达的效果。通过 CCK-8 实验、划痕修复实验及 Transwell 小室等实验分别检测 LDH-C4 对 HCC 细胞 Bel-7402 在体外的增殖、迁移及侵袭能力的影响。基于建立的 LDH-C4 稳定过表达的 Bel-7402 细胞系基础上，对各组细胞中乳酸、丙酮酸等细胞能量代谢产物含量进行检测，同时检测各组肿瘤细胞中葡萄糖消耗水平，探究 LDH-C4 过表达对 Bel-7402HCC 细胞能量代谢的影响；通过 Western blot 实验检测 AKT/mTOR 信号通路中相关蛋白表达水平受 LDH-C4 过表达的影响。

结果：HCC 中的 LDH-C4 呈现高表达状态，主要表达于 HCC 细胞的细胞质中，且 LDH-C4 的表达水平与 HCC 患者的 T 分期、临床分期及瘤体大小明显相关（$P<0.05$）；生存分析结果提示：LDH-C4 高表达患者的预后较低表达者更差（$P<0.05$）。CCK-8 实验、划痕修复实验及 Transwell 小室实验检测结果提示：LDH-C4 过表达可提升 Bel-7402HCC 细胞在体外的迁移侵袭能力，但对生长增殖无明显影响。3.能量代谢实验结果显示：Bel-7402 细胞中 LDH-C4 过表达可提高乳酸产生含量，降低丙酮酸含量，提高细胞对葡萄糖的利用；Western blot 结果提示：过表达 LDH-C4 可上调 AKT/mTOR 信号通路中 AKT 蛋白及 mTOR 蛋白的表达。

结论：HCC 组织中 LDH-C4 呈现较高表达状态，与 HCC 患者的肿瘤大小、T 分期以及临床分期呈现明显正相关；LDH-C4 可作为 HCC 患者预后监测的一项重要参考指标。Bel-7402HCC 细胞中 LDH-C4 过表达可促进该细胞在体外的迁移和侵袭能力,促进 Bel-7402HCC 细胞的能量代谢水平，可能与 AKT/mTOR 信号通路的激活有关。

关键字： 乳酸脱氢酶 C4, HCC, 增殖, 迁移, 侵袭, 机制

502. 乳酸脱氢酶 C4 在骨肉瘤中的表达与生物学功能研究

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目的：通过分析乳酸脱氢酶 C4（LDH-C4）在骨肉瘤（OS）组织中的表达情况，探讨其表达水平与骨肉瘤患者临床病理资料之间的相关性，明确 LDH-C4 表达上调后对骨肉瘤细胞 MG63 生物学行为能力的影响及相关分子机制。

方法：采用免疫组织化学染色方法对高通量骨肉瘤组织芯片进行检测，分析骨肉瘤组织中 LDH-C4 蛋白的表达水平与骨肉瘤患者临床病理特征的相关性。构建 LDHC 慢病毒过表达载体并感染骨肉瘤细胞 MG63，采用不同感染复数（MOI）和嘌呤霉素浓度筛选稳定感染的 MG63 细胞系。采用 RT-PCR 方法检测各组骨肉瘤细胞蛋白和 LDHC mRNA 表达情况。通过 CCK-8 实验、平板克隆形成实验、划痕修复实验以及 Transwell 细胞迁移、侵袭实验，检测上调 LDH-C4 后对骨肉瘤细胞 MG63 增殖和迁移侵袭等能力的影响。通过比色法检测乳酸和丙酮酸表达水平,葡萄糖氧化酶法检测葡萄糖消耗量。通过 Western blot，分析 LDH-C4 过表达对 AKT/mTOR 信号转导通路相关蛋白表达的影响。

结果： LDH-C4 蛋白主要表达于骨肉瘤细胞的细胞质中，软骨肉瘤表达在细胞核中，低表达/阴性表达占 54.29%（38/70），相关性分析结果显示，在骨肉瘤患者中临床分期和肿块直径与 LDH-C4 的表达水平呈负相关关系（P<0.05）。过表达 LDH-C4 在 CCK-8 实验、平板克隆实验、细胞划痕实验和 Transwell 小室迁移侵袭实验显示感染组 MG63 细胞的增殖能力、克隆能力、迁移能力和侵袭能力可被明显抑制。3.能量代谢实验结果显示感染组骨肉瘤细胞 MG63 葡萄糖摄取率降低，乳酸生成减少，丙酮酸生成增多。Western blot 实验发现过表达 LDH-C4 后，下调了感染组 PI3K、AKT、mTOR 蛋白表达，HIF-1a 蛋白无明显变化。

结论：在骨肉瘤组织中 LDH-C4 为中低表达状态，并与骨肉瘤患者临床分期及瘤体直径相关。上调 LDH-C4 可明显降低 MG63 骨肉瘤细胞体外的生长增殖、克隆形成以及侵袭和迁移能力。LDHC 过表达抑制细胞正常氧化耗能，通过抑制糖酵解和负向调控 PI3K/AKT/mTOR 信号通路发挥其生物学功能。

关键字： 骨肉瘤；乳酸脱氢酶 C4；过表达；分子机制

503. 乳酸脱氢酶 C4 在乳腺癌中的表达及临床意义

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目的：检测 LDH-C4 在乳腺癌中的表达，明确其表达阳性率，分析 LDH-C4 表达与乳腺癌临床病理特征和预后的关系。

方法：基于高通量乳腺癌组织芯片 HBre-Duc140Su02，通过免疫组化技术检测 LDH-C4 蛋白在乳腺癌细胞中的表达水平。基于 HBreD145Su02 高通量组织芯片已建立的临床资料和随访数据库，分析 LDH-C4 表达与肿瘤组织分化程度、淋巴结转移、肿瘤大小、临床分期等临床病理特征的关系，应用 Kaplan–Meier 法绘制生存曲线，估计生存率，分析 LDH-C4 表达与乳腺癌预后的关系。采用 COX 比例风险模型进行多因素风险分析。

结果：LDH-C4 在乳腺癌细胞中的表达率为 91.5%，其阳性表达与患者年龄、肿瘤大小、临床分期、病理分级、淋巴结是否转移均无关（P 均>0.05），LDH-C4 阳性患者的十年生存率显著低于 LDH-C4 阴性表达患者（P<0.05）。

结论：LDH-C4 表达与乳腺癌预后相关，可作为乳腺癌预后判断的一项重要指标。

关键字： 乳酸脱氢酶 C4；乳腺癌；预后

504. 乳酸脱氢酶 C4 在乳腺癌中的表达及其对乳腺癌细胞生物学功能的影响

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目的：研究乳酸脱氢酶 C4（LDH-C4）在乳腺癌组织中的表达，探讨 LDH-C4 对乳腺癌预后判断的价值；探讨 LDH-C4 表达上调对 MCF-7 乳腺癌细胞中的生物学影响及分子机制。

方法：通过免疫组织化学分析 158 例乳腺癌石蜡组织中 LDH-C4 蛋白在的表达情况。分析乳腺癌不同临床病理参数与 LDH-C4 蛋白表达的相关性。对随访资料进行 Cox 回归模型，研究 LDH-C4 蛋白在乳腺癌预后判断的临床价值。通过慢病毒载体将外源 LDHC 基因导入 MCF-7 乳腺癌细胞中，通过稀释法结合绿荧光蛋白表达筛选 LDH-C4 阳性表达的单克隆细胞系。通过平板克隆、CCK-8 细胞增殖、细胞划痕、Transwell 小室等细胞生物学实验，

研究 LDH-C4 表达上调对 MCF-7 细胞生物学行为的影响；Western blot 法检测 PI3K/AKT/mTOR 信号通路相关分子，探讨 LDHC 基因上调对乳腺癌 MCF-7 细胞生物学影响的可能机制。

结果： 158 例乳腺癌石蜡组织切片免疫组化染色，LDH-C4 蛋白染色集中在细胞质中，呈淡棕色到深棕色，阳性率为 91.8%（145/158），其中低表达（-/+）和高表达（++/+++）分别为 41.8%（66/158）、58.2%（92/158）。经卡方检验，乳腺癌临床分期晚、腋窝淋巴结转移率高，患病年龄低者 LDH-C4 呈高表达（P<0.05）；Kaplan-Meier 法进行生存分析并经 Log-rank 检验结果显示，乳腺癌 LDH-C4 高表达者预后差（P=0.035）；Cox 回归分析显示临床分期（P=0.000）和 LDH-C4 表达水平（P=0.002）是乳腺癌预后的独立因素。2. 通过慢病毒感染成功筛选 LDH-C4 过表达的单克隆化的乳腺癌 MCF-7 细胞系；细胞学实验结果显示，LDH-C4 蛋白过表达可增强乳腺癌 MCF-7 侵袭和迁移能力，而对细胞生长增殖无显著影响；免疫印迹法初步显示，过表达 LDH-C4 蛋白可上调乳腺癌 MCF-7 细胞中 AKT 和 mTOR 蛋白的表达。

关键字： 乳腺癌，LDH-C4，预后，MCF-7

505. A specific enterotype derived from gut microbiome of the elderly enables favorable responses to immune checkpoint blockade therapy

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Purpose: This study aims to unravel the phenomenon of enhanced immunotherapy sensitivity observed in elderly cancer patients and to elucidate the underlying mechanisms, specifically focusing on age-related immune changes and gut microbiota composition. The goal is to provide insights that could contribute to tailoring cancer immunotherapy strategies based on individualized factors.

Methodology: A comprehensive meta-analysis was conducted, incorporating data from 25 small-to-mid-sized trials (total n = 4464) of immune checkpoint blockade (ICB). The focus was on understanding the efficacy of ICB in elderly cancer patients, considering variations in response compared to younger counterparts. To delve into the tumor microenvironment (TME) of elderly patients, single-cell RNA-seq data from multiple studies (n = 187) were reanalyzed. The emphasis was on identifying specific markers related to exhausted and cytotoxic T cells within the TME, aiming to correlate these markers with enhanced ICB responsiveness in older individuals. To recognize the potential role of gut microbiota in modulating immunotherapy efficacy, metagenomics analysis was performed on samples from 782 cancer patients. The study identified an aging-enriched enterotype (E/AE) associated with improved ICB outcomes in older patients. Experimental interventions, particularly Fecal Microbiota Transplantation (FMT), were explored to manipulate gut microbiota composition. FMT experiments in mice were conducted to confirm the therapeutic potential of the identified E/AE enterotype, assessing its impact on anti-PD-1 sensitivity and TME reshaping.

Results: The meta-analysis of clinical data revealed heightened immunotherapy sensitivity in elderly cancer patients. This contradicts inconclusive findings from previous studies and highlights the need to delve into the mechanisms underlying this phenomenon. Reanalysis of single-cell RNA-seq data uncovered distinct upregulation of exhausted and cytotoxic T cell markers within the TME of elderly patients. This correlation suggested a potential link between these immune cell alterations and the enhanced responsiveness to ICB therapy observed in older individuals. Metagenomics analysis identified an aging-enriched enterotype (E/AE) associated with improved ICB outcomes. This suggested a potential role of gut microbiota composition in modulating immunotherapy efficacy, particularly in the elderly population. FMT experiments in mice confirmed the therapeutic potential of the E/AE enterotype. The experiments demonstrated enhanced anti-PD-1 sensitivity and reshaping of the TME, emphasizing the impact of gut microbiota on immunotherapy outcomes.

Conclusion: This study provides a comprehensive exploration of enhanced immunotherapy sensitivity in elderly cancer patients. The integration of clinical data, TME analysis, and gut microbiota profiling reveals a multifaceted relationship between age-related immune changes and treatment outcomes. The identification of an aging-enriched enterotype associated with improved

ICB responsiveness suggests a potential avenue for tailoring immunotherapy strategies based on individual gut microbiome profiles. FMT experiments further validate the therapeutic potential of the identified enterotype, emphasizing the importance of considering age-related immune alterations and gut microbiota composition in personalized cancer immunotherapy approaches. These findings offer encouraging paths for refining and optimizing immunotherapy strategies to improve outcomes for cancer patients, especially in the context of an aging population.

Key Words： Immunotherapy, Aging, Gut microbiota, Enterotype, Tumor microenvironment, Personalized therapy

506. 早期肺癌无创甲基化检测试剂的研发与转化

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研究目的：肺癌是我国及世界上最常见的恶性肿瘤。我国每年肺癌诊断病人近 80 万，其 5 年生存率不到 20%。肺癌中以非小细胞肺癌最常见，约占 80%左右，主要组织类型有肺鳞癌及肺腺癌。影像检查是目前肺癌诊断的重要手段。早期无创检测目前起有限的辅助作用。用于小细胞肺癌诊断的肿瘤标记物，包括神经特异性烯醇化酶(NSE)、铃蟾肽(BN)、肌酸磷酸同工酶(CPK-BB)、胃泌泰(GRPC)等；用于非小细胞肺癌诊断的肿瘤标记物，包括组织多肽抗原(TPA)、癌胚抗原(CEA)、鳞癌抗原(SCC)、细胞角蛋白 19 片段(CYFRA21-1)。这些蛋白标志物的特异性与灵敏度均达不到早期检测目的。

DNA 甲基化是 DNA 表观遗传的一种修饰手段，起到对基因表达调节作用。基因启动子前后的 DNA 序列含有基因表达的正向与负向调节单元，一般来说，功能单元序列的甲基化对原始功能单元的功能起抑制作用。而对肿瘤发生发展起重要作用的基因包括癌基因（促进肿瘤细胞生长）、抑癌基因（抑制肿瘤细胞生长）、生长促进基因及免疫调节基因等。基因甲基化检测已经越来越多地被用于肿瘤的早期诊断。一般来说，特异性与灵敏度明显高于蛋白标志物可以更早期检测到肿瘤的存在。

目前检验甲基化检测的常用手段是样本 DNA 先进行亚硫酸盐处理。这样未甲基化的 C 就转化为 U，PCR 扩增时 U 同 T 与 A 配对，而甲基化的 C 不被转化，在 PCR 扩增时依然是 C 与 G 配对。根据这种差别，通过对转化后的 DNA 进行扩增，可以得出样本 DNA 某个

位点的甲基化程度。目前标准的亚硫酸盐处理时间比较长，需要 3～4 小时才能完成，加上核酸提取及 PCR 扩增，整个甲基化检测一般需要 1 天半的检测周期，而临床及实验室期望这样一个以 PCR 为基础的甲基化检测能够在半天内完成。这也是该项目的立项出发点。除了耗时耗力之外，亚硫酸盐处理法还有如下缺陷：转化百分率不是百分之百，未被甲基化的 C 会被误读为甲基化；可能会发生非正常转化，使得甲基化的 C 直接转变成 T，而被误认为没有甲基化；转化过程中 DNA 断裂、降解、碎片化，损失了绝大部分，相对提高了样本量要求；转化后的序列常常有大片段 T 序列，影响引物探针设计。同时，由于扩增是针对特定位点，勉强设计出的引物探针质量不高，可能影响其检测特异性与灵敏度；大量 T 序列的存在，在生信分析过程中会被误读为测序质量问题，从而降低了测序的有效数据量。

克服亚硫酸盐处理方法的上述缺陷也就成了该项目的立项出发点。本项目的目标是通过建立一种快速的非亚硫酸盐转化法甲基化检测方法，利用无创液体活检的方法，在外周血游离 DNA 中找到可以在肺癌早期鉴别于非肿瘤病人的甲基化位点，研发出无创早期肺癌甲基化检测试剂盒，最后产业化。肺癌是国内及世界上最常见的恶性肿瘤，目前缺乏有效的无创早期检测手段。本项目的研发具有重大的社会及经济意义。

材料与方法：（1）设计重组人甲基化结合蛋白：本项目设计高选择性选用特定的人甲基化基因结合蛋白的核心结合区域，采用蛋白 linker 将多个结合单元并行联合，重组表达。（2）建立并验证甲基化结合蛋白富集甲基化 DNA 的方法：本阶段主要采用人细胞株基因组 DNA（gDNA）进行实验，包括肿瘤细胞株的高甲基化基因位点及相对正常的对应位点，相对低甲基化的对照细胞株，将高甲基化 gDNA 与低甲基化 gDNA 配比成不同比例甲基化水平的 gDNA 组，然后以标准的亚硫酸盐试剂盒处理，以及用甲基化结合蛋白富集，对应的进行下游的 PCR 定量，以亚硫酸盐转化法甲基化百分比总体偏差最小为目标进行程序优化。（3）建立并验证快速甲基化 PCR 扩增方法。（4）筛选高质量的针对肺癌差异化的甲基化位点：本阶段采用上述建立的甲基化结合蛋白富集方法，对 25 例早期肺癌病人（病理确诊）及 20 例非肿瘤对照组病人的血浆样本进行富集，富集后的样本进行建库、高通量测序及生信分析，分析人基因组近 50 万个 CpG 位点的 reads 数，从而筛选出早期肺癌特异性的 4～8 个高质量甲基化位点。（5）用较大临床样本验证并进一步筛选针对肺癌差异化的甲基化高质量位点： 本阶段重点通过检测较大量临床样本，根据检测特异性与灵敏度进一步验证并筛选出 3～6 个甲基化位点。（6）中试转产甲基化 PCR 检测试剂盒，并用临床样本系统验证产品性能。

结果：（1）成功构建并表达了人甲基化结合蛋白。（2）成功建立并验证甲基化结合蛋白富集甲基化 DNA 的方法。（3）成功建立并验证快速甲基化 PCR 扩增方法。（4）成功筛选出高质量的肺癌特异性甲基化位点组合，并通过临床样本验证，确认其在早期肺癌无创检测中的高特异性及高灵敏度。

结论：（1）成功建立并验证了快速的非亚硫酸盐转化法甲基化检测方法。（2）成功筛选出人肺癌特异性的差异化甲基化位点。（3）开发并验证用于早期肺癌检测的快速无创甲基化检测试剂盒。

关键字： 肺癌；非亚硫酸盐转化法；甲基化 DNA；

507. CAP1/RRM2 通过影响巨噬细胞 M2 型极化从而抑制 CRC 增殖与迁移

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摘要 结直肠癌（CRC）是胃肠道中常见的恶性肿瘤，9.4%的癌症相关死亡是由 CRC 引起的。因此，深入研究结直肠癌的发生发展及侵袭转移的机制，探索新的、有效的治疗靶点具有重要的意义。腺苷酸化酶相关蛋白 1（CAP1, Adenylate cyclase-associated protein 1）是一种重要的蛋白质，在细胞生物学中发挥着多种关键作用，包括细胞骨架重塑、细胞迁移和信号传导等。CAP1 在 CRC 中的功能机制尚不清楚，本课题将对 CAP1 在 CRC 中的生物学功能展开研究。

研究目的：研究结直肠癌中 CAP1 的生物学功能及其分子机制。材料与方法：（1）通过 TCGA 数据库明确了 CAP1 在结直肠癌中的表达差异与结直肠癌患者存活率的关系；并构建 CAP1 敲低的稳转细胞系。（2）通过 CCK8、Transwell 与划痕实验研究了 CAP1 在结直肠癌细胞系 MC38 功能的影响；并利用 C57 小鼠腹腔成瘤、皮下成瘤及尾静脉注射验证了动物表型。（3）采用 C57 小鼠腹腔注射造模、上清培养及 Transwell 共培养，利用流式验证巨噬细胞极化。(4)通过蛋白组学测序寻找影响巨噬细胞极化的分子机制；通过 q-PCR、

Western blot 与 ELISA 检测 RRM2 的表达变化。(5)使用 RRM2 重组蛋白刺激巨噬细胞 48h，通过流式细胞术检测巨噬细胞极化。

研究结果：（1）TCGA 差异分析结果表明 CAP1 在结直肠癌中表达降低，生存分析结果表明在结直肠癌患者中 CAP1 低表达显著降低患者生存率。（2）细胞学功能实验结果表明，CAP1 抑制结直肠癌细胞的迁移并不影响增殖；C57 小鼠造模实验结果表明 CAP1 抑制结直肠癌的增殖与迁移。(3)附睾脂肪检测、上清液培养及 Transwell 共培养结果表明 CAP1 在体内外均影响巨噬细胞 M2 型极化。（4）Western blot 与 ELISA 实验结果表明 RRM2 在 CAP1 敲低细胞系中显著升高，而 mRNA 无变化。（5）RRM2 重组蛋白刺激巨噬细胞流式实验结果表明 RRM2 直接影响巨噬细胞 M2 型极化。

研究结论：本研究揭示了 CAP1-RRM2 轴在结直肠癌增殖和迁移中的关键作用，特别是通过抑制巨噬细胞向 M2 型极化来促进 CRC 的进展。这些发现为结直肠癌的治疗提供了新的靶点，提示 CAP1 和 RRM2 可能作为预防或治疗 CRC 的潜在靶标。

关键字： CRC；CAP1；巨噬细胞；M2 型极化；RRM2

508. 肿瘤相关真菌及其与肠道真菌在癌变和肿瘤微环境中的串扰

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Abstract

大多数描述健康和疾病状态下的人类肠道微生物群的研究都强调了细菌成分，但人们对于真菌组学的研究较少，落后于我们对细菌微生物组的理解。近年来随着检测技术的发展，对真菌的研究也是从无到有。共生真菌在健康和疾病中的影响越来越明显，并调节宿主体内的各种生理功能。真菌在免疫功能低下的患者中导致高发病率和死亡率，甚至可能会危及生命。除了细菌的生态失调外，真菌群落（“真菌组”）的改变也很重要，与许多疾病有关，包括炎症性肠病、哮喘、精神疾病和各种癌症。在研究癌症时，真菌，就像病毒和细菌一样，应该被考虑在内。在这篇综述中，我们讨论了肠道真菌和肿瘤周围真菌在肿瘤发生、发展、药物治疗等方面的作用。我们提供了真菌生物群的特异性成员参与肠道疾病的证据，包括炎症性肠病、结肠直肠癌和胰腺癌以及非肠道疾病肺癌、肝癌等；此外我们还讨论了真菌在肿瘤微环境中的作用机制。我们还探索了真菌与细菌的相互作用对肿瘤发生发展的影响，可能会用于癌症的诊断和治疗。

关键字： 肿瘤，真菌，肠道微生物

509. PD-1 抗体联合化疗一线治疗晚期胃癌临床疗效及 MicroRNA 表达情况

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目的：胃癌是消化道常见的恶性肿瘤，其恶性程度高，随着美国食品和药物管理局(FDA)批准的一系列实体肿瘤的标准治疗方法。临床试验表明，晚期胃癌患者可以从 PD-1/PD-L1 抗体治疗中获益，本文通过回顾性观察及分析 PD-1 抗体联合化疗对比单纯化疗在晚期胃癌一线治疗的临床疗效的疗效相关因素及 MicroRNA 表达情况变化。

方法：收集包头市肿瘤医院 2020 年 6 月-2022 年 6 月收治的晚期胃癌共 78 例，其中用一线化学治疗 XELOX 或 SOX 方案的晚期胃癌患者 40 例为化疗组；接受一线联合治疗在化疗组基础加用 PD-1 抑制剂的患者 38 例设置为联合组。两组的基线特征具有可比性，评估

及分析两组的临床疗效、临床疗效的影响因素、不良反应率。应用 SPSS 22.0 统计学软件进行数据分析。计数资料以频数和率表示，组间比较采用 Fisher 确切概率法；采用 Kaplan-Meier 法比较两组患者生存期。P＜0.05 为差异有统计学意义。应用 miRNA-seq 技术筛选疗效较好患者外泌体中共同差异表达 MicroRNA 对其靶基因进行生信分析。

结果：两组患者中，其中联合组临床有效率为 25/38,疾病控制率为 30/38;化疗组的临床有效率为 22/40,疾病控制率为 26/40;两组比较差异均具有统计学意义（P<0.05）；两组的中位缓解时间分别是 11.5 个月和 7.5 个月，差异有统计学意义；不良反应中联合组及化疗组三度以上不良反应发生率分别为 4/38 和 4/40,差异无统计学意义（P>0.05）;三度以上免疫治疗相关不良反应发生率为 2/38。与化疗组相比，PD-1 抗体联合化疗具有高于单纯化疗组的临床疗效，缓解深度较好，不良反应较少，安全性可控。影响因素中：HP+、营养状况好、年龄较低者从观察组中获益更多。接受 PD-1 免疫检查点抑制剂治疗后 MicroRNA 发生明显差异性改变，不同 MicroRNA 表达出现明显上调或下降。

结论：PD-1 抗体联合化疗在晚期或转移性胃癌中表现出良好的生存结局和可管理的安全性，较单纯化疗具有较好的缓解率，不良反应发生率少。在临床治疗中，免疫治疗应是晚期胃癌治疗策略中不可缺少的选择，但免疫治疗影响因素较多，需个体化治疗。同时筛选出了影响胃癌治疗的关键 MicroRNA，并对进行了全面的基因功能和通路富集分析，为利用外泌体 MicroRNA 对胃癌患者接受免疫治疗疗效及其预后情况评估进行了初步探索。

关键字： 晚期胃癌；免疫治疗；化疗；PD-1 抗体；MicroRNA

510. Prediction of prognosis and treatment response in ovarian cancer patients from histopathology images using graph deep learning: a multicenter retrospective study

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Purpose: Ovarian cancer (OV) is a prevalent and deadly disease with high mortality rates. The development of accurate prognostic tools and personalized therapeutic strategies is crucial for improving patient outcomes. We aim to develop a pathomics signature which holds promise as a

valuable and labor-saving tool for improving prognostic and predictive clinical decision-making in patients with OV.

Methods: A graph-based deep learning model, the Ovarian Cancer Digital Pathology Index (OCDPI), was introduced to predict prognosis and response to adjuvant therapy using hematoxylin and eosin (H&E)-stained whole-slide images (WSIs). The OCDPI was developed using formalin-fixed, paraffin-embedded (FFPE) WSIs from the TCGA-OV cohort, and was externally validated in two independent cohorts from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and Harbin Medical University Cancer Hospital (HMUCH).

Results: The OCDPI showed prognostic ability for overall survival prediction in the PLCO (HR, 1.916; 95% CI, 1.380–2.660; log-rank test, $P < 0.001$) and HMUCH (HR, 2.796; 95% CI, 1.404–5.568; log-rank test, $P = 0.0022$) cohorts. Patients with low OCDPI experienced better survival benefits and lower recurrence rates following adjuvant therapy compared to those with high OCDPI. Multivariable analyses, adjusting for clinicopathological factors, consistently identified OCDPI as an independent prognostic factor across all cohorts (all $P < 0.05$). Furthermore, OCDPI performed well in patients with low-grade tumors or fresh-frozen slides, and could differentiate between HRD-deficient or HRD-intact patients with and without sensitivity to adjuvant therapy.

Conclusion: The results from this multicenter cohort study indicate that the OCDPI may serve as a valuable and labor-saving tool to improve prognostic and predictive clinical decision-making in patients with OV.

Key Words： Deep learning; Ovarian cancer; Whole-slide images

511. ZNF586 通过调控 MYH9 促进食管鳞癌迁移侵袭的机制研究

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背景:食管鳞状细胞癌（ESCC）是全球癌症相关死亡的主要原因，且预后不良。锌指蛋白（ZNFs）家族在多种癌症中发挥着关键作用，探索锌指蛋白在 ESCC 中的作用，以确定 ESCC 患者的潜在靶点。

方法：据 TCGA 数据库和临床组织免疫组织化学实验，揭示了 ESCC 中 ZNF586 的表达水平。用 Kaplan-Meier 方法分析了 ZNF586 与 ESCC 患者存活率之间的相关性。慢病毒转染构建 ZNF586 过表达敲除及其分别对照组，并进行了一系列体外和体内功能验证。

结果：ZNF586 在 ESCC 中表达过高。ZNF586 的高表达与 ESCC 患者的总体生存率呈显著负相关。此外，ZNF586 的敲除抑制了 ESCC 细胞增殖、克隆形成、迁移、肿瘤形成和促进细胞凋亡。此外，GST 沉淀结合液相色谱-质谱法对与 ZNF586 相结合的蛋白进行检测，结果表明 ZNF586 与肌球蛋白-9（Myosin-9, MYH9）明显相互结合。在功能上， MYH9 敲除部分逆转了 ZNF586 对 ESCC 进展的贡献。

结论：ZNF586 通过调控 MYH9 促进 ESCC 进展，抑制该信号轴可能是 ESCC 的潜在治疗靶点。

关键字 ：食管鳞癌，锌指蛋白，转录因子

512. KLF15 通过降低 usp21 介导的 Nanog 稳定性来抑制胰腺癌的干性和耐药及临床转化

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目的：胰腺癌是高度恶性肿瘤，五年生存率低于 7%，被称为“癌中之王”。由于起病隐匿，临床约 80% 的首诊患者已丧失手术机会，而即使行根治术后，胰腺癌患者的 1 年复发转移率也大于 50%。因此，化疗是目前胰腺癌治疗不可或缺的重要手段，但极高的化疗耐药发生率是临床面临的巨大难题，解决化疗耐药始终是胰腺癌研究的焦点问题。肿瘤干细

胞（Cancer stem cell，CSC）学说认为，恶性肿瘤中存在着一类细胞亚群，它们对外源性刺激耐受性强，并且具有永久性自我更新能力和不对称分裂能力，这些能力导致肿瘤组织耐受传统化疗，且术后更易复发进一步阐明肿瘤细胞干性驱动因子的表达与调控机制，才能从根本上揭示胰腺癌干细胞的特性，为逆转化疗耐药提供干预策略。鉴于此，本研究旨在探讨 KLF15 在胰腺癌干性功能的作用，阐明 KLF15 抑制胰腺癌干性的分子机制，探索利用 KLF15 抑制 CSCs 和提高化疗敏感性的可行性，从而实现临床转化。

方法：收集胰腺癌患者手术标本，进行切片，对其免疫组化染色，分析 KLF15 在胰腺癌组织中的表达水平，统计学分析 KLF15 与胰腺癌患者病理资料特征相关性，并收集胰腺癌晚期患者穿测标本切片，分析 KLF15 与晚期患者的生存期相关性。胰腺癌组织切片及新鲜组织标本分析 KLF15 与胰腺癌干细胞比例的关系，利用极限倍比稀释实验，悬浮成球实验及流式细胞学实验从细胞学层面验证 KLF15 与干性的关系。利用 western-blot 筛选 KLF15 调控胰腺癌干性的关键分子，并从组织学和细胞学实验验证 KLF15 与干性关键分子 Nanog 的相关性。利用免疫共沉淀实验，放线菌酮实验及泛素化实验验证 KLF15 调控 Nanog 的分子机制，并利用细胞学实验，体内倍比稀释实验验证 KLF15 通过 Nanog 抑制干性的功能。利用 western-blot 和 RT-PCR 检测 Tazemetostat 促进 KLF15 的表达，并通过动物实验验证联合用药的疗效来评估通过促进 KLF15 表达增加吉西他滨敏感性。

结果：1.数据库结果显示与健康对照组比，KLF15 在胰腺癌组织中低表达，KLF15 表达量与胰腺癌患者生存预后成正比。组织化学染色显示 KLF15 与胰腺癌患者肿瘤大小，淋巴结转移病理分级等病例资料成负相关。

2.利用胰腺癌组织切片和新鲜胰腺癌组织标本从组学水平证明 KLF15 与胰腺癌干性呈负相关，通过构建 KLF15 过表达及降表达稳系，通过检测细胞干细胞比例，及悬浮成球的速率，证实从细胞学水平 KLF15 抑制胰腺癌干性。

3.KLF15 过表达后明显抑制 Nanog 的蛋白水平，组织学水平验证 KLF15 与 Nanog 的表达量呈负相关，但是 KLF15 并不影响 Nanog 的 RNA 水平。加入放线菌酮处理细胞后，KLF15 的过表达能够抑制 Nanog 的稳定性，免疫共沉淀实验证明 KLF15 能够与 Nanog 结合，并抑制 Nanog 与 USP21 的结合，从而导致 Nanog 的泛素化降解。

4.通过在 KLF15 过表达细胞中过表达 Nanog,在 KLF15 降表达细胞敲降 Nanog,细胞学实验及动物实验证明 KLF15 通过 Nanog 抑制胰腺癌干性。

5.吉西他滨处理 KLF15 过表达细胞，KLF15 降表达细胞及对照细胞，证实 KLF15 能够增加吉西他滨的敏感性。利用 Tazemetostat 处理胰腺癌细胞，Tazemetostat 明显增加 KLF15 的

蛋白水平及 RNA 水平。Tazemetostat 和吉西他滨联合用药处理小鼠，与对照组和单药处理组比较，联合用药组明显抑制小鼠肿瘤的生长。

结论：1. KLF15 在胰腺癌中降表达，其表达量与患者的 OS 和 RFS 呈正相关，并且与患者肿瘤大小，淋巴结转移及 TNM 分期呈负相关。

2.KLF15 在胰腺癌中能够抑制干性。

3.KLF15 与干性关键因子 Nanog 的表达量呈负相关，通过直接与 Nanog 结合，抑制 USP21 与 Nanog 的结合，从而抑制 Nanog 的去泛素化，导致 Nanog 的泛素化降解。

4. KLF15 抑制胰腺癌的干性功能是通过抑制 Nanog 的表达。

5.过表达 KLF15 能够促进吉西他滨的敏感性。Tazemetostat 能够通过增加 KLF15 的表达增加吉西他滨的敏感性。

关键字： 胰腺癌 干性与耐药 临床转化

513. The Prediction and Diagnosis Model of Lung Adenocarcinoma was Constructed Based on Novel Autoantibody Markers

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Background

Autoantibodies against tumor-associated antigens (TAAbs) have emerged as promising biomarkers for the early detection of cancer. This research aimed to identify potential markers and to develop optimal prediction and diagnosis models for lung adenocarcinoma (LUAD).

Materials and methods

This study was conducted in three phases (screening, verification, and model building phase), including a total of 321 LUADs, 249 Benign Lung Diseases (BPDs) and 321 Normal Controls (NCs). Initially, Single-cell RNA-sequencing (scRNA-seq) data and Cell literature validation were utilized to identify out 10 tumor-associated antigens (TAAs). Subsequently, these TAAbs were validated in validation group 1(72 LUADs and 72 NCs), and the meaningful TAAbs were further confirmed in validation group 2 (249 LUADs, 249 BPDs and 249 NCs) using enzyme-linked

immunosorbent assay (ELISA). Finally, multiple models (logistic regression, C5.0, Fisher, SVM and MLP) were constructed and verified.

Results

In the screening stage, 10 TAAs (AGR2, MDK, IGFBP3, ABCC3, DSP, MET, ASS1, PYCR1, LGALS4 and CRABP2) were selected. In the verification phase, the results of validation group 1 demonstrated that all TAAs except anti-IGFBP3 showed significant differences. Results from validation group 2 showed that, except anti-DSP, all 8 TAAbs were significant elevated in LUADs than in NCs, with AUCs ranging from 0.571 to 0.780. The 9 TAAbs also exhibited significance in distinguishing both LUADs and BPDs, with an AUC range from 0.622to 0.726. During the model building phase, logistic regression models constructed by 3 TAAbs (anti-PYCR1, anti-ABCC3 and anti-MDK) and 5 TAAbs (anti-ASS1, anti-DSP, anti-MET, anti-PYCR1 and anti-MDK) were selected as the best predictive and diagnostic models for LUAD. The AUCs of predictive and diagnostic models were 0.821 and 0.785, the sensitivities were 73.5% and 79.1%, and the specificities were 76.3% and 70.6%, respectively.

Conclusions

Anti-AGR2, anti-MDK, anti-ABCC3, anti-DSP, anti-MET, anti-ASS1, anti-PYCR1, anti-LGALS4 and anti-CRABP2 could serve as potential markers for LUAD. The prediction and diagnosis model of LUAD constructed by logistic regression demonstrates promising predictive and diagnostic capabilities.

Key Words ： lung adenocarcinoma, autoantibody diagnostic, tumor marker

514. AFP、PIVKA-II、Ferritin 联合应用在肝癌诊断及疗效监测的效能评价

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目的 评价单独及联合应用甲胎蛋白（AFP）、异常凝血酶原（PIVKA-II）、铁蛋白（Ferritin）指标在肝癌诊断及预后评估的效能。

方法：回顾性分析 10 个月内在苏州大学附属第二医院核医学科就诊的体检、门诊、住院患者的 AFP、PIVKA-II、Ferritin 检测数值，按照临床诊断信息分为健康体检组（74 例）、肝炎肝囊肿组（63 例）、肝硬化组（40 例）、腺瘤增生组（76 例）及肝癌组（788 例），比较各指标在各肝相关分组中的表达水平差异。通过 Passing-Bablok 回归性分析及 Kappa 分析评价 AFP 与 PIVKA-II 的应用特性。通过 ROC 曲线及 Kappa 分析比较各指标单独及联合应用在诊断肝恶性肿瘤的效能。比较各指标对肝恶性肿瘤预后的评估价值。

结果：三指标在各分组中的表达差异明显，AFP 在健康人群阳性检出率为 4.05%，在肝癌组阳性检出率为 57.61%；PIVKA-II 在健康体检组阳性检出率为 4.05%，在肝癌组阳性检出率为 64.47%；Ferritin 在健康体检组阳性检出率为 12.16%，在肝癌组阳性检出率为 34.90%。分析 AFP 与 PIVKA-II 指标相关性，y=0.0786x+1.5675，线性度偏差显著；一致性分析，Kappa 值为 0.381，一致性一般。多指标联合应用在肝癌组的诊断效能高于单一指标，ROC 曲线下面积为 0.802，在腺瘤增生+肝癌组中诊断的 ROC 曲线下面积为 0.771；在肝癌诊断中，AFP、Ferritin、PIVKA-II 三项联检的敏感度为 88.96%，特异度为 80.24%，高于单项目检测的敏感度，在良恶性肿瘤诊断中，三项联检的敏感度为 82.52%，特异度为 78.53。三指标在肝癌治疗前后差异明显，AFP 在治疗前后中位数由 4.11 ng/mL 下调至 3.2 ng/mL，Ferritin 在治疗前后中位数由 244 ng/ml 下调至 223 ng/ml，PIVKA-II 在治疗前后中位数由 161 mIU/ml 下调至 24.78 mIU/ml；秩和检验分析治疗前后数值差异，AFP：$P<0.0247$；Ferritin：$P<0.4842$；PIVKA-II：$P<0.0001$，AFP、PIVKA-II 指标变化有更强的临床一致性和预后指导价值。

结论：三项传统肝癌检测指标在良恶性疾病中表达差异明显，其中两个核心指标 AFP 与 PIVKA-II 一致性较差，但互补性强，联检可以有效提高阳性检出率。相较于腺瘤增生+肝癌综合诊断，多指标联检对单纯肝癌的诊断效能更高。AFP 与 PIVKA-II 的疗效监测价值更高。

关键字： AFP 与 PIVKA-II 的联合应用在肝癌诊断及疗效监测价值更高。

515. Single-cell dissection of the multicellular ecosystem and molecular features underlying microvascular invasion in hepatocellular carcinoma

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Background and Aims: Microvascular invasion (MVI) is a crucial pathological hallmark of hepatocellular carcinoma (HCC), intricately associated with poor outcomes, early recurrence and intrahepatic metastasis following surgical resection and transplantation. However, the intricate tumor microenvironment (TME) and transcriptional programs underlying MVI in HCC remain poorly understood.

Approach and Results: We performed single-cell RNA sequencing of 46,789 individual cells from 10 samples of MVI+ (MVI present) and MVI- (MVI absent) HCC patients. We conducted comprehensive and comparative analyses to characterize cellular and molecular features associated with MVI, and validated key findings using external bulk, single-cell and spatial transcriptomic datasets, coupled with multiplex immunofluorescence assays. The comparison identified specific subtypes of immune and stromal cells critical to the formation of the immunosuppressive and pro-metastatic microenvironment in the MVI+ tumors, including cycling T cells, LAMP3+ dendritic cells, TREM2+ macrophages, myofibroblasts, and arterial i endothelial cells. MVI+ malignant cells are characterized by high proliferation rates while MVI-malignant cells exhibit an inflammatory milieu. Additionally, we identified the MDK-dominated interaction between TREM2+ macrophages and malignant cells as a contributor to MVI formation and tumor progression. Importantly, we unveiled a spatially co-located multicellular community exerting a dominant role in shaping the immunosuppressive microenvironment of MVI and correlating with unfavorable prognosis.

Conclusions: This study provides a comprehensive single-cell atlas of MVI in HCC, shedding light on the complex multicellular ecosystem and molecular features associated with MVI. These findings deepen our understanding of the underlying mechanisms driving MVI and provide valuable insights for improving clinical diagnosis and developing more effective treatment strategies.

Key Words： single-cell Microvascular invasion hepatocellular carcinoma tumor microenvironment

516. Gene signature associated with ferroptosis predicts prostate cancer prognosis and immune microenvironment

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Background: The iron-dependent form of programmed cell death known as ferroptosis has a significant impact on cancer. Few studies, however, have examined the link between ferroptosis genes and prostate cancer (PCa) prognosis.

Methods: RNA sequence data of 478 PCa patients and corresponding clinical data were downloaded from the TCGA database. We investigated disease-free survival (DFS) rates in high-risk and low-risk groups using the Kaplan-Meier method. Functional differences between high-risk and low-risk groups were investigated using GSEA, GO, and KEGG pathway analysis. A link between risk score and immune status was examined using CIBERSORT. Expression levels of core prognostic genes in BPH and PCa were verified using quantitative real-time PCR (Q-PCR), Western blot, and immunohistochemistry (IHC).

Results: Tested in the GEO database was the creation of a novel ferroptosis-related prognostic signature based on univariate and multivariate Cox regression analysis. Patients with PCa were classified into high-risk and low-risk groups by this prognostic signature. Patients with high-risk PCa have poorer outcomes than those without low-risk PCa. The predictive accuracy of the model was demonstrated by receiver operating characteristic (ROC) analysis. There was a significant increase in immune-related pathways in the high-risk group, according to additional enrichment

analysis, in the TCGA cohort, where the area under the ROC curve (AUC) was 0.85 at 1 year, 0.82 at 2 years, and 0.76 at 5 years. In the GEO cohort, the area under the ROC curve (AUC) was 0.69 at 1 year, 2 years, and 0.74, respectively. Additional enrichment analysis revealed that the high-risk group significantly enriched immune-related pathways. According to the results obtained from the Q-PCR, western blot, and IHC, the expression of DRD4, SRC, AKR1C2, and AIFM2 was significantly higher in PCa than in BPH. At the same time, we showed that ferrostatin-1-treated LNCaP cells had higher levels of expression of DRD4, SRC, and AKR1C2.

Conclusion: A prognostic signature for 8 ferroptosis-associated genes that could accurately predict PCa patient outcomes was constructed and validated. For PCa, ferroptosis-related genes may contribute to antitumor immunity and serve as therapeutic targets.

Key Words: ferroptosis, prostate cancer, prognosis, immune infiltration, tumor microenvironment

517. 基于血液 DNA 甲基化构建精神分裂症诊断模型

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背景：精神分裂症是一种严重的精神疾病，不加以治疗会导致严重的残疾，大约 1-4%的人受该疾病影响。目前精神分裂症的临床诊断主要基于对行为模式、心理测试和问卷调查等主观判读，缺乏一种能够有效诊断精神分裂症的客观生物指标。

目的：本研究旨在应用血液 DNA 甲基化数据来筛选诊断精神分裂症的关键甲基化特征，并基于机器学习算法来构建可以有效区分精神分裂症患者和健康对照的模型。

材料和方法：从 GEO 数据库中获取四个包含精神分裂症患者和健康对照的血液 DNA 甲基化数据集（GSE152027、GSE147221、GSE84727、GSE80417），将数据集 GSE152027 和 GSE84727 中的一半样本来训练模型，剩下的一半样本来测试模型。利用随机森林算法计算的基尼系数和精确度来筛选精神分裂症相关的重要特征，并将筛选的特征与机器学习算法结合构建诊断模型，并用独立数据集对模型性能进行评估。

结果：首先，基于 GSE152027 和 GSE84727 数据集筛选出精神分裂症与健康对照样本之间 925 个一致差异甲基化位点，其中有 720 个位点位于基因上。根据随机森林算法中的基

尼系数与精确度的重要性排序，最终我们确定了 100 个关键位点用于诊断模型的训练。随机森林模型在训练集中的 AUC 值为 0.826，在验证集中的 AUC 值为 0.81，在测试集 GSE80417 中的 AUC 值为 0.84、GSE147221 的 AUC 值为 0.80。

结论：本研究中我们构建了一个以 100 个甲基化位点为特征的精神分裂症诊断模型，该模型在独立数据集中具有较好的效能，可协助临床医生进行客观诊断。

关键字： 精神分裂症、DNA 甲基化、诊断、生物标志物

518. Lactate regulates cell cycle by remodelling the anaphase promoting complex

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Purpose: Lactate is abundant in rapidly dividing cells, especially cancer cells, owing to the requirement for elevated glucose catabolism to support proliferation. However, it is not known whether accumulated lactate can act as a critical signal transduction molecule in cancer. This study is aim to explore how protein function can be directly modified by accumulated intracellular lactate and the novel relationship between lactate and cancer progression.

Methods: Here we use a systematic approach to determine lactate-dependent regulation of proteins across the human proteome. And a series of biochemical and genetic methods were used to determine how lactate regulates APC4 SUMOylation and the remodelling of APC/C.

Results: We find that accumulated lactate binds and inhibits SENP1 by forming a complex with zinc in the SENP1 active site. SENP1 inhibition by lactate stabilizes SUMOylation of two residues on APC4, which drives UBE2C binding to APC/C. This direct regulation of APC/C by lactate stimulates timed degradation of cell cycle proteins, and efficient mitotic exit in proliferative human cells. This mechanism is initiated upon mitotic entry when lactate abundance reaches its apex. In this way, accumulation of lactate communicates the consequences of a nutrient-replete growth phase to stimulate timed opening of APC/C, cell division and proliferation. Conversely, persistent accumulation of lactate drives aberrant APC/C remodelling and can overcome anti-mitotic pharmacology via mitotic slippage.

Conclusion: In sum, we define a biochemical mechanism through which lactate directly regulates protein function to control the cell cycle and proliferation.

Key Words: Lactate; Cell Cycle; APC/C complex; Mitotic Slippage; Drug Resistance

519. Ferroptosis-related LINC02535/has-miR-30c-5p/EIF2S1 axis is a novel prognostic biomarker associated with immune infiltration and promotes progression of PDAC

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PDAC, also known as pancreatic ductal adenocarcinoma, is often diagnosed at a late stage due to nonspecific symptoms and a distinct lack of reliable biomarkers for timely diagnosis. Ferroptosis, a novel non-apoptotic cell death mode discovered in recent years, is strongly linked to the progression of PDAC and the evasion of the immune system. The objective of this study is to discover a novel ceRNA biomarker associated with ferroptosis and investigate its possible molecular mechanisms and therapeutic potential in PDAC. Through comprehensive bioinformatics analysis, we first discovered a novel LINC02535/miR-30c-5p/EIF2S1 axis associated with ferroptosis and created a nomogram for prognosticating overall survival. Meanwhile, the high immune infiltration subtype exhibited elevated ceRNA risk scores and EIF2S1 expression in PDAC. The correlation analysis revealed a positive correlation between ceRNA risk scores and four immune cells, namely Activated CD4 T cell, Memory B cell, Neutrophil, and Type 2 T helper cell, as well as four immune checkpoint genes, namely CD274, HAVCR2, LAG3, and PDCD1LG2. The analysis of drug sensitivity indicated that individuals with a high-risk score may exhibit greater sensitivity to inhibitors targeting MEK1/2 compared to those with a low-risk score. In our validation experiments, it was observed that the expression of LINC02535 was increased in both PDAC tissues and cell lines. Additionally, the inhibition of LINC02535 resulted in decreased proliferation, migration, and invasion of PDAC cells. To sum up,

our investigation indicated that the LINC02535/miR-30c-5p/EIF2S1 pathway could function as a significant indicator and possible treatment target for PDAC.

Key Words： PDAC; ceRNA network; ferroptosis; prognostic; immune infiltration; drug sensitivity

520. 胃癌血浆外泌体来源的 hsa_circ_0076987 在胃癌中的作用及机制研究

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目的：胃癌是全球常见的恶性肿瘤之一，发病率与死亡率居高，严重威胁人民生命健康。胃癌早期发现隐匿，患者预后差，急需寻找新型标志物。CircRNAs 在多种疾病中异常表达，正在成为极具前景的人类标志物之一。本研究旨在检测胃癌患者，慢性萎缩性胃炎患者与健康体检者血浆外泌体内 hsa_circ_0076987(简称 circ76987)的表达情况，分析其临床价值，阐明其在胃癌发展中的作用及机制，为胃癌的早期诊断与治疗提供一种新的诊断标志物与及潜在治疗靶点。

方法：通过 circRNA 芯片技术，检测 6 对胃癌患者，慢性萎缩性胃炎患者与健康体检者血浆外泌体内 circRNA 表达情况，筛选出差异表达的 circ76987。收集胃癌患者、慢性萎缩性胃炎患者与健康体检者的血浆，分离提取外泌体，并采用 qRT-PCR 的方法检测 circ76987 在血浆外泌体中的表达情况，绘制 ROC 曲线，分析其诊断效能；结合临床病理资料，分析其临床相关性。采用过表达质粒在胃癌细胞中过表达 circ76987，通过 CCK8 和克隆形成实验检测胃癌细胞增殖能力；Transwell 迁移和侵袭实验检测胃癌细胞迁移与侵袭能力；Western blot 检测相关蛋白变化；同时收集并分离提取高表达 circ76987 的胃癌细胞上清外泌体，与胃癌细胞共培养后，检测胃癌细胞功能与蛋白表达变化。采用核质分离技术，确定 circ76987 的细胞定位；运用生物信息学软件预测与 circ76987 结合的 miRNAs，并采用双荧光素酶报告基因实验进行验证。通过基因共转实验验证 circ76987 与 miRNA 的相互作用。

结果：Circ76987 在胃癌血浆外泌体中低表达，病理资料相关性分析显示其与神经浸润相关，ROC 曲线下面积为 0.6343；过表达 circ76987 后可以抑制胃癌细胞的增殖、迁移与侵袭能力及相关蛋白变化。

讨论：circ76987 在胃癌血浆外泌体中低表达，可通过 ceRNA 机制抑制胃癌细胞的增殖，迁移与侵袭。有望成为胃癌诊断的新型标志物与治疗靶点。

关键字： 胃癌 外泌体 circRNA

521. ASF1B 在宫颈癌转移中的作用

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目的：宫颈癌是妇科癌症死亡的主要原因，其发生转移占癌症相关死亡的 80%。本研究初步探讨抗沉默功能因子（ASF1B）在宫颈癌转移中的作用及其潜在机制。

材料与方法：通过免疫印迹和免疫组化分别验证 ASF1B 在宫颈癌细胞系和宫颈癌组织中的表达。同时，构建对照组（shNC）和敲低组（shASF1B）的 Hela 及 CaSki 稳转细胞系，通过细胞划痕实验、transwell 细胞迁移实验、裸鼠肺部转移实验研究 ASF1B 对宫颈癌细胞系迁移能力的影响。通过免疫沉淀方法（IP）及液相色谱、质谱联用（LC-MS）筛选出与 ASF1B 具有相互作用的蛋白群。

结果：免疫组化方法检测了 37 对宫颈癌组织样本和配对癌旁组织样本石蜡切片中 ASF1B 表达，发现宫颈癌中的 ASF1B 的阳性染色比配对癌旁组织更强（$p<0.01$，$n=18$）；应用免疫印迹和 qRT-PCR 方法证实了宫颈癌细胞系 HeLa 和 CaSki 中 ASF1B 蛋白表达水平和 mRNA 表达水平均显著高于对照组人永生化角质形成细胞 HaCaT（$p<0.01$，$n\geq3$）；细胞划痕实验证实了 ASF1B 的敲低显著降低了 HeLa 和 CaSki 细胞的迁移能力（$p<0.01$，$n\geq3$）；Transwell 细胞迁移实验结果显示 ASF1B 的敲低可以减少 HeLa 和 CaSki 细胞迁移（$p<0.01$，$n\geq3$）；免疫印迹实验证实了在构建的 HeLa 和 CaSki 稳转细胞系中，ASF1B 的稳定敲低显著增加 E-钙粘蛋白的表达水平，并下调 N-钙粘蛋白和波形蛋白的表达水平（$p<0.01$，$n\geq3$）；通过尾静脉注射方法将 shNC 或 shASF1B 稳定转染的 CaSki 细胞注射入裸鼠体内构建裸鼠肺部转移模型，结果提示对照组肺部转移结节数显著多于敲低 ASF1B 组的肺部转移结节数，具有统计学意义（$p<0.01$，$n=3$）；将裸鼠肺组织制作病理切片，HE 染色表明敲低 ASF1B

组的裸鼠肺部肿瘤转移灶的大小明显小于对照组，免疫组化显示敲低组裸鼠肺部组织 ASF1B 阳性表达明显下降；LC-MS 分析筛选出一系列与肿瘤 EMT 发生和肿瘤发展进程密切相关的蛋白。

结论：本课题初步探讨了 ASF1B 对宫颈癌转移的作用及潜在机制。我们发现 ASF1B 在宫颈癌组织和细胞系中高表达，通过体内外实验证实 ASF1B 与宫颈癌细胞迁移能力和肿瘤 EMT 进程密切相关，进一步筛选出与 ASF1B 结合的互作蛋白群，为 ASF1B 的后续机制研究提供思路，这有可能成为宫颈癌患者的一个新治疗靶点和预后指标。

关键字： ASF1B，宫颈癌，转移

522. YAP1/DEPDC1B 调控 mTOR 信号通路促进肝母细胞瘤增殖的机制研究

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目的 研究 YAP1/DEPC1B 信号轴在调控肝母细胞瘤细胞（hepatoblastoma，HB）增殖中的作用及潜在机制。

方法 从 GEO 数据库获取相关转录组测序数据集并行相应的生物信息学分析。qRT-PCR 和 Western blot 实验检测基因表达水平变化。MTT 实验和平板克隆形成实验检测肿瘤细胞增殖能力变化。基因集富集分析（gene set enrichment analysis, GSEA）来探究 YAP1/DEPDC1B 调控的潜在信号通路。

结果 GSEA 表明与正常肝脏组织相比，Hippo 信号通路在肝母细胞瘤组织中异常激活，进一步分析证实 YAP1 在肝母细胞瘤组织中呈异常高表达。细胞学实验证实 YAP1 特异性抑制剂维替泊芬能显著抑制 HB 细胞 HUH-6 的增殖（P＜？？）。＜0.05）。韦恩图和相关性分析表明 YAP1 可能调控 DEPDC1B 的表达，qRT-PCR 和 Western blot 证实抑制 YAP1 表达后 DEPDC1B 表达量降低。GSEA 表明在 HB 组织中，高表达的 DEPDC1B 能异常激活 mTOR 信号通路，进一步研究证实敲低 DEPDC1B 后，mTOR 信号通路关键基因 HRAS、MAP2K2 的表达量明显显著降低（P＜？？）。

结论 Hippo-YAP1 信号通路在肝母细胞瘤中异常激活，YAP1 可能通过 DEPDC1B 调控 mTOR 信号通路促进肿瘤细胞增殖，YAP1 可能是治疗 HB 的潜在靶标。

关键字： 肝胚细胞瘤；细胞增殖；基因集富集分析；Yes 相关蛋白 1；DEPDC1B

523. Intestinal Lachnospiraceae bacterium-derived Propionate Inhibits Tumor Progress in Clear Cell Renal Cell Carcinoma

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Objectives： The association between gut microbiota and the development of various tumors has been reported. However, the correlation between gut microbiota and clear cell renal cell carcinoma (ccRCC) remains poorly understood. This study aimed to elucidate the specific composition of gut microbiota in ccRCC patients compared to healthy volunteers, explore the potential relationship between alterations in gut microbiota and the development of ccRCC, and elucidate the specific mechanisms underlying the interaction between microbiota and tumors. Additionally, to further advance the clinical translation of microbiota-tumor research, we designed a biotherapy aimed at improving the prognosis of ccRCC. Finally, we aimed to establish a gut microbiota-based clinical prediction model for ccRCC to provide new insights into the prognosis of ccRCC patients.

Materials and Methods:1. Utilizing 16S rRNA gene sequencing technology to analyze the relative abundance and composition of various bacterial species in the gut microbiota of ccRCC patients and healthy volunteers, and delineate the specific differences in microbiota distribution between different groups.

2. Confirmation through phenotype experiments such as EDU assay, Transwell assay, and in vivo experiments in mice that low abundance of *Lachnospiraceae bacterium* (*L. bacterium*) in the gut of ccRCC patients possesses the ability to inhibit tumor development.

3. Validation of the inhibitory effect of *L. bacterium* on ccRCC progression through its secreted metabolite propionate using targeted metabolomics, CCK8 assay, EDU assay, and in vivo experiments in mice.

4. Exploration of the specific molecular mechanism underlying the interaction between propionate secreted by *L. bacterium* and ccRCC cells using transcriptome sequencing, WB assay, CHIP assay, and other molecular experiments.

5. Designing engineered bacteria for clinical translation and confirming their efficacy and safety through simulated gastric, bile, and intestinal fluid environments as well as *in vivo* experiments in mice.

Results:1. Through a humanized mouse model, we confirmed a correlation between gut microbiota and ccRCC progression. Specific bacterial species present in the gut microbiota of healthy volunteers were associated with slowing tumor progression compared to patients' gut microbiota.

2. There were significant differences in gut microbiota between ccRCC patients and healthy volunteers, with a significant decrease in the relative abundance of *L. bacterium* in patients' intestines, and the relative abundance of *L. bacterium* had potential predictive value for tumor development.

3. Low relative abundance of *L. bacterium* in the gut of ccRCC patients can inhibit tumor progression through its secreted metabolite propionate. Propionate secreted by *L. bacterium* binds to the receptor G protein-coupled receptors 41/43 (GPR41/43) on the surface of ccRCC cells, downregulating the expression of transcription factor HOXD10 and its downstream target IFITM1, subsequently activating the JAK1-STAT1/2 pathway, thereby inhibiting tumor cell proliferation and migration.

4. To advance the clinical translation of tumor-microbiota research, we employed two approaches: dietary modulation and engineered bacteria encapsulated in biofilms, aiming to affect ccRCC progression by altering the relative abundance of *L. bacterium* in the mouse intestine. These approaches offer new directions for patient treatment from a microbiota perspective.

5. Expanded validation cohorts confirmed that the relative abundance of *L. bacterium* in the gut microbiota, along with the expression levels of IFITM1 and HOXD10 in tumor tissues, were associated with the prognosis of ccRCC patients and had predictive value.

Conclusions: There is an association between gut microbiota and ccRCC progression. Specifically, *L. bacterium*, which shows a significant decrease in relative abundance in the gut microbiota of patients, can inhibit tumor cell proliferation and migration through its metabolite propionate,

which activates the JAK1-STAT1/2 pathway. The relative abundance of *L. bacterium* in the gut serves as a novel insight for the prediction and treatment of ccRCC.

Key Words ： Clear cell renal cell carcinoma; Gut microbiota; Propionate; Biofilm

524. 肝癌新指标-异常凝血酶原在原发性肝癌诊断中的应用

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目的： 研究异常凝血酶原（PIVKA-II）原发性肝癌诊断中的临床应用价值。

材料与方法：收集 2023 年 5 月至 2023 年 12 月河南省肿瘤医院收治的 203 例原发性肝癌（HCC）患者血清，95 例良性肝病（肝炎、肝硬化）患者血清，及同期进行体检的 206 名健康者血清。采用郑州安图生物工程股份有限公司全自动化学发光仪器 A2000 Plus 分别检测 HCC 患者、良性肝病患者和健康体检者血清的 PIVKA-II、AFP 水平，所有数据采用 SPSS 25.0 分析软件进行统计学分析。

结果：HCC 患者血清的 PIVKA-II、AFP 检测值均高于良性肝病及健康体检者的检测值。血清 AFP 单独检测 HCC 的灵敏度为 64.31%，特异性 86.24%；血清 PIVKA-II单独检测 HCC 的灵敏度为 77.59%，特异性 92.69%；血清 AFP 和 PIVKA-II联合检测 HCC 的灵敏度为 84.26%，特异性 99.13%。PIVKA-II和 AFP 联合检测可提高原发性肝癌检测的灵敏度和特异性。

结论：PIVKA-II在原发性肝癌中诊断价值要高于 AFP，PIVKA-II和 AFP 联合检查优势更明显，更利于肝癌的早期诊断，有助于肝癌的早期筛查和治疗。

关键字： 原发性肝癌；良性肝病；异常凝血酶原；甲胎蛋白；联合诊断

525. Piezo2 调控 RhoA-cofilin 通路在结直肠癌侵袭转移中的相关研究

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目的 本研究通过 Piezo2 调控 RhoA-cofilin 通路进行 CRC 增殖侵袭转移相关研究，明确 Piezo2 对结直肠癌发生发展的干预机制。

方法 通过免疫组化法检测正常肠上皮、癌旁组织及癌组织中 Piezo2 的蛋白表达；将 Piezo2 的抑制剂钌红抑制结肠癌细胞（SW620 和 HCT116）后计算半数致死浓度并通过流式细胞术检测钙离子的表达；通过蛋白免疫印迹法 检测钌红抑制 Piezo2 后侵袭转移相关的 E-cadherin、VEGF、YAP、MMP-2、vimentin、β-catenin 蛋白的表达。通过构建慢病毒载体转染法敲低结直肠癌细胞系中 Piezo2 和过表达 RhoA，荧光显微镜下观察 GFP 荧光；通过流式细胞术检测 SW620 细胞敲低 Piezo2 后钙离子的表达；通过蛋白免疫印迹法检测敲低 Piezo2 表达的稳转细胞系以及敲低 Piezo2 并过表达 RhoA 细胞的 Piezo2、RhoA、ROCK、Limk、cofilin、E-cadherin、VEGF、YAP、MMP-2、vimentin、β-catenin 蛋白的表达；通过 CCK8、Transwell 及 Wound-healing 法检测敲低 Piezo2 的稳转细胞系和敲低 Piezo2 并过表达 RhoA 稳转细胞系的增殖、迁移及侵袭能力；通过裸鼠皮下成瘤检测 HCT116 和 SW620 细胞敲低 Piezo2 后肿瘤大小变化,通过免疫组化检测 ki67 表达。

结果 在人结直肠癌癌组织、癌旁组织和正常组织中 Piezo2 表达情况结果显示：癌组织中 Piezo2 明显高于正常组织和癌旁组织 （距离肿瘤 5cm）（P<0.001）;应用 Piezo2 的抑制剂钌红干预后 HCT116 细胞和 SW620 细胞的生存曲线。结果显示：HCT116 细胞半数致死浓度（IC50）的 95%可信区间为（3.119-5.222mg/L）SW620 细胞半数致死浓度（IC50）的 95%可信区间为（ 4.521-6.578mg/L）。钌红抑制 Piezo2 后 SW620 和 HCT116 细胞内 Ca^{2+} 的浓度变化。结果显示：钌红抑制后 SW620 细胞内 Ca2+浓度降低（P＜0.001）；钌红抑制后 HCT116 细胞内 Ca^{2+}浓度降低（P＜0.001）;钌红抑制 Piezo2 后上皮间质化、机械转导蛋白等相关蛋白表达情况。结果显示：与对照组相比，经钌红培养 8h、16h 、24h 组的 E-cadherin、 VEGF、YAP、MMP-2 、Vimentin、β-catenin（P 均＜0.001）蛋白表达随着钌红培养时间增加而降低;敲低 Piezo2 表达后 SW620 细胞内钙离子的浓度变化情况。结果显示：慢病毒敲低组 Ca2+浓度低于对照组（P<0.001）。转染敲低 Piezo2 和过表达 RhoA 的 SW620 细胞系的蛋白表达情况。结果显示：敲低 Piezo2 的细胞系内 Piezo2、RhoA、ROCK、LIMK、cofilin、E-cadherin 、VEGF、YAP、MMP-2、Vimentin、β-catenin（P 均<0.01）蛋白表达降低。敲低 Piezo2 并过表达 RhoA 的细胞 Piezo2 蛋白的表达低、但是 RhoA 、ROCK、LIMK 、cofilin、E-cadherin、VEGF、YAP、MMP-2、 Vimentin、β-catenin（P 均<0.01）蛋白表达较敲低 Piezo2 组增加。敲低 Piezo2、过表达 RhoA 后结肠癌细胞 HCT116 和 SW620 的增殖能力变化。结果显示,与对照组相比敲低 Piezo2 组的增殖能力降低，敲低 Piezo2 并过表达 RhoA 组增殖能力较只敲低 Piezo2 组增加（P<0.001）。敲低 Piezo2、过表达 RhoA 后对 HCT116 和 SW620 结肠癌细胞的迁移影响。结果显示，对照组迁移能力高于敲低 Piezo2

组（P<0.001），敲低 Piezo2 并过表达 RhoA 组迁移能力高于敲低 Piezo2 组（P<0.001）。敲低 Piezo2、过表达 RhoA 后对 HCT116 和 SW620 结肠癌细胞的迁移影响。结果显示：对照组迁移能力高于敲低 Piezo2 组（P<0.001），敲低 Piezo2 并过表达 RhoA 组迁移能力高于敲低 Piezo2 组（P<0.001）;皮下成瘤结果显示,Piezo2 敲低组肿瘤体积和质量少于对照组（P 均＜0.01）,免疫组化检测显示 Piezo2 敲低组肿瘤组织中的 ki67 表达弱于对照组（P＜0.01）;

结论 Piezo2 结直肠肿瘤造成的机械应力变化可以激活 Piezo2 通道，诱发细胞 Ca^{2+} 内流进而调控下游的 RhoA 信号通路表达，使得细胞的收缩功能、增殖、迁移、黏附等功能发生改变，影响肿瘤的侵袭转移。Piezo2 可能是针对肿瘤发生发展的潜在治疗靶标，抗肿瘤血管生成的有效治疗药物可能也包括了 Piezo2 抑制剂。

关键字： 机械应力，Piezo2，钌红，钙离子，结直肠癌侵袭转移

526. GULP1 may be a potential biomarker for cancer, validated from a comprehensive pan-cancer analysis to pancreatic cancer

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GULP1 protein is involved in regulating biological processes such as endocytosis and apoptosis. The function of GULP1 in cancer, however, has been the subject of fewer studies; its importance as a potential prognostic factor in pancreatic cancer is still uncertain. Thus, the purpose of this work was to investigate GULP1's immunologic and oncogenic activities in a range of malignancies, as well as any potential relevance to pancreatic cancer. Using multiple bioinformatic databases, GULP1 expression, prognostic significance, mutation status, methylation and phosphorylation levels, biological functions, immune cell infiltration and immunotherapeutic responses and drug sensitivity were comprehensively assessed in pan-cancer and functionally validated in pancreatic cancer. The results revealed that GULP1 was differentially expressed in most tumors and correlated with unfavorable prognosis, which may be connected

to GULP1's engagement in the regulation of apoptosis pathway. In addition, the differential expression of GULP1 was linked to immune cell infiltration levels, immunotherapy response, and chemotherapy resistance. GULP1 could hinder the body's ability to fight tumors and respond to immunotherapy by promoting the accumulation of immune cells and suppressing the activity of cytotoxic T lymphocytes. In pancreatic cancer, down-regulation of GULP1 expression inhibits proliferation, invasion and migration of pancreatic cancer cells. These phenotypic changes may be achieved by regulating HIPPO, mTOR, and RTK signaling pathways. Taken together, it makes sense to think that GULP1 could be a biomarker for immunotherapy and prognosis in pan- and pancreatic cancer.

Key Words： GULP1, tumor immunity, prognosis, pan-cancer, pancreatic cancer

527. HDAC1 下调 CALM3 K76 位点巴豆酰化促进 CRC 转移

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目的：转移是肿瘤进展的标志之一，是癌症治疗的一大障碍，也是癌症死亡的主要原因。赖氨酸巴豆酰化作为一种新型蛋白修饰类型，在多种生理及病理过程中发挥着重要作用，包括干细胞分化、精子发生、急性肾损伤、HIV 潜伏期、自噬、DNA 修复以及癌症进展等。钙调蛋白 3（calmodulin 3, CALM3）作为第二信使 Ca2+的结合载体，参与肿瘤发生发展的各个阶段，但其功能是否存在巴豆酰化修饰调控，以及巴豆酰化修饰的功能及机制，目前还没有研究涉及。本研究旨在阐明 CALM3 76 位赖氨酸的巴豆酰化修饰在结直肠癌转移中的作用及机制。

材料与方法：定制 CALM3 K76 位点巴豆酰化特异性抗体，采用免疫组化方法研究 CALM3 K76 位点巴豆酰化与结直肠癌转移的相关性；采用 DNA 点突变技术，构建 CALM3 K76A 慢病毒，模拟 76 位点去巴豆酰化修饰，利用 MC38 及 CT26 细胞进行划痕、Transwell 实验研究细胞迁移功能，进一步通过小鼠尾静脉注射慢病毒感染细胞，构建 CRC 细胞肺转

移模型，在体外及体内阐明 CALM3 K76 位点修饰在结直肠癌转移中的作用。接着利用去巴豆酰化酶抑制剂和靶向 HDAC1 的 siRNA，研究影响 CALM3 K76 位点巴豆酰化水平的去巴豆酰化酶。最后，过表达 CALM3 K76 位点突变质粒，检测 MMP9 的表达，探究 CALM3 K76A 发挥促癌功能的下游分子。

结果：临床样本的免疫组化结果显示，CALM3 K76 位点巴豆酰化修饰在 CRC 转移样本中明显减少，与病人的临床分期负相关。与野生型相比，CALM3 K76A 能显著促进 CRC 细胞的迁移能力，促进细胞在小鼠体内的肺转移。HDAC 家族抑制剂 Trichostatin A（TSA）而非 SIRT 家族抑制剂 Nicotinamide（NAM）能显著提高 CALM3 K76 位点巴豆酰化水平。进一步敲低 HDAC1 能显著提升 CALM3 K76 位点巴豆酰化水平。最后，过表达 CALM3 K76 位点突变质粒，与野生型组相比，MMP9 表达量明显上升。

结论：研究结果表明 HDAC1 下调 CALM3 K76 位点巴豆酰化水平，促进 MMP9 的表达，进而促进 CRC 转移。CALM3 K76 位点有望成为 CRC 诊断和治疗的新靶点。

关键字： 结直肠癌 巴豆酰化 CALM3

528. Calcium-sensing receptor and NF-κB pathways in TN breast cancer contribute to cancer-induced cardiomyocyte damage via activating neutrophil extracellular traps formation

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Cardiovascular disorders are commonly prevalent in cancer patients, yet the mechanistic link between them remains poorly understood. Because neutrophil extracellular traps (NETs) have implications not just in cardiovascular diseases (CVD), but also in breast cancer (BC), it was hypothesized to contribute to CVD in the context of oncogenesis. We established a mouse model using nude mice to simulate liver metastasis of triple-negative BC (TNBC) through the injection of MDA-MB-231 cells. Multiple imaging and analysis techniques were employed to assess the cardiac function and structure, including echocardiography, HE staining, Masson staining, and

transmission electron microscopy (TEM). MDA-MB-231 cells underwent treatment with a CaSR inhibitor, CaSR agonist, and NF-κB channel blocker. The phosphorylation of NF-κB channel protein p65 and the expression and secretion of IL-8 were assessed using qRT-PCR, Western Blot, and ELISA, respectively. In addition, MDA-MB-231 cells were co-cultured with polymorphonuclear neutrophils (PMN) under varying conditions. The co-localization of PMN extracellular myeloperoxidase (MPO) and DNA were observed by cellular immunofluorescence staining to identify the formation of NETs. Then, the cardiomyocytes were co-cultured with the above medium that contains NETs or not, respectively; the effects of NETs on cardiomyocytes apoptosis were perceived by flow cytometry. The ultrastructural changes of myocardial cells were perceived by TEM, and ELISA detected the levels of myocardial enzyme (LDH, MDA and SOD). Overall, according to our research, CaSR has been found to have a regulatory role in IL-8 secretion in MDA-MB-231 cells, as well as in the formation of NETs by PMN cells. These findings suggest CaSR-mediated stimulation in PMN can lead to increased NETs formation and subsequently to cytotoxicity in cardiomyocytes, which potentially via activation of the NF-κB signaling cascade of BC cell.

Key Words ： TNbreast cancer, Calcium-sensing receptor, Neutrophil extracellular traps, Myocardial injury, NF-κB signaling pathway

529. GD2 electrochemical immunosensor effectively diagnoses of minimum residual disease of bone marrow in neuroblastoma

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Neuroblastoma (NB) is known as the "king of childhood tumors" due to its high metastatic, recurrence-prone, and difficult-to-treat characteristics. International Neuroblastoma Risk Grading Group (INRG) has recommended GD2, a disialoganglioside expressed on neuroectodermal tumor cells, as the target for detecting minimal residual disease in bone marrow metastases in high-risk neuroblastoma children. Therefore, accurately identifying GD2-positive cells is crucial for

diagnosing children with high-risk NB. Here, we designed a Graphene/AuNPs/GD2 Ab-functionalized electrochemical biosensor for GD2 detection. A three-electrodes system was processed by screen printed technique with a working electrode of indium tin oxide, a counter electrode of carbon, and a reference electrode of silver/silver chloride. Graphene/AuNPs were modified on the indium tin oxide electrode by chronoamperometric scans, and then GD2 antibody was modified on the biosensor by electrostatic adsorption to achieve sensitive and specific detection of GD2-positive cells in bone marrow fluid. Results showed that Graphene/AuNPs/GD2 Ab-functionalized electrochemical biosensor achieved the GD2-positive cells detection in the range of 102 cells/mL~105 cells/mL by differential pulse voltammetry. Bone marrow fluid samples from 12 children with high-risk NB were retained for testing on our biosensor and showed 100% compliance with the clinical application of the gold standard-immunocytochemical staining technique for detecting GD2-positive cells qualitatively. The GD2-based electrochemical assay can accurately detect children with high-risk NB, providing a rapidly quantitative basis for clinical diagnosis and treatment.

Key Words ： neuroblastoma, bone marrow, GD2, electrochemical sensor, Graphene/AuNPs

530. Plasma D-dimer and Interleukin-6 are associated with treatment response and progression-free survival in advanced NSCLC patients on anti PD-1 therapy

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Response to therapy after using immune checkpoint inhibitors (ICIs) is unpredictable due to significant inter-individual variation in efficacy among advanced non-small cell lung cancer (NSCLC) patients. The current study centered on the identification of perivascular blood biomarkers for predicting the effectiveness of anti-programmed cell death- protein 1 (anti-PD-1) treatment and progression-free survival (PFS) in advanced NSCLC patients, that could be applied to help determine how to change treatment plans therapeutic regimens for optimizing clinical benefits. A comprehensive review of 100 advanced or recurrent NSCLC patients receiving

anti-PD-1 therapy (carrelixumab, pembrolizumab, sintilimab or nivolumab) was conducted between January 2018 and April 2021 in Tianjin Medical University Cancer Hospital. The cut-off values of D-dimer was selected from rom our previous study and interleukin 6 (IL-6) was divided according to the median. Using computed tomography, tumor response was evaluated in accordance with the Response Assessment Criteria in Solid Tumors, version 1.1. High IL-6 lever in advanced NSCLC patients was predictive of low efficacy and a short PFS duration after anti-PD-1 therapy. An increased D-dimer value of 981 ng/mL was significantly predictive of disease progression in NSCLC patients treated with anti-PD-1 and high D-dimer expression predictive of short duration of PFS. Further studies on the correlation between IL-6, D-dimer and anti-PD-1 efficacy in NSCLC patients stratified by gender revealed that D-dimer and IL-6 levels were significantly associated with the risk of PFS in male patients.

Key Words： NSCLC, D-dimer, IL-6

531. Recurrence or progression of neuroblastoma in children with MYCN amplification, 1p deletion or 11q deletion may due to altered immune status

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This study explored the prognosis of neuroblastoma (NB) patients with different genetic alterations, as well as altered peripheral blood immune status. We screened 31 samples of neuroblastoma for MYCN amplification status and loss of heterozygosity at chromosome bands 1p36 and 11q23. The event-free survival (EFS) was found to be worse in patients with MYCN amplification or 1p deletion than in the corresponding normal group by Kaplan-Meier analysis, whereas 11q deletion was a prognostic factor affecting EFS only in patients with unamplified MYCN. Changes in peripheral blood immune cells and cytokines detected by flow cytometry revealed a decrease in the proportion of tumor-infiltrating T cells (CD4+ and CD8+ T cells), an increase in regulatory T cells (Tregs), and an increase in immunosuppression-related factors

interleukin (IL)-6 and IL-10. In our analysis, NB with these genetic characteristics may have some regulatory network/signaling pathway to downregulate tumor-infiltrating T cells, upregulate suppressor cells such as Tregs, and promote the secretion of immunosuppressive cytokines IL-6 and IL-10, creating an immunosuppressive microenvironment that affects the immune response of patients and ultimately leads to a worse prognosis.

Key Words： Neuroblastoma; MYCN; Chromosome 1p; Chromosome 11q; Immune Status

532. USP9x 联合 SOX2 在骨肉瘤发展中的作用研究

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目的：骨肉瘤（Osteosarcoma, OS）是骨骼最常见的原发性恶性肿瘤，好发于儿童和青少年，在过去的 30 年里，随着科学的进步，患者 5 年生存率提升至 70%，但复发以及转移患者的生存率却仍在 25%以下，且耐药情况频发，其中 OS 干细胞发挥关键作用，而转录因子 SOX2 是其维持干性的关键。故阐明骨肉瘤的发病机制以及剖析 SOX2 的调控网络，发现与 SOX2 联合检测的有效标志物，对临床骨肉瘤的治疗与预后判断具有重要意义。

方法：首先我们从细胞水平，过表达一系列去泛素化酶，检测 SOX2 的表达变化，找到 USP9x 可调控 SOX2 的表达；接着通过免疫沉淀，荧光共定位，半衰期测定，共同转染等实验明确 SOX2 是 USP9x 的重要底物；再次利用基因敲低与过表达技术，通过流式分析、qPCR、Western blot、CCK8 实验、划痕实验等方法，揭露泛素特异性蛋白酶 USP9x 在骨肉瘤中的角色，明确其癌基因的作用，通过回复实验证明 SOX2 是 USP9x 发挥癌基因作用的枢纽；最后在经裸鼠皮下成瘤实验，以及临床标本免疫组化分析进行体内验证。

结果：在骨肉瘤中 USP9x 发挥癌基因作用，降低其表达，可有效抑制骨肉瘤细胞的增殖，延缓骨肉瘤进展；USP9x 与 SOX2 可发生相互作用，USP9x 可稳定 SOX2 的表达，促进 SOX2 在骨肉瘤细胞中的累积；在骨肉瘤发展中，SOX2 是 USP9x 发挥癌基因作用的枢纽，USP9x 与 SOX2 的共同检测有助于骨肉瘤诊断分析与预后判断。

讨论：已有研究证明转录因子 SOX2（SRY-Box Transcription Factor 2，SOX2）在人 OS 细胞系以及肿瘤组织中高表达，是 OS 恶性增殖，维持干性的关键。同时 SOX2 作为肿瘤标志物在临床上已有一定的开展，主要用于肺癌的辅助诊断，在骨肉瘤中尚未开展。USP9x，

作为去泛素化酶中泛素特异性蛋白酶亚家族成员，在维持体内稳态过程中具有重要作用。在非小细胞肺癌，乳腺癌，多发性骨髓瘤，乳腺癌等肿瘤的发生发展中均扮演者癌基因的角色，但在骨肉瘤中的作用尚不明确。而我们在此次的研究中发现，骨肉瘤病人癌组织中 USP9x 高表达且与预后不良有关，同时 USP9x 可稳定 SOX2 的蛋白水平，抑制其通过泛素化途径降解，其高表达是骨肉瘤中 SOX2 高表达的主要原因，反之 SOX2 也是 USP9x 发挥癌基因作用的枢纽。明确 USP9x 与 SOX2 的相互关系在骨肉瘤发生发展的作用，为临床开展新的肿瘤标志物联合检测提供理论依据，为临床检验肿瘤相关基因检测提供新方向。

关键字： USP9x；SOX2；骨肉瘤；泛素化

533. Association between high galectin expression and poor prognosis in hematologic cancers: a systematic review and meta-analysis

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Background: Galectin (Gal) is considered a promising immune checkpoint molecule. More and more studies have shown that high expression levels of galectins in hematologic cancer are positively correlated with poor clinical prognosis. However, the exact prognostic significance of galectins remains unclear.

Methods: PubMed, Embase, Web of Science, and Cochrane Library were searched for studies addressing the correlation of galectin expression levels with prognosis of hematologic cancers. Stata software was used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Result: Hematologic cancer patients with high galectin expression levels showed poor overall survival (OS, HR = 2.43, 95% CI: 1.95, 3.04), disease-free survival (DFS, HR = 3.29, 95% CI: 1.61, 6.71), and event-free survival (EFS, HR = 2.20, 95% CI: 1.47, 3.29) outcomes. Subgroup analysis revealed that high expression levels of galectins pointed to relatively poor OS in MDS (HR = 5.44, 95% CI: 2.09, 14.18), as compared to AML, CHL and CLL. No correlation was found between galectins and OS in NHL and MM. Among the three galectins, Gal-9 (HR = 3.60, 95% CI:

2.03, 6.38) showed higher correlation with poor prognosis than Gal-1 and Gal-3. In addition, use of peripheral blood (HR = 2.96, 95% CI: 2.07, 4.22) samples and qRT-PCR (HR = 2.80, 95% CI: 1.96, 4.01) method for galectin detection were shown to improve its prognostic correlation in hematologic cancers.

Conclusion: Meta-analysis revealed high expression of galectins was associated with poor prognosis in hematologic cancer patients and galectins can be considered a promising prognostic predictive

Key Words： Hematologic cancer; galectin; meta-analysis; prognosis; systematic review.

534. 炎症因子和肺癌的因果关系

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目的：流行病学和实验证据表明炎症与肺癌发生发展有关。然而，目前尚不清楚特定的炎症因子是肺癌的原因还是偏倚的结果。为了检查炎症因子浓度的遗传预测变化是否与肺癌的发生有关，我们进行了双样本孟德尔随机化分析。

方法：这项研究利用全基因组关联研究中的 91 种炎症因子和肺癌摘要数据，暴露数据来自 11 个队列的样本、多达 14824 名欧洲血统的参与者，结局数据来自芬兰数据库，包括肺腺癌、肺鳞癌以及小细胞肺癌，主要使用逆方差加权来探索暴露与结果之间的因果关系。此外，同时应用了多种敏感性分析，包括 MR-Egger、加权中位数、简单模型、加权模型和 MR-PRESSO，以增强最终结果稳健性。

结果： 该研究指出了一些提示性证据：使用 IVW 方法，我们发现较低的 CD40 水平与肺腺癌的发生呈正相关 （OR= 0.81，95% 95% CI：0.69-0.96，p = 0.0133）。对于肺鳞癌，结果显示，较高的 CXCL5、CXCL6、MCP-1 水平可能与肺鳞癌的发生呈正相关（OR = 1.28，95% CI：1.06-1.54，p = 0.0092；OR = 1.24，95% CI：1.04 -1.47，p = 0.0138；OR = 1.41，95% CI：1.02-1.96，p = 0.0393）。较低的 IL-10 水平可能与肺鳞癌的发生呈正相关 （OR = 0.66，95% CI：0.49-0.90，p = 0.0082）。此外，MCP-1、OPG 水平较高可能与小细胞肺癌的发生呈正相关（OR = 1.93，95% CI：1.25-2.97，p=0.0032），腺苷脱氨酶水平和干细胞因

子水平较低与 SCLC 的可能发生呈正相关（OR=0.74，95%CI:0.58-0.93，p=0.0097；OR=0.71，95%CI:0.52-0.97，p=0.0295）。

结论：遗传预测的 CXCL5、CXCL6、MCP-1、OPG 水平可能与肺癌风险增加有关。遗传预测的 CD40、IL-10、腺苷脱氨酶和干细胞因子水平在降低肺癌发生的风险方面具有统计学意义。总之，我们的研究证实了炎症因子对肺癌的发生发展具有关键影响，并可能为治疗这种疾病提供一种新的方法。

关键字 ：炎症细胞因子，炎症，肺癌，肺腺癌，肺鳞癌，小细胞肺癌，孟德尔随机化

535. Bortezomib depended on PRDM1 and TP53 to exert therapeutic effect in activated B-cell-like diffuse large B-cell lymphoma

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PR/SET domain 1 (PRDM1) gene was located on chromosome 6q21, encodes the B lymphocyte-induced maturation protein 1 (BLIMP1). Hereafter they were collectively referred to as PRDM1. Previously, it was suggested that the loss of PRDM1 function was exacerbated in activated B-cell-like (ABC)-DLBCL and associated with inferior survival. However, it remains unclear what leads to PRDM1 inactivation and how to address the drug resistance caused by the abnormal inactivation of PRDM1. We investigated the contribution of PRDM1 gene as a prognosis and potential therapeutic target for ABC-DLBCL patients, and further clarified the possible mechanism of PRDM1 inactivation. We first proposed that TP53 could regulate PRDM1 by histone ubiquitination modification in the post-transcriptional level. Moreover, the therapeutic effect of bortezomib was dependent on PRDM1 and TP53, and a synergistic effect was produced with lenalidomide, which provided a theoretical reference for overcoming drug resistance in PRDM1-mutated ABC-DLBCL patients.

We collected blood or tissue samples from 104 DLBCL patients to confirm the prognostic effect of PRDM1 mutation on DLBCL patients. Eight patients had PRDM1 mutations, six of them fell into

non-germinal center subtype (non-GCB) (Tab. S1). Seven patients had MYD88L265P and/or CD79B mutations. Compared with patients with wild-type PRDM1, patients with PRDM1 mutation had significantly shorter PFS and OS (Fig. S1). In ABC-DLBCL cell lines, PRDM1 overexpression led to significant increase in apoptosis (Fig. S2A and B), and inhibition on proliferation (Fig. S2C). At the same time, knocking out PRDM1 suppressed apoptosis (Fig. S2D) and promoted proliferation (Fig. S2E). In summary, the above results demonstrated that the potential of PRDM1 serving as a tumor suppressor in ABC-DLBCL cell lines.

In order to further investigate the potential mechanism of PRDM1 inactivation, we selected four ABC-DLBCL cell lines (SU-DHL2, HBL-1, U-2932, RI-1) and one multiple myeloma (MM) cell line (U-266) (Tab. S2). SU-DHL2, which had PRDM1 exon2 mutation, showed high mRNA level (both PRDM1α and PRDM1β) but low levels of PRDM1 protein expression (Fig. S3A and B). In the cycloheximide (CHX) experiment, PRDM1 protein decay rate was significantly higher in PRDM1 mutated cell lines than in PRDM1 wild-type cell line (Fig. S3C). It was discovered that PRDM1 mutation not only influence protein stability but also affects its function. Bortezomib inhibited the degradation of PRDM1 protein caused by PRDM1 mutation, restored the expression level of PRDM1 protein, inhibited the expression of downstream target genes including c-myc and BCL6 (Fig. 1A) and significantly increased apoptosis in a time and concentration dependent manner (Fig. S3D, E). PRDM1 protein level in the nucleus of SU-DHL2 cells showed a significant increase after the bortezomib treatment (Fig. S3F, G). The sensitivity of SU-DHL2 cells to bortezomib was sharply reduced after knocking-out of PRDM1, but restored by the recovery of PRDM1 expression (Fig. S3H, Fig. 1B). In contrast, treating PRDM1 wild-type cell line, U-2932, with bortezomib failed to increase the level of PRDM1 protein expression or promote tumor cell apoptosis (Fig. S3I-K).

Previous results have shown that more than 40% of the ABC-DLBCL patients lacked PRDM1 protein expression despite being of PRDM1 wild-type, and the expression level of wild-type TP53 was positively correlated with the expression level of PRDM1 protein [1]. Yan J suggested that a loop regulation relationship may exist between TP53 and PRDM1 in colorectal cancer cells, TP53 up-regulated PRDM1 transcription and PRDM1 depletion increased the level of p53 expression [2].We discovered that knocking out TP53 resulted in a down-regulation of PRDM1 protein expression, while over-expression of TP53 led to up-regulation of PRDM1 protein expression (Fig.

1C). However, mRNA levels were inconsistent with protein levels. Through CHX experiments, we observed that the degradation rate of PRDM1 protein increased after knockout of TP53, but decreased after over-expression of TP53 (Fig. S3L). The transfection of PRDM1-overexpression virus into tool cell 293T was followed by knockout and over-expression of TP53. Co-immunoprecipitation experiments were performed after 72h treatment with MG132 20 μM. It was found out that the ubiquitination degradation rate of PRDM1 protein were enhanced after TP53 knockout but suppressed after TP53 overexpression (Fig. 1D). After the knockout of TP53, bortezomib failed to restore the expression level of PRDM1 protein and slowed down the degradation rate (Fig. S3M). With the recovery of p53 expression, bortezomib resulted in a increase of PRDM1 protein expression level again (Fig. 1E). Furthermore, the sensitivity of SU-DHL2 to bortezomib was significantly reduced after the knockout of TP53, but restored after p53 expression recovered in PRDM1 mutant cell lines (Fig. 1F, 1G). As suggested by the above results, bortezomib relies on TP53 to eliminate tumor cells. There is no report on the regulatory relationship between TP53 and PRDM1 in DLBCL. Yan J suggested that a loop regulation relationship may exist between TP53 and PRDM1 in colorectal cancer cells, TP53 up-regulated PRDM1 transcription and PRDM1 depletion increased the level of p53 expression [2]. Our study is the first to propose that TP53 regulated the PRDM1 protein ubiquitination-proteasome degradation pathway in ABC-DLBCL. Post-translational modification (PTM) initiates cellular processes by regulating the physicochemical properties, folding, conformation, stability, and activity of proteins. Phosphorylation, ubiquitination, glycosylation, acetylation, and SUMOylation have all been discovered as capable to regulate signal transduction, epigenetics and protein expression. Bortezomib failed to restore PRDM1 expression after TP53 knockdown, which indicated that TP53 may also regulate PRDM1 through other posttranslational modifications.

As revealed by the studies in MM, a higher level of PRDM1 expression leads to a greater sensitivity to lenalidomide [3].CRBN has already been confirmed as the target of lenalidomide [4]. It was found out that the expression level of PRDM1 was positively correlated with that of CRBN (Fig. S3N, Fig. 1H). By combining bortezomib and lenalidomide in the PRDM1 mutant SU-DHL2 cell line, it was observed that there was a significant increase in the expression levels of PRDM1 and CRBN (Fig. 1I). The index CI showed the significance of the synergistic effect produced by the combination of the two drugs (Fig. 1J). After 24h of combined treatment with bortezomib and

lenalidomide, the apoptosis of SU-DHL2 cells was significantly increased (Fig. 1K). Moreover, the synergistic effect of bortezomib and lenalidomide was reversed in PRDM1-KO-SU-DHL2 cells, and restored when the PRDM1 expression level recovered (Fig. 1L). As confirmed by the in vivo experiments on mice, the combination of bortezomib and lenalidomide significantly reduced the tumor volume after SU-DHL2 tumor formation (Fig. 1M). However, there was no synergistic inhibitory effect observed in PRDM1 wild-type cells (Fig. 1N), which proved that the synergy in ABC-DLBCL is specific to PRDM1 mutant cells. Overall, our study confirmed that the applicability of PRDM1 gene as a prognosis and potential therapeutic target for ABC-DLBCL patients, and clarified the possible mechanism of PRDM1 inactivation. At the genetic level, PRDM1 mutation caused protein instability and degradation, while bortezomib reversed the PRDM1 inactivation caused by PRDM1 mutation. In addition, TP53 regulated PRDM1 at the post-transcriptional level and the knockout of TP53 blocked the anti-tumor effect of bortezomib on PRDM1 mutant cells. In PRDM1 mutant cell lines, the application of bortezomib and lenalidomide in combination produced a synergistic effect by improving the expression level of PRDM1 and CRBN and enhancing the therapeutic effect, which is conducive to the treatment of drug-resistant ABC-DLBCL (Fig. S4).

Key Words： Activated B-cell-like; Diffuse large B-cell lymphoma; PRDM1; p53; Bortezomib; Lenalidomide

536. TWIST1 蛋白的 G-四链体调控及其在乳腺癌侵袭转移中的分子新通路研究

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目的：乳腺癌是全球女性最常见的恶性肿瘤，也是第二大癌症死因。虽然因为术后化疗和联合治疗的应用，乳腺癌的死亡率有所下降，但仍然缺乏针对性的癌症控制干预措施。转录因子 TWIST1 是一种碱性螺旋-环-螺旋蛋白，研究表明，TWIST1 在乳腺癌患者人群中被异常激活，呈现高表达，因此，探索 TWIST1 异常激活的机制和寻找靶向 TWIST1 调控的新的分子是有必要的。G-四链体(G4)是由富含鸟嘌呤(G)的序列组成的非规范的 DNA/RNA

二级结构，最近的研究表明，G-四链体结构在癌症的发生和治疗中也具有重要的作用。本课题从 G4 调控的研究入手，基于 TWIST1 蛋白的稳定性探索 TWIST1 在乳腺癌中过度表达的机制和作用。

方法：TWIST1 的 G4 结构生物信息学分析预测：将 NCBI 找到的 TWIST1 基因序列复制至 QGRS Mapper (http://bioinformatics.ramapo.edu/QGRS/)，预测得到可能形成 G4 结构的位点序列以及形成 G4 结构的可能性（以 G-Score 值表示），并选择 G-Score 值在 19 或 20 分以上的 PQS 序列进行保守性分析；鉴定 TWIST1 基因存在的 G4 结构：分别合成预测得出的 G4 序列及其 G4 位点突变序列，通过化学实验方法荧光发射光谱测量、凝胶迁移率变化测定、圆二色谱法分析以及细胞实验免疫荧光定量分析鉴定出 TWIST1 的 G4 位点；上游基因对 TWIST1 的 G4 调节的表达分析：结合文献报道，获得候选的各解旋酶，在肿瘤细胞系 HeLa 和 HEK293 中行各解旋酶基因的过表达,检测 TWIST1 基因的蛋白和 mRNA 表达是否上调，同时构建 TWIST1 表达质粒和可诱导稳定细胞系及其突变细胞系，检测过表达或敲低解旋酶后 TWIST1 蛋白及 mRNA 表达情况；TWIST1 及其 G4 功能分析：在乳腺癌细胞系中过表达或者基因沉默上游基因，检测对细胞增殖、迁移、侵袭的影响以及同时沉默 TWIST1 检测其是否依赖 TWIST1 的表达；构建 TWIST1 G4 位点突变重组质粒，再构建 HEK293 稳定细胞系，在细胞系中过表达解旋酶, 进行肿瘤增殖，迁移，侵袭能力检测。

结果：通过生物信息学分析，预测得出 TWIST1 基因结构中的两个可能的 G4 位点 PQS-454 与 PQS-559，G-Score 值均为 21 分，且在物种间相对保守；通过荧光发射光谱测量，发现 TWIST1 两个 G4 位点 WT 序列均在 KCl、NaCl、LiCl 等促进 G4 结构形成的阳离子溶液中表现出稳定的 G4 结构的形成，而进行相应的 G4 位点突变以后，TWIST1 的 G4 二级结构的形成被抑制，并且 G4 结构的形成能力在三种溶液中呈现 KCl＞NaCl＞LiCl 的趋势；通过凝胶迁移率的测定，发现 PQS-454 在凝胶中可以形成迁移受阻的 G4 延迟带，进行相应突变的序列形成 G4 的能力减弱，而 PQS-559 未能检测到这种延迟带，因此，我们初步确定 PQS-454 为 TWIST 基因的主要 G4 位点并继续进行下一步实验的鉴定；在 HEK293-TWIST1 的稳定细胞系与 HeLa 细胞中过表达各种解旋酶后，发现解旋酶 DDX21 基因的过表达可以明显上调 TWIST1 蛋白水平的表达，初步鉴定 DDX21 为调控 TWIST1 G4 位点进而调控 TWIST1 蛋白表达的上游解旋酶基因，并进行下一步的机制验证与功能分析。

结论：解旋酶 DDX21 可能可以通过调节 TWIST1 蛋白的 G4 结构，影响 TWIST1 蛋白在乳腺癌中的表达，进而影响 TWIST1 在乳腺癌生长、侵袭与转移中的作用。

关键字： TWIST1,G-四链体，乳腺癌，侵袭，转移

537. CA15-3、CA125 及 CEA 联合检测在乳腺癌中的诊断价值

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目的： 研究 CA15-3，CA125，CEA 联合检测在临床乳腺癌诊断中的应用意义，致力于探索出一种更好服务于临床的检测模式。

方法：以病理诊断为判断标准，选取因乳腺不适来我院就诊的 70 例女性患者，35 例病理结果确诊为乳腺癌疾病的患者，将其归为乳腺癌组；另外 35 例确诊非乳腺癌，而是乳腺良性病变患者，将其归为乳腺良性组。在常规体检人群中，选择健康女性 35 例，将其归为对照组。比较各组研究对象血清中 CA15-3，CA125，CEA 的水平；判断不同检测模式下，各诊断性能指标变化。

结果：乳腺癌组患者血清 CA15-3，CA125，CEA 水平超过另外两组，乳腺癌组阳性检出率高于良性组，而且联合检测高于单一检测，这些差异在统计学上具有显著性(P<0.05)。联合检测与单一检测相比较，发现灵敏度提高到 80.1%，准确度提高到 78.6%。

结论：CA15-3、CA125 和 CEA 三项联合可弥补单项检测的不足，在乳腺疾病诊断中意义非凡，对临床的及时诊断发挥巨大价值。

关键字： 乳腺癌；糖类抗原 15-3；糖类抗原 125；癌胚抗原

538. 华氏巨球蛋白血症患者 44 例免疫球蛋白 重链序列使用特征的分析

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目的 探讨免疫球蛋白重链可变区(IGHV)基因的变异状态与华氏巨球蛋白血症(WM)患者预后的相关性.

方法 采集 2010 年 12 月至 2020 年 12 月在江苏省人民医院初诊的 44 例 WM 患者的血液和/或骨髓样本,通过直接测序确定主克隆并进行免疫球蛋白重链（IGH)基因的序列分析,描述 WM 患者 IGHV-IGHD-IGHJ 基因的使用特征。

结果 在 44 例患者中,IGHV 3 基因家族的使用率最高,该结果与中国医学科学院血液病研究所的数据相似,主要使用的片段为 IGHV 3 -23(20.45％vs．15.44％)及 IGHV 3 - 7 4 (11.36％vs．7.35％),其次为 IGHV 4 基因家族(15.91％vs.24.26％).但使用 IGHV 4 家族与预后无相关性.以 9 8％作为 IGHV 变异状态的截断值,仅 5 例患者 IGHV 无变异,且与预后无相关性.根据 XG tile 分析,选择将 92.6％作为 WM 患者 IGHV 变异状态的截断值,26 例(59.1％)IGHV 无变异患者的血清乳酸脱氢酶增高(P＜0.05),无进展生存期(P＜0.05)及 OS(P＜0.05)与 IGHV 变异组相比均显著缩短。

结论 患者 IGHV-IGHD-IGHJ 的使用特征与中国医学科学院血液病研究所的数据相似,但使用 IGHV 4 家族与预后无相关性。此外, 9 8％可能并不适用于区分 WM 患者的 IGHV 变异状态。

关键字： 免疫球蛋白重链可变区;基因变异;华氏巨球蛋白血症;预后

539. Investigating the Regulatory Mechanism of miR-1260-ZNF Family Genes in Non-Small Cell Lung Cancer

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Globally, lung cancer remains one of the most common malignant tumors. However, the molecular mechanisms involved in its pathogenesis have not been elucidated. This study aimed to investigate the specific regulatory mechanism of miR-1260 (miR-1260a)-ZNF family genes (ZNF302, ZNF439, ZNF781) action mechanism in non-small cell lung cancer (NSCLC). The expression and prognostic significance of miR-1260 and target ZNF family genes in NSCLC and its subtypes were sequentially analyzed using public datasets and bioinformatics tools. The expression of miR-1260 in cancer and normal tissues was analyzed by GEO2R, and then the downstream ZNF family genes (mRNAs) were predicted by the target gene prediction platforms Targetscan and

miRDB, while the target ZNF family genes were analyzed for their expression in cancer and normal tissues by GEPIA, and their respective prognostic significance was analyzed by the Kaplan-Meier- Plotter database to analyze their respective prognostic significance. Based on the DAVID tool, the target ZNF family genes were analyzed by functional annotation using GO and KEGG. Meanwhile, the target ZNF family genes were analyzed for immune infiltration using TIMER and TISIDB. In lung squamous cell carcinoma (LUSC) patients, low expression of miR-1260 had a poor prognosis. In lung adenocarcinoma (LUAD) patients, ZNF439 expression levels were lower than normal. There were significant differences in the expression of ZNF302 and ZNF439 at different stages of LUAD. In addition, the levels of ZNF302, ZNF439, and ZNF781 mRNA were all associated with overall survival (OS) and progression-free survival (PFS). In LUSC patients, the expression levels of ZNF302, ZNF439, and ZNF781 were lower than those of normal subjects. ZNF302, ZNF439, and ZNF781 were associated with PFS. Immune infiltration analysis showed that most immune cells regulated by target genes were significantly increased in NSCLC. This study suggests that ZNF439 is a potential diagnostic marker, whereas ZNF302, ZNF439, and ZNF781 are potential PFS markers in NSCLC patients. These highlight new targets for early detection and treatment of NSCLC.

Key Words： NSCLC; miR-1260; Zinc finger family; Prognostic value; Immune infiltration

540. VEGFA 和 SOX4 在肝癌中的表达及临床意义的生物信息学分析及验证

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目的：通过生信分析探索血管内皮细胞生长因子 A（VEGFA）和 SRY 相关 HMGbox 转录因子 4(SRY-box transcription factor-4,SOX4)在肝细胞癌中的表达特征以及与肝细胞癌患者临床病理特征关系，并分析 VEGFA 和 SOX4 与肝细胞癌患者预后的相关性，确定 VEGFA 和 SOX4 在肝癌中的作用机制并通过多重免疫荧光染色进行验证。

方法：利用癌症基因组图谱（TCGA）数据库，GETx 数据库获取肝细胞癌数据,以及正常组织数据，多种在线数据库结合 R 语言对 VEGFA 和 SOX4 在肝细胞癌中的表达情况、临

床病理特征、甲基化，以及两个基因的相关性方面等进行分析。并通过 HCC 组织芯片多重免疫荧光染色(Multiplex IHC,mIHC)来验证生物信息学分析的结果。

结果：VEGFA 和 SOX4 在 HCC 组织中较正常组织表达明显升高（$p<0.05$），并且 VEGFA 高表达与患者的生存率密切相关，即 VEGFA 高表达患者其生存率更低（$p<0.05$）。

结论：VEGFA 和 SOX4 在 HCC 诊断，诊疗等方面有重要的意义。

关键字： 肝细胞癌；VEGFA，SOX4,mIHC；表达；验证

541. A high-efficient capture-based NGS approach for comprehensive analysis of mitochondrial transcriptome

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The transcription of mitochondrial genome is pivotal for maintenance of mitochondrial functions, and deregulated mitochondrial transcriptome contributes to various pathological changes. Despite substantial progress has been achieved in uncovering the transcriptional complexity of the nuclear transcriptome, many unknowns and controversies remain for the mitochondrial transcriptome, partially owing to the lack of high-efficient mitochondrial RNA (mtRNA) sequencing and analysis approach. Here, we first comprehensively evaluated the influence of essential experimental protocols, including strand-specific library construction, two RNA enrichment strategies and optimal rRNA depletion, on accurately profiling mitochondrial transcriptome in whole transcriptome sequencing (WTS) data. Based on these insights, we developed a high-efficient approach specifically suitable for targeted sequencing of whole mitochondrial transcriptome, termed capture-based mtRNA seq (CAP), in which strand-specific library construction and optimal rRNA depletion was applied. Compared with WTS, CAP has a great decrease of required data volume, without affecting the sensitivity and accuracy of detection. In addition, CAP also characterized the unannotated mt-tRNA transcripts whose expression level is below the detection limits of conventional WTS. As a proof-of-concept characterization of mtRNAs, the transcription initiation sites and mtRNA cleavage ratio were accurately identified in CAP data. Moreover, CAP had a very reliable performance in plasma and single-cell samples, highlighting its wide

application. Altogether, the present study has established a high-efficient pipeline for targeted sequencing of mtRNAs, which may pave the way toward functional annotation of mtRNAs and mtRNA-based diagnostic and therapeutic strategies in various diseases.

Key Words ：mitochondrial RNA; capture-based sequencing; mitochondrial transcriptome profiling.

542. 腹水肿瘤细胞的内吞作用、脂类代谢以及微环境免疫活性减弱对高级别浆液性卵巢癌患者铂类治疗的影响

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研究目的：铂类药物是卵巢癌治疗的基石，但其在治疗过程中出现的耐药性备受关注。本研究从蛋白层面挖掘卵巢癌患者化疗前腹水细胞中的铂类耐药相关特征，作为化疗前对铂类耐药的提示指征，可帮助患者及时调整治疗方案。

材料与方法：本研究纳入了 18 例高级别浆液性卵巢癌患者，其中铂类敏感者 10 例，耐药者 8 例。收集化疗前的腹水离心所得细胞沉淀进行蛋白质组分析，通过免疫组织化学（IHC）、Western Blotting（WB）、CCK8 在扩大样本和细胞系（敏感株 SKOV3/耐药株 SKOV3-DDP）中验证分析结果。并援引外部公共卵巢癌组织单细胞数据描述肿瘤微环境特征。18 例样本所得特征分子和通路被作为训练集构建支持向量机模型，以 TCGA 数据库卵巢癌转录组数据作为验证集代入分型，将分型结果进行生存分析以验证这些特征的预后价值。

结果：铂类耐药患者在治疗前，内吞（尤其是巨胞饮）与其代表分子 SH3YL1 上调，脂类分解代谢与其代表分子 MLYCD 上调，免疫活性与其代表分子 CD44 下调，并表现出较高的血甘油三酯水平。公共单细胞数据表明耐药的卵巢癌组织免疫活性细胞浸润少，瘤细胞免疫原性下降，固有免疫和适应性免疫的激活程度下降。TCGA 卵巢癌公共数据代入向量机模型预测敏感耐药分型后进行生存分析，发现组间明显差异。CCK8 实验发现，巨胞饮抑制

剂 EIPA 在抑制敏感组摄取铂类继而提高敏感组半抑制浓度（IC50）的情况下，降低了耐药组的 IC50。

结论：富脂微环境使得卵巢癌细胞可以通过内吞（尤其是巨胞饮）从外界摄取丰富的脂质（如甘油三酯）而不必自行合成，从而节省大量的三磷酸腺苷和还原性物质用以应对铂类造成的损伤，同时脂质还能合成细胞膜成分及参与信号转导，进一步有利于内吞的持续和肿瘤的增殖、抗凋亡。免疫细胞中脂质积累会导致其表现出免疫衰竭表型。这三大特征可提示卵巢癌铂类耐药并预测预后，是扭转铂类耐药的可能靶点。

关键字： 卵巢癌；铂类耐药；内吞；脂代谢；肿瘤微环境

543. Integrated profiling uncovers prognostic, immunological, and pharmacogenomic features of ferroptosis in triple-negative breast cancer

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Objective: Ferroptosis is an iron-dependent type of regulated cell death triggered by the toxic buildup of lipid peroxides on cell membranes. Nonetheless, the implication of ferroptosis in triple-negative breast cancer (TNBC), which is the most aggressive subtype of breast carcinoma, remains unexplored.

Methods: Three TNBC cohorts—TCGA-TNBC, GSE58812, and METABRIC—were adopted. Consensus molecular subtyping on prognostic ferroptosis-related genes was implemented across TNBC. Ferroptosis classification-relevant genes were selected through weighted co-expression network analysis (WGCNA), and a ferroptosis-relevant scoring system was proposed through the LASSO approach. Prognostic and immunological traits, transcriptional and post-transcriptional modulation, therapeutic response, and prediction of potential small-molecule agents were conducted.

Results: Three disparate ferroptosis patterns were identified across TNBC, with prognostic and immunological traits in each pattern. The ferroptosis-relevant scoring system was proposed, with poorer overall survival in high-risk patients. This risk score was strongly linked to transcriptional

and post-transcriptional mechanisms. The high-risk group had a higher response to anti-PD-1 blockade or sunitinib, and the low-risk group had higher sensitivity to cisplatin. High relationships of risk score with immunological features were observed across pan-cancer. Two Cancer Therapeutics Response Portal (CTRP)-derived agents (SNX-2112 and brefeldin A) and PRISM-derived agents (MEK162, PD-0325901, PD-318088, Ro-4987655, and SAR131675) were predicted, which were intended for high-risk patients.

Conclusion: Altogether, our findings unveil prognostic, immunological, and pharmacogenomic features of ferroptosis in TNBC, highlighting the potential clinical utility of ferroptosis in TNBC therapy.

Key Words ： Triple-negative breast cancer, ferroptosis, prognosis, Immunological feature, Immunotherapy

544. 机器学习选取血浆外泌体生物标志物建立肺鳞癌的诊断和预后模型

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目的：本研究旨在探索使用新型纳米材料 NaY 富集血浆源外泌体作为候选生物标志物，用于区分良性和恶性肺结节，以及预测肺鳞状细胞癌患者的预后。

材料和方法：本研究收集了 128 例肺鳞癌和 84 例良性肺结节患者血浆样本，使用新型纳米材料 NaY 富集血浆中的外泌体，并通过透射电子显微镜、纳米粒子直径分析、Western blot 实验验证。利用质谱分析，得到外泌体中蛋白质丰度表达信息，进行差异分析，富集分析。使用机器学习算法 XGBOOST 计算与肺鳞癌相关的蛋白质生物标志物，并根据生物学功能挑选出 5 个蛋白，建立诊断模型，并使用验证队列检测模型诊断效能。使用 ELISA 在独立队列中验证生物标志物的诊断效能。利用单因素 cox 筛选出与肺鳞癌预后相关的蛋白，并使用 101 种机器学习算法组合建立肺鳞癌预后预测模型，并使用验证队列检测模型预测效能。根据每例样本中患者生物标志物的表达丰度，对患者进行风险评分，并将患者分为高、低风险两组，对两组患者富集分析寻找形成于后差异的原因。

结果：通过透射电子显微镜、纳米粒子直径分析、Western blot 结果显示新材料 NaY 可以富集到外泌体。针对外泌体蛋白质组的富集分析发现肺鳞癌患者血浆外泌体中与 GTP 酶活性和磷酸酶激活活性相关的蛋白质分泌增加，糖酵解/糖异生和碳代谢相关的通路在这些囊泡中得到富集。我们鉴定了 38 个与肺鳞癌相关的外泌体生物标志物，并选取了五个蛋白质（TUBB3、RPS7、RPLP1、KRT2 和 VTN）建立了一个有良好诊断效能的诊断模型，可以很好的区分良性结节和肺鳞癌结节（AUC = 0.999，95% CI = 0.995 – 1.000）。使用 ELISA 实验在独立样本中验证了 RPS7 和 VTN 的诊断效能。

此外，我们利用肺鳞癌蛋白质组数据和患者临床信息，确定了 DPYD、GLAK1、CDC23、UBE2L3、RHEB 和 PSME1 作为潜在的预后生物标志物。最后，通过采用风险预测模型，我们计算了每个样本的风险分数，并发现它们能有效预测肺鳞癌患者的预后。根据风险分数将所有患者分为高低风险两组人群，对两组人群富集分析发现高风险人群外泌体中富含促进细胞增殖、侵袭的蛋白标志物，而低风险人群血浆外泌体中富含免疫相关蛋白质标志物。

结论：新材料 NaY 可以富集到血浆中外泌体，血浆外泌体生物标志物建立的诊断模型可以很好的区分患者肺部结节的良恶性，预后模型可以很好的预测患者的预后。

关键字 ：肺鳞癌、血浆外泌体、机器学习、诊断及预后

545. Mitochondrial DNA Haplogroups and SNPs: Risk Factors in Multiple Cancers Based on a Cross-Tumor Analysis in Chinese Population

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Background: Mitochondrial DNA's haplogroups and single nucleotide polymorphisms were associated with the risk of different cancer. However, there is no evidence that the same haplogroup or mtSNP exhibits the pleiotropic effect on multiple cancers.

Methods: We recruited 2489 participants, including patients with colorectal, hepatocellular, lung, ovarian, bladder, breast, pancreatic, and renal cell carcinoma. In addition, 715 healthy individuals from Northern China served as controls. Next, cross-tumor analysis was performed to determine if mtDNA variation is associated with multiple cancers.

Results: Our results revealed a significant decrease in the occurrence risk of multiple cancers among individuals belonging to haplogroup A (OR = 0.553, 95% CI = 0.375-0.815, P = 0.003). Furthermore, we identified 11 mtSNPs associated with multiple cancers and divided the population into high-risk and low-risk groups. Low-risk groups showed a significantly reduced risk of occurrence compared with high-risk groups (OR =0.614, 95% CI = 0.507-0.744, P < 0.001). Furthermore, using interaction analysis, we identified a special group of individuals belonging to haplogroup A/M7 and the low-risk population, who exhibit a lower risk of multiple cancers compared to other populations (OR =0.195, 95% CI = 0.106-0.359, P < 0.001). Finally, GSEA confirmed that haplogroup A/M7 patients had lower expression levels of cancer-related pathway genes compared to haplogroup D patients.

Conclusions: We found that specific mtDNA haplogroups and mtSNPs may play a role in predicting multiple cancer predisposition in Chinese populations.

Impact: This may provide a potential tool for early screening in clinical settings for individuals in the Chinese population.

Key Words： haplogroup, SNP, risk factors

546. 杭州市 36603 例健康体检人群糖类抗原 72-4（CA72-4）检测结果分析

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目的 分析杭州迪安医学检验中心 36603 例健康体检人群肿瘤标志物中的糖类抗原 72-4（CA72-4）血清抗原检测结果，探究不同性别和年龄组 CA72-4 的水平差异。

方法 用电化学发光法检测健康体检人群糖类抗原 72-4 水平，按性别（男和女）和年龄段（0~18 岁、19~34 岁、35~60 岁和>60 岁）进行分组，并对统计结果进行 SPSS 软件分析。

结果 在杭州市 36603 例健康体检人群中，男女之间 CA72-4 异常比例比较，差异均有统计学意义（P<0.05)。女性>60 岁体检人群 CA72-4 异常人数最多，男性 35~60 岁异常人数最多。不同年龄段 CA72-4 异常比例比较，差异均有统计学意义（P<0.05）。

结论 杭州市健康体检人群中，性别和年龄对糖类抗原 72-4 的水平均有影响。

关键字： 肿瘤标志物；健康体检人群；糖类抗原 72-4；

547. CD47-SIRP α 相关的免疫检查点抑制剂在弥漫性大 B 细胞淋巴瘤中的作用

程明杰

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弥漫性大 B 细胞淋巴瘤（Diffuse large B-cell lymphoma，DLBCL）是一种具有高度侵袭性和异质性的非霍奇金淋巴瘤，在 WHO(2022)大 B 淋巴瘤分类中，DLBCL 最为常见。随着对 DLBC 发病机制研究的不断深入，多数 DLBCL 患者利用抗 CD20 的单克隆抗体利妥昔单抗可以达到较好的治疗效果。然而，仍有近 40%的 DLBCL 患者面临难以治愈及复发率高等问题，最终因病情恶化而死亡。因此，寻找新的治疗靶点对于 DLBCL 的治疗至关重要。CD47 是一种五次跨膜蛋白，在多种细胞均有表达，大量研究表明，CD47 在 DLBCL 中的表达量远高于正常细胞，且其表达水平与疾病的进展呈正相关。巨噬细胞表达信号调节蛋白 α（Signal Regulatory Protein α，SIRPα），其胞质内含有可与 CD47 相互作用的免疫受体酪氨酸抑制基序（ITAM），是一种可以识别 CD47 的受体，通过与 CD47 相互作用，释放抑制信号，保护正常细胞免受吞噬，是重要的免疫检查点。而肿瘤细胞通过过表达 CD47，与 SIRPα结合，释放“别吃我”信号，抑制巨噬细胞对肿瘤细胞的吞噬并抑制抗肿瘤免疫，促使其逃逸和生长。因此阻断 CD47/SIRPα轴，可重新恢复巨噬细胞的吞噬功能，以达到治疗 DLBCL 的目的。大量研究证实，CD47 的表达水平与 DLBCL 的预后密切相关,这使 CD47-SIRP 有望成为继 PD-L1 后又一重要免疫治疗靶点。目前临床对 CD47-SIRPα免疫检查点抑制剂治疗 DLBCL 已有一定的认识，但是由于 CD47 表达广泛，治疗过程中可能会出现血液毒性等靶问题，因此 CD47-SIRPα免疫检查点抑制剂治疗的安全性和有效性仍需要进一步的研究。

关键字： 弥漫性大 B 细胞淋巴瘤；CD47；SIRPα；免疫治疗

548. 血清和尿液代谢指纹图谱用于肾细胞癌的分类、早期诊断和预后评估

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研究目的：肾细胞癌（Renal cell carcinoma，RCC）是泌尿系统中一种常见的恶性肿瘤类型，近年来，其患病人数呈现出持续上升的趋势。肾细胞癌由于在不同患者之间表现出各种异质性，导致现有的临床诊疗手段在管理该病时面临诸多挑战。

随着液体活检技术的兴起，它通过实时采集和分析患者样本，已经成为疾病诊断、预后判断和治疗响应监测的一个有前景的方法。在这些生物标志物中，代谢物因其反映生物代谢途径最终产物的特性，能够为体内进行的病理过程提供一种更为深入和全面的了解。最新研究表明，基于代谢物的检测由于其最小的侵入性操作，尤其在肾细胞癌的诊断中显示出巨大的潜力。但是，这些研究大多关注于单个生物流体的代谢轮廓分析，这种方式面临样本量有限及功能不全面的局限性，从而在支持诊断和预后方面存在不足。为此我们开发了代谢检测平台，并评估了血清和尿液代谢组学在肾肿瘤分类、早期检测和预后评估中的临床应用价值。

实验设计：本研究构建了纳米颗粒增强激光解吸电离质谱(nanoparticle-enhanced laser desorption ionization mass spectrometry，NELDI MS)分析血清和尿液生物样本。我们在一个肾肿瘤(n = 456)和健康对照(n = 200)的单机构队列中表征了与临床信息相关的代谢指纹。应用自动化的机器学习方法开发了分类和早期诊断模型；通过非线性特征选择算法筛选出血清和尿液生物标志物；预后表现采用 Cox 回归进行评估。

结果：分类模型区分肾肿瘤与健康对照的曲线下面积(areas under curves，AUC)为 0.938 (95 %置信区间(CI)，0.884 ~ 0.967)；鉴别肾细胞癌良恶性的 ROC 曲线下面积为 0.850 (95 % CI : 0 . 821 ~ 0 . 915)，鉴别肾细胞癌亚型的 ROC 曲线下面积为 0.925 - 0.932 (95 % CI : 0 . 821 ~ 0 . 915)。对于早期 RCC 亚型，我们在测试集中获得了平均 90.5 %的诊断敏感性和 91.3 %的特异性。血清和尿液中的代谢物被鉴定为 RCC 亚型诊断的潜在生物标志物(p < 0.05)。为了验证预后性能，我们构建了 211 例肾透明细胞癌样本的预后系统，从而有效的预测患者的疾病(p = 0.003)。

结论：我们的研究为代谢分析工具应用于 RCC 的表征提供了良好的前景。

关键字： 肾脏诊断、亚型分类、预后、质谱、代谢指纹图谱

549. Disruption of SLFN11 deficiency-induced CCL2 signaling and macrophage M2 polarization potentiates anti-PD-1 therapy efficacy in hepatocellular carcinoma

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Background & Aims: The therapeutic effect of immune checkpoint inhibitors (ICIs) is poor in hepatocellular carcinoma (HCC) and varies greatly among individuals. Schlafen (SLFN) family members have important functions in immunity and oncology, but their roles in cancer immunobiology remain unclear. Herein, we aimed to investigate the role of the SLFN family in immune responses against HCC.

Methods: Transcriptome analysis was performed in human HCC tissues with or without response to ICIs. A humanized orthotopic HCC mouse model and a coculture system were constructed, and cytometry by time-of-flight (CyTOF) technology was used to explore the function and mechanism of SLFN11 in the immune context of HCC.

Results: SLFN11 was significantly upregulated in tumors that responded to ICIs. Tumor-specific SLFN11 deficiency increased the infiltration of immunosuppressive macrophages and aggravated HCC progression. HCC cells with SLFN11 knockdown promoted macrophage migration and M2-like polarization in a CCL2-dependent manner, which in turn elevated their own PD-L1 expression by activating the NF-κB pathway. Mechanistically, SLFN11 suppressed the Notch pathway and CCL2 transcription by binding competitively with TRIM21 to the RRM2 domain of RBM10, thereby inhibiting TRIM21-mediated RBM10 degradation to stabilize RBM10 and promote NUMB exon 9 skipping. Pharmacological antagonism of CCR2 potentiated the antitumor effect of anti-PD-1 in humanized mice bearing SLFN11 knockdown tumors. ICIs were more effective in HCC patients with high serum SLFN11 levels.

Conclusions: SLFN11 serves as a critical regulator of microenvironmental immune properties and an effective predictive biomarker of ICIs response in HCC. Blockade of CCL2/CCR2 signaling sensitized SLFN11low HCC patients to ICI treatment.

Key Words： Schlafen 11; tumor-associated macrophages; immune checkpoint inhibitors; serum biomarker; hepatocellular carcinoma

550. Bibliometric of ANGPTL and the role of ANGPTL1 Gene in Hepatocellular Carcinoma

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Objective.

In this study， to summarize the current situation and development trend of the research on the correlation between liver cancer and angiopoietin-like (ANGPTL),and to discuss the role of ANGPTL1 Gene in Hepatocellular Carcinoma.

Methods.

Web of Science was used to collect literature and conduct quantitative analysis． From the CCLE database, we studied the expression of ANGPTL1 in a range of cancer cell lines.The HCCDB and Human Protein Atlas databases were used to analyze the differences in mRNA and protein expression of ANGPTL1 in HCC tissues.Additionally, the correlation between ANGPTL1 gene and clinicopathological features were assessed in the TCGA database by BEST website. The correlation between ANGPTL1 mRNA and overall survival was determined by the Kaplan-Meier plotter.

Results.

The bibliometric analysis results show that a total of 45 documents were compiled. There was a significant correlation between the ANGPTL1 members and the prognosis of HCC patients according to the Kaplan-Meier plotter analysis (p <0:05).ANGPTL1 are involved in certain pathways that may influence the development of HCC.

Conclusion.

The research on the correlation between the two is still in its infancy stage . In summary, the expression of ANGPTL1 was significantly correlated with HCC prognosis, suggesting that the ANGPTL1 may be promising molecular marker for HCC treatment and prognosis.

Key Words ： human angiopoietin-like protein 1； liver cancer； para-cancerous tissue； recurrence

551. Analysis of risk factors and establishment of predictive nomogram model for isolated distal deep vein thrombosis in colorectal cancer patients：a retrospective analysis of 1366 consecutive operated cases

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Abstract Background: Isolated distal deep vein thrombosis (IDDVT) represents half of all lower limb deep vein thrombosis (DVT) events. However, its incidence rate, anatomic distribution and risk factors have not yet been reported in colorectal cancer (CRC) patients. The clinical diagnosis and treatment are still controversial.

Methods: We conducted a retrospective study that enrolled 1366 CRC patients at Xijing Hospital between October 2021 and October 2022, to record the incidence rate, discuss the anatomical distribution characteristics, and analyze the course of IDDVT within 90 days after surgery. In addition, we established and validated a predictive model based on independent risk factors, to diagnose high-risk patients in the early stage and provide next management or follow-up strategies.

Results: The results indicated that the incidence of IDDVT in CRC patients was 6.0%, with the most involved in the soleal vein. Univariate and multivariate analysis demonstrated that gender, age, TNM stage, varicose veins, blood type, and D-dimer had a significant impact on the

occurrence of IDDVT. The DeLong test and decision curve analysis results indicated that the model was superior to Caprini and D-dimer in terms of discriminative performance and clinical utility. The nomogram of the model had an AUC of 0.846 (95% confidence interval (CI): 0.803-0.889) in the training group and 0.839 (95% CI: 0.767-0.911) in the testing group. Meanwhile, the Hosmer-Lemeshow goodness of fit test, decision curve analysis, net reclassification improvement, and integrated discrimination improvement showed excellent predictive performance.

Conclusion: The nomogram model can predict preoperative IDDVT in CRC patients more accurately.

Key Words： colorectal cancer; isolated distal deep vein thrombosis; Caprini; venous thrombosis; ultrasonography

552. 基于集成机器学习构建肝细胞癌的免疫系统发育相关预后模型及机制研究

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背景:免疫系统发育(immune system development, ISD)影响肿瘤的发生和发展，但其在肝细胞癌(hepatocellular carcinoma, HCC)中的作用和潜在机制尚不清楚。肝癌是世界上最常见和最致命的恶性肿瘤之一。尽管过去几十年肝癌得到了有效控制，但2021年全球仍有905677例新发病例和830,180例新死亡。肝细胞癌(HCC)是肝癌的主要组织学亚型，约占原发性肝癌病例的90%。精准医疗是改善HCC预后的关键。由于肝细胞癌的异质性，靶向治疗和免疫治疗对不同的肝癌人群治疗效果不一。因此，迫切需要一种新型、有效的生物标志物对HCC患者进行分层，精准预测患者预后、分子靶向药物及ICIs的疗效究。

方法：本研究通过整合机器学习对不同肝细胞癌人群进行分层，精准预测患者预后、分子靶向药物及ICIs的治疗疗效，并研究其中的潜在机制。通过单细胞组学，转录组学等对模型以及机制进行验证。

结果:在本研究中，我们开发了 167 种算法，通过整合 10 种机器学习算法来筛选一个最优和强大的 isd 相关签名(ISDRS)。由 7 个 ISDRS 相关基因组成的新风险评分在 3 个公共队列中具有最高的平均一致性指数(0.740)，多变量分析显示 ISDRS 是总生存的独立危险因素。此外，新的风险评分也优于已发表的 73 个模型。此外，在本研究中，我们试图探索在接受 ICIs 和 MTGs 的耐受患者中基于肿瘤免疫微环境的潜在机制。在本研究纳入的所有队列中，ICIs 和 MTGs 耐药患者的 Treg 浸润均显著增加，且与 ISD 和 ISDRS 均显著正相关(均 P<0.05)。此外，IL-6 作为调节 Treg 的重要细胞因子，激活由 IL-6 受体(IL-6R)和信号转导受体亚基 gp130 组成的受体复合物，促进初始 T 细胞分化为 Th17 细胞，而不是 Treg 细胞。在我们的研究中，Th17 信号通路在所有队列的 GO 和 KEGG 中均显著富集，Treg 浸润在高 ISD 水平组中显著增加，而 IL-6R 则相反。进一步证实 ISD 水平可能通过 IL-6R 的表达影响 Treg 的浸润。相关性分析显示，ISD 水平与 Treg 浸润呈正相关，而 IL-6R 与之呈负相关。有趣的是，在接受 ici 的两个外部队列和接受索拉非尼的另一个队列中也观察到这种相关性，并且基于 ISD 水平构建的 ISDRS 具有更高的相关系数。高 ISD 水平引起的 IL-6R 表达下调导致 Treg 细胞浸润增加，可能是导致 HCC 患者对 ICIs 和 MTGs 耐药的潜在机制，值得更深入的探索和验证。

结论:新的风险评分不仅可以作为预测 HCC 患者预后的生物标志物，而且可以作为指导 HCC ICIs 管理的替代指标。

关键字： 肝细胞癌，机器学习，单细胞，靶向药物

553. Identification of novel DNA methylation markers for early detection of cardia gastric adenocarcinoma and esophageal squamous cell carcinoma

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Aim: Cardia gastric adenocarcinoma (CGA) and esophageal squamous cell carcinoma (ESCC) remain major health burdens in China. Most of cases are diagnosed at advanced stages and carry a dismal prognosis. However, biomarkers for early detection of CGA and ESCC are still lacking. Here, we aim to integrate methylome and transcriptome data and identify DNA methylation markers for early detection of CGA and ESCC.

Material and Method: Infinium MethylationEPIC array was performed on 36 paired CGA and non-tumor adjacent tissues (NAT) in the discovery stage and differentially methylated CpG sites (DMCs) were identified between CGA/ESCC and NAT by combined analyses of in-house data and public database. Targeted pyrosequencing and quantitative real-time RT-PCR were performed to validate the methylation levels of candidate markers and expression levels of targeted genes on paired tumor and NAT from 50 CGA and 50 ESCC patients from an independent validation cohort. An independent cohort of 438 CGA, ESCC, high- and low-grade dysplasia (HGD/LGD), and normal control biopsies was tested for selected DMCs using pyrosequencing. For separate analysis of two disease entities, logistic regression was performed to assess the diagnostic performance of individual biomarkers and their combined discriminatory ability as a marker panel, respectively. For combined analysis of two disease entities, we randomly divided the subjects into training (80%) and test (20%) sets to test performance of a multivariable stepwise logistic regression model. These analyses were performed on “normal/LGD” versus “HGD/cancer”, because patients

with HGD or cancer are recommended to receive endoscopic or surgical therapy. Model discrimination was assessed through ROC analysis and AUC.

Results: We identified and validated three CGA-specific, two ESCC-specific, and one tumor-shared DMCs, which were significantly hypermethylated with lower expression of their located genes in tumor compared with NAT samples. Using these DMCs, we developed a CGA-specific 4-marker panel (cg27284428, cg11798358, cg07880787, and cg00585116) achieving the area under ROC curve (AUC) of 0.995 (95% CI: 0.982-1.000) and 0.962 (95% CI: 0.920-1.000) for early-stage and all-stage CGA, respectively, and an ESCC-specific 3-marker panel (cg14633892, cg04415798, and cg00585116) with an AUC of 0.970 (95%CI: 0.939-1.000) and 0.978 (95%CI: 0.958-0.999) for detecting early-stage and all-stage ESCC, respectively. We then evaluated the performance of DMCs for detecting cancerous and precancerous lesions, the CGA-specific 4-marker panel discriminated cardia HGD/CGA patients from cardia LGD/normal controls with AUC of 0.917, and the ESCC-specific 3-marker panel distinguished esophageal HGD/ESCC with AUC of 0.865. Integrating cg00585116, age, and alcohol drinking, the tumor-shared model showed good discrimination for two cancer/HGD in the training set with AUC of 0.740, which was confirmed in the test set with AUC of 0.841.

Conclusion: Collectively, novel DNA methylation markers could differentiate CGA/ESCC and HGD from LGD and normal controls with promising accuracy. Our findings pave the way for targeted DNA methylation assays in future minimally invasive cancer screening methods.

Key Words： cardia gastric adenocarcinoma, esophageal squamous cell carcinoma, high-grade dysplasia, DNA methylation markers, early detection

554. Novel signature of ferroptosis-related long non-coding RNA to predict lower-grade glioma overall survival

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Background: Ferroptosis is a novel type of programmed cell death in various tumors; however, underlying mechanisms remain unclear. We aimed to develop ferroptosis-related long non-coding

RNA (FRlncRNA) risk scores to predict lower-grade glioma (LGG) prognosis and to conduct functional analyses to explore potential mechanisms.

Methods:LGG-related RNA sequencing data were extracted from The Cancer Genome Atlas (TCGA) and Chinese Glioma Genome Atlas (CGGA) databases. Pearson correlation analysis was used to identify the FRlncRNAs, univariate Cox regression analysis was for identify the prognostic FRlncRNAs, and then intersection FRlncRNAs were screened between TCGA and CGGA. Least absolute shrinkage and selection operator (LASSO) Cox regression was used to develop a risk score to predict LGG prognosis.

Results: A total of nine FRlncRNAs were screened to construct the novel prognostic risk score of LGG, and high-risk score patients had a worse overall survival than low-risk score patients both in TCGA and CGGA datasets. The risk score was quite correlated with clinicopathological characteristics (age, WHO grade, status of MGMT Methtlation, IDH mutation, 1p/19q codeletion，and TMB), and could promote current molecular subtyping systems. Comprehensive analyses revealed that signaling pathways of B-cell receptor and T-cell receptor, immune cells of macrophage cell and CD4+T cell, tumor microenvironment of stroma score and immune score, and immune checkpoints of PD-1, PD-L1, and CTLA4 were all enriched in the high-risk score group.

Conclusion: The nine FRlncRNAs risk scores was a promising biomarker to predict the LGG's prognosis and distinguish the characteristics of molecular and immune.

Key Words： Ferroptosis · Long non-coding RNAs · Lower-grade glioma · Risk score · Immune checkpoints

555. HIF-1α 通过抑制 CXCL9、-10 和-11 介导的结直肠癌免疫抑制的作用研究

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研究目的：缺氧诱导因子 1alpha（HIF-1α）是缺氧条件下的典型标志，在某些癌症中起到致癌基因的作用。然而，缺氧诱导因子（HIF）如何调控 $CD8^+$ T 细胞迁移到肿瘤微环境的机制尚不明确。本研究旨在探索 HIF-1α在结直肠癌中介导免疫抑制的机制。

材料与方法：使用结直肠癌细胞系 DLD1 和 HT29，分别对 HIF-1α进行敲低或过表达，通过 QPCR 和 ELISA 检测 CXCL9、-10 和-11 的 mRNA 和分泌蛋白水平变化。利用免疫组化在人体结直肠癌组织切片中评估 HIF-1α蛋白表达与 CD8a 蛋白的相关性。通过基因集变异分析（GSVA），研究 HIF-1α靶向基因集的 GSVA 分数与结直肠癌患者预后、病理分期、免疫细胞浸润程度以及抗肿瘤免疫相关通路的关系。在免疫健全荷瘤小鼠模型中，研究敲低 HIF-1α及其上游调节蛋白 BIRC2 对肿瘤生长及 $CD8^+$ T 细胞浸润程度的影响。

结果：体外实验表明，HIF-1α敲低或过表达分别导致 CXCL9、-10 和-11 的表达水平增加或减少。人体结直肠癌组织中，HIF-1α蛋白表达与 $CD8^+$ T 细胞浸润程度呈负相关。GSVA 结果显示，HIF-1α水平升高与结直肠癌患者预后差、病理分期严重以及肿瘤微环境中 $CD8^+$ T 细胞缺失相关。HIF-1α与有利于抗肿瘤免疫治疗和细胞因子/趋化因子功能的通路表达呈负相关。体内实验表明，抑制 HIF-1α或其上游调节因子 BIRC2 可以显著抑制肿瘤生长，促进 $CD8^+$ T 细胞浸润。CXCR3 中和抗体逆转了这些作用，暗示了 CXCL9、-10 和-11/CXCR3 轴的参与。

结论：研究结果表明，HIF-1α可通过下调 CXCL9、-10 和-11 的表达来阻碍结直肠癌肿瘤微环境中 $CD8^+$ T 细胞的浸润，从而促进肿瘤的生长和发展。

关键字： HIF-1α；CD8+ T 细胞；免疫治疗；结直肠癌

556. DNA Methylation Profile in CpG-depleted Regions Uncovers a High-risk Subtype of Early-stage Colorectal Cancer

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Background: The current risk stratification system defined by clinicopathological features does not identify the risk of recurrence in early-stage (stage I-II) colorectal cancer (CRC) with sufficient accuracy. We aimed to investigate whether DNA methylation could serve as novel biomarkers for predicting prognosis in early-stage CRC patients.

Methods: We analyzed the genome-wide methylation status of CpG loci using Infinium MethylationEPIC array run on primary tumor tissues and normal mucosa of early-stage CRC patients to identify potential methylation markers for prognosis. The machine learning approach was applied to construct a DNA methylation-based prognostic classifier for early-stage CRC (MePEC) using the 4 gene methylation markers, including FAT3, KAZN, TLE4, and DUSP3. The prognostic value of the classifier was evaluated in two independent cohorts (n = 438 and 359, respectively).

Results: The comprehensive analysis identified an epigenetic subtype with high risk of recurrence based on a group of CpG loci in CpG-depleted region. In multivariate analysis, the MePEC classifier was independently and significantly associated with time to recurrence in the validation cohort one (HR 2.35, 95% CI 1.47-3.76, p < 0.001) and cohort two (HR 3.20, 95% CI 1.92-5.33, p < 0.001). All results were further confirmed after each cohort was stratified by clinicopathological variables and molecular subtypes.

Conclusions: We demonstrated the prognostic significance of DNA methylation profile in CpG-depleted region, which may serve as a valuable source for tumor biomarkers. MePEC could identify an epigenetic subtype with high risk of recurrence and improve the prognostic accuracy of current clinical variables in early-stage CRC.

Key Words： colorectal cancer; early-stage; recurrence; DNA methylation; biomarker

557. 血清细胞外囊泡 miRNA 作为肾透明细胞癌新型液体活检指标的临床价值研究

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目的 探讨肾透明细胞癌（ccRCC）患者血清特定变化细胞外囊泡（extracellular vehicles，EVs）miRNA 作为 ccRCC 新型分子标志物潜能。

方法 收集治疗前 ccRCC 患者血清 126 例，同时收集 124 例年龄、性别匹配的正常对照血清。分别提取患者和对照组血清 EVs 后，运用低密度芯片技术检测 miRNA 表达谱。运用 qRT-PCR 分别在复筛组（27 例 ccRCC 和 26 例正常）、验证组（72 例和 72 例正常）和测试组（27 例 ccRCC 和 26 例对照）逐步进行验证。对部分 ccRCC 患者术前、术后样本比较分析。最后评价特定变化 EVs miRNA 及其组合的临床价值。

结果 低密度芯片显示 ccRCC 患者血清 EVs 中 miRNA 的表达谱与正常对照有明显差异，44 种 miRNA 在 ccRCC 中明显上调（变化倍数 ＞5）。qRT-PCR 技术验证发现 6 种 miRNA 包括 miR-28-3p、miR-200a、miR-1826、miR-103、miR-1249 和 miR-640 在 ccRCC 患者中的

水平均显著且稳定高于正常对照，在早期 ccRCC 中即显著升高，且在患者术后明显下降。ROC 曲线下面积（AUC）分析显示，6 种 miRNA 及其组合对复筛组、验证组、测试组诊断的 AUC 范围分别是 0.751 ～ 0.893、0.620 ～ 0.808、0.744 ～ 0.920，具有较高的诊断准确性。此外，6-miRNA 组合对早期 ccRCC 诊断的 AUC 为 0.832（95%CI = 0.774 ～ 0.889），敏感度 84%，特异性 83%。逻辑回归分析显示，6 种 miRNA 及 6-miRNA 组合的 OR 值均具有统计学意义。

结论 6 种血清 EVs miRNA miR-28-3p、miR-200a、miR-1826、miR-103、miR-1249 和 miR-640 组合在一起对 ccRCC 早期诊断、手术效果评估方面具有较高的准确性，有望成为 ccRCC 潜在的液体活检指标。

关键字： 肾透明细胞癌；血清；细胞外囊泡；miRNA；液体活检；分子指标

558. 基于 LC-MS/MS 技术的乙肝相关性肝癌尿液代谢组学研究

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目的：应用尿液代谢组学技术寻找乙肝相关性肝癌的潜在代谢标志物，基于差异代谢物的调控基因建立新的肝癌分子亚型并对不同亚型的预后、差异基因、免疫治疗和靶向药物的敏感性进行分析。

方法：利用 LC-MS/MS 非靶向代谢组学技术对 10 名未经过系统抗病毒以及抗肿瘤诊治的乙肝相关性肝癌患者和 8 名健康体检人员的尿液进行分析，通过 PCA、OPLS-DA，阈值 VIP≥1 且 T 检验 P<0.01 确定组间的差异代谢物，结合 ROC 曲线和十折交叉验证寻找潜在生物标志物；基于 HMDB 数据库收集差异代谢物的调控基因，结合 TCGA-LIHC 通过聚类分析建立肝癌分子亚型，采用 KM 生存曲线评估不同亚型的预后；展示差异代谢物的调控基因在不同肝癌分子亚型中的表达情况以及不同亚型差异基因的表达。利用 TIDE 评分工具比较不同亚型间的免疫治疗效果；基于 GDSC 数据库分析不同分子亚型中每个样本的转录组结果，对分子靶向药物敏感性进行分析。

结果：通过 PCA 分析发现两组样本间有较大的差异性，组内重复性良好；OPLS-DA 得分图 R2X=0.213、R2Y=0.962、Q2Y=0.556，表明所建立的模型有较好的预测能力，置换检

验验证了该模型较可靠且不存在过度拟合；筛选得到 53 个差异代谢物，其中 44 个显著上调，9 个显著下调；结合 ROC 曲线和十折交叉验证发现 3 种差异代谢物的 AUC 平均值大于 0.9，分别是辛二酸、2'-O-甲基胞苷和 3'-唾液酸乳糖。KEGG 分析显示差异代谢物主要富集在泛酸和辅酶 A 的生物合成、2-氧代羧酸代谢、丁酸代谢、氰基氨基酸代谢、不同环境中的微生物代谢、烟酸和烟酰胺代谢以及甘氨酸、丝氨酸和苏氨酸代谢通路（P<0.05）。将差异代谢物的 98 个调控基因结合 TCGA-LIHC 的 371 个肝癌样本的基因表达数据进行聚类，将其分成两个分子亚型 C1 和 C2，代谢物的调控基因在不同肝癌分子亚型中具有较大的差异性，KM 生存曲线预测生存率 C2 亚型＞C1 亚型。C1 和 C2 肝癌分子亚型的差异基因结果显示 CA9、KRT19 等共 1894 个基因上调，HPR、APOC3、RTP3 等 438 个基因下调（P<0.05）。在免疫治疗中，TIDE 评分工具分析发现 C1 亚型患者的免疫逃逸潜力更大，ICI 的疗效可能较差。在分子靶向药物治疗中，显示索拉非尼在 C1 亚型中的 IC50 低于 C2 亚型，表明索拉非尼在 C1 亚型患者中可能更有效。

结论：辛二酸、2'-O-甲基胞苷和 3'-唾液酸乳糖因其较高的 AUC 均值、灵敏度和特异性有望成为乙肝相关性肝癌的潜在生物标志物；建立基于代谢物调控基因表达谱的肝癌分类的方法，从代谢物的角度了解人类肝癌基因表达谱的多样性。预测生存率 C2 亚型＞C1 亚型，C1 亚型的免疫逃逸潜力更大，即使用 ICI 治疗效果可能更差，但使用索拉非尼治疗效果可能比 C2 亚型更好。

关键字： 肝癌；尿液；代谢组学；生物标志物；调控基因

559. miR-494-3p 通过靶向调控 PRR14 表达参与食管鳞状细胞癌发生发展的分子机制

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目的 探讨 miR-494-3p 通过调控 PRR14 (proline rich 14)蛋白表达参与食管鳞状细胞癌（ESCC）发生发展的分子机制。

方法 收集 ESCC 组织及癌旁正常组织 20 对，Western blot 和免疫组化检测组织中 PRR14 蛋白表达变化情况； qRT-PCR 检测 PRR14 信使 RNA（mRNA）表达水平；生物信息学方

法预测可调控 PRR14 表达的 miRNA，分析 PRR14 蛋白和 mRNA 水平与 miRNA 表达相关性，荧光素报告试验证实 miRNA 与 PRR14 调控关系； RNAi 技术敲除 ESCC 细胞株（TE-10 和 ECA109）PRR14 基因表达后，利用 CCK8、EDU、克隆形成实验检测细胞的增殖能力，利用 Trans well，划痕实验和流式细胞术检测 PRR14 对细胞侵袭和凋亡的影响；进一步通过瞬时转染或慢病毒稳转过表达或抑制 miRNA、miRNA 过表达同时靶基因功能回复实验（ORF 过表达）重复上述检测指标。

结果 Western blot 和免疫组化结果显示，与癌旁正常组织相比，PRR14 蛋白在 ESCC 组织中显著高表达（$P < 0.05$）；qRT-PCR 显示，PRR14 mRNA 水平在 ESCC 组织中表达升高（$P < 0.05$）；生物信息学分析结果表明，miR-494-3p 可调控 PRR14 表达，且 miR-494-3p 在 ESCC 组织中表达显著降低，与 PRR14 蛋白和 mRNA 水平呈显著负相关（$P < 0.05$）；荧光素报告试验证实 miR-494-3p 可与 PRR14 3'UTR 结合并调控其表达；RNA 干扰、miRNA 过表达及回复实验显示，敲除 PRR14 或过表达 miR-494-3p 可抑制 TE-10、ECA109 细胞增殖，侵袭能力，并促进细胞凋亡。

讨论 miRNA-494-3p 可通过调控 PRR14 蛋白表达抑制 ESCC 增殖、侵袭能力和促进细胞凋亡，与 ESCC 的发生发展密切相关。

关键字： miR-494-3p；食管鳞状细胞癌；PRR14；分子机制

560. 肿瘤外泌体适配体传感器的制备研究

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研究目的：近年来，肿瘤对人类健康造成越来越大的威胁，已经严重危害到人类的生命安全。因此，如何尽早发现肿瘤，并及时治疗，成为了人们关注研究的热点话题。外泌体作为细胞通讯关键的参与者，其对肿瘤的发生发展产生重要的影响。肿瘤外泌体携带肿瘤细胞众多信号分子，成为肿瘤诊断的重要标志物。适配体生物传感器的检测方法具有快速、灵敏等诸多优势，广泛应用于非创伤性液体活检。本研究旨在通过不同化学连接构建信号分子-适配体偶联物，为后续新型肿瘤外泌体适配体传感器的构建提供重要基础，为肿瘤外泌体的检测研究提供重要支撑。

材料与方法：采用高效化学合成方法，通过不同化学连接将信号分子与适配体进行偶联，并通过高效液相色谱法、质谱等方法进行表征。

结果：实验数据表明已成功合成具有不同化学连接结构的信号分子-适配体偶联物。

结论：本研究成功构建了具有信号分子-适配体偶联物，为新型外泌体检测策略的开发奠定重要基础，有望进一步开发成为早期肿瘤诊断的新方法。

关键字： 适配体传感器；肿瘤外泌体；肿瘤标志物

561. 异常细胞自噬和蛋氨酸代谢介导EGFR/TP53共突变肺腺癌患者不良结局

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研究目的：肺癌作为全球肿瘤相关死亡的主要原因，五年的生存率不到25%。其中，肺腺癌作为最常见的病理亚型，已确定与KRAS、EGFR、TP53突变等致癌驱动因素显著相关。研究发现，合并EGFR和TP53突变的肺腺癌患者较单独EGFR突变的患者，预后显著降低。本研究旨在探究肺腺癌患者发生EGFR-TP53共突变时，引起临床不利预后的分子机制。分析EGFR-TP53共突变与EGFR单突变时患者肿瘤组织的蛋白和代谢物组差异，以识别预测患者的生物标志物。

材料与方法：本研究纳入53例肺腺癌患者，对患者的肿瘤和非肿瘤组织进行蛋白和代谢组学检测，过滤缺失值较多的蛋白和代谢物后，剩余6831个蛋白和1642个代谢物进一步分析。根据EGFR/TP53突变情况，进行分组差异生存分析。进一步探究分组后差异代谢物和蛋白，对差异代谢物进行KEGG通路富集和差异蛋白GSEA分析，识别EGFR-TP53共突变相比EGFR单突变的分子特征。

结果：对53例患者根据EGFR/TP53突变情况分组进行生存分析发现，EGFR突变（10例）与EGFR-TP53共突变（20例）之间的无病生存期（DFS）有显著差异，共突变组的DFS显著降低（p=0.016）。进一步探究共突变患者无病生存期显著降低的原因，根据EGFR突变与EGFR-TP53共突变分组，分析代谢和蛋白组学的差异代谢物和蛋白，发现在共突变组中，蛋白和代谢物水平均出现自噬通路，及半胱氨酸/蛋氨酸通路显著上调。ATG3、ATG7、PIK3R4等代表性细胞自噬相关蛋白，及与细胞膜合成相关的磷脂酰肌醇的显著上调，伴随

HIF-1α通路在蛋白水平上的激活，促进细胞自噬水平的上调、能量转换和利用及肿瘤细胞的存活和增殖。而在半胱氨酸/蛋氨酸代谢通路中，关键的蛋氨酸调节因子 MAT2A、转录靶点 LDHB 上调，伴随牛磺酸、N-甲酰-L-蛋氨酸等主要氧化产物显著增加和牛磺酸代谢通路上调，提升肿瘤抵抗氧化应激损伤的水平。因此，肿瘤细胞在 EGFR 和抑癌基因 TP53 同时突变的情况下，通过蛋氨酸代谢通路重编程和自噬水平提高，促进能量转换和抵抗氧化应激的能力上升，支持肿瘤细胞的生存和繁殖，对患者预后产生不利影响。

结论：在肺腺癌患者中，EGFR-TP53 共突变介导细胞自噬和半胱氨酸/蛋氨酸代谢水平上调，提升肿瘤细胞能量的转换利用和抵抗氧化应激的能力，导致患者的不良预后，可能成为影响肺腺癌预后的潜在靶点。

关键字： 肺腺癌，EGFR 突变，TP53 突变，自噬，蛋氨酸代谢，肿瘤预后

562. Comparative Efficacy of Prophylactic Protocols in Reducing Perioperative Nausea and Vomiting During Video-Assisted Thoracoscopic Radical Resection of Lung Cancer

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Background: Lung cancer, a global mortality leader, often necessitates Video-Assisted Thoracoscopic (VATS) surgery. However, post-operative nausea and vomiting (PONV) is common, highlighting a need for effective management and prevention strategies in this context.

Method: A retrospective case-control study at Fujian Medical University Union Hospital evaluated patients undergoing VATS radical resection of lung cancer between May and September 2022. Patients were categorized based on PONV prevention methods, and data encompassing demographics, surgical history, and postoperative adverse events s were analyzed to assess the association between prophylactic protocols and PONV incidence.

Results: The Netupitant and Palonosetron Hydrochloride (NEPA) group showed a significant reduction in PONV occurrences post-surgery compared to Ondansetron (ONDA) and Normal

Control (NC) groups, emphasizing NEPA's efficacy in alleviating PONV symptoms ($P<0.05$). Furthermore, following VATS radical resection of lung cancer, NEPA markedly reduced the intensity of PONV symptoms in patients. Both univariate and multivariate logistic analyses corroborated that NEPA independently reduces PONV risk, with its protective effect also apparent in susceptible populations like females and non-smokers.

Conclusions: NEPA utilization markedly reduced both the incidence and severity of PONV in patients undergoing VATS radical resection of lung cancer, serving as an independent protective factor in mitigating PONV risk post-surgery.

Key Words ： Lung Cancer; Perioperative Nausea and Vomiting(PONV); VATS

563. Peripheral blood lymphocytes differentiation patterns in responses / outcomes to immune checkpoint blockade therapies

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Objective： α-PD-1 / PD-L1 immune checkpoint blockade (ICB) therapies targeting immunocytes induce persistent tumor remission in various kinds of cancers. However, the appropriate biomarkers for the therapeutic efficacy of PD-L1 and PD-1 blockade still remain elusive.

Methods： For a comprehensive analysis of peri-treatment lymphocytes differentiation, in the current study, we enrolled 116 non-small cell lung cancer patients who received α-PD-1 therapies for exploring the peripheral blood lymphocytes differentiation pattern at baseline and post-treatment (dynamic changes) by flow cytometry.

Results： At baseline, CD4+ / CD8+ T cell ratio predicts good responses and outcomes, but activated T cell and CTL counts predict poor responses and outcomes. And for dynamic changes, after 6 weeks of ICB treatment, compared with baseline level, the elevation of total T and B cell counts indicate poor responses, and total T and TH cell counts indicate poor prognosis while activated T cells predict good prognosis. And after 12 weeks, elevated total lymphocyte, CTL

counts and decreased total T cell counts and CD4+ / CD8+ T cell ratio predicts good responses / outcomes.

Conclusion： Patients with favorable clinical responses / outcomes have distinctive peripheral blood immunocytes differentiation characteristics, indicating the potential of utilizing the peripheral immunocytes differentiation patterns for predicting ICB responses / outcomes.

Key Words： Lymphocytes differentiation; Immunotherapy; Therapeutic efficacy prediction; NSCLC; α-PD-1 / PD-L1

564. dPCR 检测尿 cfDNA 中 TERT 突变对尿路上皮癌诊断的临床应用研究

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目的：尿路上皮癌（Urothelial Cancer, UC）是泌尿系统常见的恶性肿瘤，易复发，早诊早治是提高生存率的关键。目前可靠的诊断方法是膀胱镜活检和尿细胞学，但前者有创，后者敏感性低，因此迫切需要开发无创、准确的分子诊断方法辅助 UC 的临床诊断。端粒酶逆转录酶（Telomerase Reverse Transcriptase, TERT）启动子区域的体细胞突变是 UC 中的常见事件，它们以上清液无细胞 DNA 或来自脱落细胞 DNA 的形式存在于尿液中，可作为 UC 检测和监测的非侵入性生物标志物。数字 PCR（Digital PCR, dPCR）具有高灵敏度高精准度的特点，可以在液体活检中检测出微量的目标基因突变，因此在肿瘤早期诊断、监测、复发方面具有重要应用价值。本文利用非侵入性方法收集尿液样本，对 TERT 热突变位点进行 dPCR 检测，探讨尿液 cfDNA TERT 突变作为生物标志物联合尿脱落细胞学检查对 UC 的诊断效能。

材料与方法：前瞻性收集中国医学科学院肿瘤医院有泌尿系统占位或症状的患者及 UC 监测患者自然排空尿液样本 300 例，健康对照组尿液 48 例，收到尿液后及时离心，尿沉渣用于细胞学诊断，尿上清用于提取尿 cfDNA，应用 dPCR 检测尿 cfDNA 中 TERT C228T/C250T

突变，以组织病理和临床随访为金标准，分析尿 cfDNA TERT C228T/C250T 突变情况与突变拷贝数浓度在不同临床资料组中的分布，与细胞学结果相结合评价该生物标志物模型对 UC 的诊断效能。

结果：临床随诊结果显示恶性肿瘤 165 例（其中有组织病理证实的 UC107 例，非尿路上皮恶性肿瘤 16 例，临床及影像提示泌尿道恶性 42 例），良性 101 例，失访或诊断不明确 34 例。TERT C228T/C250T 的检出限（Limit of Detection, LoD）分别为 0.546cp/μl 和 0.545cp/μl，高于此界值被定义为突变阳性。在健康对照组中 TERT C228T/C250T 的突变率为 0。在 UC 中 TERT C228T 的突变率为 43.0%（46/107）;TERTC250T 的突变率为 15.0%（16/107）。在临床病例组中，以任何一个突变为阳性，TERT C228T/C250T 诊断恶性的敏感性为 46.1%(76/165)，特异性为 87.1%(88/101)；细胞学以可疑癌为诊断恶性界值，敏感性为 60.0%(99/165)，特异性为 93.1%(94/101)，二者联合诊断的敏感性提升至 79.4%(131/165)，与单独细胞学诊断差异有统计学意义（P<0.001），特异性为 80.2%（81/101）（P=0.007）。TERT C228T/C250T 的突变与 UC 组织学分级无关。定量分析发现：TERT C228T/C250T 突变拷贝数浓度随着 T 分期增高而增高（P<0.001）。

结论：尿液 cfDNA TERT 228T/250T 突变可作为 UC 诊断的生物标志物，与尿脱落细胞学优势互补，二者联合可明显提高诊断敏感性。作为非侵入性检查，可应用于 UC 的诊断及监测复发。

关键字： 数字 PCR；尿路上皮癌；TERT；诊断效能

565. Role of Immunophenotypic Characterization in Prognostic Subtyping of Intrahepatic Cholangiocarcinoma

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Background: Intrahepatic cholangiocarcinoma (iCCA) is classified by the 5th WHO classification of tumours of the digestive system as large duct type (LDT) and small duct type (SDT), based on the anatomic location, morphological appearances, immunophenotype, and gene

events. We evaluated that subtyping system using real-world data and established a supplementary method using IHC detection.

Methods: We retrospectively investigated 190 cases of surgically resected iCCA and classified them according to histological evaluations and gene detection. The prognostic value of the IHC markers were evaluated according to the relapse-free survival (RFS) and OS.

Results: Basic HE classification was insufficient, with 61 cases classified as uncertain. This method showed no prognostic value for RFS or OS. The four-marker IHC detection, including EMA, S100P, N-cadherin, and CRP, which classified 68 cases as LDT, 108 cases as SDT, and 14 cases as uncertain, was highly efficient in subtyping and prognosis. The seven-marker method, including CD56, MUC5AC, and MUC6 was consistent with the four-marker method. FGFR2 gene fusion was exclusively detected in 20 cases of SDT iCCA, according to the four- and seven-marker IHC detection.

Conclusions: This novel method of iCCA classification exhibited diagnostic, prognostic, and therapeutic value in clinical practice.

Key Words： iCCA subtype, IHC, EMA, S100P, CRP, N-cadherin, prognosis

566. Multi-Omics Analysis Elucidates the Relationship between Intratumor Microbiome and Host Immune Heterogeneity in Breast Cancer

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Objective: Research has indicated that intratumor microbiomes affect the occurrence, progression, and therapeutic response in many cancer types by influencing the immune system. We aim to evaluate the characteristics of immune-related intratumor microbiomes (IRIMs) in breast cancer (BC) and search for potential prognosis prediction factors and treatment targets.

Materials and methods: The clinical information, microbiome data, transcriptomics data of TCGA-BRCA patients were obtained from Kraken-TCGA-Raw-Data and TCGA portal. The core tumor-infiltrating immune cell was identified using univariate Cox regression analysis. Based on

Consensus clustering analysis, BC patients were categorized into two immune subtypes, referred to as immune-enriched and immune-deficient subtypes. The immune-enriched subtype, characterized by higher levels of immune infiltration of CD8+ T and macrophage M1 cells, demonstrated a more favorable prognosis. Furthermore, significant differences in alpha-diversity and beta-diversity were observed between the two immune subtypes, and the Least discriminant analysis (LDA) effect size method identified 33 types of IRIMs.

Result: An intratumor microbiome-based prognostic signature consisting of 4 prognostic IRIMs (Acidibacillus, Succinimonas, Lachnoclostridium, and Pseudogulbenkiania) was constructed using the Cox proportional-hazard model, and it had great prognostic value. The prognostic IRIMs were correlated with immune gene expression and the sensitivity of chemotherapy drugs, specifically tamoxifen and docetaxel.

Conclusion: Our research has successfully identified two distinct immune subtypes in BC, which exhibit contrasting prognoses and possess unique epigenetic and intratumor microbiomes. The critical IRIMs were correlated with prognosis, tumor-infiltrating immune cells abundance, and immunotherapeutic efficacy in BC. Consequently, this study has identified potential IRIMs as biomarkers, providing a novel therapeutic approach for treating BC.

Key Words： Intratumor microbiome, breast cancer, tumor immune microenvironment, immunotherapy, prognostic factors.

567. Causal Effects of COVID-19 on Cancer Risk: A Mendelian Randomization Study

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Objective: In contemporary literature, little attention has been paid to the association between COVID-19 and cancer risk.

Materials and methods: We performed the Mendelian randomization (MR) to investigate the causal associations between the three types of COVID-19 exposures (critically ill COVID-19,

hospitalized COVID-19, and respiratory syndrome coronavirus 2 (SARS-CoV-2) infection) and 33 different types of cancers in European population.

Result: The results of the inverse-variance-weighted model indicated that genetic liabilities to critically ill COVID-19 had causal associations with the increased risk for HER2-positive breast cancer (odds ratio [OR] = 1.0924; P = 0.0116), oesophageal cancer (OR = 1.0004; P = 0.0226), colorectal cancer (OR = 1.0010; P = 0.0242), stomach cancer (OR = 1.2394; P = 0.0331), and colon cancer (OR = 1.0006; P = 0.0453). The genetic liabilities to hospitalized COVID-19 had causal associations with the increased risk for HER2-positive breast cancer (OR = 1.1096; P = 0.0458), oesophageal cancer (OR = 1.0005; P = 0.0440) as well as stomach cancer (OR = 1.3043; P = 0.0476). The genetic liabilities to SARS-CoV-2 infection had causal associations with the increased risk for stomach cancer (OR = 2.8563; P = 0.0019), but with the decreasing risk for head and neck cancer (OR = 0.9986, P = 0.0426).

Conclusion: Together, our study indicated that COVID-19 had causal effects on cancer risk.

Key Words： Coronavirus disease-2019 (COVID-19), Cancer, Mendelian randomization, Genome-Wide Association Study (GWAS), Causal association.

568. 基于 GEO 的 TEP lncRNA 非小细胞肺癌肿瘤标志物研究

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目的： 探究肿瘤教化血小板（Tumor-educated platelets，TEP）长链非编码 RNA（long noncoding RNA，lncRNA）在非小细胞肺癌（Non-Small Cell Lung Cancer ,NSCLC）患者与健康对照（HC）间的差异表达，为 NSCLC 的筛查诊断发掘新的具有诊断价值的非侵入性肿瘤标志物。

方法：在 GEO 数据库中检索同时包含 NSCLC 和 HC 的血小板转录组高通量测序数据集，分别基于 GSE183635 数据集（518 例 NSCLC 和 388 例 HC）和 GSE207586 数据集（399 例 NSCLC 和 367 例 HC）做差异分析，将两数据集的差异表达 lncRNA(differentially expressed lncRNA，DElncRNA)取交集得到公共 DElncRNA。将基于 PLTDB 整合后的来自 GSE68086、

GSE89843 和 GSE156902 的复合数据集（共 453 例 NSCLC，409 例 HC）作为测试集进行受试者工作（receiver operator characteristic，ROC）曲线分析，评价公共 DElncRNA 的诊断效能。

结果：GSE183635 数据集差异分析得到 595 个 DElncRNAs， 410 个上调 lncRNA， 185 个下调 lncRNA。GSE207586 数据集差异分析得到个 18 个 DElncRNAs，1 个上调 lncRNA，17 个下调 lncRNA。取交集后获得 9 个公共 DElncRNA：ZNF667-AS1、WDR11-DT、VIM-AS1、LOC101928834、MEF2C-AS1、LINC01088、LINC00989、LOC101927636、LINC02384 均为下调 lncRNA。在测试集中，WDR11-DT 的诊断效能最佳，对 NSCLC 诊断的曲线下面积（area under the curve，AUC）为 0.8545，灵敏度为 78.4%，特异度为 80.2%。

结论：WDR11-DT 在 NSCLC 患者血小板中表达下调，TEP WDR11-DT 对于 NSCLC 具有良好的诊断效能，可以作为 NSCLC 诊断的非侵入性肿瘤标志物。

关键字： 非小细胞肺癌；肿瘤教化血小板 ；长链非编码 RNA；WDR11-DT

569. 原创性 GlyExo-Capture 技术捕获糖基化细胞外囊泡 miRNA 在肝细胞癌诊断中的应用价值

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目的：肝细胞癌（HCC）作为一种全球广泛流行的恶性肿瘤，以其症状轻微、进展迅速和预后不佳而特征明显。目前用于早期 HCC 检测和筛查的临床方法，如腹部超声和α-胎球蛋白（AFP）检测，敏感性和特异性有限。因此，迫切需要探索更精确的指标用于早期 HCC 诊断。最新证据表明，糖基化细胞外囊泡（EVs）miRNA 具有作为早期癌症筛查生物

标志物的前景。本研究介绍了独创性 GlyExo-Capture 技术，该技术可特异性快速分离糖链 EVs，旨在通过基于该技术获得 HCC 的 miRNA 靶标和诊断模型，实现 HCC 早期诊断。

方法： 本研究采用 GlyExo-Capture 技术，利用凝集素偶联磁珠对 EVs 膜表面的糖链亲和性，分离血清中糖链 EVs。使用二代测序（NGS）检测了 84 例 HCC 患者和 172 例非 HCC 对照中 EVs miRNA 表达谱。随后进行差异表达分析，确定了显著改变的 miRNAs。利用机器学习算法对这些 HCC 患者中差异表达的 miRNAs 进行排序。将候选 miRNAs 配对，利用逆转录荧光定量 PCR（qRT-PCR）在独立队列（398 例）中进行训练和验证，评估其作为生物标志物的效果。

结果：GlyExo-Capture 技术可以在 11 分钟内完成 96 个血清样本的 EVs 提取，对比鉴定 GlyExo-Capture 技术与超速离心法提取的 EVs 表型一致。在 HepG2 细胞上清中，GlyExo-Capture 可捕获到 58.8%的岩藻糖基化 EVs。NGS 分析获得了 100 个 HCC 和非 HCC 队列之间的差异表达 miRNAs（DEM）。随后，使用机器学习对排名前 10 的 DEM 进行配对，并通过 qRT-PCR 进行验证。最终，一个由 3 个 miRNA 靶标对组成的模型展现出了优秀的诊断性能，在训练集和验证集的 AUC 分别为 0.962 和 0.922。值得注意的是，其对早期 HCC 的高符合率，对 BCLC 分期 0 期和 A 期的 HCC 符合率分别达到 80.0%和 89.8%。此外，该模型能够检出 82.9%的 AFP 阴性 HCC 样本。将 miRNA 靶标对与 AFP 联合分析提高了整体诊断准确性，在训练集和验证集中 AUC 分别为 0.982 和 0.947。

结论：我们成功开发了一种高通量、快速和高效的捕获富含糖链 EVs 的 GlyExo-Capture 技术。从基于该技术分离的 HCC 血清糖链 EV-miRNA 中，我们建立了一种 3 个 miRNA 靶标对的分类模型，实现了对早期 HCC 患者的精确识别。

关键字： GlyExo-Capture，细胞外囊泡，miRNA，HCC

570. 血浆外泌体 hsa_circ_0005756 在胃癌诊断及促进胃癌进展的作用机制研究

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目的：胃癌作为全球高发且预后较差的癌症之一，寻找灵敏、稳定且特异的胃癌诊断标志物及治疗靶点是解决胃癌难治问题的关键，本研究旨在找寻外泌体 circRNA 能否作为新型胃癌诊断标志物，探讨其胃癌进展中的作用与分子机制。

方法：利用血浆外泌体 circRNA 芯片筛选差异性表达的 circRNA 分子，在健康体检者、慢性萎缩性胃炎患者和胃癌患者血浆外泌体中进行验证并分析诊断效能，结合病理资料进行临床相关性分析。通过基因沉默和过表达检测 hsa_circ_0005756 的功能，细胞增殖、Transwell 迁移和 Western Blot 检测细胞增殖和迁移功能及蛋白表达。构建慢病毒稳转细胞株，利用超速离心法收集外泌体并进行鉴定。通过生物信息学分析、RIP 实验、RNA pulldown 实验寻找 hsa_circ_0005756 的结合蛋白。并在后续实验中寻找 hsa_circ_0005756 促进胃癌进展的机制以及其是否可以作为胃癌淋巴结转移的标志物。

结果：血浆外泌体 hsa_circ_0005756 在胃癌患者中较健康体检者和慢性萎缩性胃炎患者中高表达，基于 59 例健康体检者和 67 例胃癌患者所作 ROC 曲线下面积为 0.70（灵敏度=93.22%，特异度=43.28%），基于 19 例慢性萎缩性胃炎患者和 67 例胃癌患者所作 ROC 曲线下面积为 0.78（灵敏度=90.55%，特异度=47,23%），且术后显著下调，其表达量与胃癌的淋巴结转移密切相关。核质分离和 FISH 实验显示 hsa_circ_0005756 大多分布于细胞质中。在功能学实验中，使用 SNU-1 与 HGC-27 两个细胞系，结果显示，敲减 hsa_circ_0005756 抑制胃癌的增殖、迁移、侵袭、EMT 进程，过表达则相反。使用多个数据库分析预测 hsa_circ_0005756 的结合蛋白，并且查阅文献寻找淋巴结转移标志物，预测结果显示 hsa_circ_0005756 可能会相关的淋巴结转移标志物有 PROX1、TRAP1、LASP1、IMP3、FABP5、FASN，后续将进行验证。

讨论：血浆外泌体 hsa_circ_0005756 作为早期和鉴别诊断慢性萎缩性胃炎患者和胃癌淋巴结转移的标志物，并从淋巴结转移角度探讨其促癌机制。

关键字：外泌体；胃癌；circRNA;LNM

571. 人工合成多肽 cSN50.1 对肝癌细胞 HepG2 恶性行为的影响及其机制

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目的 探讨 cSN50.1 对 HepG2 细胞增殖、迁移、侵袭和集落形成能力的影响及机制 。

方法 将 HepG2 细胞分为 6 组：cSN50.1 0 μmol/L、10 μmol/L、30 μmol/L、50 μmol/L、70 μmol/L、90 μmol/L 组，采用 CCK－8 实验研究不同浓度 cSN50.1 对 HepG2 细胞增殖的影响，并计算半数抑制浓度（ IC50）将；HepG2 细 胞分为 4 组：cSN50.1 0 μmol/L、10 μmol/L、 30 μmol/L、50 μmol/L ，采用细胞划痕 、Transwell 和细胞克隆 实验研究不同浓度 cSN50.1 对 HepG2 细胞迁移 、侵袭和集 落形成能力的影响；将 HepG2 细胞分为 3 组 ：Control 组 、SP600125 组（ AP －1 信号通路抑制剂）和 cSN50.1 组 ，研究 AP －1 信号通路在 cSN50. 1 对肝癌细胞作用中的影响，采用 RT－PCR 和 Western Blot 检测 CXCL5 和 TNF-α 的表达以 及细胞质 和细胞核中 c－Jun 蛋白的表达；将 HepG2 细胞分为 3 组： Control 组 、PDTC 组（ NF -κB 信号通路抑制 剂）和 cSN50. 1 组 ，研究 NF -κB 信号通路在 cSN50. 1 对肝癌细胞作用中的影响 ，采用 RT－PCR 和 Western Blot 检测 CXCL5 和 TNF- α 的表达以 及细胞质和细 胞核中 NF - κB 蛋白的表达 。多组间 比较采用单因素方差分析，进一步两两比较 采用 SNK －q 检验 。

结果 与 0 μmol/L 相比 ，10 μmol/L 组的增殖 、迁移 、侵袭和集落形成能力无明显变化（ P 值均> 0.05 ）；30 μmol/L 组的增殖能力 无明显变化（ P>0 . 05 ），迁移 、侵袭和集落形成能力均明显降低（ P 值均<0 . 05 ）；50 μmol/L 组的增 殖、迁移、侵袭和集落形成能力均明显降低（ P 值均<0. 01）； 70 μmol/L 和 90 μmol/L 组的细胞增殖能力 均 明显降低（ P 值均<0. 01），但细胞存活率低于 50% 。与 Control 组相比，SP600125 组、PDTC 组和 cSN50.1 组 中 CXCL5 和 TNF-α 的基因和蛋白表达均明显降低（ P 值均<0. 05 ）。 与 Control 组相比， SP600125 组 、 PDTC 组和 cSN50.1 组中细 胞核蛋白 c－Jun 和 NF-κB 表达均明显降低（ P 值均<0. 05 ），SP600125 组 和 PDTC 组中细胞质蛋白 c－Jun 和 NF-κB 表 达均明显降低（ P 值均<0. 05），cSN50.1 组中细胞质蛋白 c - Jun 和 NF -κB 表达明显增高（ P<0. 05 ）。

结论 cSN50. 1 可 以抑制肝癌细胞的恶性行为 ，可抑制肝 癌细胞中 c 一 Jun 和 NF- κB 的入核转运来降低 CXCL5 和 TNF- α 的表达。

关键字： 肝肿瘤；cSN50. 1；TNF-α； 趋化因子 CXCL5；主动转运；细胞核

572. Population-based BRCA germline mutation screening in the Han Chinese identifies individuals at risk of BRCA mutation-related cancer: Experience from a clinical diagnostic center from Greater Shanghai Area

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Background: Deleterious BRCA1/2 (BRCA) mutation raises the risk for BRCA mutation-related malignancies, including breast, ovarian, prostate, and pancreatic cancer. Germline variation of BRCA exhibits substantial ethnical diversity. However, there is limited research on the Chinese Han population, constraining the development of strategies for BRCA mutation screening in this large ethnic group.

Methods: We profile the BRCA mutational spectrum, including single nucleotide variation, insertion/deletion, and large genomic rearrangements in 2,080 apparently healthy Chinese Han individuals and 522 patients with BRCA mutation-related cancer, to determine the BRCA genetic background of the Chinese Han population, especially of the East Han. Incident cancer events were monitored in 1,005 participants from the healthy group, comprising 11 BRCA pathogenic/likely pathogenic (PLP) variant carriers and 994 PLP-free individuals, including 3 LGR carriers.

Results: Healthy Chinese Han individuals demonstrated a distinct BRCA mutational spectrum compared to cancer patients, with a 0.53% (1 in 189) prevalence of pathogenic/likely pathogenic (PLP) variant, alongside a 3 in 2,080 occurrence of LGR. BRCA1 c. 5470_5477del demonstrated

high prevalence (0.44%) in the North Han Chinese and penetrance for breast cancer. None of the 3 LGR carriers developed cancer during the follow-up. We calculated a relative risk of 135.55 (95% CI 25.07 to 732.88) for the development of BRCA mutation-related cancers in the BRCA PLP variant carriers (mean age 42.91 years, median follow-up 10 months) compared to PLP-free individuals (mean age 48.47 years, median follow-up 16 months).

Conclusion: The unique BRCA mutational profile in the Chinese Han highlights the potential for standardized population-based BRCA variant screening to enhance BRCA mutation-related cancer prevention and treatment.

Key Words ： BRCA mutation related-cancer, germline mutation, population screening

573. Prognostic signifcance of absolute monocyte count and lymphocyte to monocyte ratio in mucosa-associated lymphoid tissue (MALT) lymphoma

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To investigate the prognostic signifcance of peripheral blood absolute monocyte count (AMC) and lymphocyte to monocyte ratio (LMR) in mucosa-associated lymphoid tissue (MALT) lymphoma, we retrospectively analyzed 316 newly diagnosed patients with MALT lymphoma. The best cut-of value of AMC was 0.6×10^9/L and LMR was 1.8 by x-tile according to progression-free survival (PFS). Multivariate analysis showed that MALT-IPI ($p < 0.001$), Eastern Cooperative Oncology Group performance status (ECOG PS) ($p = 0.010$), and LMR ($p = 0.003$) have independent prognostic signifcance for PFS, MALT-International Prognostic Index (MALT-IPI) ($p = 0.018$), β2-microglobulin (β2-MG) ($p = 0.015$), and LMR ($p = 0.029$) predicted poor overall survival (OS). Receiver-operator characteristic (ROC) curves were used to compare the prognostic prediction capability of MALT-IPI and MALT-IPI-M (MALT-IPI combined with LMR); area under the curves (AUCs) for MALT-IPI-M were larger than that for MALT-IPI both PFS (0.682 vs 0.654) and OS (0.804 vs 0.788). Our results indicated that that low level LMR at

diagnosis was associated with inferior prognosis. The new prognostic index, MALT-IPI-M, enabled the risk stratifcation capability for MALT lymphoma survival.

Key Words： Mucosa-associated lymphoid tissue (MALT) lymphoma · Absolute monocyte count · Lymphocyte to monocyte ratio · MALT-Lymphoma International Prognostic Index · Prognosis

574. 血清 TK1、CA125、HE4 对卵巢癌诊断的价值研究

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目的： 研究血清胸甘激酶 1(TK1)、糖类抗原 125(CA125)及人附睾蛋白 4(HE4)对卵巢癌(OC)诊断的临床价值。

材料与方法：收集 2023 年 5 月至 2023 年 12 月河南省肿瘤医院收治的 156 例 OC 患者血清，58 例卵巢良性肿瘤患者血清。采用郑州安图生物工程股份有限公司全自动化学发光仪器 A2000 Plus 分别检测 OC 患者和良性肿瘤患者血清的 TK1、CA125 和 HE4 水平，所有数据采用 SPSS 25.0 分析软件进行统计学分析。

结果：OC 患者血清的 TK1、CA125 和 HE4 检测值均高于卵巢良性肿瘤患者血清的检测值。OC 患者中，血清 TK1、HE4 及 CA125 水平均与患者 TNM 分期成正相关。当单独用于区别诊断 OC 与卵巢良性肿瘤时，TK1 的 AUC 为 0.856，HE4 的 AUC 为 0.868，CA125 的 AUC 为 0.806。TK1 联合 HE4 诊断 OC 的 AUC 为 0.895，TK1 联合 CA125 诊断 OC 的 AUC 为 0.852，TK1 联合 HE4 及 CA125 诊断 OC 的 AUC 为 0.936。

结论：血清 TK1、HE4 及 CA125 对 OC 的诊断具有较高的临床价值，联合诊断价值更优。

关键字： TK1；CA125；HE4；卵巢癌；临床价值

575. 炎性细胞因子联合细胞角蛋白 19 片段在肺恶性肿瘤诊断中的应用

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目的：研究细胞角蛋白 19 片段（Cytokeratin 19 fragment，CYFRA21-1）、白细胞介素 6（Interleukin 6, IL-6）、 白细胞介素 10（Interleukin 10, IL-10）在肺恶性肿瘤诊断中的价值，并探讨三项指标联合应用以期提高肺恶性肿瘤的诊断水平。

方法：收集 2023 年 6 月-2023 年 12 月在南京医科大学第二附属医院就诊的肺恶性肿瘤患者的临床信息及实验室资料进行回顾性分析，并与健康对照进行对比。对两组人员的炎性细胞因子及 CYFRA21-1 水平差异比较。利用单因素分析进行统计，根据受试者工作特征曲线（receiver operating characteristic curve, ROC）进一步分析细胞因子 IL-6、IL-10 及 CYFRA21-1 在人群中的诊断效能。上述标志物 IL-6、IL-10 采用 iMatrix100 流式细胞仪进行检测，CYFRA21-1 采用 Roche Cobas e801 全自动免疫分析仪进行检测。

结果：结果显示肺恶性肿瘤患者血清 CYFRA21-1 水平较健康人血清对照组差异无统计学意义（P=0.555），表明患有肺恶性肿瘤时 CYFRA21-1 水平仅有轻微升高，在进行肺恶性肿瘤诊断时灵敏度仍需提高。肺癌患者血清 IL-6 水平较健康人血清对照组有明显升高，差异有统计学意义（P=0.005），IL-10 水平较健康人血清对照组有明显升高，差异有统计学意义（P=0.017）。对三项指标分别做 ROC 分析。单独使用 CYFRA21-1 进行诊断时 ROC 曲线下面积（AUC）为 0.583，而单独使用血清 IL-6、IL-10 进行诊断时 ROC 曲线下面积（AUC）分别为 0.896 及 0.859，而当联合 CYFRA21-1、IL-6 及 IL-10 进行肺恶性肿瘤诊断时，ROC 曲线下面积（AUC）为 0.906（P=0.004），诊断能力有了进一步加强。

结论：

1. IL-6 及 IL-10 可以用于肺恶性肿瘤的辅助诊断。
2. 联合 CYFRA21-1、IL-6、IL-10 可以进一步提高诊断能力。

关键字 ：肺恶性肿瘤，细胞角蛋白 19 片段，细胞因子

576. 基于 NETs 的结直肠癌预后特征及 CXCL5 在其化疗耐药中的相关性研究

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目的：探究 NETs 相关基因对结直肠癌的影响，明确 NETs 标志物 CitH3 作为结直肠癌诊断和预后的血清标志物，探究中性粒细胞与结直肠癌化疗反应的相关性以及 CXCL5 的作用。

方法：首先，从 NETs 中性粒细胞的转录组数据中提取 NETs 相关基因并对其进行 GO、KEGG 富集分析。其次，下载公共数据库中结直肠癌患者的基因数据和临床资料，使用 LASSO Cox 回归分析精简 NRGs。使用 Cox 回归构建 NETs 风险评分模型，并分析其对肿瘤免疫浸润的影响。接着，收集 155 例结直肠癌患者和 55 例健康人，使用 ELISA 检测血清中 CitH3 水平，评估其在结直肠癌诊断和预后的应用价值。然后，使用单细胞分析比较结肠癌患者治疗前后肿瘤中免疫细胞的浸润情况，计算化疗反应好组和不好组治疗前后中性粒细胞数量的变化。用结直肠癌耐药细胞培养基与中性粒细胞孵育，使用迁移测定法评估中性粒细胞趋化性，使用 WB 评估 NETs 的形成。最后，对耐药细胞进行 RNA 测序和基因集富集分析，筛选下游靶点并进行敲低验证。

结果：1.对 NETs 数据进行提取，获得 670 个候选 NRGs。GO 富集分析结果表明，NETs 形成与细胞因子和白细胞趋化性有关。KEGG 富集分析结果表明，炎症因子的产生和 Toll 样受体信号通路在 NETs 的形成中发挥作用。2.通过 LASSO Cox 将 NRGs 筛选缩小到 13 个基因。Cox 回归分析构建 NETs 风险评分模型，该模型能够在训练集和验证集中按预后状况将结直肠癌患者划分为高低风险组。构建的诺莫图能够更好地预测结直肠癌患者的生存率。3.低风险组患者浸润更多的 CD4 T 细胞和 CD4 记忆 T 细胞，及更少的趋化因子水平。4.在结直肠癌尤其是不良预后的患者中观察到更高水平的 CitH3。5.化疗反应好的结肠癌患者治疗后肿瘤中中性粒细胞显著减少。同样，临床数据表明化疗反应好组中性粒细胞的数量显著减少。耐药细胞能趋化中性粒细胞迁移并促进 NETs 形成。6.对耐药细胞进行 RNA 测序和基因集富集分析，发现 CXCL5 上调并进行 qRT-PCR 验证。对 CXCL5 进行敲低，发现中性粒细胞迁移减少 75%，NETs 形成减少 80%。

结论：本研究成功构建 NETs 风险评分模型，能够有效预测结直肠癌患者的 1、3、5 年的生存。血清 CitH3 水平可作为结直肠癌患者诊断和预后的生物标志物。耐药细胞通过上调 CXCL5 来趋化中性粒细胞迁移和促进 NETs 形成。

关键字： NETs 结直肠癌 中性粒细胞 CitH3 CXCL5

577. 基于孟德尔随机化的类风湿性关节炎、炎症因子与恶性骨肿瘤发生的因果关系研究

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目的 通过孟德尔随机化（MR）方法研究类风湿性关节炎（RA）、炎症因子与恶性骨肿瘤发生之间的因果关系。

方法 使用单变量 MR 探究 RA 和炎症因子（白细胞计数、中性粒细胞计数、嗜酸性粒细胞计数、嗜碱性粒细胞计数、单核细胞计数、淋巴细胞计数、红细胞沉降率、C-反应蛋白、白介素-6）与恶性骨肿瘤发生的因果关系，对单变量 MR 中有统计学差异的变量进行双向 MR 和多变量 MR，使用逆方差加权法进行分析，同时使用加权中位数估计法和 MR-Egger 回归法作为补充验证。对最终筛选出的工具变量进行 GO 和 KEGG 富集分析。

结果 RA 会导致恶性骨肿瘤发生风险上升（OR=1.366，95%CI：1.118～1.669，P=0.002），嗜酸性粒细胞（EOS）计数的增加会导致恶性骨肿瘤发生风险上升（OR= 1.909，95%CI：1.021～3.567，P=0.043），RA 与 EOS 之间存在双向因果关联，二者在多变量 MR 中也具有统计学差异，P<0.05。GO 和 KEGG 富集分析表明，RA、EOS 对恶性骨肿瘤的相关基因在 T 细胞分化、细胞因子受体、JAK-STAT 信号通路、NF-κB 通路等方面显著富集。

结论 RA、EOS 计数的增加与恶性骨肿瘤发生存在基因层面的正向因果关联，其潜在机制可能包括免疫应答调控、炎症过程等。

关键字： 类风湿性关节炎；骨肿瘤；嗜酸性粒细胞；孟德尔随机化；富集分析

578. 基于结构色水凝胶微载体的膀胱癌尿液外泌体多元分析

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【目的】本文旨在探讨通过结构色水凝胶微载体富集并多元分析膀胱癌尿液外泌体的技术可行性，以提高膀胱癌的实验室诊断及预后监测效能。

【方法】结构色微载体基于周期性有序纳米结构，具有独特的光子带隙效应而具有稳定的光学编码性能。结合水凝胶良好的生物相容性，制备具有反蛋白石结构的壳层及结构色核芯的核-壳结构微载体，为生物反应提供充分的比表面积，同时实现多元编码，用于膀胱癌尿液外泌体的多元检测。通过化学偶联法修饰探针分子于微载体表面，以“探针分子-外泌体-标记抗体”的双抗体夹心法为反应模型，对微载体进行结构色解码及信号强度检测，实现外泌体标志物的定性及定量分析。

【结果】结构色微载体用于膀胱癌尿液外泌体的富集与多元分析，其独特的光学编码优势及微量多元分析模式，简化了外泌体标志物的分析过程，提高了体系的检测效率。膀胱癌尿液标本的反应体积可低至 20μL，外泌体浓度检测范围从 10^3 个/mL 到 10^8 个/mL，与信号强度呈现良好的相关性($R^2 \geq 0.95$)；受试者工作特征 (ROC)曲线分析结果显示外泌体相关标志物所对应的曲线下面积(AUC)均≥0.80，表明基于该检测体系的外泌体标志物多元分析用于膀胱癌诊断与预后检测具有较好的技术可行性。

【讨论】膀胱癌是泌尿系统最常见的恶性肿瘤之一，其发病率与死亡率逐年上升，因早期症状隐匿，致使预后差甚至危及患者生命，因此，膀胱癌的早期、高灵敏诊断具有重要的临床意义。目前，膀胱镜检查与尿液脱落细胞学检查作为膀胱癌诊断的“金标准”，因其分别具有侵入性及低敏感度等问题而受限于临床诊断应用。本文提出基于结构色编码微载体的膀胱癌外泌体多元分析方法，为膀胱癌的诊断和治疗提供了新的思路和方法。结构色编码微载体作为一种基于光学特性的液相编码微载体，因其周期性有序的纳米排列而产生光子带隙效应，由此产生的特征性反射光谱及其明亮的结构色作为编码元素，具有编码稳定、信号背景低等明显优势。在核-壳结构色微载体中，壳层的反蛋白石结构为生物反应提供了充分的比表面积，核芯则保留了光学编码的特性。外泌体的高灵敏多元检测平台的构建，有望为膀胱癌的早期诊断、病情监测及预后评价提供可靠的实验室依据与技术基础。同时，通过进一步

的研究与技术开发，以期将该技术应用于其他类型肿瘤或疾病的标志物分析中，使其具有广泛的应用价值和发展前景。

关键字： 膀胱癌，结构色，编码微载体，外泌体，肿瘤标志物

579. PLA1A 调控宫颈癌细胞脂代谢重编程介导其增殖转移的机制研究

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研究目的：脂质代谢异常可引发多种疾病，包括糖尿病、心血管疾病以及癌症等。癌症的发生发展是一个多机制多因素的复杂的生物学过程，近年来脂代谢异常在癌症研究中日益受到关注。磷脂酰丝氨酸特异性磷脂酶 A1（Phosphatidylserine specific phospholipase A1，PLA1A）在生物功能上隶属于磷脂酶，其表达紊乱在胃癌和肝癌中陆续被报道，但其在宫颈癌中的表达水平、生物学功能及可能的分子机制尚不完全清楚。本文探讨了磷脂酶 PLA1A 对宫颈癌增殖、迁移和侵袭以及对磷脂代谢的影响，确定磷脂的异常代谢在宫颈癌发生中的作用。

材料与方法：通过 RNA 测序和生物信息学筛选出磷脂代谢相关的差异基因 PLA1A 并确定 PLA1A 与宫颈癌预后的关系；利用克隆形成、Transwell 等对细胞增殖、迁移和侵袭能力进行检测；裸鼠尾静脉注射过表达 PLA1A 的宫颈癌细胞进行皮下成瘤实验在动物水平验证 PLA1A 对宫颈癌发生的影响。通过液相色谱-质谱（LC-MS）对过表达 PLA1A 的宫颈癌细胞进行脂质组学分析。

实验结果：PLA1A 在宫颈癌组织中较癌旁组织显著下调，且与病人的预后密切相关。PLA1A 过表达后，宫颈癌细胞的活力和克隆数目显著降低，并引起宫颈癌的细胞周期发生 S 期阻滞，与此同时细胞周期蛋白依赖性激酶如 CDK2、细胞周期蛋白 CyclinE 的蛋白水平明显下调。PLA1A 过表达后宫颈癌细胞侵袭和迁移能力受到抑制，该过程通过影响宫颈癌细胞的上皮-间充质转化（EMT）进程实现。裸鼠皮下成瘤实验进一步证实了 PLA1A 的作用。脂质组学结果显示过表达 PLA1A 后主要的结构磷脂，即磷脂酰胆碱(PC)、磷脂酰乙醇胺(PE)、显著下调。与此同时磷脂酰丝氨酸(PS)的含量也显著下调。进一步比较 PLA1A 和

PLA1A 酶活突变质粒对细胞增殖和迁移的影响，PLA1A 介导的磷脂代谢异常在调控宫颈癌细胞增殖、侵袭及转移的过程中发挥的功能及其可能的作用机制。

结论：宫颈癌中 PLA1A 过表达后通过影响细胞周期以及 EMT 进程抑制细胞的增殖、迁移和侵袭，提示宫颈癌细胞中 PLA1A 通过介导磷脂代谢重编程进而促进宫颈癌发生发展。

关键字： 宫颈癌 脂代谢 重编程

580. Next-generation sequencing identified that PTPRD mutation is favorable to immunotherapy in human cancer

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Protein tyrosine phosphatase receptors (PTPRs) play an important role in numerous tumor processes. However, the effect of PTPR mutations on the immune checkpoint inhibitor (ICI) response is knockdown. Here, we performed next-generation sequencing (NGS) and analyzed mutation frequency and genomic mutation characteristics of 453 tumor patients. Whole-exome sequencing (WES) and NGS data from other cohorts were integrated. Notably, among 21 PTPRs, PTPRD has the highest mutation frequency and an intensified co-occurrence with other PTPRs. Patients who responded to ICI therapy were enriched with the PTPRD mutation (PTPRD-MUT). A higher objective response rate (ORR, 44.1% vs. 29.1%) was found in PTPRD-MUT patients. Compared with PTPRD-wild-type (PTPRD-WT) patients, PTPRD-MUT patients obtained a longer overall survival time. Genomic alterations with a higher mutation frequency of genes (such as LRP1B) were enriched in PTPRD-MUT patients. A higher tumor mutation burden (TMB) and neoantigens were detected in PTPRD-MUT patients.

PTPRD-MUT patients have more abundant immune cells (including CD8+ T cells and macrophages) and upregulated cytotoxic activity, immune checkpoints, and chemokine-related genes. Moreover, several antitumor immunity pathways were enhanced in PTPRD-MUT tumors. PTPRD-MUT is favorable to immunotherapy across multiple cancer types, which might be a predictive biomarker for patients' clinical outcomes.

Key Words： Protein tyrosine phosphatase receptors, PTPRD, Immune checkpoint inhibitor, Pan_x0002_cancer

581. M6A demethylase ALKBH5 promotes the proliferation of prostate cancer through immunity

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Purpose: As the most important demethylase of m6A, ALKBH5 has been found to play an important role in various cancers. However, their roles in the initiation and progression of prostate cancer remain poorly understood. Here, we aimed to investigate the functional and clinical relevance of ALKBH5 in prostate cancer.

Methods: Western blotting (WB) and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) were used to detect protein and mRNA expression levels. The proliferation and colony formation ability of cells were detected by CCK-8 method and plate colony formation assay. The invasive and migratory abilities of cells were determined by transwell assay and wound healing assay.

Results: We carried out proliferation experiments, clone formation, migration experiments, and cell scratch healing experiments after overexpression of ALKBH5 in hormone-dependent prostate cancer cells LNCaP and hormone-independent prostate cancer cells DU145. Value-added ability, migration ability is inhibited. This suggests that ALKBH5, may play a certain tumor suppressor role in prostate cancer.

Conclusions: This study revealed that the m6A demethylase ALKBH5 inhibits the proliferation and migration of prostate cancer cells by regulating total m6A levels.

Key Words ： m6A demethylase，ALKBH5，prostate cancer，m6A

582. 枯草溶菌素转化酶 9 在结直肠癌中的表达及其对细胞迁移影响的研究

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目的 探讨枯草溶菌素转化酶 9（PCSK9）在结直肠癌（CRC）中的表达水平，及其对 CRC 细胞增殖、迁移的影响。

方法 本研究通过 Sangerbox 云平台分析 TCGA、TARGET、GTEx、GEO 数据库中 PCSK9 在正常组织和 CRC 组织中的表达差异；使用 GenomicScape 数据库分析 PCSK9 与 CRC 预后的关系；使用一个包含 93 例人类结肠癌和 85 例相邻正常组织的组织微阵列芯片，通过免疫组化的方法评估 PCSK9 的蛋白表达水平；使用 TCGA 数据库进行 GSEA KEGG 及 GO 富集分析；通过人重组蛋白刺激实验探索 PCSK9 在 CRC 中的作用。

结果 CRC 中 PCSK9 的 mRNA 水平和蛋白水平在肿瘤组织中显著上调（P<0.001）。高表达 PCSK9 与 CRC 患者预后不良有关（P<0.01）。细胞实验表明重组人 PCSK9 可以增加 CRC 细胞的迁移能力（P<0.05）。

结论 PCSK9 在 CRC 组织中高表达，并与不良预后相关。此外，PCSK9 的刺激可能促进 CRC 细胞的迁移。

关键字： 枯草溶菌素转化酶 9；结直肠癌；细胞迁移

583. TBNK 淋巴细胞亚群及血清学检测在高危人群早期胃癌筛查中应用

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目的：探究患者外周血 TBNK 淋巴细胞亚群水平及血清胃蛋白酶原I、II(PG I, PG II)、胃泌素-17(G-17)、幽门螺杆菌(HP)抗体水平在早期胃癌筛查中的临床应用。

方法：选取 2018 年 11 月至 2020 年 6 月 160 位患者作为研究对象，根据胃镜检查、病理学诊断异常或可疑病变分为 4 组，胃癌组 17 例、早期胃癌组 9 例、低级别瘤变组 24 例、胃炎组 110 例。流式细胞技术检测受试者外周血 T 淋巴细胞亚群(CD3+、CD3+CD4+、CD3+CD8+及 CD4+/CD8+比值)、B 淋巴细胞(CD3-CD19+)、NK 细胞(CD3-(CD16+CD56)+)水平；荧光免疫层析技术测定血清 PG I、PG II、G-17，计算 PG I/PG II比值(PGR)；胶体金方法检测 HP 抗体。采用方差分析和 F 检验，分析组间差异；Logistic 回归分析早癌诊断效能，受试者工作特征曲线(ROC)计算诊断胃癌的最佳临界值。

结果：方差分析结果发现年龄、CD4+T、CD8+T、B 细胞、NK 细胞、CD4+T/CD8+T、CD3+CD4+T、B(CD3-CD19+)、PGR 在多组间存在显著差异，且具有统计学意义(P<0.05)；胃癌组 CD4+T、CD4+T/CD8+T 和 PGR 低于其它组，年龄、CD8+T 高于其它组，有统计学意义(P<0.05)；早癌组 CD3+CD4+T、B 细胞、B(CD3-CD19+)水平低于其它组，NK 细胞水平高于其他组，有统计学意义(P<0.05)；多元 Logistic 回归分析显示，早癌与 NK 细胞、PGR、HP 及年龄显著相关(P<0.05)；ROC 曲线显示胃癌诊断临界值为 PGR<2.850，同时四项联合指标诊断效能高于各项单独指标。

结论：联合检测患者外周血 TBNK 淋巴细胞亚群水平及胃功能血清学指标，可以评估患者机体免疫功能，判断早期癌变风险，设计切实有效的免疫治疗方案，评估抗肿瘤治疗预后，具有重要的临床意义。

关键字： 淋巴细胞；早期胃癌；胃蛋白酶原；胃泌素；幽门螺杆菌抗体

584. 靶向 FAPα+淋巴结转移的肿瘤细胞抑制结直肠癌转移的作用机制研究

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淋巴结转移是结直肠癌最重要和最常见的转移途径之一，也是导致患者复发和远端转移的重要原因。目前手术切除是治疗转移性淋巴结肿瘤的主要手段，然而，由于淋巴结转移具有隐匿性和跳跃性，手术切除的疗效有限。因此，寻找淋巴结内肿瘤细胞潜在的分子靶点，制定有效的靶向治疗策略具有重要的临床意义。本研究发现淋巴转移的结直肠癌细胞高表达FAPα，并揭示 FAPα通过激活 STAT3 通路增强肿瘤细胞的迁移、侵袭、上皮-间质转化、干性和淋巴管生成，以及通过招募调节性 T 细胞建立免疫抑制微环境和诱导淋巴结细胞外基质重塑，从而促进结直肠癌细胞淋巴转移的作用机制，为 FAPα发展成为新的结直肠癌淋巴转移分子标志物和抗淋巴转移治疗靶点提供理论依据。另外，本研究揭示 FAPα酶激活式长春碱类前药 Z-GP-DAVLBH 靶向杀伤淋巴转移结直肠癌细胞的作用，为 Z-GP-DAVLBH 发展成为一种靶点明确、机制清楚的抗结直肠癌淋巴转移新药提供科学依据。

关键字： 结直肠癌淋巴转移；成纤维激活蛋白α；FAPα酶激活式前药；细胞外基质重塑；免疫抑制

585. 临床医师如何看待肿瘤标记物肺包

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目的：寻找更加精准、完整的肺癌肿瘤标志物指导临床治疗。

方法：大量收集各医院临床数据，制定区分腺或鳞的临床公式。经反复临床数据验证，得出准确率较高的自主创新鳞腺之分数字模型。

结论：根据快速检测结果（肿瘤标志物）对病人和家属作有限的较为准确的初步分析，让临床医师为随后诊疗有大致的方向。

关键字： 肺癌；肿瘤标志物；临床特征；鳞癌；腺癌；小细胞肺癌；

586. DCE-MRI for early evaluation of therapeutic response in esophageal cancer after concurrent chemoradiotherapy and its values in predicting HIF-1α expression

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To examine the feasibility of quantitative dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in the early assessment of the therapeutic response to concurrent chemoradiotherapy (CRT) in esophageal cancer (EC) patients and to determine its value in predicting HIF-1α expression. EC patients underwent DCE-MRI 1 week pre-CRT and 3 weeks post-CRT (3w-CRT). According to tumor regression post-treatment, patients were divided into sensitive group (SG) and resistant group (RG). HIF-1α expression was assessed by immunohistochemistry (IHC). Quantitative parameters (ktrans, kep, and ve) were compared between the SG and RG groups, as well as between the HIF-1α(+) and HIF-1α(-) groups. Receiver operating characteristic (ROC) curve analysis was performed to detect the best predictor of the above parameters in the therapeutic response and in predicting HIF-1α expression. Totally 34 and 5 patients were included in the SG and RG, respectively. Pre-ktrans and pre-kep were decreased significantly in the SG at 3w-CRT ($p < 0.01$), whereas only pre-kep was decreased in the RG ($p = 0.037$). Pre-ktrans was higher in the SG com_x0002_pared with the RG ($p < 0.01$). Meanwhile, absolute Δktrans (post-ktrans–pre-ktrans) was reduced more substantially in the SG compared with the RG. Δktrans also had the highest area under the curve (AUC = 0.929) in distinguishing SG from RG. Based on IHC, 13 and 11 patients were HIF-1α(+) and HIF-1α(-), respectively. At 3w-CRT, post-ktrans was markedly lower than pre-ktrans in the HIF-1α(+) group ($p < 0.01$); however, both ktrans and kep in the HIF-1α(-) group were dramatically reduced than pre-treatment values (both $p < 0.01$). Pre-ktrans was significantly higher in the HIF-1α(-) group compared with the HIF-1α(+) group ($p = 0.002$) and constituted an excellent parameter for predicting HIF-1α expression (AUC = 0.881). DCE-MRI is effective in the early assessment of the therapeutic response after CRT, offering a novel noninvasive method for predicting HIF-1α expression in advanced EC patients.

Key Words： concurrent chemoradiotherapy, dynamic contrast-enhanced magnetic resonance imaging, early evaluation, esophageal cancer, hypoxia-inducible factor-1-alpha.

587. Improve ovarian cancer identification using machine learning based on routine clinical and laboratory data

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Objectives

Ovarian cancer (OC) is the seventh most prevalent cancer and has become the eighth leading cause of death among women worldwide. Over 300,000 women are diagnosed with OC each year with a mortality rate of 4.7% and an incidence rate of 3.4%. Early clinical indications of OC are difficult to detected in the early stage, making it easier to transmit and spread. About 70% of OC were diagnosed in the advanced stage, resulting in a 5-year survival rate of only 20%-36.1%. However, if detected earlier, the 5-year survival rate can increase to as high as 90%. According to previous research, the development of OC begins approximately 5.1 years prior to the onset of clinical symptoms, with an average 0.8 years of progression from early to advanced stages, thus providing a potential window of opportunity for early detection of OC that lasts for 4.3 years. Although carbohydrate antigen 125 (CA125) and human epididymis protein 4 (HE4) show considerable power to distinguish OC from non-OC patients, the promise of reliable early diagnosis for OC has not yet been fully realized. In this study, we aimed to develop a machine learning model and facilitate a earlier and more accurate diagnosis of OC based on routine clinical and laboratory data.

Methods

Overall, 311 patients diagnosed with OC, 56 with borderline ovarian tumors (OTs), and 368 patients with benign OTs who were treated in Tianjin Medical University General Hospital were

defined as derivation cohort and randomly divided into training set (70%) and internal validation set (30%). Patients' demographic characteristic and routine laboratory test results were obtained from the electronic medical record system of this hospital. The patients' test results were obtained within 1 month before surgery. Fasting blood were collected in non-menstrual period using standardized procedures. Blood samples were tested in accordance with the manufacturers' instructions. The parameters contained age, menopausal status, CA125, HE4, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), β-human chorionic gonadotropin (β-hcg), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E2), progesterone (P), testosterone (T), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), albumin (ALB), globulin (GLOB), alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), calcium (Ca), Kalium (K), Creatinine (CREA), fibrinogen (FIB), D-dimer, white blood cell (WBC), hemoglobin (Hb), platelet count (PLT), red blood cell distribution width (RDW), platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), and lymphocyte/ monocyte ratio (LMR). Four supervised machine learning algorithms including artificial neural network (ANN), support vector machine (SVM), random forest (RF), and extreme gradient boosting (XGBoost) were used to develop models. Machine learning algorithm models were fitted based on R studio (4.2.3) software. We employed grid search to fine-tune hyperparameters and five-fold cross-validation in our machine learning study. The models' performance were assessed by estimating the area under the curve (AUC) and 95% confidence interval (CI), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using confusion matrixes. The model with the highest AUC was deemed to be the optimal prediction model. A total of 37 patients with OC, 16 borderline OTs, and 63 benign OTs were defined as external validation cohort to examine the generalizability of these models.

Results

Epithelial ovarian cancer (EOC) was the predominant histopathologic type of OC (92.9% in derivation cohort and 97.3% in external validation cohort). All these four machine learning models acquired high accuracy in identifying OC with XGBoost achieving the highest AUC. When differentiated OC from borderline and benign OTs by XGBoost model, the AUC and 95% CI, sensitivity, specificity, PPV and NPV in training set were 0.973 (0.962-0.985), 84.2%, 96.6%,

93.9% and 90.6%, respectively; while in internal validation set, they were 0.932 (0.897-0.966), 74.7%, 92.0%, 85.5% and 85.2%, respectively. The top important eight variables were HE4, CA125, LDH, D-dimer, age, T, FSH, and Hb. In predicting early-stage OC by XGBoost, The AUC (95%CI), sensitivity, specificity, PPV, and NPV in training set were 0.954(0.934-0.974), 66.7%, 96.9%, 88.0% and 89.5%, respectively; while in internal validation set they were 0.872(0.816-0.928), 53.5%, 91.1%, 67.6% and 85.0%, respectively. FIB and CA199 also demonstrated strong important in identifying early-stage OC. In predicting EOC by XGBoost, The AUC (95%CI), sensitivity, specificity, PPV, and NPV in training set were 0.979 (0.968-0.989), 82.3%, 99.0%, 99.7% and 91.1%, respectively; while in internal validation set they were 0.928(0.882-0.963), 72.4%, 93.6%, 82.6% and 86.0%, respectively. CEA, FIB, and Ca were demonstrated as effective biomarkers in identifying EOC. The accuracy of the models were confirmed to be similar with an independent external validation cohort.

Conclusion

In conclusion, we applied machine learning techniques along with routine clinical and laboratory data and develop novel models that exhibit excellent accuracy in differentiate OC from borderline and benign OTs. Clinically, identification of primary risk factors in patients can alert doctors the possibility of OC, which may have a substantial impact on patient's therapy selection and timing.

Key Words： ovarian cancer, machine learning, prediction model, diagnosis, routine clinical and laboratory data

588. Quaking 5 suppresses TGF-b-induced EMT and cell invasion in lung adenocarcinoma

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Quaking (QKI) proteins belong to the signal transduction and activation of RNA (STAR) family of RNA-binding proteins that have multiple functions in RNA biology. Here, we show that QKI-5 is dramatically decreased in metastatic lung adenocarcinoma (LUAD). QKI-5 overexpression inhibits TGF-b-induced epithelial– mesenchymal transition (EMT) and invasion, whereas QKI-5 knock_x0002_down has the opposite effect. QKI-5 overexpression and silencing suppresses and promotes TGF-b-stimulated metastasis in vivo, respectively. QKI-5 inhibits TGF-b-induced EMT and invasion in a TGFbR1-dependent manner. KLF6 knockdown increases TGFbR1 expression and promotes TGF-b-induced EMT, which is partly abro_x0002_gated by QKI-5 overexpression. Mechanistically, QKI-5 directly interacts with the TGFbR1 30 UTR and causes post-transcriptional degradation of TGFbR1 mRNA, thereby inhibiting TGF-b-induced SMAD3 phosphorylation and TGF-b/SMAD signaling. QKI-5 is posi_x0002_tively regulated by KLF6 at the transcriptional level. In LUAD tissues, KLF6 is lowly expressed and positively correlated with QKI-5 expression, while TGFbR1 expression is up-regulated and inversely correlated with QKI-5 expression. We reveal a novel mechanism by which KLF6 transcriptionally regulates QKI-5 and suggest that targeting the KLF6/QKI-5/TGFbR1 axis is a promising targeting strategy for metastatic LUAD.

Key Words： KLF6; metastasis; QKI-5; TGF-b-induced EMT; TGFbR1

589. 血浆小细胞外囊泡中 CAIX 蛋白在前列腺癌早期诊断和初步活检筛选中的临床意义

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背景：目前用于前列腺癌（PCa）诊断的工具，如血液前列腺特异性抗原（PSA）测试、磁共振成像和穿刺活检，存在准确性和特异性不足的问题。因此，迫切需要开发创新方法来实现 PCa 的早期诊断，并准确评估癌症的进展，以便选择最佳治疗方案。肿瘤细胞释放的小细胞外囊泡（sEVs）在细胞间通信中发挥着关键作用，参与癌症的各个阶段，包括转移、免疫逃逸和治疗抵抗。因此，本研究旨在探究血浆 sEV 来源的碳酸酐酶 IX（CAIX）蛋白在 PCa 早期诊断中的潜在价值，以避免不必要的组织活检，为临床决策提供更可靠的依据。

材料与方法：我们收集了来自接受前列腺活检且 PSA 水平升高的患者的血浆样本（n=160）。我们分离并表征了 sEVs，并利用酶联免疫吸附法测量了 sEV 蛋白 CAIX 的表达水平。我们使用受试者工作特征曲线（ROC）、决策曲线分析（DCA）和瀑布图评估了 sEV 蛋白 CAIX 的诊断价值，并确定了临床显著性前列腺癌（csPCa）的独立预测因子，并建立了一个预测模型。此外，我们利用训练队列的数据开发了一个预测 csPCa 的 Nomogram。

结果：与良性患者和非临床显著性前列腺癌（nsPCa）相比，我们发现 sEV 蛋白 CAIX 在 PCa 和 csPCa 中的表达水平显著升高（P<0.001）。sEV CAIX 在区分前列腺癌和良性患者方面表现出色。多变量回归分析显示总 PSA（tPSA）、游离/总 PSA 比率（f/tPSA）、PSA 密度（PSAD）和 sEV 蛋白 CAIX 是 csPCa 的独立预测因子。由 sEV CAIX 和 PSAD 定义的预测模型显示出对 csPCa 最高的判别能力（AUC=0.895），其诊断敏感性和特异性分别为 80.6%和 82.5%。

结论：我们的研究结果表明，sEV 蛋白 CAIX 在早期 PCa 诊断中具有显著的潜力。基于 sEV 蛋白 CAIX 和 PSAD 的 csPCa 预测模型表现出强大的预测价值，并可用于临床活检

决策。因此，sEV 蛋白 CAIX 有望成为一种新型的非侵入性诊断生物标志物，有助于增强 PCa 和 csPCa 的检测。

关键字： 前列腺癌；CAIX；PSA；细胞外囊泡；诊断；生物标志物

590. Value of multi-parameter quantification combined with full-volume analysis derived from spectral CT for the differential diagnosis of solitary pulmonary nodules

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Purpose: Conventional dynamic computed tomography has a low specificity for the distinction between benign and malignant solitary pulmonary nodules, and spectral computed tomography has been proposed as a potential alternative. We aimed to investigate the role of quantitative parameters based on full-volume spectral computed tomography in the differential diagnosis of solitary pulmonary nodules

Methods and Materials: This retrospective study included spectral computed tomography images of 100 patients with pathologically confirmed solitary pulmonary nodules (78 and 22 in the malignant and benign groups, respectively). Multiple quantitative parameters derived from spectral computed tomography were extracted from whole-tumour volume and standardised.

Results: Quantitative parameters derived from spectral computed tomography were significantly higher for malignant solitary pulmonary nodules than for benign nodules (all $P < 0.05$). In the subgroup analysis, most parameters could make the distinction between benign and adenocarcinoma groups, and between benign and squamous cell carcinoma groups. Only one parameter could distinguish between adenocarcinoma and squamous cell carcinoma groups ($P < 0.05$). Receiver operating characteristic curve analysis indicated that NEF70keV, NIC, and Δ70keV had high diagnostic efficacy for differentiating SPNs between benign and malignant solitary pulmonary nodules (area under the curve: 0.867, 0.866, and 0.848, respectively) and between benign and adenocarcinoma groups (area under the curve: 0.873, 0.872, and 0.874,

respectively). The multi-parameters derived from spectral computed tomography exhibited satisfactory interobserver repeatability (intra-group correlation coefficient: 0.856-0.996).

Conclusions: Our study suggests that quantitative parameters derived from whole-volume spectral computed tomography may be useful to improve discrimination of solitary pulmonary nodules.

Clinical Relevance/Application: This is the first study to demonstrate that CT-derived parameters obtained from spectroscopic CT whole-volume analysis hold potential as reproducible imaging markers for the identification of SPNs. Multi-parameter quantitative analyses revealed significant differences in the pulmonary nodules of different pathological types. This approach may help to avoid invasive, time-consuming, and expensive tissue sampling procedures and improve the overall biology of CT scans for characterising SPNs. These parameters may help to improve discrimination of pulmonary nodule types by radiologists and establish an accurate diagnosis for more effective treatments.

Key Words： spectral computed tomography; full-volume analysis; quantitative parameters; solitary pulmonary nodules

591. 初诊多发性骨髓瘤患者外周血γδT细胞及淋巴细胞亚群的表达分析

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目的：分析γδT 细胞和淋巴细胞亚群在多发性骨髓瘤的表达意义。

方法：选取同济大学附属杨浦医院 2022 年 01 月-2023 年 8 月收治的多发性骨髓瘤患者 55 例作为疾病组。并根据多发性骨髓瘤国际分期系统(ISS)将其分为 I 期组、II 期组、III 期组。另选取同期体检健康者 30 例作为对照组。比较疾病组与对照组γδT 细胞和淋巴细胞亚群水平，利用各细胞在 MM 与对照组间的不同表达，构建多因素线性回归方程，然后比较不同分期的 MM 患者的临床指标。最后通过绘制受试者工作特征(ROC)曲线分析关键数据对 MM 的诊断价值。

结果：疾病组与对照组相比，疾病组的γδT 细胞百分比、CD8+T 细胞百分比高于对照组，外周血淋巴细胞总数(LYMT)、CD19+B 细胞百分比、CD3+T 细胞、CD4+T 细胞、CD19+B

细胞的绝对数均低于对照组(p<0.05)。对 MM 有显著影响[A1] 的因素有γδT 细胞百分比、CD19+B 细胞百分比、CD3+T 细胞、CD8+T 细胞的绝对数。与分期有关的指标有γδT 细胞百分比、中性粒细胞数(NEUT)、中性粒细胞与淋巴细胞比值(NLR)、白细胞数(WBC)。ROC 曲线提示γδT 细胞百分比对 MM 有较高的诊断价值。

结论：初诊 MM 患者的γδT 细胞及淋巴细胞亚群(CD8+T 细胞、CD19+B 细胞、CD3+T 细胞等)可以反映患者机体的免疫功能，是 MM 的影响因素。γδT 细胞影响 MM 患者的分期，具有一定的诊断价值。

关键字： 多发性骨髓瘤；淋巴细胞亚群；γδT 细胞；临床分期

592. 血浆细胞外囊泡亚群结合机器学习在前列腺癌个体化诊疗模型的应用研究

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研究目的：前列腺癌（prostatic cancer，PCa）是当今男性面对的主要健康挑战之一。目前的前列腺癌诊断工具，如 PSA 检测和穿刺活检等缺乏足够的灵敏度和特异性。液体活检是一种非侵入性的方法，细胞外囊泡(Extracellular vesicles, EV) 作为细胞之间蛋白质、脂质和遗传物质交换的转移载体，在疾病的发生和发展过程中起关键的作用，是临床诊断前列腺癌的潜在生物标志物重要来源。然而，目前对于大细胞外囊泡（large extracellular vesicles，lEVs）和小细胞外囊泡（small extracellular vesicles，sEVs）在前列腺癌中的研究尚未完善。本研究拟以血浆中的 lEVs 和 sEVs 作为研究对象，通过将液体活检和蛋白质组学相结合，发现前列腺癌患者与正常人群的蛋白质组学差异，并利用机器学习建立前列腺癌的早期诊断及风险分级预测模型，最终验证并开发出具有高灵敏度和特异性的新型肿瘤标志物。

材料与方法：本研究根据 PSA 指标、Glesaon 评分、TNM 分期等标准对前列腺癌患者进行筛选，将患者分为低中危组和高危组，并选取排除 PCa、无其他肿瘤且年龄相仿的前列腺增生患者设为对照组（每组样本为 6 例，共计 18 例）。采集符合入组标准的患者新鲜血

浆样本，采用多步离心方法获得 lEVs 和 sEVs，通过纳米颗粒示踪分析、蛋白免疫印迹、透射电镜等技术对其进行表征验证和分析。随后，使用蛋白质组学技术筛选不同患者组别来源的血浆 lEVs 和 sEVs 中差异表达蛋白，作为 PCa 的新型肿瘤候选标志物。

结果：实验结果表明，从患者血浆中成功分离出了血液 lEVs 和 sEVs，并发现二者在大小、表面标志蛋白表达等方面存在明显差异。LC-MS/MS 结果显示，lEVs 和 sEVs 中共成功鉴定出了 2125 个蛋白。与对照组相比， lEVs 中 肿瘤组共有 6 个上调蛋白，8 个下调蛋白；sEVs 中 肿瘤组共有 31 个上调蛋白，36 个下调蛋白，提示 EV 蛋白质在前列腺癌的个体化诊疗中有关键作用。后续，我们将筛选差异蛋白作为候选标志物进行下一步验证。

结论：本研究发现不同组别患者血液 lEVs 和 sEVs 蛋白表达存在差异，并运用 LC-MS/MS 对这些差异蛋白进行了初步分析，特定差异表达的蛋白有望作为前列腺癌诊疗的标志物进一步深入研究，在前列腺癌的早期诊断和风险分级等方面提供新的方向。

关键字： 前列腺癌，液体活检，细胞外囊泡，肿瘤标志物，蛋白组学

593. hccTAAb Atlas: an integrated knowledge database for tumor-associated autoantibodies in hepatocellular carcinoma

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Tumor-associated autoantibodies (TAAbs) have demonstrated potential as biomarkers for cancer detection. However, the understanding of their role in hepatocellular carcinoma (HCC) remains limited. In this study, our aim was to systematically collect and standardize information on these TAAbs and establish a comprehensive database as a platform for in-depth research. A total of 170 TAAbs were identified from published papers retrieved from PubMed, Web of Science, and Embase. Following normative re-annotation, these TAAbs were referred into 162 official symbols. The hccTAAb (**T**umor-**a**ssociated **a**utoanti**b**odies in **h**epato**c**ellular **c**arcinoma) Atlas was developed using the R Shiny framework and incorporating literature-based and multi-omics datasets. This comprehensive online resource provides key information such as sensitivity,

specificity, and additional details like official symbols, official full names, UniProt, NCBI, HPA, neXtProt, and aliases through hyperlinks. Additionally, hccTAAb offers six analytical modules for visualizing expression profiles, survival analysis, immune infiltration, similarity analysis, DNA methylation, and DNA mutation analysis. Overall, the hccTAAb Atlas provides valuable insights into the mechanisms underlying TAAb and has the potential to enhance the diagnosis and treatment of HCC using autoantibodies. The hccTAAb Atlas is freely accessible at https://nscc.v.zzu.edu.cn/hccTAAb/.

Key Words： autoantibodies, hepatocellular carcinoma, database, immune, web tool

594. 外泌体 miR-625-3p 在前列腺癌发生和发展中的作用机制

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Prostate cancer (PCa), being highly prevalent among males, emphasizes the anguish that arises from delayed detection in order to guarantee efficacious management. The limited sensitivity and specificity of conventional prostate-specific antigen (PSA) testing have stimulated the investigation of more accurate biomarkers. According to our prior investigations, extracellular vesicle miRNA plays a crucial role in both the development and advancement of malignancies; among these, miR-625-3p has been identified as being highly expressed in PCa. This work intends to investigate the mechanistic function of extracellular vesicle miR-625-3p in PCa.

Quantitative qPCR analysis of plasma from PCa patients and miRNA-seq sequencing of PCa-associated RNA were employed in conjunction with functional investigations on PCa cell lines. The findings demonstrate a gradual increase in the expression of extracellular vesicle miR-625-3p in the plasma of patients with PCa, as well as elevated levels in the extracellular vesicles of PCa cells. In contrast to the effects observed when miR-625-3p is overexpressed, experimental evidence indicates that its downregulation inhibits PCa cell migration and invasion while promoting apoptosis. Additional research suggests that transport of extracellular vesicle

miR-625-3p could potentially impact the microenvironment of PCa tumors, consequently promoting tumor growth.

Overall, extracellular vesicle miR-625-3p is a potentially promising biomarker for early diagnosis and treatment of PCa, as it plays a crucial role in its initiation and progression. This study reveals potential mechanistic targets in addition to identifying novel therapeutic targets.

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Key Words： Prostate cancer, miRNA, extracellular vesicles, biomarker, miR-625-3p

595. N6-甲基腺苷去甲基转移酶 FTO 介导雌激素受体α的 m6A 修饰在非小细胞肺癌发生发展中的作用

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目的：N6-甲基腺苷脱甲基转移酶脂肪和肥胖相关蛋白（Fat mass and obesity-associated protein，FTO）已被证实与肥胖和膳食摄入量密切相关，在饮食相关代谢性疾病中起着重要作用。然而，FTO 在非小细胞肺癌发生和进展中的作用和潜在机制仍不清楚。本研究拟对此进行探究，期望能够揭示 FTO 在非小细胞肺癌发生发展中的作用和机制，为非小细胞肺癌的治疗提供潜在靶点。

材料与方法：通过公共数据库生物信息学挖掘和分析、蛋白质免疫印迹（Western blot）、实时荧光定量 PCR（RT-qPCR）、免疫组化（IHC）、酶联免疫吸附法（ELISA）、斑点印迹实验（Dot blot）和液相色谱与串联质谱联用技术（LC/MS-MS）等方法，检测 FTO 在非小细胞肺癌组织和细胞中的表达以及 m6A 修饰水平；通过克隆形成、3D 细胞培养、划痕、Transwell 迁移和侵袭、体内异种移植等实验，检测 FTO 在非小细胞肺癌中的增殖、迁移、侵袭和成瘤能力；通过公共数据库生物信息学挖掘和分析、甲基化 RNA 免疫共沉淀（meRIP）、RNA pull down、RIP、免疫荧光（IF）、荧光原位杂交（FISH）、双荧光素酶基因报告和 RNA 稳定性实验等方法，探究 FTO 在非小细胞肺癌发生发展中的分子调控机制。

结果：FTO 在非小细胞肺癌组织和细胞中的表达明显低于相邻的癌旁组织及正常肺上皮细胞，其表达与不良预后呈负相关。功能实验表明，FTO 在体内外均能抑制非小细胞肺癌的生长和转移。进一步研究发现，雌激素受体α （ESR1）是 FTO 的靶靶基因，FTO 通过识别 ESR1 mRNA 3′ UTR 中的两个 m6A 修饰位点（5247A 和 5409A）来削弱 ESR1 mRNA 的 m6A 水平。并且，m6A 阅读器 YTHDF1 和 IGF2BP3 可识别并结合 ESR1 mRNA，从而增强其稳定性并促进肿瘤生长。此外，ESR1 对非小细胞肺癌具有良好的诊断价值。

结论：FTO-YTHDF1-IGF2BP3-ESR1 轴可调控非小细胞肺癌的发生发展，对于通过干预 m6A 基因修饰制定非小细胞肺癌治疗策略具有重要启示意义。

关键字： 非小细胞肺癌，m6A，FTO，ESR1，YTHDF1，IGF2BP3

596. A molecular classification of diseases that accurately reflects clinicalbehaviour lays the foundation of precision medicine

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A molecular classification of diseases that accurately reflects clinicalbehaviour lays the foundation of precision medicine. The development ofin silico classifiers coupled with molecular implementation based on DNAreactions marks a key advance in more powerful molecular classification,but it nevertheless remains a challenge to process multiple moleculardatatypes. Here we introduce a DNA-encoded molecular classifier that canphysically implement the computational classification of multidimensionalmolecular clinical data. To produce unified electrochemical sensingsignals across heterogeneous molecular binding events, we exploitDNA-framework-based programmable atom-like nanoparticles with nvalence to develop valence-encoded signal reporters that enable linearityin translating virtually any biomolecular binding events to signal gains.Multidimensional molecular information in computational classificationis thus precisely assigned weights for bioanalysis. We demonstrate theimplementation of a molecular classifier based on programmable atom-likenanoparticles to perform biomarker panel screening and analyse

a panel ofsix biomarkers across three-dimensional datatypes for a near-deterministicmolecular taxonomy of prostate cancer patients.

Key Words ： cancer

597. Applications of Electrochemiluminescence Biosensors in the Detection of Tumor Markers: Trends and Challenges

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Accurate detection of tumor markers is crucial for the early diagnosis and treatment assessment of cancer. Traditional detection methods generally suffer from a lack of sensitivity and accuracy. However, electrochemiluminescence (ECL) biosensors, with their high sensitivity and specificity, offer an effective analytical tool for the detection of tumor markers. This article will review the application trends and challenges of ECL biosensors in tumor marker detection. First, the article will introduce the basic principles of ECL biosensors, from the construction of the biorecognition layer to the final detection of the light signal. Additionally, the advantages and application scenarios of ECL biosensors will be discussed. Subsequently, the article will focus on the application of ECL biosensors in tumor marker detection, divided into two categories: immunosensors and RNA/DNA sensors. Finally, by synthesizing a large amount of existing experimental data, it concludes that although ECL biosensors have achieved high sensitivity, there is still room for improvement in detecting low-abundance biomarkers. Moreover, achieving high-selectivity detection in complex biological samples such as blood or urine remains a major challenge for current technology. Future development directions may include developing novel probes to enhance the selectivity and affinity of ECL biosensors for tumor markers. Additionally, interdisciplinary collaboration in materials science, bioengineering, medicine, and information technology is needed to improve stability, reproducibility, and facilitate clinical translation.

Key Words ： ECL;biosensors;tumor markers detection

598. 血浆 ctDNA 中 C14orf39、SOX17 甲基化联合影像学指标在肺癌早诊中的应用研究

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目的 探讨肺结节直径、影像学指标、CEA、CYFRA21-1、SCC 等血清肿瘤标志物以及 ctDNA 中 C14orf39、SOX17 甲基化在肺癌早诊中的价值。

方法 纳入 2021 年 9 月至 2022 年 12 月在我院就诊的恶性肺结节患者 70 例、良性肺结节患者 60 例及健康体检者 80 例，分别为肺癌组、良性结节组和对照组。比较三组患者的肺结节直径、毛刺征、血清肿瘤标志物水平以及血浆中 C14orf39 和 SOX17 的甲基化率，运用多因素回归分析筛选癌变患者的独立危险因素。根据二元 logistic 方法建立预测模型，通过 Hosmer-Lemeshow 检验评估模型的拟合性。使用 ROC 曲线法评估该模型的诊断效能，并通过 bootstrap 重采样（n=200）得出其 95%置信区间。

结果 肺癌组的肺结节直径、毛刺征、血清 CEA、ProGRP、CYFRA21-1、ctDNA 中 C14orf39 及 SOX17 甲基化率明显高于良性结节组和对照组(P＜0.05)，肺癌组的 SCC 明显高于对照组 (P＜0.05)。肺结节直径、毛刺征以及 ctDNA 中 C14orf39 和 SOX17 的甲基化率被确定为恶性肺结节的独立危险因素(P＜0.05)。预测模型的方程为 Y=ex/(1+ex)，其中 x=-7.478+(0.093*结节直径)+(2.935*毛刺征)+(0.0435* C14orf39 甲基化率)+(0.031*SOX17 甲基化率)。Hosmer–Lemeshow 检验（P =0.702）表明模型拟合良好，该预测模型的 AUC 为 0.956(95% CI 0.908-0.985)，相较于单个指标显著提升。

结论 建立了基于肺结节直径、毛刺征、ctDNA 中 C14orf39 和 SOX17 的甲基化率的多指标预测模型，该模型可以有效的在肺癌早诊中发挥作用。

关键字： ctDNA 甲基化、临床预测模型、logistic 回归、肺癌早诊

599. Effects of heterogeneous nuclear ribonucleoprotein K and E combined with human papillomavirus 16 infection in cervical cancerization

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Objective

As important members of the RNA binding proteins (RBPs), heterogeneous nuclear ribonucleoprotein K and E (hnRNP K/E) are involved in various tumor progression. Human papillomavirus (HPV) gene expression is closely linked to RBPs and is tightly regulated at the RNA processing level. However, the comprehensive role of hnRNP K/E combined with HPV16 infection in cervical cancerization remain unclear. Our study investigated the effects of hnRNP K/E combined with HPV 16 infection in cervical cancerization.

Methods

A total of 244 participants, including 177 with different grades of cervical lesions and 67 with normal cervix, were enrolled from a community-based cohort and hospital cohort established in Shanxi Province, China. Western blotting was used to detect the expression of hnRNP K/E, HPV16 E2 and E6 proteins. Additive model was used to analyze interaction between hnRNP K/E and HPV16 infection. Bayesian kernel machine regression (BKMR) was used to explore the comprehensive effects of hnRNP K/E, HPV16 E2 and E6 in cervical cancerization.

Results

HPV16 E6 protein high expression (H=20.809, P<0.001) and HPV16 E2 protein low expression (H=19.061, P<0.001) were associated with increased risk of cervical carcinogenesis. hnRNP K high expression (odds ratio [OR]=8.649, 95% confidence interval [CI]: 3.100~24.130) could increase the risk of cervical intraepithelial neoplasia of grade 2 or worse (CIN2+), while hnRNP E1(OR=0.269, 95% CI: 0.107~0.685) and hnRNP E2 (OR=0.271, 95% CI: 0.107~0.685) high expression reduced the risk of CIN2+. Additionally, we observed that there was a synergic effect between hnRNP K high expression, hnRNP E1/E2 low expression and HPV16 infection on CIN2+.

It was worth noting that there was a significantly negative overall effect of hnRNP K/E, HPV16 E2 and E6 on CIN2+.

Conclusion

There was a negative correlation between hnRNP E1/E2 and cervical carcinogenesis, while hnRNP K was positively associated with CIN2+, especially, there was a stronger risk when it combined with HPV16 infection. Notably, combination of hnRNP K/E with HPV16 E2 and E6 could reduce the risk of CIN2+ occurrence. Our results provide new insights into the combination of HPV infection control and RBPs measures to prevent cervical cancerization.

Key Words： heterogeneous nuclear ribonucleoprotein K and E, Cervical cancerization, Human papillomavirus 16, Comprehensive effects

600. 预测胃癌腹膜转移 PD-1 抗体免疫治疗疗效的生物标志物探索

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研究目的：程序性细胞死亡蛋白 1(PD-1， Programmed cell death protein-1)抗体在晚期胃癌治疗中占据重要地位，但目前关于是否应在腹膜转移胃癌患者中使用 PD-1 抗体这一问题仍然存在争议。有研究报道腹膜转移胃癌患者并不能从 PD-1 抗体治疗中获益，也有分层分析证明无腹水或仅伴有少量腹水的腹膜转移胃癌患者仍可从 PD-1 抗体中获益。因此，本研究收集胃癌腹膜转移患者临床病理资料，探索预测胃癌腹膜转移抗 PD-1 免疫治疗疗效的生物标志物，指导其临床应用。

材料与方法：本研究收集了 75 例 2020 年 3 月-2023 年 9 月在南京大学医学院附属鼓楼医院肿瘤科接受治疗的胃癌腹膜转移患者临床病理资料，其中接受过 PD-1 抗体免疫治疗的有 57 人，未接受过 PD-1 抗体免疫治疗的有 18 人。利用 Kaplan-Meier 生存分析和卡方检验评估患者预后与 PD-1 抗体免疫治疗的关系，包括总生存期(OS, Overall survival)、客观缓解率(ORR，Objective response rate) 和疾病控制率(DCR，Disease control rate)，并利用 COX 比

例风险回归模型进一步对与 PD-1 抗体免疫治疗相关的临床预后因素进行单因素、多因素分析，经多因素分析显著的则是影响胃癌腹膜转移患者生存期的独立预后因素，差异具有统计学意义(P<0.05)，纳入分析的临床预后因素主要包括患者基线资料和基线外周血指标如免疫治疗线数、ECOG PS 评分 (Eastern Cooperative Oncology group performance status)、联合阳性分数(CPS, Combined positive score)、人表皮生长因子受体-2(Her-2, Human epidermal growth factor receptor 2)表达、EBER 原位杂交、病理类型、其它转移病灶、免疫治疗前是否伴有腹水和腹水含量、治疗期间是否腹腔引流，以及血脂指标、炎症指标和肿瘤指标等。

结果：Kaplan-Meier 生存分析结果显示，接受 PD-1 抗体治疗和未接受治疗患者有相似的 OS (15.9 月 vs 13.9 月, P=0.7888)，卡方检验结果显示两组患者的 ORR (16.7% vs 28.1%, P=0.510)和 DCR (66.7% vs 78.9%, P=0.455)也无显著差异。对接受了 PD-1 免疫治疗的患者进行的多因素分析结果显示高 ECOG PS 评分 (P=0.001)、高抗 PD-1 治疗线数(P<0.001)和抗 PD-1 治疗期间进行了腹腔引流(P=0.003)是影响患者 OS 的独立预后危险因素(HR>1)。值得注意的是，我们首次分析发现低外周血载脂蛋白 A1(ApoA1, Apolipoprotein A1)是同时影响胃癌腹膜转移患者 PD-1 抗体治疗后 OS(P=0.031)和无进展生存期(PFS, progression-free survival)(P=0.005)的独立预后危险因素，而 CPS、Her-2 表达、EBER 原位杂交等患者基线资料以及其它外周血指标在多因素分析后不存在显著的统计学差异。

结论：ApoA1 是高密度脂蛋白的主要成分，由肝脏和肠道分泌，在我们的研究中首次提出了它可能是识别胃癌腹膜转移患者免疫治疗生存获益的重要预测因子。除此之外，患者治疗前的 ECOG PS 评分、抗 PD-1 治疗线数以及抗 PD-1 治疗期间是否进行了腹腔引流也对胃癌腹膜转移患者免疫治疗的生存获益产生了重要的影响。以上研究为临床工作中胃癌腹膜转移患者选用 PD-1 抗体提供参考意见。

关键字： 胃癌腹膜转移；免疫治疗；生物标志物

601. 多指标联合血浆 miRNA-574-3p、miRNA-941 在肺结节鉴别诊断中的临床应用研究

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目的：评价应用结节直径、毛刺征、癌胚抗原(CEA)、miRNA-574-3p、miRNA-941 在肺结节患者中的鉴别诊断价值。

方法：选取 2022 年 12 月至 2023 年 12 月陕西中医药大学临床附属医院收治的肺结节性患者 168 例，恶性肺结节患者 85 例作为肺癌组，良性肺结节患者 83 例作为良性结节组，另选择同期于我院行体格检查的 82 例健康体检者作为对照组。比较三组间患者结节直径、毛刺征、血清肿瘤标志物 CEA 及血浆 miRNA 水平，通过 Logistic 回归分析筛选癌变患者的独立危险因素，计算出预测模型，采用 ROC 曲线对模型的诊断效能进行评价。

结果：肺癌组结节直径、毛刺征、CEA、ProGRP、CYFRA21-1、miRNA-574-3p、miRNA-941 水平与良性结节组和健康对照组比较，差异具有统计学意义($p<0.05$)。结节直径、毛刺征、血清 CEA、miRNA-574-3p、miRNA-941 是肺癌的独立危险因素($p<0.05$)，预测模型为 $Y=ex/(1+ex)$，$x=-4.702+(0.85\times$结节直径$)+(1.505\times$毛刺征$)+(0.183\times CEA)+(0.402\times miRNA\text{-}574\text{-}3p)+(0.525\times miRNA\text{-}941)$。预测模型的 AUC 为 0.965，相较于单个指标显著提升，差异有统计学意义($p<0.05$)。

结论：结节直径、毛刺征、CEA、miRNA-574-3p 和 miRNA-941 检测对肺癌患者具有较高的诊断价值，基于以上指标建立的联合预测模型可明显提升诊断效能。

关键字： 肺癌　CEA　miRNA　结节直径　毛刺征

602. Tumor markers profile in dermatomyositis, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and ovarian cancer

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Background: Autoimmune diseases (AID) have been showed to be susceptibility to cancer. This study aimed to analyzed the profile of serum tumor markers in four common autoimmune disease.

Methods: Patients with dermatomyositis (DM, n=132), Systemic sclerosis (SSc, n=77), Systemic lupus erythematosus (SLE, n=191), Rheumatoid arthritis (RA, n=160) and ovarian cancer (n=250) were included in this study. Twelve tumor markers (CA724, AFP, FRT, NSE, CA19-9, CA125, CYFRA21-1, CA153, β-HCG and HE4) levels and abnormal rate in these patients were retrospective statistics. The tumor markers profile were compared among the different AID.

Results: Compared with ovarian cancer (OV) patients, there were no significant difference for the levels and abnormal rate of CYFRA21-1/HE4/CA50/FRT in AID patients. The levels and abnormal rate of CA724/FRT/CA125/NSE were higher in OV patients than that in AID patients. 75% AID patients have at least one elevated tumor marker. 69.46% AID patients have 2-5 elevated tumor markers. All the 12 tumor markers were negative in 16.67%, 19.74%, 27.23% and 32.70% of DM, SSc, SLE and RA patients.

Except CA50, the levels of the other eleven tumor markers were significant difference among DM/SSc/SLE/RA. Except AFP/β-HCG/SCC, the abnormal rate of the other tumor markers were difference between these AID.

Conclusion: The increased levels of tumor makers were common in four major AID, and the profile of tumor makers were significant difference among these AID.

Key Words ： Autoimmune diseases，tumor markers，cancer

603. 凝血因子Ⅱ凝血酶受体在胃癌患者预后和免疫浸润中的临床意义

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目的：探讨凝血因子II凝血酶受体（F2R）表达在胃癌患者中的预后价值及其与免疫浸润的关系，探索其在影响胃癌发生、发展中的潜在生物学机制。

方法：胃癌患者的临床病理信息和基因表达数据来源于癌症基因组图谱（TCGA）、UCSC Xena 和 GEO 数据库等。采用 Wilcoxon 符号秩和检验、配对 T 检验分析临床特征与胃癌样本中 F2R 表达的相关性。构建 Kaplan–Meier 生存曲线和 Cox 回归模型来评估 F2R 对预后的影响，并构建包括相关列线图。利用 UCSC 的 Xena 平台的数据分析 F2R 基因表达和 DNA 甲基化之间的相关性，并采用 MethSurv 方法进行生存分析。使用 TIMER2.0 来评估 F2R 表达与肿瘤免疫细胞浸润丰富度的相关性等。对 F2R 共表达基因进行 GO 功能分析和 KEGG 通路分析，并通过 TISIDB 在线网站分析与 F2R 相互作用的药物。

结果：F2R 在胃癌样本中表达显著上调（P<0.001），与肿瘤组织学分级、临床分期相关；Cox 回归的结果提示 F2R 是胃癌的独立预后因素（HR=2.004，95%CI：1.069~3.755，P<0.05）。生存分析的结果表明，F2R 高表达组、F2R 启动子区低甲基化组的患者总体生存率较低（P<0.05），预后差。免疫浸润的结果显示，F2R 的表达与 CD8+T 细胞（r=0.367）、肿瘤相关的成纤维细胞（r=0.571）、巨噬细胞（r=0.564）、中性粒细胞（r=0.347）、树突状细胞（r=0.504）等呈正相关（P<0.05）。对于单细胞检测的数据集分析发现，F2R 主要在成纤维细胞、CD8+T 细胞、浆细胞和内皮细胞中表达。GO 功能分析表明，F2R 共表达基因的生物学过程主要涉及细胞粘附、对细胞迁移的调节、细胞外基质组织等；KEGG 通路分析显示，F2R 共表达基因主要富集在癌症通路、PI3K-Akt 信号通路和 MAPK 信号通路等。多

GSEA 富集分析的结果显示，F2R 基因高表达，会通过促进 ECM 受体相互作用、局灶粘附和癌症通路等影响胃癌的发生、发展。

结论：F2R 可能是一种独立的、潜在的胃癌预后生物标志物，与胃癌的免疫浸润相关，可作为免疫治疗靶点。

关键字： F2R；胃癌；预后；免疫浸润；富集分析

604. Analysis on SQSTM1 identifies liver metastatic mechanisms in uveal melanoma

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Purpose: Uveal melanoma (UVM) is one of the most frequent adult intraocular malignant tumors, with low initial detection, increased liver metastasis, and lower survival rates. Although SQSTM1 has been identified as a new target for cancer diagnosis and treatment, its role remains unclear in UVM.

Methods: In this paper, UALCAN was used to detect SQSTM1 expression in UVM. Correlations between SQSTM1 expression and hepatic stellate cell (HSC) markers in UVM were analyzed on TIMER 2.0 and verified by qPCR. Methylation of SQSTM1 was performed on MethSurv and pyrosequencing was used to confirm methylation sites in two different UVM cell lines.

Results: SQSTM1 expression was positively associated with the epithelioid cell type of UVM and was higher in stage 4. SQSTM1 expression was associated with HSC activation and functional markers. Lower SQSTM1 expression could induce hepatic stellate cell activation markers and liver fibrosis markers. Methylation of SQSTM1 was much more stable as a malignant marker in UVM.

Conclusions: SQSTM1 expression might induce HSC activation to result in liver metastasis at some extent. Expression of SQSTM1 and its methylation sites may serve as a potential marker for screening, diagnosis, prognosis, and metastasis.

Key Words： uveal melanoma, hepatic stellate cell, liver metastasis

605. 一种兼具葡萄糖代谢调控功能的新型肝癌诊断和预后生物标志物-溶质载体家族 37 成员 3（SLC37A3）

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肝细胞癌(Hepatocellular Carcinoma,HCC)是最常见的肝癌类型,其发病隐匿，早期诊断困难，同时一线治疗药物索拉非尼也表现出较强的耐药性，因此迫切需要开发新型 HCC 诊断和预后生物标志物用于其靶向诊断和治疗。溶质载体超家族(Solute Carrier Superfamily, SLC)是一种重要的的膜转运体家族。SLC 转运蛋白形成跨膜转运通道，运输细胞所需的营养素、代谢物和药物等。SLC37 家族是位于内质网的跨膜糖转运蛋白，主要包括 SLC37A1, SLC37A2, SLC37A3 和 SLC37A4。SLC37A1 参与糖脂代谢和磷脂合成，其高表达与结直肠癌和乳腺癌的发生、增殖和转移高度相关；SCL37A2 是调控 HCC 相关的铁死亡关键基因，参与 HCC 肿瘤微环境重塑；SLC37A4 基因突变使葡萄糖-6-磷酸转移酶缺乏进而引起糖原累积病，同时其高表达也预示卵巢癌预后不良。SLC37A3 主要表达在肝脏、肾脏和胰腺，已被证实与先天性高胰岛素血症、颅内动脉瘤和视网膜疾病相关，但是其在 HCC 发生发展中的作用尚未阐明。

首先 UALCAN 数据库分析结果表明与正常肝组织相比，肝癌组织中 SLC37A1 和 SLC37A3 表达显著升高，而 SLC37A2 和 SLC37A4 表达没有显著差异。GEPIA 数据库分析结果表明在肝癌进展过程中，SLC37A1 和 SLC37A3 表达显著升高，而 SLC37A2 和 SLC37A4 表达没有显著变化；与 SLC37A1（$p=0.0491$）相比，SLC37A3 表达升高更为明显（$p=0.0107$），因此选取 SLC37A3 作为后续研究的目的基因。我们进一步分析发现性别、种族、体重、年龄、转移情况、分期、亚型及 TP53 突变等均可影响 SLC37A3 表达。为验证上述结果选取人肝实质细胞系 HL7702、肝癌细胞系 HepG2 和 HuH-7 体外培养，结果表明与 HL7702 细胞相比，HepG2 和 HuH-7 细胞中 SLC37A3 表达显著升高。选取肝癌患者肝癌组织及癌旁组织进行 SLC37A3 免疫组化染色，结果表明与癌旁组织相比，肝癌组织中 SLC37A3 表达显著升高。

然后应用 Kaplan-Meier 数据库进行生存率分析，结果表明 SLC37A3 高表达患者的总生存率、1 年、3 年和 5 年生存率均显著低于 SLC37A3 低表达患者。SLC37A3 高表达患者中位生存时间为 45.7 个月，而 SLC37A3 低表达患者中位生存时间为 82.9 个月。Cox 回归分析进一步证明 SLC37A3 是 HCC 的独立危险因素。

最后进行 SLC37A3 生物学功能检测，功能互作分析结果表明 SLC37A3 表达与 CALU、YEATS2 和 TRRAP 表达呈显著正相关，与 OCEL1、SELENBP1 和 ECHS1 表达呈显著负相关，体外细胞实验进一步验证上述结果。免疫浸润分析结果表明 SLC37A3 表达与肿瘤中浸润的 B 细胞、CD4+T 细胞、CD8+T 细胞、巨噬细胞和树突状细胞比例呈显著正相关；与经典免疫检查位点 CD274、PDCD1、CTLA4 和 TIGIT 表达也呈显著正相关。在 HepG2 和 HuH-7 细胞中敲减 SLC37A3，结果表明抑制 SLC37A3 表达可显著抑制 HepG2 和 HuH-7 细胞的增殖和侵袭，同时促进凋亡。进一步进行转录组测序分析，结果表明在最具显著性差异前 20 个 KEGG 通路中，1 型糖尿病相关通路位于其中；差异基因筛选发现胰岛素分泌和糖异生/糖酵解相关基因表达发生显著变化。分子生物学实验验证发现胰岛素分泌相关分子 IGFBP1 表达显著升高，KCNN4 表达显著下降；糖异生/糖酵解相关分子 TPI1 和 ALDH1B1 表达显著下降。最后在动物体内建立异种移植瘤模型，结果表明 SLC37A3 敲减组小鼠肿瘤明显生长缓慢，重量下降，增殖减弱，凋亡增强。综上表明，SLC37A3 是一种新型 HCC 诊断和预后生物标志物，同时可能通过调控胰岛素分泌和糖异生/糖酵解途径维持葡萄糖代谢稳态。

关键字： 肝癌；诊断和预后；葡萄糖代谢；SLC37A3

606. IL-6 通过 JAK2/STAT3 信号通路上调 IL-6R 的表达以促进 HCC 进展

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背景与目的：肝细胞癌（Hepatocellular carcinoma，HCC）是一种常见的原发性肝癌亚型，在全球癌症中排名第六，其疾病死亡率较高。尽管全身治疗取得了很大的进展，但 HCC 进展是多因素多步骤的相互作用，发病比较难以察觉，传统疗法的治疗效果有限，而靶向治疗药物的疗效受耐药性限制。有研究显示，白介素 6 受体(IL-6R)在肿瘤的发生和发展过程中扮演着重要角色，但对其功能及其调控的 HCC 表达机制缺乏足够的研究。因此，本研究

旨在探究 IL-6R 在 HCC 细胞中的生物学效应以及其受到的调控表达机制。在此背景下，本研究可以提供新的治疗策略并在 HCC 早期诊断和治疗上提供更有效的方法。

方法：本研究采用 Western blot(蛋白免疫印迹实验)方法评估正常肝细胞(如 THLE-2、THLE-5)和肝细胞癌(HCC)细胞(Huh7, HepG2, SK-Hep1)中 IL-6R 蛋白水平的差异，并通过免疫细胞化学（Immunocytochemistry，ICC）方法对其定性和定位进行分析。我们还采用转染慢病毒的方法，成功构建了 SK-Hep1IL-6R-和 SK-Hep1STAT3-细胞株。利用克隆形成实验和 EdU 检测方法，评估不同处理组间的细胞增殖能力差异。同时，使用划痕愈合实验和 Transwell 实验评估不同细胞组之间的细胞迁移和侵袭能力。此外，我们建立了人肝细胞性肝癌裸鼠移植瘤模型。通过定期监测肿瘤体积来计算肿瘤生长情况并评估 IL-6R 对体内肝癌异种移植模型肿瘤生长的效应，以验证 IL-6R 的受调表达机制。

结果：研究表明，IL-6R 在正常肝脏细胞中的表达程度较低，而在 HCC 细胞中则表现为不正常的高度。SK-Hep1 中 IL-6R 表达水平较高，而在 HepG2 中表达水平较低。相比之下，在 SK-Hep1STAT3-细胞株中，IL-6R 的表达水平下降。研究还发现，在 HepG2IL-6 细胞株中，IL-6（白介素-6）通过上调增殖分子 p-P70S6K 以及迁移分子 MMP2、MMP9 促进了细胞增殖与迁移。与此相反，干扰 IL-6R 表达的 SK-Hep1IL-6R-细胞株以及使用 Tocilizumab 阻抑 IL-6R 表达的 SK-Hep1TCZ 细胞株中，通过下调增殖分子 p-P70S6K、迁移分子 MMP2 和 MMP9 减弱了细胞的增殖和迁移侵袭能力。通过进一步研究 IL-6R 的受调控机制，我们发现通过激活转录因子 STAT3，而 JAK2/STAT3 信号通路促使其与 IL-6R 启动子区域结合，提高 IL-6R 的转录表达。在动物实验中，肿瘤生长最快的是 HepG2IL-6 处理组，终末体积最大；而肿瘤生长最慢的是干扰 STAT3 表达组，终末体积最小。蛋白免疫印迹结果表明 HepG2IL-6 处理组和 SK-Hep1 荷瘤组中 JAK2/STAT3 信号通路活化水平和 IL-6R 蛋白表达水平均上调。

结论：本研究结果显示，IL-6 可通过 JAK2/STAT3 信号通路提高表达 IL-6R，进而增强 HCC 细胞增殖、迁移能力，进而推动 HCC 进展。这一研究成果为 HCC 的治疗提供了新的目标和理论基础。

关键字：肝细胞性肝癌、IL-6R、JAK2/STAT3

607. Identification and validation of an anoikis-related genes signature for prognostic implication in papillary thyroid cancer

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Objective: Thyroid cancer, particularly papillary thyroid cancer (PTC), presents a significant global health concern with increasing incidence and morbidity. While PTC prognosis is generally favorable, a subset of patients experiences reduced survival rates due to factors such as recurrence, metastasis, and complications. This study aims to explore key molecules involved in the progression of PTC, focusing on anoikis-related genes, to enhance prognosis and improve patient outcomes.

Methods: Differentially expressed genes (DEGs) between PTC and adjacent normal tissues were analyzed using GEO (GSE29265, GSE33630, and GSE60542) and TCGA databases. Anoikis-related genes (ARGs) were identified, and a six-gene signature related to anoikis was developed by integrating clinical information. Functional enrichment analyses, prognostic model establishment, and evaluation were performed, along with nomogram construction and assessment. Additionally, the study explored immune cell infiltration patterns, functional analysis related to risk score, and tumor immune microenvironment characteristics.

Results: The study identified 64 anoikis-related DEGs in PTC patients and established a prognostic signature comprising EZH2, PRKCQ, CD36, INHBB, TDGF1, and MMP9. A risk score for each patient was calculated as follows: 1.4829 * (expression of EZH2) + (-0.2218) * (expression of PRKCQ) + (-0.0188) * (expression of CD36) + (-0.2417) * (expression of INHBB) + (-1.1662) * (expression of TDGF1) + (0.1198) * (expression of MMP9). The K-M analysis demonstrated significant prognostic value, with high-risk patients exhibiting worse progression-free survival (PFS) rates ($P < 0.05$). The AUC values for 1-, 3-, and 5-year FPS rates obtained from the prognostic signature were 0.805, 0.705, and 0.703. The nomogram (Figure 1) with clinical factors was subsequently constructed, and the C-index calculated for the nomogram

was 0.712. Functional analyses revealed biological processes and pathways associated with cancer progression. The risk model showed relevance to the tumor immune microenvironment. The high-risk group had a higher stromal score, immune score, and ESTIMATE score, and a lower tumor purity than the low-risk group. Drug sensitivity prediction findings that PTC patients in the low-risk group demonstrated greater sensitivity to Sorafenib and Axitinib. Conversely, PTC patients in the high-risk group exhibited increased sensitivity to Cisplatin, Doxorubicin, Paclitaxel, and Sunitinib. The TIDE score showed a limited immunotherapy benefit for PTC patients in the high-risk group.

Conclusion: The developed six-gene anoikis-related signature offers a promising tool for predicting PTC progression, enhancing treatment options, and contributing to precision medicine. Further exploration of the molecular mechanisms and experimental validation will provide valuable insights for improving patient outcomes in PTC.

Key Words ： Papillary thyroid cancer, anoikis, tumor microenvironment, prognostic model, nomogram

608. Hepatitis B-Related Hepatocellular Carcinoma: Classification and Prognostic Model Based on Programmed Cell Death Genes

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Background & Aims: Chronic hepatitis B virus (HBV) infection is a major risk factor for the development of Hepatocellular carcinoma (HCC), particularly in regions with high HBV prevalence. Despite advances in treatment, the prognosis of HBV-related HCC remains poor, with a high rate of recurrence and metastasis Therefore, there is an urgent need to identify novel prognostic biomarkers and therapeutic targets for HBV-related HCC. Programmed cell death (PCD) is a critical process in the regulation of tissue homeostasis and the elimination of damaged or abnormal cells. Several types of PCD have been identified, including apoptosis, necroptosis, pyroptosis, and ferroptosis. Recently, several studies have suggested that PCD plays a critical role

in the development and progression of HCC. However, the role of different types of PCD in HBV-related HCC and their clinical significance remains unclear. This study aims to develop a prognostic model that incorporates genomic and clinical information based on PCD-related genes, providing novel insights into the molecular heterogeneity of HBV-HCC through bioinformatics analysis and experimental validation.

Materials & Methods: In this study, we analyzed 139 HBV-HCC samples from The Cancer Genome Atlas (TCGA) and validated with 30 samples from the Gene Expression Omnibus (GEO) database. Various bioinformatics tools, including differential expression analysis, gene set variation analysis, and machine learning algorithms were used for comprehensive analysis of RNA sequencing data from HBV-HCC patients. Furthermore, among the PCD-related genes, we ultimately chose DLAT for further research on tissue chips and patient cohorts. Immunohistochemistry, qRT-PCR and Western blot analysis were conducted. Differences between the subgroups were statistically evaluated.

Results: Several previous studies have identified subtypes in HCC, and classified HCC patients with distinct clinical outcomes. Our study differed from those previous ones in the methods used to identify subtypes, and found specific clinical characteristics and immune features of each subtype. Through unsupervised clustering analysis, we firstly discovered three distinct subgroups of HBV-HCC patients with different clinical characteristics and survival outcomes. However, TIDE analysis showed that Cluster 2 had significantly higher exclusion scores, indicating an immunosuppressive state and inability for immune cells to infiltrate into the tumors, which may be related to its poor survival outcomes. MSI analysis also indicated that Cluster 2 was least likely to benefit from immune checkpoint blockade therapy, while both Cluster 1 and Cluster 3 had higher MSI scores, suggesting that these two subgroups may be more sensitive to immunotherapy. In our study, we performed more detailed research and found metabolic pathways were activated or inhibited in different immune subtypes of HBV-HCC. Small molecule, carboxylic acid, organic acid and other catabolic process related pathways were upregulated in Cluster 1 and downregulated in Cluster 2. Using a combination of univariate cox regression analysis, LASSO regression, and random forest analysis, we identified five genes (CHMP4C, DLAT, MMP1, NLRP6, and NOD2) associated with OS. We developed a risk score formula based on their expression levels. Furthermore, we evaluated the potential for drug sensitivity analysis based on

the risk score. These genes may serve as potential prognostic biomarkers and therapeutic targets for HBV-HCC.

Conclusions: Our study identified distinct subgroups of HBV-HCC patients with different clinical characteristics, survival outcomes, and metabolic states, providing new insights into the heterogeneity of HBV-HCC. A prognostic model based on five PCD-related genes (specifically DLAT) and tumor stage that may serve as potential biomarkers for patient stratification and personalized therapy. Finally, our study highlights the potential for drug sensitivity analysis based on the risk score, which may facilitate the development of targeted therapies for HBV-HCC.

Key Words ： Hepatocellular carcinoma, Hepatitis B virus infection, Programmed cell death, Clinical characteristics, Prognostic model

609. 基于数据库分析 TL1A 在结直肠癌中的表达及其与临床病理因素、预后的关系

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背景：结直肠癌是我国常见的恶性肿瘤，随着生物信息学的发展，寻找高效、敏感的生物标志物有助于早期疾病诊断及干预。TL1A 又称 TNFSF15，是时下热门的生物靶点，并且已被证实在多种自身免疫相关性疾病和肿瘤发病过程中发挥作用，而其与结直肠癌发生发展的关系尚不明确。

目的：本研究旨在通过查询肿瘤相关数据库对结直肠癌中 TL1A 表达水平及其与临床病理因素、预后的相关性进行分析。

方法：在 TCGA、GEPIA 和 UALCAN 数据库中检索下载结直肠癌组织样本、正常组织样本 RNA 测序表达数据和临床数据，分析比较 TL1A 在结肠癌、直肠癌组织与正常组织中的表达差异，并分析 TL1A 表达水平与临床病理因素、预后之间的关系；在 Kaplan-Meier plotter 数据库中分析 TL1A 表达高低对于评估结直肠癌患者预后的价值。

结果：1.基于 TCGA 数据库分析发现 TL1A mRNA 在结肠癌组织与癌旁正常组织中的表达存在显著差异，在结肠癌组织中的表达水平高于癌旁正常组织；而在直肠癌组织与癌旁正常组织中的表达差异无显著性；2.基于 GEPIA 数据库分析发现 TL1A mRNA 在结肠癌、直

肠癌组织中的表达均高于正常组织，但差异不具有统计学意义；进一步分析发现在结肠癌、直肠癌不同临床分期之间 TL1A 表达无显著差异，且表达高低对结直肠癌患者总体生存期无明显影响；3.基于 UALCAN 数据库分析发现 TL1A 在结肠癌、直肠癌组织中的表达水平显著高于正常组织；进一步分析发现 TL1A 高表达与结肠癌患者体重指数、直肠癌患者肿瘤分期相关；4.基于 Kaplan-Meier plotter 数据库分析发现 TL1A 高表达的结肠癌患者 OS 低于低表达的患者；而 TL1A 高表达的直肠癌患者与低表达的患者 OS 无显著差异。

结论：1. TL1A 可能是结肠癌、直肠癌的促癌基因；2. TL1A 表达量与结肠癌患者体重指数、直肠癌患者肿瘤分期相关；3. TL1A 高表达可用于预测结肠癌患者的不良预后，但与直肠癌患者预后无明显相关。

关键字 ：TL1A；TNFSF15；结肠癌；直肠癌；数据库

610. 基于 Hb/RDW 比值、CA19-9 与黏膜病理建立精准化评估 CAG 人群癌变风险的列线图预测模型

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目的：胃癌（gastric cancer，GC）是我国最常见的消化道肿瘤之一，由于其早期症状的隐匿性与非特异性，如何精准识别及诊断 GC 一直是胃癌防治的重点。慢性萎缩性胃炎（chronic atrophic gastritis，CAG）在我国发病率高且属于 GC 的癌前病变。本研究旨在探寻基于 CAG 人群分析的 GC 独立危险因素，并以此构建并验证个性化预测模型，探讨新型血液标志物血红蛋白/红细胞分布宽度比值（Hb/RDW ratio，HRR）与常规肿瘤标志物结合对 GC 的诊断价值。

方法：回顾性分析 2018 年 1 月-2024 年 1 月本院收治的经内镜病理诊断为 CAG 的患者共计 314 例。内镜及病理活组织检查记录肠上皮化生（IM）、异性增生及胃黏膜癌变情况，根据是否存在原发性胃癌，分为 CAG 组以及 GC 组。通过单因素与多因素 logistic 回归，筛选出独立危险因素并建立列线图模型。对模型使用 ROC 曲线评价区分度、Hosmer-Lemeshow 拟合优度检验校准度、绘制临床决策分析（DCA）曲线评价临床有效性。

结果：对两组研究对象的各项参数及指标对比发现，幽门螺旋杆菌（Hp）感染（53.7%，p=0.012）、重度肠上皮化生（IM）（14%，p=0.033）、黏膜异型增生（20.6%，p=0.011）

在GC组更多见。对血液学指标比较显示，GC组患者的G-17（6.87pmol/L）、CEA（3.37ng/mL）、CA199（10.81U/ml）、CA72-4（2.43U/mL）、RDW（13.91%）均显著高于CAG组（5.15pmol/L、1.96ng/mL、5.94ng/mL、1.48U/mL、12.70%）。而淋巴细胞计数（1.27×10^9/L）、Hb（111.38g/L）、HRR（9.37±2.48）、总铁结合力（44.8μmol/L）均低于CAG组（1.52×10^9/L、136.00g/L、11.29±2.32、52.2μmol/L），差异均具有统计学意义（p<0.05）。将血液学指标进行单因素与多因素logistic回归分析发现，Hp感染（p=0.002）、胃粘膜重度IM（p=0.023）及异型增生（p<0.001）、G-17（p=0.009）、CA19-9（p=0.032）及HRR（p<0.001）被筛选为GC的独立危险因素。基于这几项指标建立个性化列线图模型，该模型AUC为0.813（95% CI：0.765-0.860），Hosmer-Lemeshow拟合优度检验显示p=0.7566（P＞0.05），DCA曲线显示模型阈概率在0到70%区间内，说明模型的区分度、校准度、以及临床应用价值良好。

结论：本研究证明，基于新型血细胞比值HRR、常规肿瘤标志物CA19-9以及胃泌素-17、Hp感染与黏膜病变程度五项GC独立危险因素，建立的针对CAG人群的精准化个性化列线图预测模型，对于量化CAG患者的癌变风险具有良好的诊断和筛查价值。外周血细胞参数与肿瘤筛查标志物因其经济性和适用性在临床上广泛应用，不同标志物的联合分析可能是筛查肿瘤的一个新方向，本研究证明了其在胃癌筛查和诊断中的应用前景，值得进一步研究。

关键字： 胃癌；慢性萎缩性胃炎；危险因素；Hb/RDW比值；CA19-9；列线图模型

611. ATF3/CXCL8通过诱导中性粒细胞极化及胞外诱捕网的形成促进三阴性乳腺癌转移

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目的 探究肿瘤相关中性粒细胞极化及形成的胞外诱捕网（NETs）在三阴性乳腺癌（TNBC）转移中的作用及机制。

方法 利用TNBC细胞系MDA-MB-231小鼠尾静脉模型从转移灶中纯化、筛选和构建转移能力更强的细胞株。通过SytoxGreen染色和免疫荧光实验在高转移和低转移TNBC细胞系及动物肿瘤转移模型中比较两者招募中性粒细胞和诱导NETs形成的能力。通过NETs抑制剂，在体内外功能实验中检测NETs在TNBC转移能中的作用。通过临床数据分析结合细胞因子芯片、RNA干扰或过表达功能实验，筛选高转移TNBC趋化、极化中性粒细胞和

NETs 形成的关键细胞因子。通过启动子区转录结合位点及转录因子预测、RNA-seq、ChIP-qPCR、荧光素酶报告基因技术，敲降/过表达调控实验确定关键细胞因子的转录因子及其上下游调控机制。

结果 通过小鼠尾静脉模型成功筛选和构建转移能力更强的 4-9 细胞株，体内外功能实验表明 NETs 在 4-9 转移中发挥重要作用。4-9 细胞上清中显著高表达的 CXCL8 是促进诱导中性粒细胞在肿瘤微环境中富集、极化及 NETs 形成的关键细胞因子。ATF3 在 4-9 细胞中显著上调，并在转录水平促进 CXCL8 高表达。

讨论 TNBC 高度侵袭及转移能力与其特殊的肿瘤微环境（TME）有关。肿瘤相关性中性粒细胞（TAN）作为 TME 重要组成部分，与 TNBC 高转移密切相关。本研究发现 TNBC 与 TANs 的相互驯化是造成 TNBC 高转移的关键因素，机制上 ATF3 介导的 CXCL8 高表达促进中性粒细胞招募、极化和 NETs 形成进而促进 TNBC 转移。该研究结果有望明确驱动 TNBC 转移和复发的关键分子和机制，对 TNBC 治疗靶点的发现、鉴定和策略的选择具有重要意义。

关键字： CXCL8，中性粒细胞，三阴性乳腺癌，肿瘤转移

612. TL1A 表达及其基因特定 SNP 与胃癌的关联性研究

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目的：分析肿瘤坏死因子配体相关分子 1A(Tumor necrosis factor ligand related molecule-1A，TL1A)在胃癌组织中的表达及其特定单核苷酸多态性(Single nucleotide polymorphism，SNP)与临床病理特征之间的关联。深入探讨 TL1A 与胃癌的易感性和严重程度的相关性。

方法：（1）收集杭州师范大学附属医院 58 例胃癌患者的肿瘤组织（石蜡包埋组织）和 77 例健康人群的外周血，分别提取 DNA，进行聚合酶链式反应(Polymerase Chain Reaction，PCR)联合测序技术检测目的基因 3 个调控区 SNP 位点(rs6478106、rs7848647、rs6478109)。（2）采用免疫组织化学方法(Immuno Histo Chemical，IHC)检测 TL1A 在 58 例胃癌组织和癌旁正常黏膜组织（石蜡包埋组织）中的表达水平。

结果：（1）rs6478106 位点经测序检出 GG、GA 和 AA 三种基因型；rs7848647 位点经测序检出 AA、AG 和 GG 三种基因型；rs6478109 位点经测序检出 CC、CT 和 TT 三种基因型。

（2）胃癌患者与健康人群 rs6478106、rs7848647 位点三种基因型频率、等位基因频率的分布差异均无统计学意义(P>0.05)，提示上述两个位点与胃癌的易感性不相关。胃癌患者与健康人群 rs6478109 位点三种基因型频率的分布差异有统计学意义(P<0.05)；两组间 C、T 等位基因频率分布差异有统计学意义(P<0.05)，提示 T 等位基因是胃癌的危险因素(OR=1.82)，且该位点与胃癌的易感性相关。

（3）在胃癌患者中，rs6478106 位点基因型与年龄、性别、肿瘤最大直径、分化程度、浸润深度、淋巴结转移及远处转移均无统计学意义(P>0.05)；rs7848647 位点基因型与肿瘤最大直径(P<0.05)有统计学差异，其它均无统计学意义(P>0.05)；rs6478109 位点基因型与淋巴结转移(P<0.05)有统计学差异，其它均无统计学意义(P>0.05)。

（4）TL1A 在胃癌组织中表达明显增多，与癌旁正常黏膜组织相比差异有统计学意义(P<0.001)。在胃癌组织中，TL1A 表达水平在 rs6478106、rs6478109 位点三种不同基因型人群中有统计学差异(P<0.05)；TL1A 表达水平在 rs7848647 位点三种不同基因型人群中无统计学差异(P>0.05)。

（5）胃癌组织中 TL1A 表达水平与淋巴结转移(P<0.05)有显著相关性，与年龄、性别、肿瘤最大直径、分化程度、浸润深度及远处转移均无显著差异（P>0.05）。且高表达 TL1A 的胃癌患者发生淋巴结转移的危险性增加(OR=3.86)。

结论：（1）TL1A 编码基因特定 SNP 位点 rs6478109 的等位基因与胃癌的易感性相关，且 T 等位基因是胃癌的危险因素。

（2） TL1A 编码基因特定 SNP 位点 rs7848647、rs6478109 与胃癌的严重程度相关。其中 rs7848647 可能通过影响胃癌细胞增殖来促进胃癌的发生发展，rs6478109 位点可能参与胃癌的淋巴结转移机制来促进胃癌的侵袭与扩散。

（3）TL1A 编码基因特定 SNP 位点 rs6478106、rs6478109 与胃癌组织 TL1A 的表达水平相关。其中 rs6478109 可能通过影响 TL1A 的表达量，进而参与胃癌的淋巴结转移进程。

关键字： 胃癌；TL1A；SNP

613. Unveiling NUSAP1 as a Common Gene Signature Linking Chronic HBV Infection and HBV-Related HCC

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Background: Hepatitis B virus (HBV) is a significant contributor to the development of hepatocellular carcinoma (HCC). Chronic HBV infection (CHB) facilitates disease progression through various mechanisms. However, the specific factor responsible for the progression of HBV infection to HCC remains unresolved. This study aims to identify the hub gene linking CHB and HBV-related HCC through bioinformatic analysis and experimental verification.

Methods: Differentially expressed genes (DEGs) were identified in datasets encompassing CHB and HBV-HCC patients from the GEO database. Enriched pathways were derived from GO and KEGG analysis. Hub genes were screened by protein-protein interaction (PPI) analysis and different modules in Cytoscape software. The significance of the selected hub gene in prognosis was further assessed in validated datasets. The effects of hub genes on cell growth and apoptosis were further determined in functional experiments.

Results: The study revealed upregulation of NUSAP1 in CHBs and HBV-HCCs. High expression of NUSAP1 served as an independent predictor for poor prognosis of liver cancers. Functional experiments demonstrated that NUSAP1 promotes cell growth, influences cell cycle process, and protects cells from apoptosis in HepG2.2.15 cells.

Conclusion: NUSAP1 serves as a poor prognostic indicator for liver cancers, and potentially plays a crucial role in HBV-HCC progression by promoting proliferation and inhibiting apoptosis.

Key Words： Hepatocellular carcinoma, Chronic HBV infection, NUSAP1, Cell cycle

614. 肿瘤恶病质个体特异性：源自癌代谢物 D2HG 介导的肿瘤-骨骼肌相互作用

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背景和目的：肿瘤恶病质的特点是体重减轻和骨骼肌萎缩。基于分解代谢上调和合成代谢下调的骨骼肌萎缩机制，恶病质表现为肿瘤相关代谢产物异常产生和积累。积累的代谢物不仅作为生物标志物预后肿瘤恶病质发生发展，也会通过代谢网络调控影响机体代谢稳态和蛋白合成/分解代谢。本研究通过筛选肿瘤产生的代谢物对骨骼肌组织的影响，研究了肿瘤遗传突变介导的癌代谢物代谢积累促进肿瘤恶病质进展。

方法：我们基于文献搜索肿瘤恶病质相关代谢产物，并使用体外肌管分化模型来筛选干扰肌肉萎缩中的代谢物。在评估代谢产物功能后，我们通过癌基因突变建立了代谢微环境，以揭示代谢产物介导肌肉蛋白水解的机制。此外，我们过表达下游代谢酶基因，并且通过 IDH1 抑制剂调控代谢功能活性研究肿瘤恶病质个体化治疗的可能性。

结果：根据文献整理，共筛选出 157 种恶病质相关代谢产物和肿瘤代谢产物，并用体外肌管分化模型筛选出 19 种代谢产物。D-2-羟基戊二酸（D2HG）和富马酸盐处理导致肌管宽度缩短，并增加 E3 泛素连接酶 Trim63 和 Fbxo32 的 mRNA 表达。RNA 测序显示 D2HG 诱导了明显的转录和代谢变化。然后，我们收集了 149 名肿瘤患者，并在 19 名 D2HG 高于非突变患者的患者中证实了 IDH1 突变（$p<0.0001$）。此外，8 名患有 IDH1 突变和恶病质综合征的肿瘤患者具有更高的 D2HG（$p<0.0002$）。在小鼠癌症恶病质模型中，CT26 癌症细胞中突变的 IDH1（R132H）加速了肌肉萎缩并降低了总生存率。在携带共同 IDH1 肿瘤的小鼠中在 DPI 17 处和在携带野生型肿瘤的小鼠的 DPI 22 处观察到恶病质。在分化良好的肌管中过表达的 D-2 羟基戊二酸脱氢酶（D2hgdh）可以减轻 93μM D2HG 诱导的肌管宽度缩短和 E3 连接酶上调。转录组学和代谢组学揭示了 D2HG 诱导的 NADH/NAD+模式。此外，IDH1 抑制剂伊沃西替尼治疗通过改善肌肉面积、保留腓肠肌质量、降低 E3 连接酶 mRNA 表达和血清 D2HG 浓度，延缓了癌症恶病质的进展。

结论：晚期肿瘤恶病质也具有个体差异的遗传特异性，IDH1 突变的肿瘤患者会导致 D2HG 积累，损伤骨骼肌蛋白合成和降解，引起骨骼肌萎缩和肿瘤恶病质发病进程加快，导

致晚期恶病质死亡率升高。本文发现抑制 IDH1 抑制可以延缓肿瘤患者恶病质的发生，提示肿瘤恶病质患者进行个体化治疗的重要性，恶病质不是肿瘤发展的必然阶段。

关键字： IDH1；肿瘤代谢产物；D-2-羟基戊二酸；肿瘤恶病质；骨骼肌

615. Colonic expression of glutathione S-transferase alpha 4 and 4-hydroxynonenal adducts is correlated with the pathology of murine colitis-associated cancer

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Chronic inflammation-induced oxidative stress is an important driving force for developing colitis-associated cancer (CAC). 4-hydroxynonenal (4-HNE) is a highly reactive aldehyde derived from lipid peroxidation of ω-6 polyunsaturated fatty acids that contributes to colorectal carci_x0002_nogenesis. Glutathione S-transferase alpha 4 (Gsta4) specifically conjugates glutathione to 4-HNE and thereby detoxifies 4-HNE. The correlation of these oxidative biomarkers with the patholog_x0002_ical changes in CAC is, however, unclear. In this study, we investigated the expression of Gsta4 and 4-HNE adducts in azoxymethane/dextran sulfate sodium (AOM/DSS)-induced murine CAC, and analyzed the correlations of 4-HNE and Gsta4 with inflammatory cytokines and the pathological scores in the colon biopsies. Real-time quantitative PCR showed that expression of IL6, TNFα, and Gsta4 sequentially increased in colon tissues for mice treated with DSS for 1, 2, and 3 cycles, respectively. Moreover, immunohistochemical staining showed remarkably increased expression of 4-HNE adducts, Gsta4, TNFα, and IL6 in the colon biopsies after 3 cycles of DSS treatment. Correlation analysis demonstrated that 4-HNE adducts in the colon biopsies were positively correlated with Gsta4 expression. Additionally, the expression of Gsta4 and 4-HNE adducts were strongly correlated with the pathological changes of colon, as well as the expression of TNFα and IL6 in colon tissues. These results provide evidence for the association of oxidative biomarkers Gsta4 and 4-HNE with the pathological changes of

CAC and may help developing novel histopathological biomarkers and prevention targets for CAC.

Key Words： Colitis-associated cancer, 4-Hydroxynonenal, Glutathione S-Transferase alpha 4, AOM/DSS, Inflammatory cytokines.

616. m6A- and immune-related lncRNA signature confers robust predictive power for immune efficacy in lung squamous cell carcinoma

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Abstract

Immune checkpoint blockade has revolutionized immunotherapy of lung squamous cell carcinoma (LUSC), but the effective rate is less than 30% attributing to no effective and reliable method for predicting immune response. However, the clinical value of N6-methyladenosine (m6A) and immune-related lncRNA (mirlncRNA) concerning immune efficacy remains unknown. First, we identified a packet of specific mirlncRNA. Based on this, patients with LUSC were optimally divided into mirlncRNA clusters A, B, and C. The mirlncRNA cluster A was categorized as an immune-inflamed phenotype distinguished by infiltration of numerous immune cells such as tumor-infiltrating lymphocyte cells and highlighted by pathways such as regulation of myeloid leukocyte differentiation, while clusters B and C were found to correspond to immune-desert and immune-excluded phenotypes, respectively. Furthermore, the immuneinflamed phenotype was shown to possess the highest immune infiltration, the lowest chromatin accessibility, survival rates, half inhibitory concentration (IC50), and the best immune efficacy. Finally, risk scores derived from the mirlncRNA signature helped identify subgroups of patients who could significantly benefit from immunotherapy. Encouragingly, in the population with poor response to the three targeted drugs, the immune response of patients with low drug sensitivity is significantly

improved, indicating the vitality of combined therapy. The mirlncRNA signature not only identifies molecular typing and distinguishes chromatin accessibility, but also further highlights the immune efficacy and drug sensitivity, which might contribute to developing a new strategy for immunotherapy-based individualized treatment.

Key Words： chromatin accessibility, immune efficacy, long-chain non-coding RNA, lung squamous cell carcinoma, N6-methyladenosine (m6A) methylation

617. A prospective, multicenter, real-world study of the incidence of chemotherapy-related malignant vomiting （CINV） and its influencing factors in cancer patients in China

Purpose Nausea and vomiting are the most painful and feared side effects for patients during chemotherapy. In the absence of effective intervention, highly emetogenic chemotherapy can cause nausea and vomiting in about 90% of patients.Many previous clinical studies have shown that standardized use of antiemetic therapy can protect more than 70% of patients at risk for the incidence of chemotherapy-related malignant vomiting （CINV） chemotherapy.Although the relevant NCCN guidelines have been published for many years, it has been reported in Germany that only 2.8-20.1% of patients in the HEC group received the prophylactic antiemetic therapy recommended by the guidelines.A prospective study conducted in developed countries in Europe and the United States showed that 55%, 46% and 29% of patients in the HEC/MEC group, respectively, received prophylactic antiemetics in accordance with guidelines during the respective acute, delayed, and global stages during the first cycle.In 2020, we conducted the first prospective real world study on chemotherapy-related vomiting.In this study, the incidence of acute CINV and delayed CINV was 55.3% and 62.3%, respectively,and another 36% of patients developed CINV after the risk period.The compliance rate of all antiemetic regimens was 21.5% , within which the rate was 47.06% in the MEC group and 4.64% in the HEC group. The incidence of CINV and

treatment norms rate in real world are not optimistic. In order to further investigate the real world incidence of CINV in cancer patients in China and the influencing factors for CINV control, we conducted this study. In order to reduce the incidence of CINV in cancer patients in China, and to provide a certain research basis for the development of CINA treatment strategies for cancer patients with Chinese characteristics.

Methods This prospective real-world study was conducted at 27 major cancer centers in Sichuan, China.Cancer patients who were about to be treated with moderate/highly emetogenic chemotherapy drugs were included in the study. The main learning tool consists of two parts. In the first part, the investigators of the medical institutions involved in the study filled in a questionnaire to record the age, gender, diagnosis, stage, ECOG score, chemotherapy stage, chemotherapy regimen, antiemetic drugs and other basic information of the enrolled patients. The second part is the patient diary , which records the occurrence of nausea and vomiting on the 1st to 21st day of chemotherapy. The severity of nausea was recorded using a visual analog scale (a line 10 cm long, on a scale of 0-10).The incidence of CINV is the frequency with which chemotherapy-related nausea and/or vomiting occurs after chemotherapy has begun. Nausea and/or vomiting are recorded as CINV; The absence of both was recorded as no CINV. A delay period occurs within 4 days after treatment with moderate/high emetogenic chemotherapy drugs (e.g., D4-7 is recorded if cisplatin is given for 3 days). Days of complete protection Days free of nausea and vomiting. The risk phase, the acute phase plus the delayed phase. After the risk period, it continues from the risk period until day 21 of chemotherapy (for example, if cisplatin is given for 3 days, D8-21 is recorded). Acute phase + Delayed phase + phase beyond the risk phase (e.g., if cisplatin is given for 3 days, D1-21 is recorded).

Results A total of 2078 patients were enrolled in the study between March 2023 and October 2023. After quality inspection, a total of 1985 questionnaires were included in statistical analysis after rejecting 93(4.4%) unqualified questionnaires.The mean age of the patients was 61 years, and the age range was 17-90 years. Among them, 1177 (59.2%) were males and 808 (40.07%) were females. The top 3 primary tumor sites were lung cancer in 536 cases (27.00%), colorectal cancer in 388 cases (19.54%), and esophageal cancer in 218 cases (10.98%). There were 844 patients (42.51%) with stage IV cancer. All enrolled patients had physical performance scores within 0-2 (ECOG).There were 840 (42.3.%) patients receiving moderately emetogenic chemotherapy (MEC)

and 1145 (57.7%) patients receiving highly emetogenic chemotherapy (HEC).The results showed that, at all stages, the overall incidence of CINV was 57.7%, the incidence of acute CINV was 43.8%, the incidence of delayed CINV was 30.3%, and the incidence of CINV beyond the critical stage was 23.9% in both hyperemetogenic and moderately emetogenic chemotherapy regimens. The proportion of patients receiving standardized antiemetic therapy mentioned in the NCCN guidelines was 51.9%, among which 43.2% received standardized antiemetic therapy in patients receiving high antiemetic chemotherapy drugs, and 63.9% received standardized antiemetic therapy in patients receiving moderate antiemetic chemotherapy drugs. The proportion of patients treated with NK-1 receptor antagonist (NK-1 RA) was 45.9%, and the proportion of patients treated with NK-1 RA was 53.1% in patients receiving hyperemetic chemotherapy.The main factors affecting the incidence of CINV in acute stage, delayed stage and outside risk stage were related to the use of chemotherapy drugs and NK-1 RA, and had nothing to do with metastasis site and administration mode.There are many major factors affecting the proportion of patients receiving standardized antiemetic therapy mentioned in the NCCN guidelines, including chemotherapy drugs, chemotherapy regimen, administration mode, combination therapy mode, and the use of NK1 RA.

Conclusion In the real world, the incidence of CINV is high in patients receiving moderate/high emetic chemotherapy, and nausea and vomiting may still occur after the risk period. Compared with the results of the first real-world study in 2022, the decrease in the incidence of CINV is associated with the use of standardized antiemetic protocols and the use of NK-1 RA.

Keywords： Chemotherapy-induced nausea and vomiting (CINV) · CINV beyond the risk period · Standardized antiemetic therapy · Real world

618. LKB1 抑制 NLRP3 炎症小体减轻放射性肠炎的机制研究

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【目的】放射治疗是一种精准的肿瘤局部治疗方法，提高了盆腔恶性肿瘤的局部控制率和总生存率，在放疗过程中或结束后均可出现不同程度的放射性肠炎，严重影响患者生存质量及预后。因而，如何预防放射性肠炎便成为一个非常重要且亟待解决的环节。前期研究结果初步证实了 LKB1 可显著改善炎症损伤反应，因此，本研究从介导炎症小体活化的角度研究 LKB1 减轻放射性肠炎的作用机制。

【材料与方法】本研究采用 qRT-PCR 检测 lkb1、foxo1、il-1b 的表达，WB 检测 LKB1、FoxO1 的表达，ELISA 检测 TNF-α、IL-6、IL-1β的表达。我们构建小鼠放射性肠炎模型，采用 WB 检测 FoxO1、NLRP3、IL-1β、IL-18 表达水平，ELISA 检测细胞因子表达水平，观察调控 LKB1 对 FoxO1 及肠道炎症反应的严重程度的影响。

【结果】研究发现，当放射性肠炎发生时，LKB1 可减轻炎症损伤反应。可通过 FoxO1 抑制 NLRP3 炎症小体的活化，从 RNA 和蛋白质层面下调 NLRP3 水平，减少细胞因子 IL-1β、IL-18 释放水平，减轻肠道组织凋亡水平，从而减轻肠道炎症损伤反应的发生。

【结论】本研究明确 LKB1 对放射性肠炎的缓解作用，并探讨 LKB1 通过抑制 NLRP3 炎症小体的作用机制。

619. Zinc-finger protein 382 antagonises CDC25A and ZEB1 signaling pathway in breast cancer

Abstract： Our previous studies found that Zinc-finger protein 382 (ZNF382) played as a tumor suppressor gene in esophageal and gastric cancers, and a positive correlation between the high expression of ZNF382 and better outcome in breast cancer patients. However, the biological roles and mechanisms of ZNF382 in breast cancer remains unclear. We detected ZNF382 expression by reverse-transcription PCR (RT-PCR) and real-time quantitative PCR (qRT-PCR) in breast cancer cells and tissues, and explored the impacts and mechanisms of ectopic ZNF382 expression in

breast cancer cells in vitro and in vivo, respectively. Our results revealed that ZNF382 was significantly down-regulated in breast cancer tissues compared with adjacent non-cancer tissues. Restoration of ZNF382 expression in silenced breast cancer cells not only inhibited tumor cell colony formation, viability, migration and invasion, and epithelial-mesenchymal-transition (EMT), but also induced apoptosis and G0/G1 arrest. In conclusion, ZNF382 could induce G0/G1 cell cycle arrest through inhibiting CDC25A signaling, and, inhibit cell migration, invasion and EMT by antagonizing ZEB1 signaling in breast cancer cells.

620. Prognostic role of RNA modified regulatory genes in patients with colorectal cancer

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Background: Colorectal cancer (CRC) is one of the top three malignant tumors in the world in terms of morbidity and mortality, which has caused a serious economic burden worldwide. There were approximately 147 950 new cases and 53 200 deaths from CRC in 2020. Surgery, chemotherapy, molecular targeted therapy and radiotherapy are considered to be the main treatments for patients with CRC. Even if the patients have received sufficient and reasonable treatment in the early stage, nearly 40% of the patients will still experience recurrence and metastasis. Late diagnosis and high recurrence rate are the main causes of high mortality of CRC. Among patients with advanced metastatic CRC, about 70% to 75% survived for more than one year, no more than 35% survived for more than 3 years, and only less than 20% survived for more

than 5 years. Chemotherapy resistance, gene mutation, epigenetic modification, tumor cell proliferation and invasion are the main reasons for the recurrence and metastasis of CRC. Therefore, it is urgent to develop some new treatment strategies, including chemotherapy drugs, molecular targeted drugs, immunotherapy, etc., to improve the prognosis of CRC patients and reduce the recurrence and metastasis rate. However, further elucidation of the molecular mechanisms and epigenetic features of CRC will provide a theoretical basis for new therapeutic strategies.

A key factor in the pathogenesis of CRC is epigenetics, which is the dynamic and genetic remodeling of independent DNA or RNA sequences without permanently altering their sequences. Oncogene and tumor suppressor gene expression levels can be destroyed by the aberrant epigenetic effects of alterations, which can then increase carcinogenesis. DNA methylation, coding or non-coding RNA alteration, and histone acetylation are frequent epigenetic modifications that are thought to be the primary regulatory mechanisms in the development of cancer. CRC pathogenesis is associated with continuous changes and gradual accumulation of epigenetics, which makes normal colonic epithelium transform into colonic adenocarcinoma. Furthermore, epigenetic molecular markers have become an important tool for early screening, diagnosis, prognosis evaluation, drug sensitivity screening and treatment response of CRC. Both the hypomethylation of oncogenes and the hypermethylation of tumor suppressor genes are involved in the occurrence and development of cancer, which is also a consensus of many researchers.

Recently, researchers also have discovered that in addition to DNA methylation, gene transcription product RNA can also be modified by methylation. N6 methyl adenosine (m6A) modification of RNA during transcription can directly regulate the demethylation of adjacent DNA, which is of great significance for further understanding the complex mechanisms of gene expression regulation. With the development of bioinformatics, RNA modification is gradually known, including writers, erasers and readers of modifications. RNA modification, as a key process in epigenetics to regulate post transcriptional gene expression, is considered to be one of the main regulatory mechanisms in cancer progression. Recent studies have found that RNA not only acts as an intermediate or effector of protein synthesis, but also participates in the modification of many other RNAs, through which various functions of RNA can be controlled. The most

well-known and distinctive RNA alteration is m6A. In mRNA, long coding RNA, and other RNAs, m6A is modified by methylation. At present, common RNA modifications include m6A, 5-methylcytosine (m5C), N1-methyladenosine (m1A) and 7-Methylguanosine (m7G).

However, the majority of earlier research lacked a comprehensive examination of CRC and instead concentrated only on the sole role of genes connected to epigenetics. In addition, the relationship between these epigenetic modification-related genes and CRC is still in the preliminary exploration stage. For this reason, this study intends to explore the role of RNA modification related genes in the diagnosis and prognosis of CRC. Moreover, the diagnostic significance and prognostic value of epigenetic modifier genes in CRC are still unclear. In order to further reveal the answers to the above-mentioned questions, this study aims to explore the role of RNA modification-related genes in the diagnosis and prognosis of CRC.

Methods: To better investigate RNA modification in CRC, we firstly obtained microarray gene expression profiling data and transcriptome expression data of CRC from different public databases. Then, RNA modification-related genes (RMRGs) were collected from the GeneCards database. Next, LASSO regression, functional enrichment analysis, Cox risk model, immunohistochemistry, RT-qPCR、Western Blot (WB) and single-cell analysis were used to screen out clinically significant CRC methylation-related genes.

Results: We constructed a prognostic model of RMRGs consisting of six genes, namely EPO, EPOR, GSTM1, MYB, SRSF3 and YTHDC2. RMRGs prognostic model has significant significance in prognostic judgment and clinical decision-making. RT-qPCR and WB further confirmed that only SRSF3 is highly expressed in tumors. Further analysis of the correlation between RMRGs and clinicopathological features also found that only SRSF3 had a statistically significant relationship with Overall Survival (OS) in CRC patients.

Conclusions: In summary, our study is the first to explore the interaction of four types of RNA modification-related genes in CRC and their correlation with clinicopathological features. A scoring system based on four RNA modification types was constructed to predict the survival outcome of CRC patients. Further in-depth analysis of the clinical significance of each element in the RMRGs prediction model and its relationship with the tumor infiltrating immune microenvironment found that SRSF3 may be the most meaningful molecular target for colorectal cancer. Finally, through mutation site analysis, it was found that R119del in the exon 4 region was

the most important mutation site of SRSF3. This study raises the importance of RNA modifying genes in CRC and provides a new direction for future research on colorectal cancer. Therefore, we believe that the SRSF3 may become an important target for the diagnosis and prognosis of CRC patients.

Keywords： Colorectal cancer, RNA modification-related genes, SRSF3, prognostic indicator

壁报交流

1. ERRα，潜在的卵巢癌耐药治疗的靶点

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目的：卵巢癌年发病率居我国女性生殖系统恶性肿瘤第 3 位，病死率更是居于首位。由于难以早期诊断以及对于耐药复发卵巢癌缺乏有效的治疗，卵巢上皮癌的总体预后较差，多数患者死于肿瘤复发耐药。本文探讨了雌激素相关受体α（Estrogen associated receptor alpha, ERRα）在预测卵巢癌耐药和靶向治疗中发挥的作用，以期为临床攻克耐药难题提供一定的参考。

方法：计算机检索了 CNKI、Wanfang、PubMed 等数据库中近 5 年发表的 ERRα与细胞周期性死亡，ERRα与血管内皮生长因子（vascular endothelial growth factor, VEGF），紫杉醇、卡铂、贝伐珠单抗与卵巢癌耐药的相关文献。纳入相关研究并筛选，对最终纳入的文献进行归纳综述。

结果：（1）ERRα作为一种核转录因子，对卵巢细胞发生恶性转变至关重要，是卵巢癌发生、发展的重要分子事件，可作为早期筛查和评估预后的潜在靶点，同时也是卵巢癌靶向治疗的潜在靶标之一。（2）铂类药物能通过 NLRP3/Caspase-1/GSDMD 途径诱导细胞焦亡，实现对肿瘤的杀伤作用。ERRα的上调通过靶向 NLRP3 诱导对细胞焦亡的抵抗，从而导致体内和体外肿瘤细胞的铂类抗性。（3）紫杉醇通过多种信号传导途径诱导癌细胞凋亡，而改变凋亡基因表达以抵抗细胞死亡是紫杉醇的耐药机制之一。在膀胱癌、多发性骨髓瘤、骨肉瘤中 ERRα的敲低均增加了肿瘤细胞凋亡的发生。ERRα的反向激动剂 XCT790 能以浓度和时间依赖性方式诱导细胞凋亡，从而改善紫杉醇的耐药。（4）ERRα能通过独立于 HIF 途径以外的方式促进 VEGF 的表达，抑制 ERRα能与贝伐珠单抗产生协同抗血管生成作用，增强对肿瘤的杀伤效果。

结论：卵巢癌的一线化疗方案是紫杉醇联合卡铂，根据具体指征选择是否联用贝伐珠单抗。抑制 ERRα能增强化疗引起的焦亡、凋亡，减弱血管生成，从而在紫杉醇、卡铂、贝伐珠单抗杀伤卵巢癌细胞中发挥协同作用，ERRα的反向激动剂 XCT790 联合化疗可能对改善化疗耐药，提高卵巢癌患者的预后有重要意义，应用前景广阔，期待更多体内外研究进一步证实。

关键字： ERRα；卵巢癌耐药；化疗

2. TBC1D3 作为一种新型肌动蛋白结合蛋白通过上调 KCC3 的表达促进乳腺癌细胞迁移

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TBC1D3 在许多肿瘤中高表达。我们之前的研究表明，TBC1D3 是一种核浆蛋白。然而，对 TBC1D3 在细胞核中的作用知之甚少。在目前的工作中，我们采用免疫沉淀法联合质谱检测获得肌动蛋白 ACTB，作为 TBC1D3 的一种新的结合蛋白；ACTB 通过抑制 FCS 诱导的泛素化和降解来增强 TBC1D3 核浆蛋白的稳定性。此外，ACTB 还能增强 TBC1D3 诱导的乳腺癌细胞迁移。关于 TBC1D3 在细胞核中的功能，我们采用染色质免疫沉淀法对其结合 DNA 进行了测序，结果显示 TBC1D3 结合 KCC3 启动子区可促进 KCC3 的表达，此外，TBC1D3 通过上调 KCC3 的表达激活 MAPK 通路，促进乳腺癌细胞迁移。总之，本研究揭示了一种新的肌动蛋白结合蛋白 TBC1D3 在促进乳腺癌细胞迁移的分子机制。

关键字： TBC1D3；ACTB；泛素化降解；乳腺癌

3. 染色体 8q24.21 扩增与卵巢浆液性癌预后关系的研究

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背景与目的：已发现泛癌组织中 8q24.21 扩增，最常见扩增基因是 MYC，同时常伴有浆细胞瘤变异体易位 1（Plasmacytoma variant translocation 1, PVT1）、gasdermin 家族蛋白 C（gasdermin C, GSDMC）、SMC5/6 复合物的非 SMC 元素 2（Non-SMC element 2, NSMCE2）和 RecQ 蛋白样 4（RecQ like helicase 4, RECQL4）等基因共扩增，且与患者不良预后相关。然而，8q24.21 扩增对卵巢癌免疫微环境及其预后影响尚未完全明确。本研究旨在探讨 8q24.21 相关基因扩增与卵巢癌免疫细胞浸润状态和预后的相关性，为卵巢癌临床治疗反应与预后判断提供依据。

方法：本研究通过癌症基因组图谱（The Cancer Genome Atlas, TCGA）分析泛癌组织中染色体 8q24.21 区域相关基因扩增频率，及染色体 8q24.21 基因扩增与卵巢癌患者临床病理特征和预后相关性。通过 TIMER2.0 在线分析卵巢癌中 8q24.21 常见扩增基因及 8q24 常见 DDR 基因扩增与免疫细胞浸润亚型及丰度相关性。通过免疫组织化学（immunohistochemistry, IHC）检测 92 例上皮性卵巢癌组织蜡块中 c-Myc、GSDMC、RECQL4 及 TP53 蛋白表达水平，分析其与卵巢癌组织学分型、分级及预后的关系。

结果：（1）染色体 8q24.21 扩增子在卵巢癌、乳腺癌、食管-胃癌和肝细胞性肝癌中扩增频率最高，分别为 45.4%、22.7%、19.4%及 18.9%，但该位点在其他癌种中的扩增频率相对较低。

（2）MYC、PVT1、CASC8、RAD54B 和 ADCY8 等基因在卵巢癌中 mRNA 表达水平较低，或者检测不到；GSDMC、NSMCE2 等基因扩增与 mRNA 高表达基本相对应；MYC 扩增常见于晚期、更具侵袭性的浆液性卵巢癌中。

（3）在卵巢癌中，MYC、PVT1、GSDMC、NSMCE2 和 RECQL4 扩增或高表达与 B 细胞和/或树突状细胞浸润丰度呈正相关（$P<0.05$），与 CD4+/CD8+T 细胞的浸润丰度未存在显著相关性（$P>0.05$）。

（4）在卵巢癌患者中，MYC、PVT1、GSDMC、NSMCE2 和 RECQL4 mRNA 水平高表达较低表达患者无进展生存期（progression-free survival, PFS）短（$P<0.05$）；类似的是，在 TP53 突变型浆液性卵巢癌患者中，MYC、GSDMC、NSMCE2 及 RECQL4 mRNA 水平过表达患者者 PFS 显著缩短（$P<0.05$）。

（5）c-Myc 蛋白在晚期上皮性卵巢癌中表达上调，RECQL4 蛋白水平表达多见于低分化上皮性卵巢癌，且 c-Myc 和 RECQL4 蛋白共高表达者 PFS 短于低表达者（$P<0.05$）。

结论：本研究结果提示染色体 8q24.21 位点上共扩增的基因常出现在晚期、更具侵袭性的卵巢癌中，并且与卵巢癌患者预后不良密切相关。此外，MYC 与 PVT1、GSDMC、NSMCE2 及 RECQL4 基因的共扩增可能降低卵巢癌的抗肿瘤免疫活性，提示 8q24.21 上的基因与 DDR 相关基因共扩增可能是病变耐药的关键因素，促进卵巢癌侵袭与进展。

关键字 ：卵巢癌；染色体扩增；染色体 8q24.21；DNA 损伤反应；免疫微环境

4. 中国高等教育收费制度急需改革--

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概述和目的：据中央电视台 2023-9-06 日《朝闻天下》栏目报道，今年专科以上的大学生报到时，截至目前以贷款来交学费的人数为 581 万人，截至目前贷款金额为 594 亿元，较 2022 年全年贷款金额 571.14 亿元，增加 4%，【1】这不是学生越来越穷吗？每年一半多大学生都贫困？本人感到很震惊，另外，不断有媒体报道和网传，很多人因上大学交学费，不断给很多家庭生活、工作、家庭和睦、健康造成严重影响，更是有些学生因交不起学费而遗憾终生放弃上大学，或者即使上了大学后因交学费、生活费贫困而走上犯罪的道路，随着中国复兴、走出贫困、走向致富和小康生活水平，那么，大学生因交不起学费和生活费及靠贷款来上大学的压力，与中国的小康水平相差甚远，大学生交不起学费和生活费及靠贷款来上大学，必定会造成背负经济压力的包袱，给他们的学习和生活造成不可磨灭的影响，他们已成了身背责务的人，若能挺过这些压力的大学生，可能会胜利毕业参加工作，若挺不过去的大学生，可能会学业无成，甚至走上歧途、沦落，给个人、家庭、社会和国家造成严重不良影响。

作为高校学生，还未完全步入社会，本应该专心学习，在学业上掌握真正的专业本领，但却为学费、学校住宿费及生活费发愁，奔波，肯定影响学业。

因此，随着社会的发展，中国经济实力的增强，为了更好地培养一代又一代国家栋梁之材，大学生自己缴费上大学的政策应该改革，本研究特提出这方面的建议，供相关部门参考。

方法：结合本人的生活经历，所听、所见、所闻、所读的事实和新闻，研究总结，提出中国大学生缴费上大学政策的改革建议。

结果：研究建议如下：

1、取消各级各地公立大中专高等院校大学生必须交学费和住续费的政策，也即是所有公立大中专高等院校停止向入学大学生索要学费和住续费。

2、民营大中专高等院校大学生，可继续实施入学交学费和住续费的政策，但应设立缴学费和住续费最高限额。

3、国家鼓励民营大中专高等院校实行不向入学大学生索要学费和住续费的政策。

4、公立和民营大中专高等院校，可以向学生收取教科书的费用。

5、公立和民营大中专高等院校，应该继续建立勤工俭学、助学金、奖学金、贫困生补助等制度，以此来弥补学生的生活费。

6、各级各类研究生的收费政策，也类同大学生的收费政策和相关管理政策。

7、中外合资办学的高等大中专高等院校，按照上述政策管理，是公立的，按照公立的大中专高等院校政策管理，是民营的，按照民营大中专高等院校的政策管理。

8、国家应建立法规、制度，杜绝对大中专、研究生非法收取额外费用，加重学生的负担，对违反法规的责任人和单位，给以相应的处罚。

结论：为了充分体现中国社会主义国家的优越性，为了给各地各级大中专高等院校学生提供一个安心学习的场所，为了强国和国家复兴，为了培养好一代又一代优秀的专业技术人才，从而更好地为人民服务，维持世界和平和可持续发展，结合当前形势和事实，特研究总结了中国高等教育收费制度急需改革的建议，这八条建言献策，值得相关部门参考应用。

这些建言献策若能被实施，理论上肯定能激发学生的学习热情，减轻学生全家的压力，全心全意地争取考取高质量学校和热门专业，同时还能促进民营高校，全力提高教学质量，招收优质学生，降低学费，共同促进高等学校教育的高质量发展，为国家、为世界不断培养出高质量的人才。

关键字： 高等教育；管理制度；收费管理；社会生活；健康成长教育；建言献策。

5. 100 个已知和可疑的影响因素与总卵巢癌及其六种组织学类型发病风险的关联：一项孟德尔随机化研究

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Background: Observational studies have linked various exposures to ovarian cancer (OC) risk, but the findings are potential subject to reverse causation and confounding. Herein, we performed comprehensive Mendelian randomization (MR) analyses to systematicly evaluate potential causal associations of known and suspected influencing factors with risk of OC and six common histotypes.

Methods: Two-sample MR analyses were applied to data from the genome wide association study summary results comprising a total of 25,509 women with epithelial OC and 40,941 controls of

European descent in the Ovarian Cancer Association Consortium. Genetic instrumental variables associated with influencing factors were selected. Inverse-variance weighted method was used as the primary analysis, and the MR assumptions were evaluated in sensitivity analyses. MR-PRESSO method was applied for the detection and correction of potential horizontal pleiotropy.

Results: OC and six histotypes were considered in this study. Of 100 known and suspected influencing factors, 46 were identified to be related to OC risk. Notably, alcohol drinking, cigarette smoking, chronotype, time spent driving, sugar or poultry or vegetable intake, linoleic acid or saturated fatty acids (FA), age at first birth or at menopause, hysterectomy, several body size factors, endometriosis, schizophrenia, and telomere length were significantly positively associated with risk of OC or six histotypes. In contrast, income, past tobacco smoking, time spent using computer, 25 hydroxyvitamin D, cheese or fruit intake, dietary change, omega-3 FA, parity, C-reactive protein, HDL cholesterol, and tumor necrosis factor were significantly inversely associated with risk of OC or histotypes.

Conclusions: Our study adds to current knowledge on the causal effect of known and suspected influencing factors on OC and six histotypes. Further investigation is needed to better understand potential pathways or mechanisms of these factors.

关键字： Association; Histotypes; Mendelian randomization; Ovarian cancer; Risk factor.

6. 基于 WGCNA 筛选及鉴定肝细胞癌预后相关基因

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背景与目的

肝细胞癌（Hepatocellular carcinoma，HCC）是我国常见恶性肿瘤。早期 HCC 患者主要治疗手段是手术切除和肝移植，而晚期患者多采取全身治疗，免疫治疗在 HCC 患者中显示良好效果，但不同患者对治疗药物敏感性、毒副作用、存在差异 HCC 预后并不理想。近年来基因芯片和高通量测序技术的广泛应用，基因测序和生物信息学分析已被广泛用于筛选基

因组水平改变。因此，本研究旨在通过生物信息学技术筛选预测 HCC 预后和免疫治疗反应的相关基因标记。

方法

（1）从 TCGA、GEO 中下载 HCC 的转录组、临床及肿瘤突变数据。以 CIBERSORT 和 WGCNA 算法相结合，识别出最显著相关的基因模块，将模块中的基因进行单/多因素 Cox 和 LASSO 回归分析，构建多基因预后模型。

（2）研究风险模型与肿瘤突变负荷及免疫微环境中的潜在作用，并进行基因富集分析（GSEA）、基因集变异分析(GSVA)和免疫检查点相关性分析。

（3）收集 2016 年 1 月至 2021 年 12 月暨南大学附属第一医院共 117 例 HCC 患者肿瘤组织，用免疫组化检测模型基因的蛋白表达水平，分析它们与 HCC 临床病理特征的相关性，评估其对 HCC 患者的预后价值。

结果

（1）由 S100A9、IL15RA、KLRB1 和 ADA 组成的免疫相关基因预后模型经 TCGA 队列证实，该模型高风险组患者预后比低风险组差（$P < 0.001$）。

（2）高风险组的 TMB 水平比低风险组更高（$P = 0.03$），相关分析显示 TMB 与风险评分呈正相关（$r=0.11, P = 0.037$）。风险评分与 CD8+T 细胞亚群和静息记忆 CD4+T 细胞亚群呈显著负相关。GSEA/GSVA 分析显示四基因高/低表达组中存在各自最显著的信号通路；免疫检查点相关分析发现大多数基因与风险评分呈正相关，而与 PDCD1 并无相关性。

（3）免疫组化结果显示：S100A9（$X2=27.065$，$P = 0.000$）、IL15RA（$X2=4.808$，$P = 0.028$）和 ADA（$X2=4.028$，$P = 0.045$）高表达组较低表达组在的 TNM 分期（III+IV）高，KLRB1（$X2=7.384$，$P = 0.007$）则相反；S100A9（$X2=5.110$，$P = 0.024$）、KLRB1（$X2=16.405$，$P = 0.000$）高低表达组与 MVI 之间具有显著相关性。

结论

本研究构建并验证一种新的免疫相关基因的 HCC 预后预测模型，临床样本检测结果显示 S100A9、IL15RA 和 ADA 在晚期 HCC 中高表达，KLRB1 则相反。S100A9、KLRB1 高低表达组与 MVI 存在相关性。提示该模型可以很好地预测 HCC 患者的预后，为临床患者分层提供参考依据。

关键字： 肝细胞癌；加权基因共表达网络分析（WGCNA）；免疫相关基因；预后。

7. 组蛋白甲基化修饰基因 KDM5B、NSD3 与染色体 8q 共扩增对乳腺癌预后影响研究

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目的

基因扩增与乳腺癌进展及不良预后密切相关，但乳腺癌演进中染色体/基因组扩增机制目前尚未完全清楚。本研究主要分析乳腺癌中组蛋白甲基化修饰相关基因 KDM5B 及 NSD3 表达水平及其与染色体 8q 扩增之间关系，探讨组蛋白甲基化状态与 8q22.3 及 8q24.21 位点相关基因共扩增之间关系及其与乳腺癌中免疫细胞浸润状态和预后相关性，为临床预后判断和治疗靶点筛选提供线索。

方法

（1）通过 TCGA、GeneCards 和 cBioPortal 数据库分析泛癌及乳腺癌中 8 号染色体上各基因的扩增频率，明确 KDM5B、NSD3 与 8q22.3、8q24.21 扩增的临床病理特征及预后关系。

（2）通过 TIMER2.0 分析乳腺癌中 KDM5B 及 NSD3、GRHL2、RRM2B（P53R2）、MYC、TP53 基因扩增与免疫细胞浸润亚型及丰度的相关性。

（3）收集乳腺浸润性导管癌 124 例标本并伦理获批后，以免疫组化检测 MYC、RRM2B、GRHL2、KDM5B、NSD3、TP53 蛋白表达情况，分析以上基因蛋白表达水平与乳腺癌组织学分级、分型及预后关系。

结果

（1）NSD3、KDM5B、8q22.3、8q24.21 在各泛癌种中乳腺癌扩增频率均排前五，分别为：11.16%，14.48%，11.2%，8.12%。

（2）乳腺癌中 KDM5B、NSD3、GRHL2、MYC、RRM2B、TP53 基因扩增与中性细胞、CD4+T 细胞浸润丰度呈正相关，与 NK 细胞浸润呈负相关($P < 0.05$)。NSD3 与 RRM2B 蛋白表达与各免疫细胞浸润丰度的相关性高度相似。

（3）临床免疫组化结果示：NSD3 表达水平与 GRHL2、RRM2B 及 MYC 显著相关，KDM5B 与 RRM2B 呈中度显著相关。KDM5B 阳性表达率及强度随组织分级增高而增高；RRM2B、MYC 和 TP53 蛋白在 Luminal B 型乳腺癌中阳性表达率及强度较其他分型高($P < 0.05$)。

（4）NSD3、GRHL2、MYC 和 TP53 高表达患者无转移生存期较低表达患者明显缩短 (P ＜ 0.05)。

结论

乳腺癌中存在组蛋白甲基化修饰基因 NSD3、KDM5B 与染色体 8q 共扩增，且共扩增基因常出现在高级别及 Luminal B 型乳腺癌中。NSD3、KDM5B 表达水平与 8q 位点上 GRHL2、RRM2B、MYC、TP53 密切相关，与肿瘤组织中免疫细胞亚型浸润、患者预后显著相关，提示组蛋白甲基化修饰基因与染色体 8q 基因共扩增可能是乳腺癌耐药及不良预后密切相关，靶向组蛋白修饰相关基因可能成为克服耐药手段之一。

关键字： 乳腺癌；组蛋白甲基化；染色体扩增；免疫微环境；预后

8. 非编码 RNA 调控细胞焦亡参与肺癌发病机制的研究进展

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肺癌是我国最常见的癌症类型，其高发病率和高死亡率使其成为我国面临的重大公共卫生问题。细胞焦亡是一种新的程序性细胞死亡方式，越来越多的研究证实了非编码 RNA（如 miRNA、lncRNA、circRNA）通过调节细胞焦亡在肺癌的发生发展中起着重要作用。本文旨在揭示非编码 RNA 调控肺癌细胞焦亡的机制，从而以非编码 RNA 的角度为阐明细胞焦亡参与肺癌发生发展提供新的思路，进而为肺癌的治疗提供新靶点和新策略。本文通过查阅近年来非编码 RNA 调控细胞焦亡参与肺癌发生发展的相关文献，对非编码 RNA 调控肺癌细胞焦亡的分子机制加以阐述，并论述其与肺癌发生、发展和预后的关系。目前关于非编码 RNA 调控细胞焦亡的研究主要集中在改善肺癌放化疗敏感性，肺癌预后及协同增效等方面。因此本文证实了非编码 RNA 通过调节细胞焦亡在肺癌的发生发展中起着重要作用。

关键字： 非编码 RNA；细胞焦亡；肺癌

9. 基于 Warburg 效应探讨肿瘤相关基因在消化道肿瘤中的研究进展

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Warburg 效应，即有氧糖酵解，是恶性肿瘤细胞的代谢标志，Warburg 效应的高产能速率和产生的代谢中间产物促进了癌细胞的存活、增殖、侵袭及转移。消化道肿瘤发病率高、早期诊断率低、预后不佳，目前的治疗手段尚存在不足，需要找到更有力的生物标志物及更有效的治疗方法，提高早期诊断率，延长消化道肿瘤患者生存期。许多研究证实肿瘤相关基因可通过调控 Warburg 效应影响消化道肿瘤的发生发展，本文旨在揭示肿瘤相关基因在消化道肿瘤中调控 Warburg 效应的分子机制，以期为消化道肿瘤的早期诊断、治疗和预后提供借鉴。本文通过查阅相关文献发现肿瘤相关基因通过介导 Warburg 效应相关因子的氧化磷酸化、蛋白质泛素化、甲基化、miRNA 海绵化或琥珀酰化，进而促进或抑制 Warburg 效应相关因子表达，最终影响 GI 肿瘤细胞中的有氧糖酵解，参与 GI 细胞增殖、细胞侵袭、细胞迁移、细胞凋亡，细胞自噬和耐药。因此本文证实了肿瘤相关基因通过调节 Warburg 效应在消化道肿瘤的发生发展中起着重要作用。

关键字： Warburg 效应；基因；消化道肿瘤

10. GNG2 在结肠癌中的表达及其发生、发展的意义

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目的 探讨 GNG2 在结肠癌癌变过程中的表达差异及其表达与临床指标的相关性；分析 GNG2 表达差异对患者生存率的影响，并分析结肠癌预后的独立相关因素；分析 GNG2 与 MMR 主导蛋白、PDL1、ERK 的相关性。

方法 采用免疫组化 EnVision 法检测 GNG2 在 98 例结肠癌和 73 例癌旁组织样本中的表达情况。

结果 GNG2 蛋白在结肠癌组织中的表达明显高于癌旁组织 (P<0.001)；GNG2 表达与病理分级、PDL1 密切相关（P＜0.05）。即结肠癌病理分级越高，GNG2 蛋白表达越高。此外，随着 PDL1 蛋白表达增加，GNG2 蛋白表达量下降；生存分析显示，GNG2 低表达组生存率为 58.6%，GNG2 高表达组生存率为 33.3%，癌组织 GNG2 表达低的结肠癌病人拥有更长的总生存期(P=0.025)；患者年龄、N 分期、PDL1 间质是结肠癌预后的独立预测因素(P＜0.05)；GNG2 表达与 PDL1 间质 2 之间存在着显著的负向的弱相关关系(P=0.034，rs=-0.226)，GNG2 表达与 ERK 之间存在着显著的正向的中等相关关系(P＜0.001，rs=0.563)。

结论 GNG2 在结肠癌中呈高表达，且与患者的病理分级、ERK 的表达、肿瘤细胞表面的 PDL1 的表达密切相关，并可能作为结肠癌诊断及判断患者预后的重要生物标志物。

关键字： 结肠癌；GNG2；组织芯片

11. Dickkopf 3 抑癌基因在不同癌症中的作用:一个潜在的生物标志物和治疗靶点？

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Dkk3 与 LRP、克莱曼和表皮生长因子受体（EGFR）相互作用以阻断 Wnt 和 EGFR 信号传导，与 SGTA 相互作用以破坏动力蛋白运动依赖性 AR 转运和信号传导，抑制糖皮质激素受体胞质转运，在血管生成期间将 Smad4 招募到血管内皮生长因子（VEGF）启动子，并通过下调 ID-1 诱导细胞凋亡。Dkk3 参与免疫抑制微环境诱导的单核细胞树突状细胞（DC）样分化，对细胞毒性 T 淋巴细胞、DC 和自然杀伤（NK）细胞活化发挥抗癌作用，介导 CD8+ T 细胞耐受，并限制外周 B1 细胞的自我维持。Dkk3 在口腔鳞状细胞癌（OSCC）和食管腺癌（EA）中也上调，但在卵巢癌、宫颈癌、乳腺癌、肺癌、胆囊癌（GBC）、胰腺癌（PCa）和结直肠癌（CRCs）等恶性肿瘤中下调，主要是由于启动子甲基化。Dkk3 低表达、缺失和高甲基化与不同癌症的侵袭性特征或短生存率正相关。Dkk3 过表达或重组 Dkk3 治疗通过 PI3K/Akt/NF-κB、VEGFR-2/Akt/mTOR、Wnt/β-连环蛋白/TCF-4、MAPK、p53、线粒体、Hedgehog、JAK-STAT、Toll 样受体、钙、BiP/GRP78 和 TGF-β/Smad 途径抑制增殖、耐药、抗凋亡、迁移、侵袭、肿瘤生长或肺转移特征。

在这篇全面的 Dkk3 综述中，我们研究了基因和蛋白质结构、生物学效应以及在肿瘤发生和发展中的作用。我们假设 Dkk3 可以作为不同癌症的肿瘤发生、肿瘤侵袭性和预后不良的生物标志物，并可能成为基因治疗的合适靶点。

关键字： Dkk3，癌症

12. BTG4 在肺癌中的表达及其临床病理和预后意义

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背景：BTG4 通过阻止细胞周期而具有抗增殖特性，并可抑制卵母细胞和胚胎发育及致癌作用，但其在肺癌中的作用尚未发现。

目的：探讨 BTG4 在肺癌中的表达及其临床病理和预后意义。

方法：我们通过 Oncomine、TCGA、仙桃、UALCAN 和 Kaplan-Meier 绘图仪数据库对 BTG4 mRNA 表达进行生物信息学分析。我们用免疫印迹和免疫组织化学方法研究了 BTG4 在肺癌中的表达。所有生物信息学分析均在开放数据平台上进行，所有患者样本和实验均在锦州医科大学第一附属医院和承德医科大学附属医院进行。参与者为 1993 年至 2020 年锦州医科大学附属第一医院和中国医科大学附属第一医院的肺癌患者。

结果：肺癌组织中 BTG4 mRNA 表达低于正常组织（p＜0 . 05），且与 BTG4 启动子甲基化呈负相关（p＜0 . 05）。BTG4 表达与肺癌患者的年龄（＞65 岁）、R0 残留、中央型肺癌、较大烟包数/年和无进展生存期呈正相关（p＜0.05）。BTG4 在鳞癌中的表达高于腺癌患者（p＜0.05）。Cox 比例分析显示，年龄较小、T 分期较低、无淋巴结转移和 BTG4 mRNA 高表达是癌症患者预后较差的独立因素（p＜0 . 05）。免疫组化和 western blot 显示 BTG4 在肺癌组织中的表达低于正常组织（p＜0.05）。

结论：BTG4 表达可能是肺癌发生、组织发生、侵袭性行为和预后的潜在标志物。

关键字： BTG4, 肺癌

13. RNF180 通过结肠直肠癌细胞中 ACC1 和 ACLY 的蛋白酶体降解减弱脂滴形成，从而抑制化学诱导的结肠直肠癌发生和耐药性

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背景：无名指蛋白 180（RNF180）是一种 E3 泛素蛋白连接酶，促进多泛素化和降解。

方法: 通过字母分析、体内实验和体外实验分析 RNF180 的表达及其与结直肠癌发生发展的关系。

结果：RNF180 在结直肠癌中高表达，并与浸润深度、淋巴结转移、远处转移、TNM 分期或分化程度呈正相关。RNF180 通过与 Notch1、TRIM24 和 FOXC1 相互作用并降解它们以及通过激活 Akt 通路来抑制增殖、促进凋亡并抑制 CRC 细胞的迁移和侵袭。RNF180 可能通过脂滴组装和 ACC1 和 ACLY 介导的结直肠癌细胞脂肪生成抑制化疗耐药性。它的敲除可能增加 Lgr5-cre/RNF180 f/f 小鼠模型中化学诱导的结直肠癌发生的敏感性。RNF180 相关基因参与 CRC 的神经活性配体-受体相互作用、糖胺聚糖结合、ECM 结构成分和组织、受体配体活性、细胞粘附、mRNA 剪接等。

结论： RNF180 的表达可作为结直肠癌诊断的生物标志物、预后指标和基因治疗靶点。

关键字： 大肠癌,RNF180,预后,基因治疗

14. LDHA 在卵巢癌耐药中的研究进展

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目的：卵巢癌是妇女中最常见的致死性妇科恶性肿瘤之一。尽管应用了手术切除、放射治疗和化学药物等多种治疗手段，但卵巢癌的耐药性仍然是导致治疗失败和死亡的主要原因之一。在当前研究中，越来越多的证据表明乳酸脱氢酶 A（Lactate dehydrogenase A，LDHA）

在卵巢癌耐药中发挥着重要的作用。本文探讨了 LDHA 与卵巢癌耐药的关系及其在治疗卵巢癌耐药中的潜在作用，以期为今后临床工作中卵巢癌精准治疗提供个体化方案和参考。

方法：计算机检索了 CNKI、Wanfang、PubMed 等数据库中近 5 年发表的 LDHA 与卵巢癌的相关文献。纳入关于 LDHA 与卵巢癌耐药的相关研究并筛选，对最终纳入的文献进行归纳综述。

结果：（1）在卵巢癌细胞中，LDHA 的表达水平明显升高，与卵巢癌细胞的代谢重塑和增殖有关。这意味着 LDHA 在卵巢癌细胞生长和存活中起到了重要的作用。（2）在卵巢癌耐药中，LDHA 的过度表达与多种耐药机制有关。首先，LDHA 通过维持细胞内乙酸水平变化而保护卵巢癌细胞免受化学药物的损害。其次，LDHA 过度表达导致肿瘤细胞产生过剩的乳酸，酸化肿瘤微环境，降低化疗药物对癌细胞的效力，从而导致耐药性的产生。此外，LDHA 的过度表达还能促进上皮间质转化（Epithelial-Mesenchymal Transition ，EMT）的发生，提高肿瘤细胞的侵袭和迁移能力，使得肿瘤在初治时对化疗药物具有抗性。（3）一些前瞻性的研究表明，抑制 LDHA 活性可以显著增加卵巢癌细胞对化疗药物的敏感性。此外，使用 LDHA 抑制剂与其他化疗药物联合应用能够改善化疗效果，并减轻耐药性的发生。（4）一些实验研究还发现，通过靶向 LDHA 来调节肿瘤相关微环境，可以阻断肿瘤侵袭和转移的过程。

结论：在卵巢癌耐药的研究中，LDHA 作为一个重要的分子标志物和治疗靶点，受到了越来越多研究人员的关注。对 LDHA 在卵巢癌耐药中的研究将有助于我们深入了解卵巢癌的耐药机制，并为开发新的治疗策略提供了有力的理论支持。然而，目前有关 LDHA 在卵巢癌耐药中的研究还相对较少，未来还需要进一步的临床研究来验证其在卵巢癌耐药治疗中的临床应用潜力。

关键字： LDHA；卵巢癌；耐药

15. 肿瘤标志物在卵巢癌耐药中的研究进展

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目的：卵巢癌是一种常见的妇科恶性肿瘤，治疗效果受到耐药性的限制。肿瘤标志物能够为卵巢癌的早期诊断、预后评估和治疗反应监测提供重要指导。然而，肿瘤标志物的表达水平可能受到卵巢癌细胞的耐药性影响，因此研究肿瘤标志物在卵巢癌耐药中的作用具有重要意义。本综述将介绍当前关于肿瘤标志物在卵巢癌耐药中的研究进展，包括抗肿瘤药物耐药与标志物表达的关联、耐药相关标志物的发现和应用，以及未来可能的研究方向。

方法：计算机检索了 CNKI、Wanfang、PubMed 等数据库中近 8 年发表的肿瘤标志物与卵巢癌的相关文献。纳入相关研究并筛选，对最终纳入的文献进行归纳综述。

结果：（1）卵巢癌细胞对化疗药物的耐药性与肿瘤标志物的表达水平之间存在着密切的关联。一些研究发现，耐药细胞株的标志物表达模式与耐药性相关，如多药耐药相关蛋白（MDR）家族的成员 P-glycoprotein（P-gp）的高表达与化疗药物耐药性相关。其他标志物如 PARP、BRCA 等也与针对 DNA 损伤修复的药物耐药性相关。（2）许多研究致力于寻找新的耐药相关标志物，以便更早地预测卵巢癌细胞的耐药性和选择更合适的治疗方案。例如，某些研究已经发现某些长非编码 RNA（lncRNA）在卵巢癌耐药过程中起到重要作用，其表达水平与耐药性相关。另外，一些循环肿瘤 DNA（ctDNA）和细胞外泡球（EV）中的特定突变、融合基因和表观遗传标志物也被认为可能与卵巢癌的耐药性相关。（3）未来的研究方向包括发掘更多的耐药相关标志物，建立多种标志物的联合检测体系以提高预测准确性。此外，可以将肿瘤标志物应用于耐药治疗的监测和评估中，及时调整治疗方案，提高患者的治疗效果。同时，结合新技术如人工智能和基因组学，将寻找耐药相关标志物与个体化治疗相结合，以更好地管理卵巢癌耐药性。

结论：肿瘤标志物在卵巢癌耐药方面的研究持续发展，为早期诊断、预后评估和治疗反应监测提供了重要基础。寻找更多的耐药相关标志物以及建立综合评估体系，将有助于提高卵巢癌治疗的效果，并为患者提供更个体化的治疗选择。

关键字： 肿瘤标志物；卵巢癌；耐药

16. DEPDC1B 促进肾透明细胞癌血管生成及影响其转移及侵袭的机制研究

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研究目的：肾癌为最常见的泌尿系统肿瘤恶性肿瘤，约占 80%，我国每年约有 40 万例新增病例，其中肾透明细胞癌（Kidney renal clear cell carcinoma，KIRC）在肾癌中约占 70%。大多数 KIRC 患者起病隐匿，大多数患者就诊时进入晚期阶段，对化疗和放疗都不敏感，术后 5 年生存率低。因此，寻找能够早期诊断和评估预后的生物标志物就显得极为有价值。DEPDC1B 为包含 1B 的 DEP 结构域，已有研究表明 DEPDC1B 可以作为黑色素瘤、肝癌等多个癌种的潜在生物预测标志物，但在 KIRC 中尚未有研究，本研究旨在应用生物信息学、分子生物学等实验，证明 DEPDC1B 在 KIRC 中的研究价值，通过实验进一步阐明其导致 KIRC 转移及侵袭的机制，以期为临床制定更有效的检查方式及治疗策略提供新思路，提高肾透明细胞癌患者的生存。

材料与方法：1. 从公共数据库 TCGA、GEO 中下载 KIRC 相关数据，GEPIA、UALCAN 等在线网站分析 DEPDC1B 在 KIRC 及癌旁、KIRC 分级及分期等中的差异表达，临床预后。

2. 将构建好 DEPDC1B 敲减的质粒稳转入 786-O、Caki-1 细胞系中。采用细胞增殖及克隆形成实验、划痕实验、Transwell 小室实验、流式细胞术等测定 DEPDC1B 对 KIRC 细胞恶性生物学能力，细胞周期及细胞凋亡的影响，并应用 NU/NU 小鼠行体内成瘤实验。

3. 在线工具分析并验证 DEPDC1B 在 KIRC 中的甲基化程度；双荧光素酶报告基因实验、实时荧光定量反转录多聚核苷酸酶链式反应（Quantitative real-time PCR，qRT-PCR）等方法探索并验证 DEPDC1B 的上游调控转录因子。

4. 筛选 DEPDC1B 影响 KIRC 进展的下游分子，并运用 qRT-PCR，蛋白免疫印迹（ Western blot，WB）等方法进行验证；收集 DEPDC1B 敲减后 KIRC 细胞的上清行血管生成实验，KIRC 细胞行索拉非尼 IC50 药物浓度实验及细胞活力抑制实验。

结果：1. DEPDC1B 在 KIRC 中较癌旁正常组织低表达，与淋巴结转移、分级和 TNM 分期显著相关，DEPDC1B 可以作为 KIRC 的独立影响因素，影响 KIRC 患者的无疾病进展生存及总生存率。

2. 敲减 DEPDC1B 后可抑制 KIRC 细胞增殖、迁移和侵袭能力，增加细胞凋亡，并将细胞阻滞于 S 及 G2/M 期；同时 DEPDC1B 敲减组小鼠瘤体积显著小于对照组。

3. DEPDC1B 在 KIRC 组织较正常组织低表达可能与甲基化、E2F1 调控相关；DEPDC1B 可能通过 CDK1、CDC20、ERK 磷酸化、细胞凋亡、细胞迁移相关分子影响 KIRC 进程。

4. 经敲减 DEPDC1B 后 KIRC 细胞的上清液培养 HUVEC 细胞发现，其血管生成节点数、成环数、成管长度、成环面积以及平均网格大小等显著减小，且成管形态较差；此外 DEPDC1B 稳定敲减的 KIRC 细胞系索拉非尼 IC50 药物浓度更低，应用相同浓度索拉非尼处理后的细胞活力下降更为显著。

结论： DEPDC1B 可以作为 KIRC 生物标志物，可能通过影响血管生成及 E2F1-DEPDC1B-CDC20/CDK1 轴增强 KIRC 细胞恶性生物学能力促进其进展，且敲减 EDPDC1B 后可减少索拉非尼用药，提示联合应用可能有助于降低索拉非尼不良反应。

关键字： DEPDC1B；肾透明细胞癌；生物标记物；血管生成

17. DNA 甲基转移酶 3a 促肺鳞癌增殖的机制与预后相关性研究

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目的：研究 DNA 甲基转移酶 3a（DNMT3a）表达与肺鳞癌预后的相关性及其介导肺鳞癌增殖的潜在分子机制。

方法：回顾性研究纳入 47 例肺鳞癌患者，通过免疫组织化学染色检测 DNMT3a 在肺鳞癌组织的表达情况，结合临床病理信息进行预后相关性分析。为探索 DNMT3a 介导肺鳞癌增殖的分子机制，采用慢病毒感染法构建 DNMT3a 过表达的肺鳞癌 H1703 细胞系，Western blot 检测相关蛋白的表达情况。通过细胞克隆实验、CCK-8 增殖实验、EdU 染色增殖实验检测 DNMT3a 过表达在体外对细胞增殖能力的影响，通过裸鼠皮下肿瘤异种移植实验验证 DNMT3a 过表达的体内促增殖能力。此后，采用 DNMT 特异性抑制剂 SGI-1027 在体外处理

细胞，观察降低 DNMT3a 表达后对肺鳞癌细胞增殖的影响。进一步地开展功能回复实验，采用 c-Myc 特异性抑制剂 10058-F4 药物处理 DNMT3a 过表达细胞检测增殖能力。

结果：回顾性研究结果显示，肺鳞癌组织 DNMT3a 水平明显高于癌旁组织（图 1A，图 1B，$p<0.01$），其高表达与患者预后不良相关（图 1C）。DNMT3a 高表达与淋巴结转移（$p<0.05$）、临床分期高（$p<0.05$）、肿瘤分化程度差（$p<0.01$）等因素呈正相关（表 1），是肺鳞癌患者预后不良的独立危险因素（HR=2.073，95%CI 1.017-4.222，$p<0.05$，表 2）。基础实验表明，DNMT3a 过表达能够显著肺鳞癌细胞的在体外（图 2）与体内（图 3A）的增殖能力。Western blot 与功能回复实验进一步证明了 DNMT3a 上调 c-Myc 促进增殖能力的分子机制（图 3B）。

结论：DNMT3a 高表达是肺鳞癌患者预后不良的独立危险因素，DNMT3a 可能通过上调 c-Myc 的表达促进肺鳞癌的增殖功能。

关键字： DNA 甲基转移酶 3；肺鳞癌；肿瘤增殖；预后

18. Programming Super DNA-Enzyme Molecules for On-Demand Enzyme Activity Modulation

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Abstract: Dynamic interactions of enzymes, including programmable configuration and cycling of enzymes, play important roles in the regulation of cellular metabolism. Here, we constructed a super DNA-enzymes molecule (SDEM) that comprises at least two cascade enzymes and multiple linked DNA strands to control and detect metabolism. We found that the programmable SDEM, which comprises glucose oxidase (GOx) and horseradish peroxidase (HRP), has a 20-fold lower detection limit and a 1.6-fold higher reaction rate than free enzymes. An SDEM can be assembled and disassembled using a hairpin structure and a displacement DNA strand to complete multiple cycles. An entropically driven catalytic assembly (catassembly) enables different SDEMs to switch from an SDEM with GOx and HRP cascades to an SDEM with sarcosine oxidase (SOX) and HRP cascades in over six orders of magnitude less time than without the catassembly to detect different metabolisms (GO and sarcosine) on demand.

Key Words Catassembly · Enzyme Cascade · Programmable Modulation · SDEM · Strand Displacement

19. 外周血细胞计数综合评分作为结直肠癌患者预后的影响因子的研究

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目的：探究术前外周血细胞计数对结直肠癌患者预后的预测能力。

方法：使用 R 软件中的“surv_cutpoint”函数分析中性粒细胞、淋巴细胞及血小板的最佳界值，依据最佳界值建立外周血细胞评分系统。应用单多因素 Cox 回归分析探究患者临床病理特征与预后的相关性，并在 Cox 回归分析的基础上构建列线图以预测患者预后。使用 C 指数、校准曲线及决策曲线分析验证列线图预测模型的准确性。

结果：中性粒细胞、淋巴细胞和血小板的最佳界值分别为 4.40 ×109 /L, 1.41 ×109 /L 和 355 × 109 /L。外周血细胞评分系统（PBCS）评分规则如下：中性粒细胞和血小板低于最佳界值= 1 分，否则记为 0 分；淋巴细胞高于最佳界值=1 分，否则记为 0 分。三种细胞的得分情况相加，即为外周血细胞评分。多因素 Cox 回归分析结果显示 PBCS 是影响患者总生存期(P= 0.034, 1 分 vs0 分：P=0.045，HR=1.472, 95%CI: 1.315-2.109；2 分 vs0 分：P=0.021，HR=1.919, 95%CI: 1.527-2.691；3 分 vs0 分：P=0.013，HR=2.981, 95%CI: 2.174-5.711)和疾病相关生存(P= 0.005, 1 分 vs0 分：P=0.009，HR=1.601, 95%CI: 1.115-2.143；2 分 vs0 分：P=0.038，HR=1.917, 95%CI: 1.419-2.873；3 分 vs0 分：P=0.034，HR=2.915, 95%CI: 1.922-6.349)的独立保护因素。C 指数（0.873）、校准曲线和决策曲线分析（阈值概率：0%-75.2%）均表明列线图预测模型对患者的总生存期具有良好的预测效能。

结论：构建了基于患者术前外周血中性粒细胞、淋巴细胞和血小板水平构建的外周血细胞评分系统，其分值是影响结直肠癌患者预后的独立危险因素。本研究中所构建的列线图模型对于患者的预后具有较好的预测效能。

关键字： 结直肠癌；中性粒细胞；淋巴细胞；血小板；预后

20. Associations between reproductive-related factors with risks of overall and 4 specific cancers in women: Insights from a UK Biobank Cohort

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Background: Limited knowledge exists regarding the associations between reproductive-related factors and the risks of overall or specific cancers in females.

Methods: In this study, we leveraged a cohort of 242,789 females from the UK Biobank to investigate the impact of reproductive factors, including the number of live births, age at first live birth, and oral contraceptive pill use, on the risks of overall cancer and four specific cancers: breast, corpus uteri, cervix uteri, and ovary cancers. Applying Cox proportional hazards models, we assessed the relationships between reproductive-related factors and cancer risks. Additionally, mediation analysis was conducted to explore the role of metabolites in mediating the effects of these reproductive factors.

Results: For overall cancer, an increased number of live births showed a significantly negative association (HR: 0.915 (95%CI: 0.901, 0.929) per child increase). Conversely, a higher age at first live birth (HR: 1.013 (95%CI: 1.009, 1.016) per year increase) and oral contraceptive pill use (HR: 1.703 (95% CI: 1.647-1.762)) were positively associated with overall cancer risk. Similar patterns were observed for breast, corpus uteri, and ovary cancers. Specific metabolites, including albumin,

histidine, and citrate, were identified as crucial mediators in these associations. The mediation analyses showed that each cancer type had different essential mediating metabolites. Specifically, for overall cancer, albumin and His accounted for 4.46% and 2.18% of the total effects of oral contraceptive pill usage on the risk, respectively; moreover, albumin played a mediating role in the influence of age at first live birth on overall cancer risk, contributing 6.81% to the risk, while His mediated the effects of the number of live births, contributing 6.00%. For corpus uteri cancer, we observed that the concentration of Small LDL Particles (S-LDL-P) played a significant mediating role in the association between the number of live births and the risk of corpus uteri cancer, demonstrating a substantial mediation effect of 23.56%; additionally, His was identified as a mediator, accounting for 2.70% of the association between the use of oral contraceptive pill with the risk of breast cancer. In the case of breast cancer, only 3-Hydroxybutyrate (bOHbutyrate) was found to mediate 12.6% of the effects of oral contraceptive pill usage. For ovary cancer, citrate was identified as a mediating factor in the context of oral contraceptive pill usage, with a mediation effect of 0.91%.

Conclusion: Our findings underscore the significant influence of reproductive-related factors on overall and specific cancer risks in females. Moreover, our study provides molecular insights into how these reproductive factors affect cancer risk through the mediation of specific metabolites. This research contributes valuable information to the understanding of the complex interplay between reproductive history and cancer susceptibility in women.

Key Words： Reproductive-related factors; overall cancer; female-specific cancers; metabolites; mediation analysis.

21. PNPLA8 是调控三阴性乳腺癌磷脂代谢并促进肿瘤增殖和转移的关键分子

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Background Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype and leads to the poorest patient outcomes despite surgery and chemotherapy treatment. Exploring new molecular mechanisms of TNBC that could lead to the development of novel molecular targets are critically important for improving therapeutic options for treating TNBC.

Methods We sought to identify novel therapeutic targets in TNBC by combining genomic and functional studies with lipidomic analysis, which included mechanistic studies to elucidate the pathways that tie lipid profile to critical cancer cell properties. Our studies were performed in a large panel of human breast cancer cell lines and patient samples.

Results Comprehensive lipid profiling revealed that phospholipid metabolism is reprogrammed in TNBC cells. We discovered that patatin-like phospholipase domain-containing lipase 8 (PNPLA8) is overexpressed in TNBC cell lines and tissues from breast cancer patients. Silencing of PNPLA8 disrupted phospholipid metabolic reprogramming in TNBC, particularly affecting the levels of phosphatidylglycerol (PG), phosphatidylcholine (PC), lysophosphatidylcholine(LPC) and glycerophosphocholine (GPC). We showed that PNPLA8 is essential in regulating cell viability, migration and antioxidation in TNBC cells and promoted arachidonic acid and eicosanoid production, which in turn activated PI3K/Akt/Gsk3β and MAPK signaling.

Conclusions Our study highlights PNPLA8 as key regulator of phospholipid metabolic reprogramming and malignant phenotypes in TNBC, which could be further developed as a novel molecular treatment target.

关键字： PNPLA8, Breast cancer, Triple negative, Phospholipid, Metabolism reprogramming, Eicosanoids, Migration, Invasion, Proliferation

22. SESN2 参与肺癌细胞自噬过程中的 m6A 调控

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N6-甲基腺苷（m6A）是真核生物中最丰富的 mRNA 修饰，参与肺癌的自噬和进展，然而其基本的分子机制仍未知。在本研究中，我们在自噬激活的 H460 细胞中发现了 GGACU 共识别基序，表明自噬过程中 m6A 修饰显著富集。通过机器算法我们获得了自噬过程中参与 m6A 调控的核心靶点 SESN2。MeRIP-seq 数据显示，自噬过程中 SESN2 mRNA 中多个 m6A 丰度增加，SESN2 m6A mRNA 主要富集于 3'UTR 和 CDS 区域。此外，在具有两个 5'-GGAC-3' 序列的自噬激活的 H460 细胞中，第 9 号外显子的 m6A 峰（chr1:28,605,611-chr1:28,605,750）高度富集。进一步的，我们发现当放线菌素 D 阻断转录后，与 FTO 敲低细胞相比，siFTO 和 siIGF2BP1 共同处理显著提高了 SESN2 mRNA 的降解效率。IGF2BP1 的缺失不仅降低了 SESN2 mRNA 的稳定性，还促进了放线菌素 D 转录阻断过程中 FTO 缺失引起的 SESN2 mRNA 降解。RNA 免疫沉淀证实 IGF2BP1 抗体在 FTO 缺陷细胞中显著富集 SESN2 mRNA，提示 IGF2BP1 与 SESN2 mRNA 结合。更重要的是，我们通过荧光素酶报告基因和诱变实验证实 SESN2 第 9 号外显子中的 m6A 参与了自噬过程中 SESN2 mRNA 稳定性的调控。本研究为非小细胞肺癌中自噬的表观遗传修饰的机制研究提供了新思路。

关键字： m6A；自噬；表观遗传调控；SESN2；IGF2BP1；mRNA

23. 基于 FOLFOX 方案辅助化疗的结直肠癌患者无复发生存 microRNA 预测模型构建研究

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目的：构建辅助化疗结直肠癌患者无复发生存预测模型，实现对高复发风险患者的早期识别。

材料与方法：从 GEO 数据库下载 GSE217978 和 GSE106584 的表达数据和临床信息。GSE217978 数据集中有 71 名 CRC 患者的 RNA 测序数据，其中 30 名患者在辅助化疗后复发。GSE106584 数据集中有 156 例 CRC 患者样本的 RNA 测序数据，其中 52 例患者在辅助化疗后复发。通过差异表达分析获得辅助化疗后复发相关的 miRNA 或 mRNA。通过 LASSO 回归筛选变量，通过单因素和多因素 cox 回归。使用诺莫图对模型进行可视化。依据最优截断值将辅助化疗患者分为高、低风险组。通过 Log Rank 检验比较两组患者无复发生存率的差异。通过受试者工作特征（receiver operating characteristic,ROC）曲线、校准曲线和决策曲线分析该模型的预测效能。使用 miRWALK 对 5 个预后 miRNA 进行靶点预测，与 GSE106584 数据集中的差异表达 mRNA 取交集后，通过 cytoscape 构建与辅助化疗无进展生存相关的 miRNA-mRNA 调控网络。使用 mirPath 和 DAVID 网站分别对差异表达 miRNA 和 mRNA 进行基因本体、京都基因与基因组百科全书富集分析。

结果：在 GSE217978 和 GSE106584 数据集中，分别发现 31 个差异表达 miRNA 和 414 个差异表达 mRNA。 通过 LASSO 回归分析，共筛选出 7 种对无复发生存有预测价值的变量。通过对上述变量进行单变量 Cox 回归分析，发现 miR-144、miR-500a、miR-592、miR-942、miR-379 等 5 种 miRNA 与辅助化疗 CRC 复发相关，随后针对这 5 种 miRNA 进行多因素 Cox 回归分析构建了无复发生存预后模型。无复发风险评分计算公式为 Score= 0.003380*miR144+0.150653*miR379-0.042411*miR500a+0.0033134*miR592-0.0063025* miR942。风险评分的最优截止值为-0.59，据此将患者分为高风险组和低风险组。高风险组患者辅助化疗后复发的风险显著高于低风险组[HR=7.91，（95%CI:3.35-18.65），P<0.001]。高风险组患者的中位无复发生存时间为 23 个月，而低风险组患者的中位无复发生存时间长于随访时间。通过亚组分析发现，65 岁以下的患者可能比其他年龄患者更适合使用该预测模型。该模型预测 1 年、3 年和 5 年无复发生存的 AUC 值分别为 0.84（0.71,0.96）、0.88（0.79,0.96）

和 0.89（0.79,9.98），C-Index 值为 0.80（95%可信区间：0.72-0.87，P＜0.001）。 校准曲线分析显示预测曲线与标准曲线拟合情况良好，决策曲线分析证实该预测模型有较高的临床应用价值。基于 miRWALK 数据库预测得 5 个预后 miRNA 共能调控 59 个 mRNA 的表达，并绘制了调控网络图。5 个 miRNA 显著富集于肿瘤转录失调、细胞内吞、剪接体和结直肠癌信号通路，而其所调控的 59 个 mRNA 显著富集于 TGF-β和细胞因子-细胞因子信号通路。

结论：本研究基于 5 个预后 miRNA 构建了预测模型，对辅助化疗后的结直肠癌无复发生存预后具有较高的预测价值，可以辅助临床医生对高复发风险人群实现早期识别。

关键字： 辅助化疗；结直肠癌；无复发生存；微小 RNA

24. 肿瘤训导的红细胞（tumor educated RBC）在肿瘤发生发展中的功能及应用

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哺乳动物红细胞（RBC）是一类没有细胞核或线粒体的细胞，是氧气、二氧化碳和细胞代谢副产物的运输载体。在哺乳动物红细胞成熟过程中，红系前体细胞在线粒体的辅助下将细胞核排出细胞外，产生无核网织红细胞，网织红细胞成熟后被释放到血液循环中，通过清除线粒体和其他细胞器进一步成熟为红细胞。有文献报道，某些存在脾脏功能缺陷的患者循环红细胞中存在含有 DNA 的包涵体，这种包涵体被称为 Howell-Jolly 小体（HJBs），HJBs 的形成是红系发育异常过程的结果，大多数 HJBs 含有着丝粒区 DNA，只有少数 HJBs 的 DNA 来自常染色质。既往研究表明，红细胞不仅可以通过自身表面的 Toll 样受体 9（TLR9）与细胞游离 mtDNA 和致病 DNA 结合，调节机体免疫功能，还能在肿瘤进展和转移中发挥重要作用。近期我们的研究也表明，在肿瘤发生发展过程中，成熟红细胞会吸收来自肿瘤细胞的 DNA，并且红细胞吸收的 DNA 可以作为肿瘤诊断的标志物（Advance Science, 2023）。然而关于红细胞是否能够吸收肿瘤细胞来源的 RNA 和蛋白质至今尚无报道。通过高通量测序和蛋白质谱测序，我们证实在肿瘤发生发展过程中，肿瘤细胞与红细胞会通过细胞外囊泡等方式交互调控，肿瘤细胞通过分泌大量的 RNA 和蛋白“教育”红细胞，将红细胞转变为肿瘤训导的红细胞（tumor educated RBC）。肿瘤训导的红细胞（tumor educated RBC）能够通

过调控免疫细胞等方式促进肿瘤的生长和转移。此外，肿瘤训导的红细胞包含的肿瘤细胞来源的 RNA 和蛋白质可以作为肿瘤早期诊断和转移预测的新型生物标志物。

关键字： 肿瘤训导的红细胞，肿瘤，RNA，蛋白质

25. METTL14 通过介导促凋亡蛋白 Bim m6A 修饰抑制 EGFR 突变 NSCLC 奥希替尼耐药

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Resistance to osimertinib represents a significant challenge for the successful treatment of non-small cell lung cancer (NSCLC) harboring activating mutations in epidermal growth factor receptor (EGFR). N6-methyladenosine (m6A) on mRNAs is critical for various biological processes, yet whether m6A regulates osimertinib resistance of NSCLC remains unknown. In this study, we demonstrated that developing osimertinib-resistant phenotypes depends on m6A reduction resulting from downexpression of m6A methyltransferase METTL14 and METTTL3 in EGFR-mutant NSCLCs. Both in vitro and in vivo assay showed that specific knockdown of METTL14 but not METTL3 was sufficient to confer osimertinib resistance and elevated expression of METTL14 but not METTL3 rescued the efficacy of osimertinib in the resistant NSCLC cells. Mechanistically, METTL14 promoted m6A methylation of pro-apoptotic Bim mRNA and increased Bim mRNA stability and expression, resulting in activating the Bim-dependent pro-apoptotic signaling and thereby promoting osimertinib-induced cell apoptosis. Analysis of clinical samples revealed that decreased expression of METTL14 was observed in osimertinib-resistant NSCLC tissues and significantly associated with a poor prognosis. In conclusion, our study reveals a novel regulatory mechanism by which METTL14-mediated m6A methylation of Bim mRNA inhibited osimertinib resistance of NSCLC cells. It offers more evidences for the involvement of m6A modification in regulation of osimertinib resistance, and provides potential therapeutic targets for novel approaches to overcome the drug tolerance of osimertinib and other EGFR-TKIs.

关键字： Osimertinib resistance, METTL14, m6A modification, Bim, NSCLC

26. CRISPR-based rapid and convenient diagnostic test for ALDH2 gene mutation.

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The ALDH2 gene encodes enzymes such as aldehyde dehydrogenase and nitrate reductase. The gene is polymorphic, prone to mutations that affect enzyme activity, leading to the progression of gastrointestinal tumors and liver cancer. Studies have shown that in treating cardiovascular diseases, individuals with the ALDH2*2 mutation exhibit significantly reduced nitrate reductase activity, affecting the efficacy of nitroglycerin. Timely and effective detection of ALDH2 mutations provides clues for relevant treatments, reducing ineffective medication use. CRISPR Cas12a, due to its collateral cleavage activity, is used for specific nucleic acid molecule detection, combined with RPA nucleic acid amplification technology, offering advantages such as speed and convenience. Based on it, we introduced mismatched points in the guide RNA to eliminate Cas12a's tolerance of mismatch, for ALDH2 mutation detection. Our designed RPA combined with the CRISPR Cas12a detection platform can rapidly detect ALDH2 gene mutations within 30 minutes, with an accuracy rate as high as 97%.

Key Words： ALDH2 mutation CRISPR cas12a RPA

27. Proteomics of plasma extracellular vesicles reveals a panel of diagnostic biomarkers for Non-Small Cell Lung Cancer

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Background The global incidence and mortality rates of non-small cell lung cancer (NSCLC) remain high. Timely screening and early diagnosis are crucial for improving patient outcomes and reducing cancer-related fatalities. Extracellular vesicles (EVs) offer a promising approach for liquid biopsy-based disease screening and therapy monitoring. This study aims to develop a multi-protein signature derived from plasma tumor cell-derived extracellular vesicles (TDEVs) for effective NSCLC screening.

Methods A label-free data-independent acquisition (DIA) quantitative proteomics of EVs derived from 4 typical NSCLC cell lines and 3 human normal lung epithelial cell lines was employed to analyze the differentially expressed proteins (DEPs). Among the DEPs, X (unpublished data) was exclusively detected in the NSCLC EVs by western blot (WB) and flow cytometry (FC). To further assess X expression, immunohistochemistry (IHC) assays and Enzyme-linked immunosorbent assay (ELISA) were developed using NSCLC tumor tissue microarrays (TMAs) and plasma EVs from NSCLC patients, respectively. Bead-based flow cytometry assays and immune-captured assays were used to validate the membrane localization of X on the EVs. Then a proteomic signature of immune-captured EVs from clinical pooled plasma in a discovery cohort was processed to obtain a diagnostic model with a random forest machine learning method. Finally, these candidate proteins were validated by parallel reaction monitoring (PRM) -based targeted proteomics in a validation cohort.

Results Differential proteomics of cell lines derived EVs revealed that 430 proteins were differentially expressed, among which, 129 proteins and 44 proteins were exclusively detected in the NSCLC group and control group, respectively. Among the DEPs, X was exclusively identified

in the NSCLC EVs compared to the control group. Moreover, X was upregulated in the tumor cells while it was barely expressed in the stromal cells examined by the IHC staining. In addition, X was much higher in the NSCLC plasma EVs compared with the healthy control (HC) samples. Co-localization analyses of X with CD63/Rab5 and cell surface biotinylated X pull-down assay suggested that EVs X originated from the internalized plasma membrane. EVs membrane-localized X enabled to immune-capture TDEVs from total circulating EVs. According to the machine learning processed proteomics data of the discovery cohort, 49 candidates were subsequently quantified in the validation cohort. Finally, for PRM-based target proteomics, a seven-protein panel for classifying NSCLC and HC with area under curve (AUC) of 1.000, sensitivity of 100%, and specificity of 100%.

Conclusions Taken together, these findings indicated that a seven-protein panel exhibited promising biomarkers for classifying NSCLC and HC with high accuracy by integrated analysis of proteomics of TDEVs, which would provide an alternative approach for developing a liquid biopsies test for NSCLC screening.

Key Words ： NSCLC, extracellular vesicles, proteomics, machine learning, diagnostic panel

28. Comprehensive characterisation of cell disulfidptosis in human cancers: an integrated pan-cancer analysis

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A recent study has reported a novel programmed cell death pathway, called “disulfidptosis”, due to increased disulfide stress. A total of 10 genes were identified in the disulfidptosis pathway, including 6 pro-disulfidptosis genes (NUBPL, NDUFA11, LRPPRC, OXSM, NDUFS1, and GYS1) genes and 4 anti-disulfidptosis genes (SLC7A11, SLC3A2, RPN1, and NCKAP1). By mining multi-omic profiling data, we performed a systematic and comprehensive bioinformatics analysis of the disulfidptosis gene set across human cancers. We comprehensively clarified the genomic pan-cancer profiles of the disulfidptosis gene set regarding the SNV, CNV, methylation

across 32 tumors. Furthermore, we revealed that the gene expression of disulfidptosis pathway is dysregulated in some cancer and the dysregulated disulfidptosis genes may affect the activation or inhibition of diverse cancer-related pathways. Meanwhile, disulfidptosis gene expression is related to the prognosis in multiple cancers and has a significant correlation with stromal and immune scores in pan-cancer. Besides, disulfidptosis gene set also has a significant correlation with RNA stemness score, DNA stemness score, and may affect the drug sensitivity of various chemotherapy agents. Generally, this study not only revealed diverse mechanisms of the gene expression regulations of the disulfidptosis gene set in cancers but also analyzed the potential associations between disulfidptosis and other cancer pathways, providing a new insight of disulfidptosis for future clinical cancer researches and treatment.

Key Words ： Cell death, Disulfidptosis, Bioinformatics analysis, Pan-cancer

29. The establishment of prognostic model of uterine corpus endometrial carcinoma based on antigen presentation-related genes

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Background: Uterine corpus endometrial carcinoma (UCEC) is the major gynecologic tumor in most countries around the world with a poor prognostic in the late stages. The down-regulation of the antigen presentation pathway serves a pivotal strategy employed by tumor cells to evade the immune system, leading to diminished neoantigen presentation. However, the function of antigen presentation-related genes (APGs) in UCEC is still unknown, and a prognostic model for UCEC with high accuracy is urgently needed.

Methods: RNA-seq data and the clinical information on 544 UCEC patients are provided from the Cancer Genome Atlas database (TCGA) and 177 normal samples are provided from TCGA and Genotype-Tissue Expression (GTEx). Then we used the information to analyze the corresponding

differentially expressed genes (DEGs) and prognostic genes. We chose important genes using statistical methods, and then the analysis of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment were performed. In order to identify molecular subtypes, consensus clustering was used. These antigen presentation-related subtypes' clinicopathologic characteristics, immune cell infiltration, and somatic mutation profile were contrasted. APGs were also used to create a prognostic model for UCEC with machine learning algorithms. And we performed immune correlation analysis and single gene analysis to check the model's correctness.

Results: UCEC was divided into two subtypes according to APGs, each of which has unique clinicopathologic characteristics, prognostic indicators, tumor microenvironment characteristics, and microsatellite instability. In general, the immunosuppressive microenvironment and a higher frequency of oncogene mutations resulted in a poorer prognosis for the antigen presentation-low subtype. In contrast, the immunoreactive microenvironment was related with the best clinical results for the antigen presentation-high subtype. Additionally, we created a prognostic model based on APGs with a strong prognosis evaluation capability. The best prognostic model was established based on Random Survival Forest (RSF) algorithm (1-, 3- and 5-year AUC are 0.81, 0.84 and 0.85).

Conclusion: We identified molecular subtypes based on APGs and compared specific clinical features between subtypes. Besides, a prediction model with accurate prediction ability was developed.

Key Words ： uterine corpus endometrial carcinoma, antigen presentation-related genes, prognostic model, machine learning

30. sST2 /NT-proBNP levels predict early cardiac toxicity in breast cancer chemotherapy

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Objectives ：Cardiovascular biomarkers act crucially in monitoring cancer therapy-related cardiac dysfunction (CTRCD), but the effects on early stage of CTRCD are still inadequate. To screen biomarkers for CTRCD in patients with breast cancer receiving anthracycline-containing chemotherapy, we studied the behaviors of six biomarkers during chemotherapy and the associations with CRTCD.

Methods ： In a prospective cohort of 73 patients treated with anthracycline-containing chemotherapy, soluble ST2 (sST2), high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), Myoglobin (Myo), Creatine kinase isoenzyme MB (CK-MB) and heart-fatty acid binding protein (H-FABP) were measured at baseline, during chemotherapy cycle (C1-C6). According to whether arrhythmia occurred, patients were divided into two groups (healthy group or arrhythmias group), and basic clinical characteristics were collected and compared. Logistic regression analyses and receiver operating characteristic (ROC) curves were conducted to investigate the associations of changes in biomarkers with CTRCD.

Results： sST2 levels increased significantly from baseline to C1 (P<0.01). NT-proBNP levels decreased from baseline to C1, C5 (P< 0.01). Logistic regression analysis showed a greater risk of CTRCD was associated with interval changes in sST2 (OR: 1.27; 95% CI: 1.03 to 1.56; P= 0.024) and NT-proBNP (OR: 0.83; 95% CI: 0.70 to 0.98; P = 0.029). ROC curves showed that △sST2, △NT-proBNP and △sST2+△NT-proBNP had good predictive value for CTRCD (areas under the curves were 0.631, 0.633, and 0.735, respectively, P<0.05).

Conclusions ： Early changes in sST2 and NT-proBNP levels offer additive information in early CTRCD prediction in breast cancer patients receiving anthracycline-containing chemotherapy.

Key Words ： chemotherapy, CTRCD, sST2, NT-proBNP

31. 铁死亡相关基因 GPT2：胃腺癌潜在的治疗靶点及预后标志物

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目的：应用生物信息学方法分析胃腺癌铁死亡相关基因（ferroptosis-related genes, FRGs），筛选关键枢纽基因并明确其表达与预后意义，预测以关键枢纽基因为治疗靶点的中药，为胃腺癌的预后及治疗提供新的思路和生物标记物。

材料与方法：从 GEO 数据库检索得到基因芯片数据集 GSE13861，利用 GEO2R 分析工具，筛选出差异表达基因（differentially expressed genes，DEGs）；随后，从 FerrDb 数据库下载铁死亡相关数据集，并与前面筛选获得的 DEGs 利用韦恩图取交集获得胃腺癌 FRGs；然后，通过 DAVID 数据库对胃腺癌 FRGs 进行 KEGG 通路富集分析，采用 STRING 数据库构建蛋白相互作用（protein-protein interaction, PPI）网络，利用 Cytoscape 软件从胃腺癌 FRGs 中筛选出关键枢纽基因并通过 GEPIA2 及 Kaplan-Meier Plotter 数据库分析关键枢纽基因的表达及预后意义；最后，选取本院胃腺癌标本组织切片，通过免疫组织化学方法分析胃腺癌中关键枢纽基因的表达水平，同时验证癌和癌旁差异，并利用 Coremine Medical 数据库进行分析获得以关键枢纽基因作为治疗靶点的中药。

结果：差异表达分析共获得 552 个 DEGs，其中 185 个基因上调，367 个基因下调；DEGs 与铁死亡数据集取交集后共得到 30 个胃腺癌 FRGs，其中 10 个属于铁死亡驱动基因，15 个属于铁死亡抑制基因，5 个属于铁死亡未分类基因，且大多数胃腺癌 FRGs 的表达均下调；KEGG 通路分析显示胃腺癌 FRGs 主要富集在 2-氧代羧酸代谢、半胱氨酸和甲硫氨酸代谢、氨基酸的生物合成及 FoxO 信号通路；PPI 网络图及枢纽基因网络图结果表明 GPT2 可作为胃腺癌 FRGs 的关键枢纽基因，且 GPT2 在胃腺癌中的表达明显低于癌旁正常组织（$P<0.05$），GPT2 高表达组患者总生存率（OS）显著高于 GPT2 低表达组（logrank $P=0.016$），且发现本院胃腺癌患者免疫组化结果与上述结果一致；另外，针对关键枢纽基因 GPT2，应用 Coremine medical 数据库预测得到 3 味中药，分别为丹参、浮小麦及玉米须，其中仅丹参和浮小麦具有统计学意义。

结论：铁死亡相关基因 GPT2 可能是胃腺癌潜在的治疗靶点及预后标志物。

关键字：胃腺癌；铁死亡；GPT2；靶点；预后标志物

32. Dissecting the Cell States Unveils a Cellular Ecosystem Enhancing Risk Stratification in Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) exhibits enormous cellular heterogeneity in both leukemic and tumor microenvironment (TME) cells, presenting valuable insights for clinical outcomes. However, our understanding of these heterogeneity is limited to relative small, isolated cohorts. Here, we described sciNMF framework to dissect heterogeneous cell states from large-scale scRNA-seq datasets. Notably, sciNMF identified 26 leukemic and TME cell states that linked to clinical variables, mutations, and prognosis. By examining the co-existence patterns among these cell states, we highlighted a unique AML cellular ecosystem (ACE) that signifies aberrant TME and poor survival, which is confirmed in two large bulk AML cohorts. We further developed a 12-gene signature (aScore) on the basis of ACE signature genes, accurately predicting AML prognosis and exhibiting superior performance in comparison to existing methods. Our results demonstrate that large-scale systematic characterization of cellular heterogeneity has the potential to enhance our understanding of AML heterogeneity and contribute to more effective risk stratification strategy.

Key Words ： Acute myeloid leukemia; cell states; cellular ecosystem; risk stratification

33. Pan-cancer Single Cell Analysis Revealed the Role of Cancer-associated Fibroblast-Specific LncRNA MEG3

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Objective: The limited efficacy and high recurrence rates associated with immunotherapy in solid tumors underscore the critical need for identifying biomarkers targeting cancer-associated fibroblasts (CAFs). In light of their strong tissue and cell type specificity, CAF-specific long non-coding RNAs (lncRNAs) emerge as promising targets. This study endeavors to pinpoint CAF-specific lncRNA biomarkers across diverse cancer types by leveraging single-cell pan-cancer datasets, thereby elucidating their role in CAFs' aberrant activation.

Methods: Integrated single-cell sequencing datasets were analyzed to identify differentially expressed lncRNAs in CAFs, focusing on MEG3. MEG3's expression patterns and its effects on CAF activation and transformation were examined by employing activation trajectory inference and cell–cell interactions analysis in the TME. Survival and TIDE analysis were utilized to evaluate the potential of MACAFS score for evaluating cancer progression and response to therapy.

Results: Our analysis revealed a consistent CAF-specific downregulation of MEG3 expression but not positive rate at pan-cancer level, which may be driven by m6A-related post-transcriptional modifications. Through activation trajectory analysis of the major CAF types, MEG3 activation in CAFs was detected to upregulate PDGFRA receptor expression. This process facilitates CAF activation and transformation into a distinct MEG3+ adiCAF subtype (i.e., MACAFS). Further CAF-related cell–cell interactions investigation highlighted the pivotal role of MACAFS subtype in remodeling the tumor microenvironment. Importantly, our findings indicate that patients undergoing ICB therapies with higher MACAFS score tend to experience unfavorable prognosis

and poor response rates, implying the correlation between MACAFS and immunosuppressive microenvironment shaping.

Conclusion: Collectively, our findings provide novel insights into MEG3's role in CAF activation and transformation, presenting new insight for potential therapeutic interventions in cancer treatment.

Key Words： cancer-associated fibroblast, LncRNA, MEG3, PDGFRA, immunotherapy, m6A

34. 血清肿瘤相关自身抗体检测在胃癌筛查与诊断中的价值

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目的：探讨血清自身抗体在胃癌筛查与诊断中的应用价值。

方法：570 例胃癌患者以及 373 例对照被纳入本课题研究。运用酶联免疫吸附法（ELISA）对被测血清的自身抗体进行定量检测，并对结果进行统计建模，分析其与各临床病理参数的关系。

结果：胃癌患者组的自身抗体检测结果与对照组的检测结果存在显著性差异。结果筛选 claudin18.2、CAGE、NY-ESO-1、PBRM1、RASSF7、IMP2、COPB1 等 7 种自身抗体组合建模（AUC=0.885）。联合 7-TAAs 与幽门螺杆菌后的诊断特异性约 0.86，而阳性预测值提升至 0.94。胃癌患者群体内不同 TAAs 蛋白的异常升高与疾病分期、肿瘤分化程度及浸润深度等因素相关。

结论：血清自身抗体谱的测定在胃癌的筛查与预测疾病进程中具有一定的临床应用价值，可作为临床诊断的辅助指标。联合 7-TAAs 与幽门螺杆菌后可有效提高筛查特异性和阳性预测值。不同蛋白的检测结果与疾病分期、肿瘤分化程度及浸润深度等因素相关。

关键字： 胃癌；多中心研究；自身抗体谱；NOMOGRAM；诊断

35. Exosomes Homogeneously Enriched Using a Functionalized Temperature-Responsive Polymer for the Early Detection of Bladder Cancer

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Objective: Currently, the methods for detecting bladder cancer (BCa) often exhibit invasiveness or unsatisfactory diagnostic performance, especially for low-grade and early-stage tumors. Therefore, novel biomarkers for BCa detectable through non-invasive means are urgently needed. Urine exosomes have excellent potential for improving non-invasive early diagnosis of BCa. However, the lack of a highly efficient exosome isolation strategy poses a challenge for the clinical application of exosomes biomarkers. This study aims to develop an efficient and cost-effective exosome extraction method suitable for clinical application, and identifying the potential value of urinary exosome biomarkers in early-stage bladder cancer diagnosis.

Methods: Nucleic acid aptamers were employed as capture probes and conjugated to the temperature-responsive polymer PNIPAM. Homogeneous exosome capture and heterogeneous separation were achieved by controlling the reaction temperature and centrifugation steps. Through integrative analysis of BCa transcriptomic data, BCa-derived exosomes genes and single-cell analysis, we identified potential BCa exosome biomarkers. Exosomes from urine samples were enriched using a functionalized temperature-responsive polymer to develop an exosomes-based diagnostic model.Lastly, the diagnostic performance. of this diagnostic model was compared to FISH detection.

Results: The developed novel method for homogeneous exosome capture does not require specialized equipment. Exosomes can be efficiently separated from the batch samples through centrifugation at 37 ° C and 12,000g for 5 minutes. The diagnostic model, UExo-2R, demonstrates excellent performance in distinguish between benign urological diseases and bladder cancer. In the training set, the area under the curve (AUC) is above 0.9, while in the testing and validation sets, the AUC is above 0.85, indicating a robust and stable diagnostic

performance. UExo-2R showed a significant sensitivity improvement over FISH, particularly for early-stage (88.7% vs. 49.1%) and low-grade BCa (82.6% vs. 26.1%).

Conclusion: We have successfully developed a highly efficient, rapid, cost-effective, and clinically applicable method for exosomes enrichment and a excellent BCa diagnostic model. This non-invasive, reliable BCa detection method has good potential for clinical application.

Key Words：bladder cancer; exosome; enrichment; diagnosis; temperature-responsive polymer

36. HER2 阳性晚期乳腺癌临床药物治疗的定量系统药理模型研究与应用

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目的：针对 HER2 阳性转移性乳腺癌（HER2-positive metastatic breast cancer，HER2+ mBC）二线治疗存在的问题，如新组合方案的疗效、药物最佳治疗顺序、药物耐药及潜在的应对策略、新靶点的临床价值等，本研究旨在利用新型模型引导的药物研发方法对上述问题的解答提供新见解，以指导 HER2+ mBC 患者的治疗。

方法：采用定量系统药理学（Quantitative systems pharmacology，QSP）的建模研究思路，针对 HER2+ mBC 的病理生理机制和药物作用机制构建了一个机理性 QSP 模型。随后利用大量体内外多尺度数据（包括已发表和内部实验数据）对模型进行校准与验证。运行参数敏感性分析以识别对模型输出影响最大的参数。对不同治疗策略下的临床前疗效进行模拟，并通过动物实验对模拟结果进行验证。最后，通过虚拟患者生成和虚拟临床试验模拟预测新治疗方案在临床层面的疗效与安全性。

结果：该模型重点关注 HER2+ mBC 二线治疗的三类药物，即酪氨酸激酶抑制剂（Tyrosine kinase inhibitor，TKI）、抗体药物偶联物（Antibody-drug conjugate，ADC）和化疗，定量重现了大量体外细胞信号转导、细胞活性数据以及体内小鼠肿瘤生长数据。敏感性分析和随后的异质性耐药表型模拟为设计新的药物组合以有效克服各种耐药情况提供了重要见解。模型预测 TKI 与 ADC 的新组合即使在更低剂量下对诱导肿瘤消退仍优于传统的 TKI 联合卡培他滨。同时，模型表明 ADC 后 TKI 联合卡培他滨的序贯治疗与直接使用 TKI

联合卡培他滨相比，将延长反应持续时间，这对于部分因 ADC 的不良反应而停药的患者具有治疗意义。以上两项发现均得到了动物实验的验证。此外，模型分析表明 NRG1 高表达和 PI3K 通路异常激活可诱导 TKI 耐药，HER3 抗体和 PI3K 抑制剂则分别有效逆转耐药性。虚拟临床试验结果进一步表明 TKI 联合 ADC 的新组合方案即使在更低剂量下仍具有较好的临床疗效，尤其是吡咯替尼联合 T-DM1。模型预测吡咯替尼（320 mg，qd）联合 T-DM1（3.0 mg/kg，q3w）的客观缓解率（Objective response rate，ORR）可达到 50% [95%CI 41.7-58.3]，同时降低了 T-DM1 的不良反应，≥3 级血小板减少的发生率为 15%，提示该方案可作为 HER2+ mBC 二线治疗的可选方案。

结论：该模型是第一个从机理上整合了 HER2+ mBC 研究中多种关键药物模式的模型，对 HER2+ mBC 的二线治疗具有指导意义。它可以作为一个高通量计算平台，指导未来模型引导的药物研发和临床转化。

关键字：定量系统药理学，HER2 阳性转移性乳腺癌，治疗策略，药物耐药，模型引导的药物研发

37. 肺腺癌原代细胞培养及在不同模型中的药物敏感性研究

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目的：体外培养人肺腺癌原代细胞，构建二维药筛和三维药筛体系，观察细胞在不同体系中的药物敏感性。

材料与方法：收集肺腺癌手术标本，利用自建的 SZC 培养法培养原代细胞；通过免疫荧光、核型分析、小鼠成瘤，免疫组化验证原代细胞是肿瘤细胞；培养所得的原代肿瘤细胞与海藻酸钠溶液混合后滴进氯化钙溶液中形成稳定的海藻酸钙凝胶微球（水凝胶），凝胶微球为细胞提供一个模拟的三维生长环境；CCK8 细胞毒性实验检测药物分别在二维与三维体系中的敏感性。

结果：培养所得的肿瘤细胞贴壁聚集，紧密排列，成鹅卵石铺路石状；免疫荧光结果显示 CK7 为强阳性，NapsinA 和 TTF-1 均为阳性表达。细胞核型分析鉴定显示染色体为 58-64，异常比例为 100%。细胞可在 NCG 小鼠中形成肿瘤，且组织的 HE 鉴定表明见异性细胞，结合形态及免疫组化结果（ck7+，NapsinA+，TTF-1+，p63-），符合肺腺癌；细胞毒性实验表明，顺铂、卡铂、多西他赛、吉西他滨、紫杉醇、培美曲塞，及长春瑞滨在细胞中的抑制率明显不同，且与二维体系中相比，在三维体系中不同药物均呈现出更好的敏感性。

结论：建立了一株肺腺癌原代细胞，且细胞在三维模型中药物的敏感性更高，为体外药物试验及耐药相关机制研究提供了实验依据。

关键字： 肺腺癌、原代细胞、药物敏感性

38. 联合单细胞及空间转录组解析肿瘤细胞来源的 SPP1 胞内外作用促进肝内胆管癌进展机制

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肝内胆管癌（iCCA）是一类发病隐匿，进展迅速，预后极差的原发性肝脏恶性肿瘤。近年来 iCCA 发病率呈上升趋势，约占所有原发性肝脏肿瘤的 10%-20%，复发率高，由于患者初诊时已是晚期，总体五年生存率不足 10%，手术切除并不能达到可治愈的生物学获益。iCCA 具存在不同的肿瘤病变模式，风险因素及遗传特征多样，造成其高度异质性的特征。同时，iCCA 具有促纤维增生的微环境，在肿瘤发生发展、免疫逃逸和治疗抵抗中至关重要，这两大特征是导致 iCCA 耐药难治及恶性复发的根本原因。

为了深入研究瘤内瘤间异质性以及复杂的肿瘤微环境，我们联合单细胞转录组测序技术及空间转录组测序技术，整合公开的 iCCA 单细胞转录组数据，构建了共约 25w 细胞的大规模样本 iCCA 单细胞转录组图谱。首先，基于特征基因相似性聚类，将所有胆管上皮细胞分为 6 种细胞亚型，应用 Scissor 算法发现 SPP1+肿瘤细胞高度浸润患者预后较差。骨桥蛋白（SPP1）是一种分泌型蛋白，于是将从胞内外两方面探究其在 iCCA 进展中的关键作用。一方面，基于单细胞 Progeny 通路分析以及 scMetabolism 代谢分析结果，发现在 SPP1+肿瘤

细胞中缺氧通路特异性激活，并且发现 SPP1+肿瘤细胞特异性激活氧化磷酸化等代谢通路。肝内胆管癌细胞系的细胞迁移、平板克隆、细胞增殖检测实验证明，SPP1 可促进 iCCA 肿瘤细胞增殖、侵袭和转移，进一步结合 SPP1 特异性敲除肝内胆管癌细胞系的 RNA 测序及非靶向代谢测序分析发现，SPP1 特异性敲除后缺氧特征及氧化磷酸化相关代谢产物特异性降低。另一方面，通过 CellChat 细胞互作及空间共定位分析，发现 SPP1+肿瘤细胞与间充质细胞（成纤维细胞与内皮细胞）有着较强的相互作用，并且 SPP1+肿瘤细胞基于 SPP1-ITGAV/ITGB1/ITGB5 配受对与 POSTN+成纤维细胞、PLVAP+内皮细胞存在空间共定位现象，进一步分析发现该生态位存在与 Treg 细胞浸润、CD8+T 细胞的排斥密切相关，提示 SPP1+肿瘤细胞-POSTN+成纤维细胞-PLVAP+内皮细胞的生态位诱导免疫抑制微环境形成。

综上所述，基于整合的单细胞转录组及空间转录组测序数据，我们的研究揭示了 iCCA 差异特征的分子分型及其复杂的转录调控互作网络，系统地研究了预后较差 SPP1+肿瘤细胞的胞内外作用机制，为深入了解 iCCA 发生发展机制、个体化精准诊疗的临床运用提供崭新的生物标志物以及分子靶点。

关键字： 肝内胆管癌；单细胞转录组；空间转录组；骨桥蛋白；免疫抑制生态位

39. Clinical value of soluble fms-like tyrosine kinase 1 (sFlt-1) in adult secondary hemophagocytic lymphohistiocytosis

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Background: Secondary hemophagocytic lymphohistiocytosis (sHLH) is a syndrome characterized by an excessive systemicinflammatory response, manifested by multiple organ dysfunction, lacking reliable immune biomarkers for predicting their inflam-matory status and

prognosis. Soluble fms-like tyrosine kinase 1 (sFlt-1) is associated with various inflammation-related diseases,including sepsis and severe organ failure.

Methods: This study retrospectively included 32 adult sHLH patients diagnosed from January 2020 to December 2021. Theexpression of Flt-1 in peripheral blood CD14+ monocytes was detected by flow cytometry, and the level of plasma sFlt-1 wasdetected by ELISA.Results: In our study, the results of flow cytometry reveal that the Flt-1 expression on CD14+ monocytes of peripheral blood fromsHLH patients was higher than that in normal control. In plasma samples of sHLH patients, sFlt-1 levels were 677.8 (463.2 – 929.7)pg/mL, significantly higher than in normal controls 377.18 (350.4 – 424.6) pg/mL and sepsis group 378.3 (257.0 – 499.1) pg/mL.Besides, a positive correlation was found between sFlt-1 and IL-6 in sHLH patients. The analysis of univariate Cox regressionindicated that sFlt-1 >681.5 pg/mL demonstrated unfavorable overall survival ($p = 0.022$). Multivariate analysis demonstrated thatsFlt-1 >681.5 pg/mL was an independent factor associated with OS ($p = 0.041$) after adjustment for confounders. Restricted cubicspline confirmed a linear and positive association between sFlt-1 and mortality risk.

Conclusion: Retrospective analysis showed that sFlt-1 was a promising prognostic factor.

Key Words : Fms-like tyrosine kinase 1; Prognosis; Secondary hemophagocytic lymphohistiocytosis

40. Single-cell RNA sequencing indicates cordycepin remodels the tumor immune microenvironment to enhance TIGIT blockade's anti-tumor effect in colon cancer

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Both preclinical and clinical studies have extensively proven the effectiveness of TIGIT inhibitors in tumor immunotherapy. However, it has been discovered that the presence of CD226 on tumor-infiltrating lymphocytes is crucial for the effectiveness of both anti-TIGIT therapy alone and when combined with anti-PD-1 therapy for tumors. In our investigation, we observed that cordycepin therapy significantly augmented the expression of the Cd226 gene. As a result, it was

hypothesized that cordycepin therapy could enhance the effectiveness of anti-TIGIT therapy. By employing single-cell RNA sequencing analysis of immune cells in the MC38 tumor model, we discovered that cordycepin combined with anti-TIGIT therapy led to a significant increase in the proportion of NK cells within the tumor immune microenvironment. This increased NK cell activity and decreased the expression of inhibitory receptors and exhaustion marker genes. In the combination therapy group, CD8+ T cells had lower exhaustion state scores and increased cytotoxicity, indicating a better immune response. The combination therapy group increased DCs in the tumor immune microenvironment and promoted cellular interaction with CD4+ T cell and CD8+ T cell populations while decreasing Treg cell interactions. In conclusion, cordycepin with anti-TIGIT therapy in colon cancer could reshape the tumor immune microenvironment and have notable anticancer effects.

Key Words ： Cordycepin, anti-TIGIT, NK cells, CD8+ TILs, DCs, Tumor immune microenvironment.

41. LINC00969 调控 NLRP3 介导的细胞焦亡促进肺癌 EGFR-TKIs 耐药机制研究

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目的：大量临床试验表明，包括吉非替尼和奥希替尼在内的表皮生长因子受体酪氨酸激酶抑制剂（epidermal growth factor receptor tyrosine kinase inhibitors，EGFR-TKIs），是 EGFR 突变肺癌患者标准一线治疗方法，其能延长患者的生存时间。不幸的是，在治疗过程中，患者会不可避免地出现获得性耐药，导致肿瘤复发和转移。目前较为明确的获得性耐药机制为 T790M 突变，c-MET 扩增，HER2 突变和上皮细胞-间质转化等。但目前还有许多患者对 EGFR-TKIs 耐药的分子机制仍尚未明确。因此，深入研究肺癌获得性耐药的新机制，寻找耐药相关基因和逆转耐药途径，对于改善肺癌患者的预后，延长其生存时间具有重要意义。

方法：通过生物信息学分析，筛选出 LINC00969 在 EGFR-TKIs 获得性耐药肺癌细胞中表达上调。qRT-PCR 实验分析 LINC00969 在 EGFR-TKIs 耐药及敏感组织和细胞中的表达差

异。通过体外和体内实验证实 LINC00969 在肺癌 EGFR-TKIs 耐药中的作用，并通过 RNA pull down、RNA 免疫共沉淀（RNA Immunoprecipitation，RIP）、染色质免疫共沉淀（Chromatin Immunoprecipitation，ChIP）、RNA 甲基化免疫沉淀（Methylated RNA Immunoprecipitation，MeRIP）和 Western blot 等实验探索其对靶基因的调控机制。

结果：LINC00969 在体内外均能增强肺癌细胞对 EGFR-TKIs 的耐药性。在机制探究发现 H3K4me1 和 H3K27Ac 可调控 LINC00969 的转录激活，从而促进其表达。LINC00969 能与 EZH2 和 METTL3 特异性结合，EZH2 在转录水平调控 NLRP3 启动子区 H3K27me3 水平，METTL3 以 YTHDF2 依赖的方式通过 m6A 修饰在转录后水平调控 NLRP3 表达，两者在表观遗传上共同抑制 NLRP3 的表达，抑制 NLRP3/Caspase-1/GSDMD 相关经典焦亡信号通路的激活，从而抑制肺癌细胞焦亡，促进肺癌 EGFR-TKIs 耐药。

讨论：细胞焦亡是一种全新的程序性细胞死亡形式，由炎性小体介导的细胞肿胀甚至膜破裂引起。先前的研究表明，细胞焦亡在肿瘤发生和耐药中起着至关重要的作用。长链非编码 RNA 通过调控细胞焦亡通路在多种疾病的治疗中发挥重要作用。我们的研究结果同时从组蛋白甲基化和 RNA 甲基化调控肺癌细胞焦亡的新角度丰富了 EGFR-TKIs 耐药的分子机制。本研究首次证明 LINC00969 通过该机制调控 EGFR-TKIs 耐药性。我们还证实了 LINC00969 在肺癌肿瘤发生中的功能作用。LINC00969 作为组蛋白甲基化、RNA 甲基化和细胞焦亡三者相互作用的关键分子，调控肺癌耐药细胞焦亡。LINC00969 介导的 EGFR-TKIs 耐药调控机制可以丰富我们对肿瘤耐药的认识，LINC00969 可能成为克服肺癌 EGFR-TKIs 耐药的新型潜在靶点。

关键字：LINC00969，EGFR-TKIs，耐药，m6A，焦亡

42. 三级淋巴结构对黑色素瘤预后及肿瘤免疫微环境的影响

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目的：探究黑色素瘤肿瘤组织内三级淋巴结构对预后及肿瘤免疫微环境的影响。

方法：采用 HE 染色和免疫组化方法观察肿瘤组织内三级淋巴结构与肿瘤免疫细胞浸润特征，KM 生存曲线分析预后，T 检验分析组间差异。

结果: Kaplan-Meirer 生存曲线结果提示肿瘤内存在三级淋巴结构组患者预后较不存在组患者显著改善。免疫组化结果分析发现存在肿瘤内三级淋巴结构组患者肿瘤组织中每平方毫米内 CD3、CD4、CD8、Foxp3 阳性细胞数显著高于不存在肿瘤内三级淋巴结构组患者。

结论: 黑色素瘤患者原发灶中肿瘤内三级淋巴结构的存在与良好预后及免疫细胞浸润密切相关。

关键字: 三级淋巴结构,黑色素瘤,肿瘤免疫微环境,预后

43. 一种用于发现肺癌血液生物标志物的深度代谢组学分析方法

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【目的】寻找肺癌患者血浆的代谢物生物标志物，为肺癌的鉴别诊断、干预性治疗以及机制研究提供重要指导依据。

【方法】选择性别、年龄匹配的肺鳞癌（n=20）、肺腺癌患者（n=23）和肺良性结节（n=13），采用 DeepMarker MT 代谢组学平台对血液样本进行代谢组学分析，其中，基于高效化学同位素标记（High Performance Chemical Isotope Labeling, HP-CIL）结合 Agilent 6546 超高效液相色谱-串联四极杆飞行时间质谱联用技术对血浆样本进行代谢组学分析，利用 IsoMS Pro 软件的三层级代谢物数据库对代谢物鉴定，采用主成分分析(principal component analysis，PCA)、t 检验、偏最小二乘判别分析(partial least square-discriminant analysis,PLS-DA)、分层聚类分析（hierarchical cluster analysis, HCA）等统计方法，分析不同人群患者的血液代谢差异，筛选有意义的差异代谢产物，并建立可以区分不同肺癌进程患者人群的诊断模型。

【结果】在血浆中共检测到 9783 个色谱峰对，其中有 8620 个代谢物（88.11%）可以被准确鉴定或者是推定得到。通过火山图与 PLS-DA 等分析筛选并鉴定出肺鳞癌与肺腺癌血浆中有 381 种代谢物存在显著差异（FC > 1.2 或< 0.83，$p < 0.05$ 以及 $q < 0.25$），通过 ANOVA（one-way）分析三组血浆样本，发现有 2017 种（$p < 0.05$ 以及 $q < 0.25$ ）代谢物显著差异，主要集中在氨基酸代谢、嘌呤代谢等通路。采用 LASSO 回归分析确定的 34 种

代谢物，绘制受试者工作特征（ROC）曲线，表明代谢物可有效区分不同肺癌类型和分期，AUC >为 0.91，特异性>为 82%，敏感性>为 84%。

【结论】本研究通过 DeepMarker MT 代谢组学平台对肺良性结节与肺恶性肿瘤（肺腺癌、肺鳞癌）患者的血浆的代谢组学分析，独有的 HP-CIL 技术为所有的物质生成同位素内标，有效克服检测时仪器漂移、基质效应等影响，使定量更加精准，提高 10-1000 倍检测灵敏度，扩大代谢组覆盖率，寻找到多个潜在的生物标志物，有助于促进肺癌早诊领域的研究。

关键字： 肺癌；代谢组学；高效化学同位素标记；生物标志物；DeepMarker MT 代谢组学平台

44. Single-cell Sequencing and Transcriptome Analysis Identified a Comprehensive Risk Score Model Based on Immune-Related Metabolic Genes

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Background: The immunotherapy of breast cancer (BC) has garnered significant attention in recent years, and metabolic reprogramming is associated with immune infiltration in the tumor microenvironment. Consequently, it is imperative to comprehensively investigate the involvement of immune-related metabolic genes in breast cancer.

Methods: In this study, we utilized the Limma method to identify differentially expressed immune-related genes (DEGs) between various tissue states. Subsequently, the intersection of DEGs and metabolic genes (MRGs) is selected to ascertain immune-related metabolic genes (IRMGs) for subsequent analysis. Additionally, unsupervised clustering was employed to group BC patients based on IRMGs. The Least Absolute Shrinkage and Selection Operator (LASSO) regression and univariate, multivariable Cox analysis were subsequently performed to optimize the gene sets and construct a comprehensive risk-sharing index model to prognostic metabolism-immune status-related signature. Finally, the single-cell sequencing data mining and analysis aimed to explore the immunometabolic heterogeneity of human breast cancers.

Results: We identified 46 IRMGs mainly clustered in regulating lipid localization and transport. Through this process, a scoring model consisting of 14 genes has been identified and validated, demonstrating exceptional accuracy and clinical applicability. The high-risk group was characterized by poorer prognosis, fewer activated immune cell infiltration and poorer treatment response to immune checkpoint inhibitors (ICIs). A prognostic nomogram based on the 14-gene signature and combined with clinical parameters exhibited a best predictive performance. Our model and corresponding nomogram are optimal and independent prognosis factors compared to other traditional clinical variables. In addition, ten hub genes were also selected from the Protein-protein interaction (PPI) network using the cytoHubba and MCODE plug-in.

Conclusions: An in-depth analysis of immune-related metabolic genes was conducted, culminating in the development a combined model for predicting susceptibility to immunotherapy in BC, thus helping guide patient management and providing a reference for further analysis and drug development in target discovery.

Key Words： breast cancer, biomarker, immunotherapy, metabolic, prognostic model, scRNA-seq

45. Identification of SFRPs family expression, prognosis, immune infiltration, and DNA methylation in colorectal cancer

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Objective: Colorectal cancer (CRC) is a common malignancy of the digestive tract. Patients always have progressed when they were diagnosed due to the early symptoms of CRC are not specific, which caused the 5-year survival rate lower than 4%. Secreted frizzled-related protein (SFRP) is an extracellular tumor suppressor gene of Wnt signaling pathway, which plays an important role in embryogenesis and tumorigenesis. However, the features of SFRPs family members in CRC are not fully elucidated. The purpose of this study was to discovery the expression, prognosis, DNA methylation and immune invasion levels of SFRP1-5 in colorectal cancer, and to explore the relationship between SFRP1/2 methylation and immune infiltration.

Methods: The GEPIA database (based on TCGA and GTEx data) was used to explore the expression and prognosis of SFRP1-5 in the CRC. Meanwhile, 4 GEO databases (GSE23878, GSE113513, GSE79793, GSE156355) also been selected to conducting the analyze differentially of SFRP1-5 through limma package of R software. STRING website was adopted to provide the information of molecular interactions and conducted the correlations between SFRPs and related proteins. Subsequently, the cytoscape software was used to choose the hub genes. And the protein function including GO and KEGG pathway was showed by DAVID website, the corresponding charts were draw by using ggplot2 package. The role of SFRPs in immune infiltration was found in TIMER database. MSP and BSP experiments were conducted to find the methylation level of SFRP1/2 in colorectal cancer. Flow cytometry and CCK8 experiments were used to determine the apoptosis and proliferation of colorectal cancer cells after knockdown the expression of SFRP1/2. TISIDB database was used to analyze the relationship between the methylation level of SFRP1/2 and its immune infiltration.

Results: The analysis results of GEPIA and GEO found the expression of SFRP1, SFRP2 and SFRP5 in colorectal cancer patients was significantly lower than normal tissues compared with normal colorectal tissues, but the SFRP4 was higher. And the prognosis analysis indicated that the increased mRNA expression of SFRP2 was significantly associated with the overall survival, disease-specific survival and progress free survival, however, only SFRP1 was associated with the progress-free survival. The prediction of function showed SFRPs family mainly participated in the regulation of Wnt signaling pathway. Immune infiltration analysis found that SFRP1, SFRP2, SFRP4 were positively correlated with the expression of CD274, while SFRP5 was negatively correlated with CD274. Meanwhile, the results also showed the correlation between the main immune cells infiltration and SFRPs family. The TIMER database was adopted to explore the relationship between the SFRPs family and CD4+T cells, CD8+T cells, macro cells, neutral cells and B cells, this study found that SFRP1/2/3/4/5 were positively correlated with the CD4+T cells ($P<0.01$), the SFRP1/2 were positively correlated with the CD8+T cells ($P<0.01$), SFRP1/2/3/4/5 were positively correlated with the macro cells ($P<0.01$), SFRP1/2/5 were positively correlated with the neutral cells ($P<0.01$) and SFRP1/2/4 were positively correlated with the B cells ($P<0.01$). Through the TCGA database, the results showed that the expression of SFRP1/2 in colorectal cancer was negatively correlated with the expression of methyltransferase

DNMT1/DNMT3A/DNMT3B. According to the results of prognosis analysis, this study chose SFRP1/2 to further verify the methylation level. BSP experiment confirmed that DNA methylation analysis of SFRP1 promoter region contained − 351 to − 93 positions and 42 CG sites. Through MSP experiment, it was found that the unmethylation level of SFRP1/2 in colorectal cell lines was increased, while the methylation level was significantly reduced. Compared with normal colorectal tissues, the methylation level in colorectal cancer tissues was significantly increased. HCT116 and SW620 cell lines were selected as experimental cell lines to verify the effect of the methylation level of SFRP1 and SFRP2 on the proliferation and apoptosis of colorectal cancer cells. After the cells were treated with A-zad C, it can inhibit the proliferation of colorectal cancer cells and promote apoptosis, while the use of si-SFRP1 or si-SFRP2 can promote the proliferation of colorectal cancer cells and inhibit apoptosis. When A-zad C and si-SFRP1/si-SFRP2 were used at the same time, it can save the effect of inhibiting proliferation and promoting apoptosis caused by simple A-zad C. When the expression of SFRP1/2 is knocked down, the proliferation ability of colorectal cancer cells increases, and its methylation level is inversely related to immune cells.

Conclusion: This investigation was the first relatively comprehensive to explore the features of the expression, prognosis, methylation and immune cell infiltration of SFRPs family in CRC. The results indicated that SFRPs family could be potential therapy targets and to identify as the key genes related to immune cell infiltration in CRC.

Key Words： SFRP, immune infiltration, DNA methylation, colorectal cancer

46. N-糖基化修饰的 CD276 通过诱导免疫逃逸促进胃癌进展的机制研究

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背景：根据 GLOBOCAN 2020 数据统计，全球胃癌发病率在所有恶性肿瘤中排名第五，死亡率排名第四，其中我国胃癌每年新发病例约占全球一半。我国胃癌诊断时多以进展期为主，传统手术联合放化疗的治疗效果欠佳，预后较差。当下，免疫治疗成为癌症研究与治疗的前沿热点，其在胃癌中也展现出了令人振奋的疗效，为晚期胃癌患者带来了新的希望。然而胃癌免疫治疗获益人群仍十分有限，提高总体获益率成为其发展的关键。因此，探究影响免疫治疗疗效因素，扩大免疫治疗获益人群，寻找新的免疫治疗靶标，改善胃癌总体疗效有着深远的临床意义。B7 家族是一系列免疫检查点相关蛋白家族，其中 PD-L1/CD274 已经被广泛报道其在肿瘤免疫治疗中的作用，并应用于临床。由于胃癌具有显著的异质性，使得 PD-L1 的治疗在胃癌中的效果并没有很显著，因此迫切需要寻找新的免疫治疗靶点。而作为 B7 家族另一个成员的 B7-H3/CD276，其在胃癌的作用机制尚不明确。

方法：TCGA、GEO 等公共数据库分析 B7 家族在胃癌中的差异表达。本中心的胃癌样本进一步验证 CD276 在胃癌中的表达水平。Kaplan-Meier Plotter 生存分析探索 CD276 与胃癌患者生存的关系。Cibersort 免疫浸润联合组织芯片 CD8、CD4 染色分析预测 CD276 与免疫细胞的关系。利用 CRISPR/Cas9 技术构建 CD276 敲除的胃癌细胞系。CCK8、平板克隆、皮下成瘤实验研究 CD276 对胃癌细胞增殖能力的影响。Transwell、划痕、小鼠肝转移模型探索 CD276 对胃癌细胞转移能力的作用。Western blot、糖苷酶以及糖基化抑制剂的使用探究 CD276 的蛋白翻译后修饰水平。CHX、MG132 和泛素化质粒转染验证糖基化对 CD276 蛋白稳定的作用。流式细胞学技术检测糖基化修饰对膜表达的 CD276 的作用。构建鼠源胃癌细胞 MFC 细胞 CD276 敲除，利用 cyTOF 技术探索 CD276 对免疫胃癌环境的影响。CD276 KO 细胞联合 PD-L1 抑制剂注射探索 CD276 KO 联合 PD-L1 抑制剂对胃癌的治疗作用。

结果: CD276 在胃癌高表达且与不良预后相关。CD276 能够在体内外促进胃癌细胞的增殖和转移。CD276 在胃癌中主要受到 N-糖基化修饰，且 N-糖基化修饰导致其蛋白稳定和膜表达增多。机制上，CD276 的 N-糖基化发挥其对其免疫抑制的功能。CD276 的敲除可以增加 PD-L1 抑制剂对胃癌的治疗效果。

结论：我们的结果发现 N-糖基化修饰的 CD276 能够通过诱导免疫逃逸从而促进胃癌的恶性进展。CD276 与胃癌患者的临床病理相关且能增加 PD-L1 抑制剂的疗效。因此 CD276 有望成为胃癌潜在的治疗靶点。

关键字： CD276，免疫，糖基化

47. Mutational profiling of mitochondrial DNA reveals an epithelial ovarian cancer-specific evolutionary pattern contributing to high oxidative metabolism

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Background: Epithelial ovarian cancer (EOC) heavily relies on oxidative phosphorylation (OXPHOS) and exhibits distinct mitochondrial metabolic reprogramming. Up to now, the evolutionary pattern of somatic mitochondrial DNA (mtDNA) mutations in EOC tissues and their potential roles in metabolic remodelling have not been systematically elucidated.

Methods: Based on a large somatic mtDNA mutation dataset from private and public EOC cohorts (239 and 118 patients, respectively), we most comprehensively characterised the EOC-specific evolutionary pattern of mtDNA mutations and investigated its biological implication.

Results: Mutational profiling revealed that the mitochondrial genome of EOC tissues was highly unstable compared with non-cancerous ovary tissues. Furthermore, our data indicated the delayed

heteroplasmy accumulation of mtDNA control region (mtCTR) mutations and near-complete absence of mtCTR non-hypervariable segment (non-HVS) mutations in EOC tissues, which is consistent with stringent negative selection against mtCTR mutation. Additionally, we observed a bidirectional and region-specific evolutionary pattern of mtDNA coding region mutations, manifested as significant negative selection against mutations in complex V (ATP6/ATP8) and tRNA loop regions, and potential positive selection on mutations in complex III (MT-CYB). Meanwhile, EOC tissues showed higher mitochondrial biogenesis compared with non-cancerous ovary tissues. Further analysis revealed the significant association between mtDNA mutations and both mitochondrial biogenesis and overall survival of EOC patients.

Conclusions: Our study presents a comprehensive delineation of EOC-specific evolutionary patterns of mtDNA mutations that aligned well with the specific mitochondrial metabolic remodelling, conferring novel insights into the functional roles of mtDNA mutations in EOC tumourigenesis and progression.

Key Words： epithelial ovarian cancer; evolutionary selection; metabolic remodelling; mitochondrial DNA; somatic mutations

48. REEP4 是一种与预测肾透明细胞癌的预后和免疫反应相关的潜在生物标志物

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目的：评估 REEP4 作为预测肾透明细胞癌预后和治疗效果的生物标志物的潜力。

方法：使用 TCGA 数据库分析 REEP4 在泛癌和肾透明细胞癌中的表达水平以及 REEP4 表达水平与肾透明细胞癌临床病理特征的关系；使用 K-M 生存曲线、ROC 曲线和 COX 回归分析评估 REEP4 与肾透明细胞癌的预后价值的关系；使用 R 语言对 REEP4 的基因功能进行评估；分别采用 TIMER 在线网站和 TICA 数据库对 REEP4 在肾透明细胞癌中的免疫特点和 REEP4 对肾透明细胞癌免疫治疗的影响进行评估；单细胞 RNA 测序分析了

REEP4 在免疫细胞中的表达情况；实时荧光定量 PCR 和 Western blotting 用于检测 REEP4 在肾透明细胞癌组织和细胞中的表达水平。

结果：通过 TCGA 数据库，我们观察到 REEP4 在肾透明细胞癌肿瘤组织中的表达相较于癌旁组织显着上调，且较高水平的 REEP4 与更高的临床分期相关，高表达 REEP4 的肾透明细胞癌患者的预后更差。进一步的 COX 回归分析以及单因素和多因素生存分析证实，高表达 REEP4 导致肾透明细胞癌患者的存活率较低。基因功能分析还确定了 REEP4 与细胞周期、蛋白质结合等关键途径之间的关联。此外，免疫反应的实验表明，良好的免疫治疗反应与 REEP4 低表达有关。最后，我们进行了体外实验来证实了 REEP4 在肾透明细胞癌组织和细胞中的高表达。

结论：我们的研究揭示了 REEP4 表达与肾透明细胞癌之间的密切相关性，强调了其与肾透明细胞癌预后和免疫反应的相关性。这些发现表明 REEP4 有希望作为肾透明细胞癌的潜在生物标志物。

关键字： REEP4；肾透明细胞癌；生物标志物；预后

49. LY6E reveals the new prognostic biomarker of multiple myeloma-related bone disease signature

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Background： Osteolytic bone disease is a typical complication of multiple myeloma (MM), affecting in terms of survival and the patient’s quality of life. We identified lymphocyte antigen 6 complex (LY6E) involved in osteoclast differentiation and unfavorable prognosis in MM, which might shed light on novel treatments.

Methods： We screened the differentially expressed genes (DEGs) in the Gene Expression Omnibus (GEO) databases. Kaplan-Meier (K-M) curves, univariate and multivariate Cox analysis were applied to identify the prognostic implications of LY6E in MM. Using CCK-8 assay detected the effect of LY6E on cell proliferation in vitro. Bone lesions were designed using TRAP staining.

The hallmark of osteoclast differentiation genes was verified by qRT-PCR. Potential pathways of LY6E were analyzed by gene set enrichment analysis (GSEA).

Results： 27 upregulated and 36 downregulated DEGs were identified in GSE2658. 21 DEGs were significant after magnetic resonance imaging (MRI) defined focal lesions grouped based on the median counts in GSE24080. Then, 5 DEGs (including LY6E, BMPR1A, CSF2RB, CST6 and ADTRP) were shared between the two GSE datasets (GSE24080 and GSE6477). Survival analysis of the GEO databases revealed that LY6E suggests a poor prognosis of MM. Furthermore, elevated LY6E expression increased MM cell proliferation in vitro. In addition, LY6E promoted osteoclast differentiation by up-regulating the expression of TRAP, CTSK and NFATC1. It is suggested that LY6E is related to osteoclast formation. GSEA analysis showed that high expression of LY6E was mainly concentrated in the proteasome pathway.

Conclusion： Our study clarified LY6E accelerates MM bone disease (MBD) and osteoclast differentiation, which probably is the novel prognostic factor for MM.

Key Words： LY6E, multiple myeloma, bone disease, osteoclast

50. Cysteine metabolism related ferroptosis sensitivity in trastuzumab resistant HER2 positive breast cancer

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Background： Trastuzumab has shown great effectiveness in HER2 positive breast cancer treatment, but about 50% patients would undergo resistance during or after treatment. Although previous research has suggested several potential reasons for trastuzumab resistance, the metabolic reprogramming during resistance formation remains largely unclear. Here we identified aberrant ferroptosis associated cysteine metabolism in trastuzumab resistant HER2 positive breast cancer, which might become a novel target for overcoming resistance.

Methods： Trastuzumab sensitive HER2 positive breast cancer cell SKBR3 and resistant JITM1 were obtained for transcriptomics, proteomics, metabolomics and epigenomics analysis. Gene silencing was mediated by siRNAs. CUT&Tag was applied to compare H3K4me3 and H3K27me3 binding regions. DNA methylation levels and different methylated regions were evaluated by WGBS-seq. CRISPRi with dCas9-DNMT3A was applied to regulate specific DNA methylation in CpG islands. Lipid ROS was measured by flow cytometry with BODIPY-C11.

Results： Joint analyses of transcriptomics and proteomics according to ferroptosis pathways revealed downregulated glutathione metabolism, glutamate transmembrane and homocysteine metabolism processes, as well as upregulated fatty acid metabolism and iron metabolism pathways in JIMT1. Metabolomics verified that JIMT1 increased cysteine metabolism and decreased glutathione metabolism. SLC7A11 expression and GSH/GSSG ratio were increased in JIMT1, while no difference was observed in free cysteine. JIMT1 featured significant higher UGC codon usage bias and increased cysteinyl-tRNA synthetase. The abundance of H3K4me3 other than H3K27me3 in SLC7A11 promoter region was found increased in JIMT1, and the 5-mC level of CpG islands in SLC7A11 promoter region was shown decreased. Using dCas9-DNMT3A, the methylation of SLC7A11 promoter was enhanced and SLC7A11 expression was reduced in JIMT1. Inhibition of SLC7A11 by siRNAs, CRISPRi or Erastin all indicated a higher ferroptosis sensitivity in JIMT1.

Conclusion： Trastuzumab resistant HER2 positive breast cancer features aberrant cysteine metabolism resulting from altered H3K4me3 modification and DNA methylation in SLC7A11 promoter region. This might provide novel targets for further anti-HER2 treatment.

Key Words： breast cancer; trastuzumab resistance; metabolism; ferroptosis

51. Identification of Diagnostic Biomarkers for FOLFOX Resistance in Colorectal Cancer and Selection of Second-line Therapeutic Agents

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Background： Colorectal cancer is the third most malignant tumor in the world. 5-fluorouracil (5 - FU) - based chemotherapy is the first-line chemotherapy scheme for CRC, whereas acquired drug resistance poses a huge obstacle to curing CRC patients and the mechanism is still obscure. Therefore, identification of genes associated with 5- FU chemotherapy and seeking second-line treatment are necessary means to improve survival and prognosis of patients with colorectal cancer.

Methods： The bulk RNA sequencing data of FOLFOX-resistant and FOLFOX-sensitive CRC tissues were enrolled from the GEO datasets. GO and KEGG pathway analyses were performed using the DAVID database. The Therapeutic Response Portal (CTRP) database and the Cancer Drug Sensitivity Genomics (GDSC) database were used to identify CRC-related genes and potential second-line therapies for FOLFOX-resistant CRC. The single-cell RNA sequencing (scRNA-seq) data for CRC tissues were obtained from a GEO scRNA-seq dataset which was deposited in the Tumor Immune Single-cell Hub (TISCH) database. The relationship between ITGA2 and FOLFOX-resistant was investigated in vitro and in vivo models.

Results： Hundreds of differentially expressed genes (DEGs) were selected in FOLFOX-resistant CRC tissues compared to FOLFOX-sensitive CRC tissues, which were associated with the positive regulation of lipid metabolic processes and alkaline phosphatase activity and were primarily located on the cell membrane. Based on two publicly available databases (GDSC and CTRP), ACOX1 and ITGA2 were identified as risk biomarkers associated with FOLFOX resistance. The single-cell sequencing data showed that ITGA2 was mainly enriched in malignant cells. ITGA2, as a gene associated with DNA damage repair, was negatively correlated with IC50 values of most small molecule inhibitors, among which selumetinib had the highest negative correlation. Finally, in vivo and in vitro experiments confirmed that knocking down ITGA2 can

make CRC-5-FU-resistant cells sensitive to 5-FU and combining selumetinib can improve the therapeutic effect of 5-FU-resistant cells.

Conclusion：Our results confirmed that ITGA2, as an important driver of CRC FOLFOX-resistant, is closely related to the small molecule inhibitor selumetinib. Interfering ITGA2 in combination with selumetinib has the potential to be a promising adjunctive therapy to enhance the clinical efficacy of 5-FU in the treatment of colorectal cancer.

Key Words：Colorectal cancer (CRC); FOLFOX resistance; ITGA2; Selumetinib.

52. KLF13 通过抑制肺腺癌中的 GPX4 促进铁死亡和化疗敏感性

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目的：铁死亡是一种依赖于铁代谢紊乱和脂质过氧化的细胞死亡形式，已成为缓解肿瘤耐药性的一个有前景的研究方向。KLF13 是 Kruppel 样锌指转录因子家族的成员，已有研究报告了其在肿瘤自噬、脂质代谢和增殖中的调节作用。本研究的目的是揭示 KLF13 在肺腺癌（LUAD）铁死亡和化疗敏感性中的潜在分子机制。

方法：我们使用铁死亡诱导剂处理 LUAD 细胞，并进行 RNA 测序以筛选转录因子 KLF13。接下来，对肿瘤细胞进行 KLF13 的过表达和敲除处理，并使用细胞毒性实验、铁含量、ROS 检测和电子显微镜评估 KLF13 在铁死亡和化疗耐药性中的作用。然后，我们进行 RNA-seq、qPCR、WB、ChIP 和双荧光素酶报告基因测定，以研究 KLF13 对下游靶标 GPX4 的直接调节。然后，我们研究了 GPX4 的过表达和敲低对 KLF13 促进铁死亡和化疗敏感性的影响。最后，进行免疫组织化学（IHC）染色和异种移植物小鼠模型，以验证 KLF13 在体内的作用。

结果：我们发现当铁死亡发生时，KLF13 的表达水平会发生变化，这表明 KLF13 可能与铁死亡有关。抑制 KLF13 的过表达，沉默 KLF13 可促进 IKE 和 RSL3 诱导的癌症细胞铁死亡。同时，KLF13 的过表达提高了顺铂和培美曲塞的疗效。通过对下游靶基因的筛选，发现 KLF13 抑制了 GPX4 的表达。进一步验证表明，KLF13 直接与 GPX4 启动子区结合，

抑制其转录功能，从而抑制其脂质过氧化的还原功能。然而，GPX4 过表达和敲低可以逆转 KLF13 对铁死亡和化疗药物敏感性的影响。患者的 IHC 染色和小鼠的异种移植实验也验证了上述结果。

结论：我们的研究发现，KLF13 通过抑制 GPX4 来促进 LUAD 的铁死亡，从而提高对化疗药物的敏感性。总的来说，靶向 KLF13 可能有助于建立治疗 LUAD 的新策略。

关键字： KLF13；肺腺癌；铁死亡；化疗敏感性；GPX4

53. PREX2 mediates radiation resistance via inhibiting the cGAS-STING axis in colorectal cancer

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Background: Colorectal cancer (CRC) lacks established biomarkers or molecular targets for predicting or enhancing radiation response. Phosphatidylinositol-3,4,5-triphosphate-dependent Rac exchange factor 2(PREX2) exhibits intricate implications in tumorigenesis and progression. Nevertheless, the precise role and underlying mechanisms of PREX2 in CRC radioresistance remain unclear.

Methods: RNA-seq was employed to identify differentially expressed genes between radioresistant CRC cell lines and their parental counterparts. PREX2 expression was scrutinized using Western blotting, real-time PCR, and immunohistochemistry. The radioresistant role of PREX2 was assessed through in vitro colony formation assay, apoptosis assay, comet assay, and in vivo xenograft tumour models. The mechanism of PREX2 was elucidated using RNA-seq and Western blotting. Finally, a PREX2 small-molecule inhibitor, designated PREX-in1, was utilised to enhance the efficacy of ionizing radiation (IR) therapy in CRC mouse models.

Results: PREX2 emerged as the most significantly upregulated gene in radioresistant CRC cells. It augmented the radioresistant capacity of CRC cells and demonstrated potential as a marker for predicting radioresistance efficacy. Mechanistically, PREX2 facilitated DNA repair by upregulating DNA-PKcs, suppressing radiation-induced immunogenic cell death, and impeding

CD8+ T cell infiltration through the cGAS/STING/IFNs pathway. In vivo, the blockade of PREX2 heightened the efficacy of IR therapy.

Conclusion: PREX2 assumes a pivotal role in CRC radiation resistance by inhibiting the cGAS/STING/IFNs pathway, presenting itself as a potential radioresistant biomarker and therapeutic target for effectively overcoming radioresistance in CRC.

Key Words : Colorectal cancer; PREX2; Immunogenic cell death; Radioresistance; cGAS/STING/IFNs

54. HBx Integration in Diffuse Large B-cell Lymphoma Inhibits Caspase-3-PARP Related Apoptosis

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common pathological type of non-Hodgkin lymphoma, and is closely associated with hepatitis B virus (HBV) infection status and hepatitis B X (HBx) gene integration.

Methods: This project investigated the cellular biological effects and molecular mechanisms responsible for lymphomagenesis and the progression of HBx integration in DLBCL.

Results: The data showed that clinical DLBCL cells demonstrated HBx integration, and the sequencing analysis of integrated sites validated HBx integration in the constructed HBx-transfected cells. Compared with control cells, HBx-transfected cells had a significantly reduced proportion of apoptotic cells. Further studies found that this decreased apoptosis level was associated with a significant reduction of cleaved Caspase-3 and downstream poly ADP-ribose polymerase (PARP) proteins, revealing the molecular mechanisms of HBx-associated apoptosis in DLBCL. Animal experiments also demonstrated that the protein expression of cleaved Caspase-3 and PARP was prominently reduced in HBx-transfected cells from subcutaneous tumors in mice. Furthermore, the HBx-integrated cells in clinical tissues had significantly lower cleaved PARP levels than the HBx-negative samples.

Conclusion: HBx gene integration inhibits cell apoptosis through the Caspase-3-PARP pathway in DLBCL indicating a potential biomarker and therapeutic target in HBV related DLBCL.

Key Words ： Diffuse large B cell lymphoma; hepatitis B virus; HBx integration; apoptosis

55. Diagnosis and Monitoring of Breast Cancer with a Novel Circulating Tumour Cells enrichment Device and Ultrasonography

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Background and aims: More excellent detection system of circulating tumor cells (CTCs) is demand. Here we performed CTCs detection with a novel automatic device, CytoBot.

Materials and methods: Commercial cell lines of breast cancer were used to assess the performance by spiking assays. 137 breast cancer patients, 97 patients with benign breast diseases and 42 healthy volunteers were enrolled for clinical validation. 4 ml of peripheral blood was obtained and followed CTCs detection. The performance was assessed by receiver operator characteristic curve.

Results: The sensitivity and specificity of 89.8% and 98.6% respectively when the cut-off was 1.5. The significant differences of CTC level were found between malignant and non-malignant group ($P < 0.0001$), tumor progression ($P < 0.0001$) and tumour size ($P < 0.0001$). In follow-up, the 82.61% of patients exhibited reduction in CTCs count which correspond with medical observation that benefit from clinical treatment. Additionally, CD45+ positive CTC (/CK+) showed with anomalous pattern during treatment.

Conclusion: A qualified performance of this novel platform was validated in our study. CTCs and this platform both have practical implications in clinical breast cancer diagnosis and monitoring.

Key Words： Breast cancer, Circulating tumour cells, Tumour progression, Cancer diagnosis and monitoring

56. OTUB1 Recruits Tumor Infiltrating Lymphocytes and Is a Prognostic Marker in Digestive Cancers

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Aim: OTUB1 can regulate the process of ubiquitination as a de-ubiquitinating enzyme (DUB). Whereas the influence of OTUB1 on immunity, apoptosis, and autophagy and the prognosis of digestive cancers need further exploration.

Materials and methods: OTUB1 expression was analyzed with Oncomine and TIMER database. Kaplan-Meier plotter was used to calculate the association between OTUB1 and clinical prognosis. The regulation of OTUB1 on cancer immunocyte infiltration was determined by TIMER database. The interaction between OTUB1 and immune genes, gene expression profiling (GEP), key genes of apoptosis and autophagy were analyzed via GEPIA. Protein-protein interaction (PPI), gene expression profiling (GEP), and functional pathway enrichment were also performed with STRING and Pathway Common database respectively.

Results: High OTUB1 expression was found in CHOL, LIHC, READ, ESCA, and COAD, which was significantly associated with poorer OS of LIHC (HR = 2.07, 95% CI = 1.30-3.30, P = 0.002) with modifications by stage, grade and mutant burden. OTUB1 can promote the recruitment of B cells, CD8+ T cells, macrophages in ESCA, and B cells, neutrophils in LIHC.. The significant interaction between OTUB1 and USP8, RNF128, LRIG1, UBB, UBC, STAM2, RNF41, EGFR, RPS27A, and HGS was determined by PPI. The functional pathway enrichment further classified the regulatory role of OTUB1on immune, apoptosis, and autophagy through its interaction with TP53 and ATG.

Conclusions: OTUB1 performed as a molecular indicator of poor prognosis in digestive cancers, and modified the infiltration of tumor immunocytes and exerted a significant moderating effect on apoptosis and autophagy. OTUB1 is a potential antitumor target for digestive tumors.

Key Words： digestive cancers, OTUB1, bioinformatics, prognosis, immunotherapy

57. TMEM173 is a prognostic biomarker and recruit tumor infiltrating lymphocyte in head and neck squamous cell carcinomas

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Aim: TMEM173 gene is an innate immune regulatory gene. The protein encoded by TMEM173 is an occasional facilitator of innate immune signaling that acts as a sensor of cytosolic DNA and promotes the production of type I interferon. While it can exert an effect on oncotherapy and prognosis in several cancers, further bioinformatics analysis in head and neck cancer (HNSCC) has yet to be performed. We aimed to explore the expression and prognostic values of TMEM173 in HNSCC, and its relationship with HPV P16/ CDKN2A gene. The regulatory function of TMEM173 in immunity and other pathways was also investigated.

Materials and methods: The data used for analysis was mainly from TCGA dataset. The online analysis tools, including GEPIA, Reactome Pathway Database, and KM plotter database, UCSC Xena browser and cBioPortal for Cancer Genomics database, were used for the analysis of gene expression, tumor infiltrating lymphocyte and survival prognosis.

Results: We observed that TMEM173 expression was not significantly elevated in HNSCC tissues, but its expression was higher in HPV-positive HNSCC compared with HPV-negative HNSCC. The expression of TMEM173 could recruit tumor infiltrating lymphocyte. Furthermore, TMEM173 involved in multiple functional regulations and its expression was regulated by p16/CDKN2A gene, apoptosis- and autophagy-related genes. Higher expression of TMEM173 correlated with a favorable OS (HR=0.72, p=0.021) in HNSCC patients.

Conclusions: Above all, TMEM173 involved in recruiting tumor infiltrating lymphocytes in the tumor microenvironment and high expression of TMEM173 predicted favorable OS of HNSCC patients, recommending it as a promising therapeutic target.

Key Words： HNSCC, TMEM173, bioinformatics, prognosis

58. Enzyme Reaction-Assisted Programmable Transcriptional Switches for Bioactive Molecule Detection

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Bioactive molecules are highly worthwhile to recognize and explore the latent pathogenic mechanism. Conventional methods for bioactive molecule detection, including mass spectrometry and fluorescent probe imaging, are limited due to the complex processing and signal interference. Here, we designed enzyme-reaction-assisted programmable transcriptional switches for the detection of bioactive molecules. The approach is based on the use of programmable enzyme site-specific cleavage-assisted DNA triplex-based conformational switches that, upon responding to bioactive molecules, can trigger the transcription of fluorescent lightup aptamers. Thanks to the programmable nature of the sensing platform, the method can be adapted to different bioactive molecules, and we demonstrated the enzyme-small molecule catalytic reaction combination of myeloperoxidase (MPO)−hydrogen peroxide (H2O2) as a model that transcriptional switches was capable of detecting H2O2 and possessed the specificity and antiinterference ability in vitro. Furthermore, we successfully applied the switches into cells to observe the detection feasibility in vivo, and dynamically monitored changes of H2O2 in cellular oxidative stress levels. Therefore, we attempt to amalgamate the advantages of enzyme reaction with the pluripotency of programmable transcriptional switches, which can take both fields a step further, which may promote the research of biostimuli and the construction of DNA molecular devices.

Key Words： transcriptional switch, enzyme reaction, bioactive molecule detection, real-time monitoring

59. AHSA1 promotes cell survival, EMT, and EGFR-TKI resistance in EGFR-mutated lung adenocarcinoma through HSP90/TGFB1/IFI6 axis

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Purpose： AHSA1 is an activator Of HSP90 ATPase, which is a biomarker associated with oncogenesis in pan-cancer. The significance of AHSA1 in EGFR mutated lung adenocarcinoma (LUAD) remains uncertain. The purpose of the research is to uncover the function of AHSA1 in EGFR mutated lung adenocarcinoma.

Materials and Methods： In EGFR mutated LUAD tissues, the examination of AHSA1 and other gene expressions was carried out using tissue microarrays. Date from TCGA-LUAD were employed to explore AHSA1's expression, potential regulatory pathways, and prognostic significance. The protein expression of AHSA1 and other gene products was evaluated using Western blotting (WB) or flow cytometry. Stable overexpression or knock-down of AHSA1 was achieved through lentivirus. Following that, employing EdU, Annexin V/PI staining, Caspase 3/7 staining, TMRM staining, Fluo4-AM staining, and Transwell assay and Xenograft models, in vitro experiments and in vivo expreiments were performed to investigate greater insight regarding the cellular functions of AHSA1 in LUAD. Co-immunoprecipitation and WB experiments were employed to explore potential mechanisms through which AHSA1 may regulate LUAD progression.

Results： the knock-down of AHSA1 impaired cell proliferation, apoptotic evasion, epithelial to mesenchymal transition (EMT) capacity and EGFR-TKI resistance. AHSA1 activated HSP90 stabilizes TGFB1, which binds to the promoter of IFI6. IFI6 subsequently maintains the integrity of mitochondrial membranes through downregulating expression of BAX. Furthermore, elevated TGFB1 can also promote the EMT process through the classical TGFB1-SMAD3 pathway and enhance EGFR-TKI resistance.

Conclusion： Our research has unveiled that AHSA1 assumes a central and oncogenic role in EGFR-mutated LUAD through its influence on downstream HSP90/TGFB1/IFI6 axis. Targeting

AHSA1 alleviates the progression of EGFR-mutant lung adenocarcinoma and EGFR-TKI resistance, and brings potential clinical application value.

关键字 ： EGFR-TKI resistance, EMT, TGFB pathway, mitochondrial membranes stability

60. EGFR 突变肺腺癌小细胞转化模型构建及机制初探

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目的：接受 EGFR-TKIs 治疗的肺腺癌（Lung Adenocarcinoma, LUAD）对于环境压力的适应不同于正常细胞的渐进性特异表型状态，其采取了更多变的组织结构谱系可塑性。如靶向治疗后转化为小细胞肺癌以逃避药物压力。囿于肺癌神经内分泌转化前、后临床样本的匮乏，我们拟构建体外转化模型作为研究平台，模拟谱系转化各阶段，初步揭示肺癌小细胞转化的分子机制，为肺癌治疗提供新靶标。

材料与方法：采用体外给予药物压力和营养匮乏压力的方式模拟肺腺癌体内治疗真实微环境，通过长期体外诱导 EGFR 突变的细胞株，得到具有神经内分泌特性的肺腺癌细胞，结合动物荷瘤模型，并通过单细胞转录组测序、全外显子组测序等方法监测生长过程并进行多组学分析，探索转化过程依赖的表观调控。

结果：预实验确定诱导条件后，多组学动态监测奥希替尼联合血清饥饿（简称 TS）长期体外诱导的两株 EGFR 突变人源肺腺癌细胞 HCC827 (EGFR19DEL)、NCI-H1975 (EGFRL858R/T790M)（图 A）。对诱导 8 周的 HCC827 行单细胞测序发现 TS 分化方向具有较高神经内分泌转化特性（图 B），转录组特征沿着从 LUAD 到 SCLC 的轨迹发展（图 C），更趋同于 SCLC 的表达特征。建立的体内荷瘤免疫荧光示在长达 16 周后出现 SCLC 标记物和 LUAD 标记物均高强度表达的细胞（图 D）。神经内分泌谱系特征的稳定获得标志着 EGFR 突变肺腺癌小细胞转化模型的建立。TS 诱导过程中细胞活力先迅速下降至最低，进而以较低的活力维持，然后细胞活力逐渐增长（图 E）。第 4 周时细胞经历偏向滞育态的去分化、干性显著提高并获得基底细胞和基质细胞谱系分化潜能；但第 8 周时回归正常发育细胞表达谱，同时也丧失了额外获得的谱系可塑性（图 F-G）。全外显子测序分析联合分子动力学模拟发现体外神经内分泌转化过程不依赖 RB1 的变异，但诸多表观调控基因和临床样本中一

致地发生失功能突变（图 I），细胞转录频率增高（图 J），神经内分泌转录因子表达不受控（图 K），提示转化关键机制可能和表观调控失能相关。我们接下来构建了表观不稳定性评分和表观突变谱相似度，公共队列验证显示出了表观基因不稳定的变异和神经内分泌转化相关，并可作为预后指标（图 L-M）。

结论：成功构建 EGFR 突变肺腺癌小细胞转化的体外模型，机制上，表观调控失调导致神经内分泌相关转录因子表达不受控可能是转化关键。

关键字： EGFR 突变肺腺癌；谱系可塑性；神经内分泌转化；表观调控

61. 大分割放射治疗转移性实体瘤远隔效应影响因素及疗效分析

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目的 分析真实世界下大分割立体定向放射治疗（Stereotactic ody radiotherapy， SBRT）单独或联合免疫检查点抑制剂（Immune checkpoint， ICI），治疗转移性实体瘤患者远隔效应的发生率、影响因素以及远隔效应对于患者的生存意义。

方法 回顾性分析 2020 年 10 月至 2022 年 5 月在江苏省肿瘤医院行大分割治疗的转移性实体瘤患者。记录放疗前后一个月内最近一次的血液学检查结果，放疗结束后的第三个月复查一次 CT 或 MRI，后续每隔三个月对病人进行复查和随访。

结果 研究共纳入 37 名患者，包含 10 种类型实体瘤。患者接受照射剂量为 4-8Gy/f，放疗部位包括淋巴结、肺等 10 余种类型病灶。21.6%的患者治疗后出现远隔效应，其中的 4 名之前接受 ICI 治疗后发生病情进展。中位随访时间为 11 个月，所有患者 6 个月总生存率为 60.5%，中位生存时间为 20 个月，出现远隔效应的人群与其他患者相比生存曲线无统计学差异。单因素分析显示年龄、性别、原发肿瘤类型、放疗部位、之前系统治疗次数以及之前是否接受过 ICI 治疗并不影响远隔效应的发生。多因素分析显示放疗前中性粒细胞与淋巴细胞比值（Neutrophil to Lymphocyte ratio，NLR）、放疗后绝对淋巴细胞计数（Absolute lymphocyte count， ALC）影响远隔效应发生。

结论 未经挑选的转移性实体瘤患者远隔效应发生比较罕见，继续改进治疗策略是有必要的。年龄等基本生存资料并不影响患者的远隔效应发生，而一些血液学指标的联合检测具

有敏感、易获取特性，对远隔效应有潜在预测价值，有必要开展一些前瞻性临床试验来进一步证实。此外，远隔效应对患者生存获益并不确定，我们认为，在缺乏足够证据之前远隔效应不应该作为临床治疗的主要目标。最后，作为一项小样本回顾性研究，该结果存在的选择偏倚和混杂效应，但其对远隔效应的研究及继续开展的大型临床研究是提示意义的。

关键字：大分割放疗；放疗与免疫；远隔效应；生物标志物

62. Multiomics study on formation of ground-glass EGFR mutated lung adenocarcinoma induced by oxygen-rich state

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Purpose: This study aimed to investigate the association between early features of EGFR-mutated lung adenocarcinoma (LUAD) formation and the oxygen environment, along with molecular pathways. An integrated and multilevel approach was employed to further validate the role of oxygen enrichment in LUAD development.

Methods: Retrospective analysis was conducted on clinical data from 400 in-hospital patients with EGFR-mutated LUAD to compare the composition ratio of peripheral to central ground-glass nodules in the lung's coronal position. A supplementary set of 26 early-stage lung adenocarcinomas, including 13 EGFR-mutated samples, underwent single-cell sequencing. This aimed to uncover differences and potential associations at the single-cell level in early-stage LUAD with varying imaging features. Following tumorigenesis induced by the TetO-EGFR 19DEL mouse model, immunofluorescence staining and single-cell sequencing were conducted. Mice were exposed to oxygen chambers with varying concentrations (60%, 21%, and 10%) to simulate the LUAD genesis landscape under different oxygen concentrations. In vitro experiments investigated the regulation of early tumor mechanisms by oxygen levels. Retroviral vectors expressing EGFR 19DEL and EGFR L858R were used to transduce immortalized human-derived bronchial epithelial BEAS-2B cells.

Result: The analysis of clinical data revealed a higher proportion of ground-glass nodules in the periphery of the coronal lungs compared to the center, and CT values differed significantly

between groups. Human LUAD single-cell sequencing samples showed a consistent trend of hypoxic signaling in the transcriptome with the percentage of imaging solid components. Oxidative stress molecules, including HSPA1A, FOS, and JUN, were significantly up-regulated in the tumor cells of pure solid samples. Animal experiments demonstrated that TTF-1 expression was significantly higher in the 60% oxygen concentration-treated group. This was accompanied by a significant increase in activated B cells, as revealed by immunofluorescence staining and single-cell sequencing. In vitro experiments showed that hypoxia activated the RAF-MEK-ERK pathway, promoting AP-1 expression and enhancing the EMT characteristics of tumors. Conversely, the hyperoxic environment inhibited the pathway, alleviating the progression of EMT.

Conclusion: In summary, the development of lung adenocarcinoma is closely associated with the hypoxia status of tumors detected by CT imaging with solid changes. We found that the main mechanisms of early solid changes in EGFR-mutated lung adenocarcinoma involved the expression of AP-1 induced by the RAF-MEK-ERK pathway and the enhancement of EMT features. Hyperoxia treatment significantly inhibited this mechanism while promoting host innate immunity. Overall, this study offers a new perspective and experimental foundation for an in-depth analysis of the developmental process of EGFR-mutated lung adenocarcinoma. It also serves as a valuable reference for the precision of future clinical treatments.

Key Words ： EGFR; LUAD; hyperoxia; GGO

63. 基于 GEO/TCGA 数据库分析 m6A 相关基因 在乳腺癌中的表达

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目的：联合 GEO 和 TCGA 数据库，采用生物信息学方法筛选出在乳腺癌中表达具有差异的基因，筛选 m6A 相关基因并做生物信息学分析，为进一步发现 m6A 在乳腺癌中的作用提供思路，从而为探究乳腺癌新的治疗靶点和预后标志物提供理论依据。

方法：在 R 语言中利用 limma 包对 GSE7904、GSE10780、GSE10810、GSE29431、GSE42568、GSE61304 原始数据进行差异分析后，筛选出 m6A 相关基因的表达情况，统计

差异有统计学意义的基因（P<0.05），以差异较为显著的基因作为目的基因。目的基因的表达在 UALCAN 中分析目的基因在乳腺癌及乳腺正常组织的表达情况，并分析目的基因在乳腺癌临床分型中的表达。利用 Coexpedia 数据库估计了与目的基因功能相关的共表达基因，目的基因及其共表达基因在 DAVID 数据库中分析 KEGG 通路富集情况，最后在 STRING 数据库中构建目的基因的蛋白互作网络图。

结果：筛选出 m6A 相关基因的差异表达情况后发现 FTO 在乳腺癌组织较乳腺正常 组织 mRNA 表达均下降且差异较为明显。因此，FTO 确定为后续研究的目的基因。TCGA 数据库分析结果显示，FTO 在乳腺癌中的表达明显低于乳腺正常组织（P<0.001），在所有乳腺癌临床分型中较正常乳腺组织表达较低，进一步的分析中发现 TP53 突变的乳腺癌中 FTO 的表达较 TP53 未突变乳腺癌明显下调 （P<0.05）；浸润性导管乳腺癌、化生性乳腺癌、髓样特征乳腺癌及浸润性小叶癌 FTO 的表达较粘液癌均明显下调（P<0.05）；FTO 在白种人中的表达均高于非裔美国人和亚洲人（P<0.001）；乳腺癌分子分型中 HER-2+型乳腺癌及三阴乳腺癌 较 Luminal 型乳腺癌 FTO 表达下调（P<0.001）；乳腺癌患者中绝经前患者的 FTO 表达高于更年期患者（P<0.05）。Coexpedia 数据库中分析出有 158 个基因与 FTO 存在共表达关系，FTO 及其共表达基因主要富集在错配修复、 碳代谢、代谢途径、磷酸戊糖途径、核苷酸切除修复通路上，最后 FTO 的蛋白质互作网络图在 STRING 数据库中构建。

结论：本研究分析发现，FTO 基因在乳腺癌组织中 mRNA 表达水平显著低于正常乳腺组织，其低表达可能影响乳腺癌的发生发展。

关键字： N6-甲基腺嘌呤；共表达基因；KEGG 通路；蛋白质互作网络图

64. 第二代选择性 JAK2 抑制剂 Fedratinib 对食管癌细胞增殖、转移及凋亡的作用及其相关机制

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目的：食管癌（esophageal cancer，EC）是全球最常见的恶性肿瘤之一， 目前我国食管癌 5 年生存率仍不足 30%。由于食管癌容易产生耐药性，因此寻找新的抗食管癌药物，对于改善食管癌患者的生活质量及延长生存时间有着十分重要的意义。本实验通过研究第二代选择性 JAK2 抑制剂 Fedratinib 对人食管癌细胞株 Eca109 和 KYSE150 的增殖及转移抑制

作用和对细胞周期及凋亡的影响，以及 Vimentin、Cyclin D1、Survivin 蛋白表达的影响，进一步探讨 Fedratinib 对食管癌细胞的作用及其相关机制，从而为食管癌治疗提供潜在的抗癌药物及相应的理论依据。

材料与方法： 1 细胞培养后，应用普通光学显微镜观察 Fedratinib 作用于食管癌细胞 Eca109 和 KYSE150 后细胞的形态学变化。 2 不同浓度的 Fedratinib 作用于食管癌细胞 Eca109 和 KYSE150 后，应用 Cell Counting Kit-8（CCK-8）法测定细胞光密度值(opticaldensity，OD)，计算生长抑制率，研究 Fedratinib 对食管癌细胞增殖的影响。 3 应用流式细胞仪技术(flow cytometry，FCM)研究 Fedratinib 对食管癌细胞 Eca109 和 KYSE150 凋亡率的影响。4 应用流式细胞技术检测 Fedratinib 对食管癌细胞 Eca109 和 KYSE150 细胞周期分布影响。5 蛋白免疫印迹法(Western blot)检测药物作用后食管癌细胞 JAK2/Stat3 信号通路相关蛋白 JAK2、p-JAK2、stat3、P-Stat3 及 Vimentin、Cyclin D1、Survivin 蛋白表达变化。 6 RT-PCR 检测 Vimentin mRNA、Cyclin D1 mRNA、Survivin mRNA 的变化。7 利用瞬时质粒转染方法构建过表达 STAT3 的食管癌细胞株模型,并通过 qRT-PCR 和 Western blot 验证。8 利用 CCK-8、平板克隆实验及 Transwell 检测过表达 STAT3 后对 Fedratinib 诱导的食管癌细胞增殖、迁移能力及凋亡的影响。9. 利用 Western blot 及 RT-PCR 技术检测过表达 STAT3 后 Fedratinib 对 JAK2/STAT3 信号通路相关蛋白表达的影响及其下游靶基因的 mRNA 水平变化。

结果：1. Fedratinib 呈时间和剂量依赖性抑制食管癌细胞的增殖和迁移能力。 2. Fedratinib 能够将食管癌细胞阻滞在 G2/M 期，同时促进癌细胞凋亡。3. Fedratinib 处理食管癌细胞后 p-JAK2、p-Stat3、Vimentin、Cyclin D1、Survivin 蛋白表达水平随药物浓度增加而下降 (P<0．05),并且较对照组相比有显著性差异(P<0．01)。4. 过表达 STAT3 可部分逆转 Fedratinib 对食管癌细胞增殖和迁移能力的抑制。

结论：Fedratinib 靶向 JAK2/STAT3 信号通路调控食管癌细胞内信号传导机制,最终通过下调 Vimentin 、Cyclin D1 及 Survivin 的表达影响食管癌细胞的增殖、转移并诱导癌细胞凋亡。

关键字： JAK2 抑制剂、JAK2/STAT3 信号通路、食管癌

65. Serum tumor biomarker panel as a first line for multi-cancer screening: a large-scale population-based cohort study

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Aim: Several serum tumor biomarkers have been proven to be useful in specific cancer screening with hospital-based study design (e.g. PSA for prostate cancer, AFP for liver cancer). However, the screening ability of tumor biomarkers on multi-cancer in natural population remains largely unknown. We aimed to evaluate the screening value of single tumor biomarker on common malignant cancer, as well as identify the combined panel and construct tumor biomarker score with optimal cut-off value for each cancer type to guide clinical practice.

Material and Method: 12 Serum tumor biomarkers (CA199, CA125, CA724, CEA, AFP, Cyfra21-1, PG I, PG Ⅱ, Pro-GRP, NSE, PSA (Male), F-PSA (Male), CA153 (Female), β-HCG (Female)) were measured in 519,469 participants in the Taihu Biobank of Tumor Biomarker (TBTB) study at baseline using chemiluminescence protein microarray chip. We defined diagnosed cancer as malignant cancers were diagnosed within 1 year after baseline measurement. Area under the curve (AUC), sensitivity and specificity were used to evaluate the screening ability of tumor biomarkers on common cancer types. The screening ability was also evaluated stratified by clinical stage, time interval between baseline and diagnosis, and cancer pathological or anatomical subtype. 4 strategies were used to select combined panel for each cancer type. Tumor biomarker score was generated for the combined panel to seek optimal cut-off value in clinical practice.

Results: 5553 cancer cases were diagnosed within 1 year after baseline measurement, of which, cancers of lung, gastric, colorectal, prostate, breast, esophageal, liver, pancreas, bladder and renal ranked top ten. Moderate or excellent screening (AUC>0.7) abilities were observed several single tumor biomarkers on common malignant cancer (e.g. CEA-colorectal cancer, PSA-prostate cancer, AFP-liver cancer, CA199- pancreatic cancer). Upward and downward trends of AUC were

observed with the increasement of clinical stage and time interval of baseline measurement preceding time of cancer diagnosis. Tumor biomarker combined panel consisted with only one to three tumor biomarkers could be effectively used in each common cancer screening. The screening ability was similar for tumor biomarker score with combined panel. The optimal cut-off values were also ascertained for tumor biomarker score of each cancer.

Conclusion: Traditional serum tumor biomarkers could be used in common malignant cancer screening. Selected tumor biomarker panel and optimal tumor biomarker score should be used in clinical practice to guide cancer screening.

Key Words ： Tumor marker; Malignant cancer; Screening; Cohort

66. LncRNA MAFG-AS1 promotes proliferation and immune escape of breast cancer by interaction with EZH2

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Aim: Understanding the complicated mechanisms of lncRNAs in breast cancer (BC), one of the deadliest cancers worldwide, contributes to provide potential targets for BC to assist in diagnosis and treatment.

Methods : The expression of lncMAFG-AS1 in BC cell lines were detected by qRT-PCR and immunofluorescence. Fluorescence in situ hybridization (FISH) and Nucleocytoplasmic separation assay were utilized to probe the location of lncRNA in BC cells. Bioinformatics analysis for lncRNA expression in TCGA and GEO databases, correlation of the expression with cancer-related pathways and tumor immunity. Cell cycle and apoptosis-related genes as well as target genes of lncMAFG-AS1 expression were measured by western-blot. Clone formation, EdU, flow cytometry, and nude mouse tumorigenesis assays were used to probe the function of lncMAFG-AS1 in breast cancer cells in vivo and in vitro. RNA pulldown and Chromatin immunoprecipitation (ChIP) were conducted to identify the specific binding of lncMAFG-AS1-EZH2 complex and the H3k27me3 modification of CDKN2A. CD8+ T cells

sorting and co-culture with tumor cells were used to detect the resistance of tumor cells to the damage ability of CD8+ T cells.

Results: Analyzing the openly available microarray data, MAFG-AS1 was found overexpressed in BC tissues compared with normal mammary tissues. Additional, MAFG-AS1 was up-regulated in a panel of BC cells compared with a normal mammary cell. Consistently, immunofluorescence staining results by constructing MAFG-AS1 probes on tissue microarrays containing 42 pairs of BC tissues showed that MAFG-AS1 expression was significantly elevated in BC tissues compared to the paracancerous ones. We found that proliferation ability of BC cells was suppressed when MAFG-AS1 was knocked down. EdU and clone formation assay demonstrated that loss of MAFG-AS1 could reduce the growth of BC cells, whereas overexpressed MAFG-AS1 showed higher cell proliferation ability in BC. Next, we observed Xenografts on the side of up-regulated MAFG-AS1 showed increased volume compared with that in the control side. These results suggested that MAFG-AS1 could promote breast cell growth both in vivo and vitro. Subsequently, GSEA analysis of the sequencing data showed that cycle-related gene sets were significantly enriched in response to MAFG-upregulated. Then, results of flow cytometry approved MAFG-AS1 knockdown suppressed the transition from G1 to S phase, whereas up-regulated MAFG-AS1 promoted cell cycle activity. Consistent with the data above, western bolt showed cell cycle related protein expression were reduced by si-MAFG-AS1.

We next investigated the mechanisms underlying the effect of a MAFG-AS1 on BC development. FISH and nuclear fractionation assay showed MAFG-AS1 located in both cell nucleus and cytoplasm. The significant association of MAFG-AS1 with the cell cycle inspired us to explore the mechanism of its regulation of the cell cycle. After analysis of differentially expressed genes of transcriptome sequencing, we focused on CDKN2A, a key cell cycle regulator, whose expression was significantly decreased after MAFG-AS1 knockdown. Moreover, we observed the expression of CDKN2A was negatively correlated with MAFG-AS1 both at mRNA and protein level. CCk8 assay shown that si-CDKN2A abolished the inhibitory proliferation effects of MAFG-AS1 knockdown, which further verified by the EDU assay. Recently studies revealed that nuclear located lncRNAs can play a role in recruiting PRC2 to prevent transcription of target genes by catalyzing the trimethylation of H3K27. GSEA analysis were performed to verify the correlation between MAFG-AS1 and PRC2. Further, RNA pull down assay was conducted and the

results of western blot showed MAFG-AS1-1 probe combined with EZH2 protein directly, indicating MAFG-AS1 was required for EZH2 effects. It is known that EZH2 plays pivotal functions in cell cycle via targeting tumor suppressor, and CDKN2A is thought to be one of the key targets. Accordingly, the results of ChIP-PCR shown that EZH2 and H3K27me3 were occupied at the CDKN2A promoter locus and the enrichment of EZH2 and H3K27me3 was reduced after MAFG-AS1 depletion. Then, we found loss-of-EZH2 inhibited the proliferation-promoting effects of MAFG-AS1 overexpression.

We analyzed the BRCA-TCGA data and divided the patients into low and high immunity groups, and observed high MAFG-AS1 expression was associated with low immune infiltration in BC patients ($p < 0.01$). EZH2 has been reported to play an important regulatory role in the immune microenvironment of cancer, which mediates CXCL9/10 to suppress its expression, thereby turning the cancer from “hot” to “cold”. Since we have found that MAFG-AS1 can be involved in its regulation by binding to EZH2, qRT-PCR was utilized to assess CXCL9/10 expression and showed that overexpression of MAFG-AS1 resulted in an expressively decrease in CXCL9 but no significant change in CXCL10 expression, indicating that MAFG-AS1 was involved in the EZH2-CXCL9 regulatory pathway. Subsequently, we co-cultured T47D cells with normal human CD8+T cells. The CXCL9/10 of the culture medium were detected by ELISA, and the results showed that overexpression of MAFG-AS1 lead to increased CXCL9 secretion with or without co-culture with CD8+T. Meanwhile, we performed crystalline violet staining and PI staining on the co-cultured cells, and it was seen that upregulated MAFG-AS1 resulted in increased resistance of damaged effect of CD8+T cells and a decreased proportion of apoptotic BC cells. Similarly, IF with constructing MAFG-AS1 and CD8 probes on BC tissue microarrays showed that MAFG-AS1 was significantly correlated with expression of CD8. Collectively lncMAFG-AS1 participated the EZH2-mediated CXCL9 level repression to inhibit immune infiltration.

Conclusions: Our data highlighted that aberrant lncMAFG-AS1 level affected tumorigenesis and correlates with immune infiltration of BC, suggesting that it might be a potential target for BC.

Key Words： Breast cancer, lncRNA, Immune, EZH2

67. TCF4N 通过减少中性粒细胞胞外诱捕网形成抑制结直肠癌转移

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目的：转移是结直肠癌（CRC）患者预后不良的主要原因。近年来研究报道中性粒细胞胞外诱捕网（NETs）具有促进癌症转移的能力，并与癌症不良预后密切相关。目前关于 TCF4N，是 β -catenin 相互作用转录因子 TCF7L2 的一种亚型，在肿瘤转移中的作用鲜有文献报道。因此，深入探究 TCF4N 与 NETs 形成在 CRC 转移中的作用及机制具有重要的理论和应用价值。

方法：通过临床数据分析，我们发现 TCF4 的新型剪切异构体 TCF4N 的高表达与 CRC 患者进展生存期有显著相关性。体内外功能实验显示 TCF4N 在 CRC 细胞转移中发挥抑癌功能。进一步临床数据分析及体内外功能实验表明 TCF4N 通过减少 NETs 形成从而抑制 CRC 转移。通过 RNA-seq、免疫沉淀和免疫荧光实验确定 TCF4N 竞争性抑制 TCF4 与 β -catenin 相结合，进一步通过细胞上清质谱分析，发现 TCF4N 通过抑制 β -catenin 通路激活从而下调胞外分泌蛋白 CD44 减少 NETs 形成抑制 CRC 转移。最后，基于 TCF4N 构建真核细胞穿透肽 4N 进一步验证其临床价值。

结果：研究结果表明， TCF4N 可作为潜在 CRC 的治疗靶点，进一步阐明 TCF4N 抑制 CRC 转移的作用机制，在此基础上证明基于 TCF4N 构建的多肽 4N 可以通过减少 NETs 形成抑制 CRC 的转移，为靶向 CRC 转移的治疗提供了新策略。

讨论：本研究明确了 TCF4N 通过抑制 NETs 形成从而抑制 CRC 转移。机制研究显示 TCF4N 竞争性抑制 TCF4 与 β -catenin 相结合，引起下游靶基因 CD44 的下调，使其分泌至胞外的蛋白量减少，从而减少 NETs 形成抑制 CRC 转移。而胞外分泌蛋白 CD44 如何影响中性粒细胞形成 NETs，是直接进入中性粒细胞核内发挥作用，还是作为配体与中性粒细胞膜受体结合进而调控 NETs 形成，这些都需要我们进一步探究。因此，本项目将在现有的研究基础上进一步解析 TCF4N 通过减少 NETs 形成抑制 CRC 转移的分子机制，研究结果有望为阐明 CRC 肿瘤转移机制提供新的理论依据，并为 CRC 治疗提供新的思路和干预靶点。

关键字： 结直肠癌；中性粒细胞胞外诱捕网；TCF4N；肿瘤转移

68. 不同标本类型检测 NSE 影响探讨

何平

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目的 探讨与血浆标本肿瘤标志物指标检测差异。

方法 以 100 例健康体检者的血清和肝素钠抗凝血浆，用罗氏 602 全自动电化学发光分析仪对癌胚抗原（CEA)、甲胎蛋白（AFP)、糖链抗原 199（CA199)、糖链抗原 125（CA125)、糖链抗原 153（CA153）、糖链抗原 724（CA724）、神经元特异烯醇化酶（NSE）、细胞角蛋白 19 片段（CYFRA211）、人副睾蛋白（HE4）、总前列腺特异抗原（PSA）和游离前列腺特异抗原（FPSA）指标进行检测，并对检测结果进行比较分析。

结果 血清与肝素抗凝血浆 CEA、AFP、CA199、CA125、CA153、CA724、CYFRA211、HE4、PSA、FPSA 检测结果差异无统计学意义（P>0.05)，NSE 结果差异有统计学意义（P<0.01）。

结论 肿瘤标志物检测除 NSE 外其他指标血清与肝素抗凝血浆标本均可使用，进行 NSE 检测时建议采用血清标本、不可用肝素抗凝血浆。脂浊标本 NSE 明显偏高，其原因有待探讨。

关键字：比较分析；血清；肝素抗凝血浆；NSE

69. STM2457 inhibits proliferation and enhances sensitivity to paclitaxel in esophageal squamous cell carcinoma

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Background: According to the 2023 Cancer Annual Report, Esophageal cancer (EC) is one of the most common malignant tumors in China, including esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinomas (EAC). Its incidence rate is the seventh, and its mortality rate is the sixth in the world. The early symptoms of esophageal cancer are not obvious, the degree of malignancy is high, and it is easy to recur. At present, the treatment of ESCC is mainly divided into surgical resection and drug treatment, but its curative effect is still

unsatisfactory. This is mainly due to the complex pathogenesis of ESCC and the resistance to drug treatment. Therefore, it is very important to find new safe and effective anti-ESCC drugs.

Methyltransferase-like factor 3 (METTL3) can catalyze methylation of adenine nitrogen atom 6 on RNA and is the main component of methyltransferase complex. Recently, it has been reported that METTL3 acts as an oncogene in esophageal cancer. Therefore, finding drugs targeting METTL3 may be an important strategy to treat ESCC. STM2457 was first identified as a METTL3 inhibitor with in vivo activity in 2021, which can significantly inhibit the progression of acute myeloid leukemia. STM2457 can directly bind to SAM active site of METTL3 protein, thus inhibiting methyltransferase activity of METTL3. At present, the role and molecular mechanism of STM2457 in esophageal squamous cell carcinoma have not been reported.

Objective: The purpose of this study is to explore the role of STM2457 in ESCC and its influence on the biological behavior of ESCC cells, explore the potential molecular mechanism of STM2457 in treating esophageal squamous cell carcinoma, and provide a new theoretical basis for STM2457 as an anti-esophageal cancer drug, so as to provide laboratory basis for clinical treatment of ESCC.

Methods: The effects of STM2457 to Eca109 and KYSE150 cells were detected by CCK8, flow cytometry, drug affinity responsive target stability and cellular thermal shift assay, xenograft model, IHC, western blot and PCR. Transcriptome sequencing, comet assay, western blot and siRNA was used to verify the intracellular DNA damage response after STM2457 treatment.

Results: The inhibitory effect of STM2457 with different concentrations on esophageal cancer was observed. The results showed that 40 μM and 80 μM had obvious inhibitory effects. STM2457 did not affect METTL3 mRNA and protein levels in Eca109 and KYSE150 cells. After treatment of Eca109 and KYSE150 with different concentrations of STM2457, starting with the drug concentration of 40 μM, the content of m6A gradually decreased with increasing concentration.STM2457 can enhance the stability of METTL3 protein. Compared with DMSO group, the proliferation and migration ability of Eca109 and KYSE150 cells treated with STM2457 were significantly decreased in a dose-dependent manner. Compared with DMSO group, STM2457 could induce the ROS production, lead to cell cycle arrest at G0/G1 phase and induce apoptosis in Eca109 and KYSE150.

GO and KEGG pathway enrichment analysis of STM2457 treated samples showed that there were 2882 genes with difference multiple greater than 1, 2084 genes were significantly up-regulated and 798 were down-regulated. ATM is one of the up-regulated genes. Further analysis of the results showed that STM2457-treated genes were involved in gene replication.

Compared with DMSO group, DNA damage in Eca109 and KYSE150 cells was aggravated after STM2457 (40 μM and 80 μM). ATM, p-ATM, p-Chk2 and γ-H2AX protein expression was increased. When Eca109 and KYSE150 cells were treated with STM2457 combined with CGK-733 (ATM inhibitor) or siATM, the levels of p-ATM, p-Chk2 and γ-H2AX in STM2457 combined with CGK-733 or siATM groups were significantly lower than those in STM2457 alone. STM2457 significantly inhibited the growth of tumor tissues in ESCC xenograft model, and down-regulated the expression of Ki67. While the expression levels of ATM, p-Chk2 and γ-H2AX related to DNA damage response pathway were significantly increased. STM2457 had no significant effect on peripheral blood indexes such as leukocyte number, erythrocyte number, hemoglobin content and platelet number in mice. In addition, STM2457 had no significant effect on the histomorphology of heart, liver, spleen, lung and kidney.

Compared with STM2457 group and paclitaxel group, the results of STM2457 combined with paclitaxel showed that STM2457 and paclitaxel significantly inhibited the ability of proliferation and migration in Eca109 and KYSE150 cells. The results of Western Blot showed that the combination of paclitaxel and STM2457 aggravated DDR more significantly than that of paclitaxel alone or STM2457 alone. STM2457 combined with paclitaxel can significantly inhibit the growth of tumor tissues in ESCC xenograft model, and the combination of the two drugs has no significant effect on the histomorphology of important organs.

Conclusion: STM2457 can bind to METTL3 protein and significantly inhibit the proliferation and metastasis of ESCC. STM2457 triggers DDR through ATM-Chk2 axis in ESCC, which leads to cell cycle arrest and induces apoptosis, and inhibits the proliferation of ESCC cells in vivo without obvious toxic. STM2457 can improve the chemosensitivity of paclitaxel to esophageal squamous cell carcinoma and provide a new treatment strategy for patients with esophageal cancer who are clinically paclitaxel resistant.

Key Words： STM2457; METTL3; Esophageal squamous cell carcinoma; ATM-Chk2 signal pathway; Paclitaxel

70. E2F-Score：一种肺腺癌临床及生物学意义的评估指标

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[摘要] 背景：肺癌是癌症致死率居于首位的恶性肿瘤，而肺腺癌是肺癌的主要病理亚型，严重危害人类健康状况。有研究表明 E2F 信号网络在肿瘤发生发展中意义重大，有望作为肿瘤分层及治疗的靶标，因此本文分析了 E2F 信号网络基因在肺腺癌中的临床及生物学意义，并建立了肺腺癌临床评估的新指标：E2F-Score。

方法：MSigDB 数据库提供了 E2F 信号网络基因。在 TCGA-LUAD 数据库中，我们收集了 515 例肺腺癌和 59 例正常组织的完整基因表达特征矩阵和详细临床分期及随访信息，通过 Logistic 回归、Cox 回归分析了 E2F 信号网络基因在肺腺癌中的表达特征及预后意义。通过层次聚类评估 E2F 信号网络基因对肺腺癌的分类效果。使用单样本基因集富集分析（single-sample gene set enrichment analysis，ssGSEA）方法建立了 TCGA-LUAD 数据集中 E2F 信号网络基因的整体表达评分（E2F-Score）。通过 Kaplan-Meier 曲线、Log-rank 检验、单多因素 Cox 分析探索 E2F-Score 和肺腺癌预后的关系。通过 Kruskal-Wallis 检验分析 E2F-Score 和肺腺癌临床分期的关系。通过基因集富集分析（the gene set enrichment analysis, GSEA）分析探索 E2F-Score 在肺腺癌中的生物富集特点。使用 maftools 包、ssGSEA 探索 E2F-Score 和肺腺癌基因突变及免疫浸润的关系。三个独立数据集（GE68465/GSE72094/GSE31210）作为 E2F-Score 在肺腺癌中临床意义和生物学意义的验证数据集。

结果：E2F 信号网络基因在肺腺癌中具有明显的差异表达和预后提示意义，大部分基因呈现对总生存期（overall survival，OS）和无进展生存期（progression free survival，PFS）的预测能力。E2F-Score 和肺腺癌临床特征和生物学行为密切相关，高得分的 E2F-Score 是预后的独立危险因素，预示着较差分期，以及更剧烈的基因突变紊乱和免疫浸润。

结论：肺腺癌中，E2F 信号网络基因具有显著的临床意义和生物学意义，E2F-Score 可作为肺腺癌的潜在临床评估指标。

关键字： E2F；肺腺癌；预后

71. 肺腺癌中 m6A/m5C/m1A/m7G 相关基因风险模型的构建及其预后的综合分析

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研究目的：肺癌的发病率和死亡率在世界范围内居高不下，而肺腺癌是最常见的肺癌病理类型。RNA 甲基化修饰是在特定修饰酶的调控下，对底物 RNA 进行的动态、可逆的化学修饰，在多种疾病及肿瘤的许多生物学过程中发挥着重要的调节作用。然而，m6A/m5C/m1A/m7G 相关基因在肺腺癌中的具体作用和机制尚不明确。因此，本研究将基于生物信息学方法分析 m6A/m5C/m1A/m7G 相关基因在肺腺癌中的功能和作用，研究这些基因在肺腺癌中的表达及其临床预后价值，并全面探讨这些基因与肿瘤发生和预后之间的关系。

材料与方法：我们从癌症基因组图谱(TCGA)数据库中获得了总共 535 例具有临床随访数据的 LUAD 患者的 RNA 测序数据。接着在肺腺癌中鉴定不同表达的 m6A/m5C/m1A/m7G 相关基因（DERGs）。通过单变量 COX 回归分析鉴定具有潜在预后价值的基因，并利用 LASSO-COX 回归分析筛选预后特征基因并建立风险模型。运用生存曲线以及 ROC 曲线等方法验证模型敏感性和特异性。根据中位风险评分，将肺腺癌患者样本分为两组。运用 ssGSEA 等生信工具分析高低分风险组免疫浸润情况、免疫微环境情况以及预测免疫治疗疗效。利用 qRT-PCR 验证临床样本中肺腺癌样本与配对正常肺组织中模型基因的表达情况。

结果：对与 m6A/m5C/m1A/m7G 相关的 71 个调控基因进行了单变量 Cox 回归分析，得到了 19 个潜在的预后基因（$P<0.05$），它们之间存在显著的正相关关系。通过整合生信分析我们构建出包含 3 个基因的预后预测模型（HNRNPC, IGF2BP1, IGF2BP3）。进一步的验证证明该模型对于预测肺腺癌预后具有良好的敏感性和特异性。我们发现高风险患者中 γ δ T 细胞和活化的 CD4 T 细胞更多。而肥大细胞休眠和 NK 细胞激活的表达水平与风险评分呈负相关。结果显示，在高风险患者中，CD274 和 CD276 等八个免疫检查点显著高表达；而在低风险患者中，BTLA 和 IDO2 等八个免疫检查点显著高表达。后续的验证试验发现模型基因在 LUAD 癌组织中显著上调。

结论：本研究加深了我们对 LUAD 发病机制中 RNA 甲基化相关调节机制的认识。并且构建出相关的可以预测 LUAD 免疫治疗疗效和预后的预测模型。m6A/m5C/m1A/m7G 相关的基因在 LUDA 的发生和发展中发挥了重要的作用，有望成为潜在的治疗靶点。

关键字： 肺腺癌、甲基化、免疫治疗、预后

72. Transcription factor DDIT3 is a potential driver in pancreatic cancer

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Objectives: Pancreatic ductal adenocarcinoma (PDAC) is associated with high mortality and poor survival rates, and it is the most malignant tumour of the digestive tract. The purpose of this study was to evaluate the expression of DNA damage-inducible transcript 3 (DDIT3) in pancreatic cancer and furthermore investigate its effects on the proliferation and invasive properties of pancreatic cancer cells.

Methods: Immunohistochemical assays conducted to evaluate the expression levels of DDIT3 protein in human pancreatic tissue. Real time PCR, western blotting and flow cytometry were conducted to evaluate the expression levels of DDIT3 gene or protein in human pancreatic cancer cells, respectively. Lentivirus-mediated shRNA interference was used to generated DDIT3 gene knock-down pancreatic cancer cell. Cell proliferation viability, migration and invasion were evaluated in colony formation and transwell chamber assays in DDIT3 gene knock-down pancreatic cancer cell.

Results: DDIT3 was positive or strong positive expression in high-grade pancreatic ductal adenocarcinoma, and no or weak expression in normal pancreatic tissue. It is also highly expressed in pancreatic cancer SW1990, PANC-1 and PATU8988T cells, whereas human pancreatic normal ductal epithelial (HPNE) cells do not express DDIT3. Lentivirus-mediated shRNA interference targeting DDIT3 gene reduces its proliferation, migration and invasion in PANC-1 cell line.

Conclusions: DDIT3 represents a novel a predictive biomarker for the potential treatment of patients presenting with pancreatic ductal adenocarcinoma.

Key Words： Pancreatic ductal adenocarcinoma, DNA damage-inducible transcript 3 (DDIT3), Bioinformatics, Proliferation, Invasion, In situ implantation tumor model

73. 激活转录因子 2 调节胰腺癌增殖和凋亡的实验研究

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目的：探讨胰腺癌组织中激活转录因子 2（ATF2）的表达情况，并通过体外实验评估 ATF2 对人胰腺癌细胞增殖的影响。

方法：收集 2021 年 5 月至 2023 年 5 月于江苏省肿瘤医院就诊的胰腺癌病理蜡块，通过免疫组化检测胰腺癌和对应癌旁组织中 ATF2 的表达情况。构建 shRNA/PATU8988T-ATF2 敲减稳转株，检测敲减后胰腺癌细胞增殖情况。

结果：ATF2 在胰腺癌中呈阳性或强阳性表达，而在正常胰腺导管组织中不表达或弱表达。ATF2 敲减后，胰腺癌细胞增殖能力较对照组减弱。

结论：ATF2 在胰腺癌组织中高表达，ATF2 敲减后，细胞增殖能力减弱。

关键字： 胰腺癌；激活转录因子 2；增殖；侵袭

74. Trends in research on circulating tumour cells in cancer from 2014 to 2024: bibliometric and visualized analysis

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Background: Circulating tumor cells (CTC) are malignant cells in the peripheral blood originating from primary tumors or metastatic sites, and their isolation holds promise for the diagnosis and analysis of cancer from blood samples. Circulating tumor cells are important biomarkers for several cancers and strong predictors of many cancer outcomes. It has significant potential value for the clinical management of cancer patients, monitoring treatment response and

selecting targeted therapies. This study analyzes the research on circulating tumor cells in cancer therapy by bibliometrics from 2014-2024 with the aim of assessing the general state of research in this field and identifying potential new research directions.

Methodes: Literature published between 1 January 2014 and 10 February 2024 was searched in the Web of Science Core Collection database. The search strategy was TS=(Neoplasms) AND TS=(Neoplastic Cells, Circulating), and the complete records of the original studies and cited references were extracted and screened by both authors. Bibliometric analysis and visualisation were performed using CiteSpace, Microsoft Excel 2019, VOSviewer and R software. A total of 5354 documents were included in the study.

Results: Literature includes a total of 5,354 articles published in 77 countries, with China, the United States and Germany ranking in the top three. USA, China and Germany are the three countries with the highest frequency of articles. National-Keywords-Agency Sankey reflects the data flow of the article focused on circulating tumor cells. Cancer-CTC research peaks in 2017 to 2020, with overall research showing a normal distribution trend between 2014 and 2024. Major research institutions include University of Texas System, University of California System, Harvard University and Chinese Academy of Sciences. The University of Texas System had the highest number of postings with 206. CLINIC CANCER RESEARCH is the most cited journal with 3195 times citations. A close second is CANCER RESEARCH, which has 2,585 citations. Detection of circulating tumor DNA in early-and-late-stage human malignancies is the most cited literature with 3134 times citations. The journals with the most publications between 2014 and 2024 are SCIENTIFIC REPORTS, ONCOTARGET and PLOS ONE. SCIENTIFIC REPORTS had the highest number of publications, with 1,179 during the period. CANCERS had the most publications with 731 in 2023. Among the authors included in these journals, the most published author and the most co-authored author is Pantel Klaus. Pantel Klaus has 109 articles and the articles of Pantel Klaus have been cited 841 times. In terms of the number of articles, Wang Yang and Riethdorf,Sabine respectively ranked second and third with 66 and 63 articles. Cristofanilli Massimo is the most cited author and the fourth co-authored author. Cristofanilli Massimo has 53 articles and the articles of Cristofanilli Massimo have been cited 1233 times. The study of circulating tumor cell (CTC) counting liquid biopsy and the clinical utility of CTC assessment in patients with cancer have been a topical trend in this field in recent

years. According to the keyword hotspot map, “circulating tumor cells”, “breast cancer”, “peripheral blood”, “cancer cell metastasis” and “liquid biopsy” are the main keywords of emerging research hotspots.

Conclusions: This is the first article to summarise the research trends and potential hotspots of circulating tumour cells in cancer, providing valuable directions for future research in this field and laying the foundation for future studies.

Key Words： Circulating tumor cells, Cancer, tumor, liquid biopsy, bibliometric analysis, visualized analysis

75. Mitochondrial Enzymes Mediate Cisplatin Resistance in Hypopharyngeal Squamous Cell Carcinoma Cells

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Cisplatin, a widely used chemotherapeutic drug, faces significant challenges due to drug resistance, which hinders its clinical effectiveness. However, the molecular mechanism underlying cisplatin resistance remains unclear. Previous studies have shown that tumor cells rely on glycolysis for energy and nutrients due to mitochondrial dysfunction. Yet, limited research has explored changes in energy metabolism after the development of drug resistance in tumor cells. In this study, we investigated the relationship between changes in key enzymes involved in aerobic respiration in

mitochondria and cisplatin resistance. Our findings revealed enhanced synthesis of citrate synthase (CS), succinate dehydrogenase (SD), and cytochrome oxidase (CCO) in drug-resistant cancer cells, with CCO showing the greatest increase. Notably, inhibiting CCO activity reversed drug resistance in cancer cells. These findings shed light on a new mechanism of cisplatin resistance related to energy metabolism and offer a promising approach to overcoming resistance and improving clinical anticancer effects.

Key Words： Cisplatin Resistance, Mitochondria, Cytochrome Oxidase, Energy Metabolism, Aerobic Respiration

76. 多灶微结节性肺泡上皮增生一例并文献复习

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目的：总结多灶微结节性肺泡上皮增生(multifocal micronodular pneumocyte hyperplasia，MMPH)的临床特点及病理特征，以提高临床医生对该病的诊疗水平。

方法：回顾性分析中山大学附属第五医院收治的1 例MMPH临床特点并进行文献复习。

结果：患者女，39岁，因“阵发性呼吸困难1月余”于2021年11月30日入院诊治。1月余前无明显原因出现呼吸困难，自述有喘憋感，持续10余秒后可自行缓解，不伴咳嗽、咳痰等不适。否认抽烟史、长期粉尘接触史、肿瘤家族史。胸部CT检查示：双肺弥漫结节，大部分为纯磨玻璃或混杂磨玻璃，少部分呈实性，最大7mm，病灶以双肺上叶较多，随机分布；胸椎及部分肋骨内可见广泛密度减低并斑点状硬化。于2021年12月7日行 “单孔胸腔镜下左侧胸腔探查+左上肺楔形切除+肺门纵隔淋巴结采样术”。 肉眼观：楔形切除肺组织一块，体积6*4.5*1cm，切面见淡褐色结节十余枚，直径0.2-0.7cm，切面实性、质软，与周围组织分界清。镜下观察：低倍镜肺组织内多枚结节随机分布，大部分结节内肺泡腔塌陷，少部分结节内肺泡腔扩张，病变与周边肺组织界限清楚；高倍镜见结节内II型肺泡上皮沿肺泡壁增生，大部分细胞呈立方、扁平和多边形，个别呈鞋钉样，细胞及细胞核均增大，胞浆丰富，核浆比未见明显异常，细胞异型性不明显，部分细胞可见小核仁，未见明确的病理性核分裂象；肺泡腔内见组织细胞灶状聚集，偶见多核巨细胞；肺泡间隔轻度均匀增宽，间质纤维组织增生，散在淋巴细胞、浆细胞等炎细胞浸润。免疫组织化学结果：增生的肺泡

上皮 TTF-1、CK7、NapsinA 均为阳性，p40 及 SMA 为阴性，Ki67 阳性指数约 1%，组织细胞 CD68 为阳性。弹力纤维染色显示肺泡间隔弹力纤维呈团块状增生。基因检测：病变组织行 NGS 检测出两个突变位点：TSC2 2714 点突变及 TSC2 4290 截断突变。最终病理诊断为 MMPH。患者术后 11 个月，病情稳定，呼吸困难症状好转，未行药物治疗。

结论：MMPH 是结节性硬化症的肺部病变之一，因临床症状不明显，常于偶然或体检中发现，影像学示多个小的磨玻璃样结节影，病理表现为多个 II 型肺泡上皮细胞沿肺泡壁增生灶。现有报道中几乎所有经过基因检测的病例均具 TSC1 和 TSC2 的基因突变，口服依维莫司是治疗 MMPH 的潜在候选药物。在临床工作中，对于年轻患者影像学表现为双肺多个混杂及磨玻璃结节，且数目超过 10-30 个者需排除 MMPH 的可能，以避免过度治疗。MMPH 较为罕见，容易误诊肺恶性肿瘤为或各种感染病，需结合临床、影像及病理结果最终明确诊断。

关键字： 多灶微结节性肺泡上皮增生；结节性硬化症

77. Spatial distribution and molecular characteristics of the tertiary lymphoid structures in esophageal squamous cell carcinoma

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Background： Mounting evidence underscores the pivotal role of the tumor microenvironment in the initiation, progression, and treatment resistance of esophageal squamous cell carcinoma (ESCC), often leading to unfavorable patient prognoses. Recent studies have indicated a correlation between the presence of tertiary lymphoid structures (TLS) and better patient outcomes. These outcomes include more favorable prognoses, improved responses to chemotherapy, and enhanced efficacy of immunotherapy. This correlation suggests that TLS may serve as biomarkers of a more robust immune response, potentially influencing treatment outcomes. But increasing evidence indicates that the contradictory role of TLS in some cancer. Meanwhile, a study on intrahepatic cholangiocarcinoma suggests that the spatial distribution of TLSs in tumors are

closely related to its ability to predict clinical outcome. Therefore, understanding the morphological characteristics and spatial location of TLS can provide further insights for ESCC.

Methods： Initially, we investigated the morphological characteristics and spatial distribution of TLS in 196 ESCC patients by Hematoxylin and Eosin (H&E) staining. The chi-square tests were employed to analyze the relationship between different spatial distributions of TLS and clinical pathological parameters. The TLS at different anatomic subregions (invasive margin (IM) and mucosal lamina propria (LP)) were quantified and correlated with survival by Kaplan-Meier analyses. Subsequently, we explored the characteristics of different spatial distributions of TLS in ESCC tissue by GeoMx digital spatial Profiler, as well as the Differential analysis and WGCNA analysis were performed. The results were further tested by immunofluorescence staining and imaging mass cytometry (IMC) analysis.

Results： We found that TLS were widely distributed in the LP and IM, furtherly, the chi-square tests showed a significant association between spatial distribution of TLS to pTNM staging. Kaplan-Meier survival analysis indicated that the distribution of TLS was associated with different prognosis, especially those located in IM subregion, which was contrary to the positive clinical significance. The GeoMx Digital Spatial Profiler combined Differential analysis and WGCNA analysis revealed that the characteristic gene expression and signal pathways and simultaneously, identified the main phenotype of infiltrating help T cells (nTreg, Th1 and Th17) of TLS in IM subregion compared to LP. IMC and IF confirmed that the abundant nTreg (CD4+FOXP3+) cells in TLS at invasive front related to unfavorable prognosis. Finally, a risk prediction mode based on the spatial distributions of TLS and the infiltrating help T cells immunophenotype was successfully constructed and showed higher accuracy in predicting survival or recurrence in ESCC patients compared with pTNM staging.

Conclusion： Herein, we sought to characterize the tissue distribution and significance of TLS in ESCC patient tissues. We identified a subpopulation of CD4+FOXP3+ nTreg cells infiltrating TLS at the invasive front that associated with ESCC progression and poor prognosis. In addition, we defined a novel prognostic model, with the characteristic of TLS, that shows superior predictive power than the current TNM staging system. This study may provide novel potential targets for optimal immunotherapy against ESCC.

Key Words： Esophageal squamous cell carcinoma；Tertiary Lymphoid Structures；nTreg cells；prognostic model

78. USP5 promotes ripretinib resistance in gastrointestinal stromal tumors by MDH2 deubiquition

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Ripretinib, a broad-spectrum inhibitor of the KIT and PDGFRA receptor tyrosine kinases, is designated as a fourth-line treatment for gastrointestinal stromal tumor (GIST). It is tailored for patients resistant to imatinib, sunitinib, and regorafenib. As its increasing use, instances of resistance to ripretinib are becoming more frequent. Unfortunately, there are currently no scientifically mature treatment options available for patients resistant to ripretinib. Posttranslational modifications (PTMs) such as ubiquitination, in conjunction with its interplay with other modifications, play a collective role in regulating tumor initiation and progression. However, the specific association between ubiquitination and ripretinib resistance has not been reported. Through proteome–ubiquitinome sequencing, we detected increased levels of the USP5 protein and decreased ubiquitination in ripretinib-resistant GISTs. Subsequent examination of the mass spectrometry findings validated the interaction through which TRIM21 governs USP5 expression via ubiquitination, and USP5 regulates MDH2 expression through deubiquitination, consequently fostering ripretinib resistance in GIST. Moreover, ZDHHC18 can palmitoylate MDH2, preventing its ubiquitination and further increasing its protein stability. Our research underscores the correlation between posttranslational modifications, specifically ubiquitination, and drug resistance, emphasizing the potential of targeting the USP5-MDH2 axis to counteract ripretinib resistance in GIST.

Key Words： Mesothelial and soft tissue tumors, Gastrointestinal stromal tumor, Ripretinib resistance, Ubiquitination

79. GPR56 的抗氧化作用促进胃癌失巢凋亡抵抗及腹膜转移

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目的：胃癌腹膜转移严重影响胃癌患者的预后。失巢凋亡是一种细胞离开细胞外基质，而后发生凋亡现象的死亡方式。肿瘤细胞具有的抗失巢凋亡特性，是其在血液、淋巴、腹腔中可以存活以及远处转移关键之处，失巢凋亡抵抗是肿瘤转移的先决条件。先前的研究表明，GPR56 在多种类型的肿瘤中起着抵抗失巢凋亡作用，然而，GPR56 在胃癌腹膜转移中的确切作用和机制仍有待阐明。本文研究了 GPR56 在胃癌腹膜转移中的生物学功能和分子机制，旨在为胃癌腹膜转移发展提供潜在的治疗靶点。

方法：RT-qPCR 和 WB 检测胃癌细胞以及胃癌组织标本中 GPR56 的 mRNA 和蛋白表达水平。IHC 检测胃癌标本中 GPR56 的表达情况。KMPLOT 数据库验证 GPR56 水平对胃癌患者预后的影响。对胃癌细胞及胃粘膜正常上皮细胞（GES-1）进行贴壁、悬浮及再贴壁培养。慢病毒构建 GPR56 敲降胃癌稳定细胞株（MKN45,AGS）。悬浮培养后，检测 GPR56 敲降组和对照组胃癌细胞 NADPH/NADP+和 GSH/GSSG 含量。流式细胞术检测线粒体及总 ROS 水平和 Annexin V/PI 染色后的细胞凋亡情况。软琼脂克隆形成实验检测胃癌细胞的非锚定生长能力。细胞粘附实验检测胃癌细胞的粘附能力。检测敲低 GPR56 后凋亡通路的变化。向 BALB/c 裸鼠腹腔中注射构建好的 GPR56 敲低胃癌稳定细胞系以探究 GPR56 表达水平对胃癌腹膜转移能力的影响。

结果：（1）GPR56 在胃癌患者腹膜转移组织中较原发灶高表达，且 GPR56 高表达的患者预后更差，在腹膜转移胃癌患者中,高表达 GPR56 的胃癌患者生存时间较短；（2）GPR56 在胃癌细胞中的蛋白相较 GES-1 而言水平升高，并且胃癌细胞 MKN-45 和 AGS 在模拟失巢状态下 GPR56 的表达水平增加，而在 GES-1 中无明显变化；（3）常规贴壁培养的胃癌细胞的凋亡率较 GES-1 细胞低但差异无统计学意义；在悬浮培养状态下，胃癌细胞的凋亡率显著小于 GES-1 细胞；（4）悬浮培养后，GPR56 敲低组 GC 细胞的 NADPH/NADP+和 GSH/GSSG 的含量均显著降低，且线粒体及细胞总的 ROS 水平升高；（5）MKN-45 及 AGS 细胞系在常规贴壁培养状态下敲低 GPR56 后细胞凋亡率变化不显著，而在悬浮培养状态下细胞凋亡率显著升高；（6）敲低 GPR56 后 MKN-45 和 AGS 细胞系的增殖和细胞粘附

能力显著减弱；（7）敲低 GPR56 表达后，凋亡通路相关蛋白表达水平升高；（8）在体内实验中，敲低 GPR56 组中腹膜转移灶的数目和大小均显著小于对照组。

结论：GPR56 可以调节胃癌中 NADPH 生成和氧化还原稳态，有助于细胞在脱离细胞外基质期间的存活，促进肿瘤的生长和转移。针对 GPR56 的特异性靶向药物有望成为抑制胃癌腹膜转移的潜在治疗策略。

关键字： 胃癌，腹膜转移，失巢凋亡，GPR56

80. Preoperative peripheral inflammatory markers are predictors of postoperative central diabetes insipidus in craniopharyngioma patients: a retrospective study

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Background： Postoperative central diabetes insipidus (CDI) is commonly observed in craniopharyngioma (CP) patients, and the inflammatory response plays a pivotal role in CPs. We aimed to evaluate the predictive value of preoperative peripheral inflammatory markers and their combinations regarding CDI occurrence in CPs.

Methods： The clinical data including preoperative peripheral inflammatory markers of 208 CP patients who underwent surgical treatment were retrospectively collected and analyzed. The preoperative peripheral white blood cells (WBC), neutrophils, lymphocytes, monocytes, platelet (PLT), neutrophil-to-lymphocyte ratio (NLR), derived-NLR (dNLR), monocyte-to-lymphocyte ratio (MLR) and PLT-to-lymphocyte ratio (PLR) were assessed in total 208 CP patients and different age and surgical approach CP patient subgroups. Their predictive values were evaluated by the receiver operator characteristic curve analysis.

Results： Preoperative peripheral WBC, neutrophils, NLR, dNLR, MLR, and PLR were positively correlated and lymphocyte was negatively associated with postoperative CDI

occurrence in CP patients, especially when WBC ≥ 6.66 × 109/L or lymphocyte ≤ 1.86 × 109/L. Meanwhile, multiple logistic regression analysis showed that WBC>6.39 × 109/L in the >18 yrs age patients, WBC>6.88 × 109/L or lymphocytes ≤ 1.85 × 109/L in the transcranial approach patients were closely associated with the elevated incidence of postoperative CDI. Furthermore, the area under the curve obtained from the receiver operator characteristic curve analysis showed that the best predictors of inflammatory markers were the NLR in total CP patients, the MLR in the ≤18 yrs age group and the transsphenoidal group, the NLR in the >18 yrs age group and the dNLR in the transcranial group. Notably, the combination index NLR+dNLR demonstrated the most valuable predictor in all groups.

Conclusions：Preoperative peripheral inflammatory markers, especially WBC, lymphocytes and NLR+dNLR, are promising predictors of postoperative CDI in CPs.

Key Words： Craniopharyngioma; Diabetes insipidus; Inflammatory marker; Lymphocyte; Neutrophil-to-lymphocyte ratio

81. Upar，一种有潜力的肿瘤标志物

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目的：尽管肿瘤治疗领域取得了巨大的进展，但肿瘤的复发和转移仍然是主要的治疗障碍之一。本文综述了一种与肿瘤相关的受体 Upar（尿激酶型纤溶酶原激活物受体）在肿瘤发展和治疗中的新发现、新技术和新成果，以期为进一步研究和治疗提供启示和指导。

方法：采用系统性文献回顾，涵盖近 5 年在 CNKI、Wanfang、PubMed 等发表的相关研究文献，结合实验和临床数据，全面展示 uPAR 在肿瘤中的作用和应用

结果：（1）研究表明，Upar 在多种肿瘤中过度表达，与肿瘤的侵袭性、转移性和预后密切相关。Upar 还参与调控肿瘤细胞的干细胞特性、肿瘤血管生成以及肿瘤免疫逃避等关键过程。（2）通过对 Upar 进行靶向治疗，可以抑制肿瘤细胞的增殖和转移过程。近年来，研究人员开发了多种基于 Upar 的靶向治疗方法，如抗体药物联合免疫疗法、基因治疗以及纳米技术等。（3）Upar 在肿瘤治疗中的研究取得了一些重要的突破。例如，某些抗体药物

对抑制 Upar 与其配体之间的相互作用具有高效性和选择性。此外，最新的研究表明 Upar 在肿瘤靶向治疗中的联合应用可以提高治疗效果。

结论：Upar 在肿瘤发展和治疗中具有重要的作用，并为开发新的治疗策略提供了潜在的靶点。未来的研究应该进一步探索 Upar 的生物学功能和新的治疗方法，随着对 Upar 的进一步研究，我们可以更好地理解其在肿瘤发展和治疗中的生物学功能。此外，针对 Upar 的靶向治疗策略的不断发展和优化将为肿瘤治疗领域带来新的机会和挑战。

关键字： Upar;肿瘤

82. 儿童白血病罕见遗传变异识别及临床表型组研究

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目的：急性淋巴细胞白血病（acute lymphoblastic leukemia, ALL）是儿科最常见的恶性肿瘤，遗传因素对其发病和预后都有一定影响。本研究拟基于全外显子组测序，识别和中国汉族儿童 ALL 发病有关的罕见遗传变异，同时结合临床表型组研究，探讨这些易感变异在疾病发展中的作用，为细化疾病分型和改善疾病预后提供线索。

方法：收集 89 名病例外周血样，按照 1:4 比例，使用倾向性评分匹配对照。测序数据清洗质控后，把次等位基因计数大于 1、并且次等位基因频率小于 5%的变异定义为罕见，次等位基因计数大于 20 的变异归为常见。第一阶段采用病例对照设计，常见变异使用 Logistic 回归，罕见变异使用以基因为中心的 STAAR-O 检验；第二阶段依然用 STAAR-O 方法检验病例临床表型和发病相关变异的关联。用 Firth Logistic 回归计算罕见变异的效应值。使用 Bonferroni 方法进行多重校正。

结果：单位点分析未发现和儿童 ALL 有关的常见编码变异。4 个罕见变异集合与儿童 ALL 发病有关，包括 NOL8 错义变异、MFAP3L 同义变异、CARD11 错义变异、OR7G2 错义变异。集合内有 6 个显著变异：NOL8 rs183819692、MFAP3L rs188150392、CARD11

rs199873591 和 rs202014429、OR7G2 rs62621389 和 rs144836316，均为风险变异。儿童 ALL 患者临床表型组分析显示， NOL8 错义变异与红细胞计数有关，OR7G2 错义变异与促甲状腺激素水平有关。OR7G2 可能会影响儿童 ALL 生存患者的甲状腺功能。以 P=0.05 为提示性相关阈值，NOL8 错义变异与平均红细胞体积、平均血红蛋白含量、红细胞分布宽度 CV、血小板分布宽度存在提示性相关；OR7G2 错义变异与血小板分布宽度、平均血小板体积、大血小板比率、凝血国际标准化比值、尿酸水平、游离甲状腺素水平存在提示性相关；MFAP3L 同义变异与纤维蛋白原、三酰甘油水平存在提示性相关；CARD11 错义变异和总胆固醇水平存在提示性相关。

结论：NOL8 和 OR7G2 中罕见错义变异不仅与儿童 ALL 发病风险增加有关，还可能参与疾病的病理生理过程，改变某些临床特征，从而影响临床分型和治疗方案的选择

关键字：儿童急性淋巴细胞白血病，外显子，罕见变异，临床表型组

83. 单细胞和大量 RNA 测序的综合分析确定 CTHRC1+INHBA+CAF 是结直肠癌癌症进展的驱动因素

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背景：结直肠癌（Colorectal cancer，CRC）是最常见的肿瘤之一，在全球癌症发病率和死亡率中分别排名第三和第二。由于 CRC 患者发病较晚，进展迅速，且有明显的异位转移。因此，CRC 患者的预后极差。癌症相关成纤维细胞（Cancer related fibroblasts，CAFs）是肿瘤微环境（Tumor microenvironment，TME）的重要组成部分，其在肿瘤转移、耐药性、炎症和免疫中的作用越来越重要。CAFs 可以通过调节肿瘤细胞生长、转移、血管生成和免疫逃避来促进肿瘤进展。CAFs 能够衍生出多种分子来促进 CRC 转移和免疫逃避，包括金属蛋白酶、细胞因子趋化因子和生长因子等。因此，寻找 CAFs 关键靶点是 CRC 的一种很有前途的治疗策略。

方法：在本研究中，基于单细胞测序和批量测序数据，并使用加权基因共表达网络分析（Weighted Gene Co-expression Network Analysis，WGCNA）和机器学习鉴定 CAF 的关键基因。同时基于多个数据库和体外实验对 CAF 关键基因进行了一系列全面分析，包括其表达、预后、免疫浸润、免疫逃逸、免疫治疗、药物敏感性、调节机制和转移。

结果：本研究结果显示，CRC 组织中 CAF 的比例显著增加，高比例的 CAF 与 CRC 的免疫逃逸和不良预后有关。Collagen triple helix repeat containing 1 (CTHRC1)和 Inhibin beta A (INHBA)被鉴定为 CRC 进展的关键基因，主要在 CAFs 中表达，并在 CRC 组织中显著上调。本研究将 CTHRC1 和 INHBA 定义为癌症相关的成纤维细胞相关基因（Cancer related fibroblast related genes，CAFRGs）。CAFRGs 与 CRC 和巨噬细胞极化的不良预后相关。CAFRGs 促进 CRC 的免疫逃逸和转移，是免疫治疗反应的良好预测因子。药物敏感性分析显示，CAFRGs 高表达组对 15 种化疗药物敏感，而低表达组仅对 3 种药物敏感。本研究对单细胞测序数据中的 CAFs 进行了聚类和分群，并确定了 CAFs 的七种亚型（F1-F7）。CTHRC1 和 INHBA 在 F1 和 F5 中高表达。因此，本研究中将 F1 和 F5 定义为 CTHRC1+INHBA+CAF。进一步分析显示 CTHRC1+INHBA+CAF 是 CRC 的不良预后因素，并与细胞外基质重塑和免疫调节有关。

结论：本研究证实 CTHRC1 和 INHBA 是肿瘤相关成纤维细胞相关基因（CAFRGs），CTHRC1+INHBA+CAF 是 CRC 发生发展的关键因素。综上所述，本研究为 CRC 制定有效的治疗策略和寻找新的治疗靶点提供理论依据。

关键字： 结直肠癌（CRC），癌症相关成纤维细胞相关基因（CAFRGs），预后，转移，免疫逃逸

84. 基于癌症相关成纤维细胞相关亚型揭示结直肠癌异质性并鉴定 BGN 作为结直肠癌的生物标志物和治疗靶点

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背景：结直肠癌（Colorectal cancer，CRC）是常见的恶性肿瘤，发病率位居第三位，死亡率位居第二位。肿瘤微环境（TME）在 CRC 发生发展中发挥重要作用，研究表明 TME 不仅为肿瘤生长转移提供环境，同时能够调控肿瘤免疫反应，影响肿瘤免疫治疗应答。肿瘤相关成纤维细胞（CAFs）是 TME 基质细胞的主要成分，在 CRC 转移和免疫治疗抵抗中发挥了重要作用。迄今为止，尚未有基于 CAFs 对 CRC 分型的研究。因此，从单细胞层面，

基于 CAFs 相关基因对 CRC 进行分型，揭示 CRC 异质性及为临床提供合理的治疗策略是非常有必要的。

方法：本研究基于单细胞测序数据和 bulk RNA 测序数据，采用共识聚类分析鉴别 CRC 亚型。随后，本研究对这两种亚型进行异质性解析。这些异质性包括 CRC 亚型的预后、生物特征、TME、免疫逃逸、免疫治疗、药物治疗和基因组突变。本研究基于 CRC 亚型并结合多种算法开发一种风险预后模型用于预测 CRC 病人的总生存期。最后，鉴别 CRC 亚型之间的枢纽基因并结合体外实验对其进行分析。

结果：本研究基于单细胞测序数据鉴别了 4 种 CAF 亚型，并结合 bulk 测序数据鉴别两种 CRC 亚型（C1 和 C2）。C2 相较于 C1 具有更差的预后。C1 主要与代谢有关，C2 主要与细胞转移及免疫调节有关。C2 相较于 C1 具有更高的基质评分、免疫评分、巨噬细胞浸润和免疫逃逸。而 C1 相较于 C2 具有更高的免疫治疗敏感性。我们还发现了多种对 C1 和 C2 敏感的潜在药物，这可能有利于未来的临床转化。我们基于 C1 和 C2 亚型开发一种风险特征，在预测 CRC 患者总生存率方面具有较高的可靠性。此外，我们鉴别 BGN 作为 C1 与 C2 之间的枢纽基因及 CRC CAFs 的特征基因。BGN 不仅与肿瘤微环境（TME）密切相关，它还能够作为 CRC 的独立预后标志物。免疫荧光实验表明 BGN 主要表达在肿瘤成纤维组织和 CAF 中。Transwell 实验表明下调 CAF 中 BGN 的表达能够减少 CRC 细胞的转移。在机制上，我们发现 BGN 通过 SPP1/ITGAV/ITGB1 轴调控 CRC 细胞。

结论：我们根据单细胞测序数据和批量测序数据确定了两种 CRC 亚型。这两种 CRC 亚型具有不同的生物学特征，产生不同的预后、TME、免疫逃逸、免疫治疗、药物治疗和基因突变。我们开发了一种基于 C1 和 C2 亚型的风险特征，在预测 CRC 患者的总体生存率方面具有高可靠性。此外，我们确定 BGN 能够作为 CRC 的生物标志物和治疗靶点。总之，我们的工作揭示了 CRC 的异质性，并能够改善 CRC 患者的预后和治疗。

关键字： 癌症相关成纤维细胞，结直肠癌，BGN，生物标志物

85. Circulating microbiome DNA as novel biomarkers for predicting recurrence after resection of stage T1 non-small cell lung cancer

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Background

Most recurrence of non-small cell lung cancer (NSCLC) occurs within three years after surgery, yet currently there are no effective methods for postoperative recurrence detection. Recent studies have proposed that specific microbial signatures could serve as prognostic biomarkers across various cancers. However, no studies have systematically investigated circulating microbiome DNA (cmDNA) signatures in NSCLC. Therefore, this study aims to characterize cmDNA signatures and identify prognostic biomarkers for recurrence in NSCLC patients.

Methods

Whole genome sequencing was conducted on plasma samples from 101 patients diagnosed with stage T1 non-small cell lung cancer (NSCLC). Of these patients, 36 had experienced tumor recurrence within three years after surgery (R group), while 65 had not experienced recurrence (NR group). Microbial DNA was obtained by removing the host genome and relative abundance was measured by mapping reads into microbial genomes. A random forest model was developed to distinguish the R group from the NR group. Patients were randomly split into the training dataset (n = 61) and the test dataset (n = 40) at the ratio of 6:4.

Results

Through LEfSe analysis, we identified 23 cmDNA taxa enriched in the R group and 39 cmDNA taxa enriched in the NR group, which may possibly relate to postoperative recurrence. Of note, Candidatus Nanosynbacteraceae family, Staphylococcus genus, Candidatus Nanopelagicales order were the most enriched taxa in the R group (LDA >2, $p<0.05$). A machine learning model was implemented using these significant features. Specifically, our model exhibited a sensitivity of 72.7% and a specificity of 84.6% in the training set, with an AUC of 88.1% (95%CI, 79.7% –

96.6%). Additionally, in the test set, the model achieved a sensitivity of 71.3% and specificity of 84.6%, with an AUC of 80.9%. Furthermore, patients were categorized into high- and low-risk groups according to the median of model predicting scores. The Kaplan–Meier survival curve revealed that recurrence-free survival in the high-risk group was significantly shorter ($p < 0.001$) than that of the low-risk group.

Conclusions

In summary, our study provides valuable insights into the significant alterations in circulating microbiome DNA signatures in postoperative recurrence patients. We developed a highly sensitive cmDNA-based model that effectively distinguished patients with recurrence from those without. Our findings suggest the potential use of cmDNA as a promising biomarker in postoperative recurrence, which could significantly improve patient outcomes.

Key Words： circulating microbiome DNA; stage T1; tumor recurrence; microbial biomarker

86. Efficacy and safety of probiotics, prebiotics, and synbiotics for the prevention of colorectal cancer and precancerous lesion in high-risk populations: A systematic review and meta-analysis of randomized controlled trials

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Objectives

Colorectal cancer (CRC) is highly prevalent worldwide and is a leading cause of cancer-related death. Probiotics, prebiotics, and synbiotics have recently attracted attention as preventive measures against colorectal neoplasms. We aimed to analyze the findings of randomized controlled trials (RCTs) on the effects of probiotics, prebiotics, and synbiotics in patients at a high risk of CRC, outlining the challenges and future prospects of using probiotics to prevent colorectal tumors and providing evidence for clinical physicians in particular.

Methods

PubMed, EMBASE, and the Cochrane Library databases were searched for relevant studies published up to January 7, 2022. RCTs conducted on populations with a high risk of CRC who received probiotics, prebiotics or synbiotics in comparison with placebo, candidate agent or no treatment were included. The primary outcome was the incidence or recurrence of any colorectal neoplasms. Additional outcomes included their effects on the diversity of gut microbiota and relevant inflammatory biomarkers. Safety outcomes were also analyzed. Two authors independently screened and selected studies based on pre-specified eligible criteria, performed data extraction and risk-of-bias assessment independently.

Results

Nine RCTs were included in the systematic review and meta-analysis. Probiotic supplementation significantly reduced adenoma incidence, but no significant benefit was observed in CRC incidence. Additionally, probiotics modulated gut microbiota and inflammatory biomarkers.

Conclusion

Probiotics may have beneficial effects in the prevention of CRC. More RCTs with larger sample sizes are warranted to further confirm these findings.

Key Words： probiotics, prebiotics, synbiotics, Colorectal cancer, RCT

87. 血清肿瘤标志物检测对系统性红斑狼疮的诊断价值

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目的：探讨肿瘤标志物 CA125、CEA、CA199 和 CA153 对系统性红斑狼疮(SLE)的诊断价值。

方法：分析 2021 年 7 月—2023 年 6 月长海医院风湿免疫科收治的 SLE 患者 95 例为 SLE 组，再按 SLEDAI 评分为 SLE 活动期亚组 59 例及 SLE 缓解期亚组 36 例。纳入同期性别、年龄相匹配的健康体检者 100 例为健康对照组。检测 2 组受试者红细胞沉降率(ESR)、C 反应蛋白(CRP)，血清 CA125、CEA、CA199、CA153 及免疫学指标(补体 C3、补体 C4、IgG、IgM、IgA)、抗 dsDNA 抗体等指标，采用 Pearson 法分析 SLE 患者中肿瘤标志物与 SLEDAI 评分的相关性,探讨血清肿瘤标志物对 SLE 诊断及活动度判断的临床意义。

结果：与健康对照组比较,SLE 组患者 ESR、CRP、IgG、IgA、IgM 及血清 CA199、CA125 水平均明显升高,补体 C3、C4 水平均明显下降,差异均有统计学意义(P<0.01),而血清 CEA、CA153 水平差异无统计学意义(P>0.05)。与 SLE 缓解期亚组比较，SLE 活动期亚组患者补体 C3、C4 水平显著下降,IgG、IgA、IgM、CA125、CA199 水平显著升高(P<0.01),而 CEA、CA153 水平差异无统计学意义(P>0.05)。经 Pearson 检验，SLE 患者的 CA125、CA199、抗 dsDNA 抗体与 SLEDAI 评分均呈显著正相关(r=0.479、0.587、0.664,P 均<0.01)，而 CEA、CA153 与 SLEDAI 无相关性(r=0.258、0.228, P>0.05)。

结论：SLE 患者血清 CA125、CA199 等肿瘤标记物水平均升高,与病情活动性相关，通过检测肿瘤标志物有助于 SLE 的诊断及疾病活动程度的判断。

关键字： 系统性红斑狼疮；肿瘤标志物；诊断

88. IFI35 regulates non-canonical NF-κB signaling to maintain glioblastoma stem cells and recruit tumor-associated macrophages

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Glioblastoma (GBM) is the most aggressive malignant primary brain tumor characterized by a highly heterogeneous and immunosuppressive tumor microenvironment (TME). The symbiotic interactions between glioblastoma stem cells (GSCs) and tumor-associated macrophages (TAM) in the TME are critical for tumor progression. Here, we identified that IFI35, a transcriptional regulatory factor, plays both cell-intrinsic and cell-extrinsic roles in maintaining GSCs and the immunosuppressive TME. IFI35 induced non-canonical NF-kB signaling through proteasomal processing of p105 to the DNA-binding transcription factor p50, which heterodimerizes with RELB (RELB/p50), and activated cell chemotaxis in a cell autonomous manner. Further, IFI35 induced recruitment and maintenance of M2-like TAMs in TME in a paracrine manner. Targeting IFI35 effectively suppressed in vivo tumor growth and prolonged survival of orthotopic xenograft-bearing mice. Collectively, these findings reveal the

tumor-promoting functions of IFI35 and suggest that targeting IFI35 or its downstream effectors may provide effective approaches to improve GBM treatment.

Key Words： Glioblastoma stem cells; Tumor microenvironment

89. B2-Microglobulin Maintains Glioblastoma Stem Cells and Induces M2-like Polarization of Tumor-Associated Macrophages

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Glioblastoma (GBM) is a complex ecosystem that includes a heterogeneous tumor population and the tumor-immune microenvironment (TIME), prominently containing tumor-associated macrophages (TAM) and microglia. Here, we demonstrated that B2-microglobulin (B2M), a subunit of the class I major histocompatibility complex (MHC-I), promotes the maintenance of stem-like neoplastic populations and reprograms the TIME to an anti-inflammatory, tumor-promoting state. B2M activated PI3K/AKT/mTOR signaling by interacting with PIP5K1A in GBM stem cells (GSC) and promoting MYC- induced secretion of transforming growth factor-b1 (TGFb1). Inhibition of B2M attenuated GSC survival, self-renewal, and tumor growth. B2M-induced TGFb1 secretion activated paracrine SMAD and PI3K/AKT signaling in TAMs and promoted an M2-like macrophage phenotype. These findings reveal tumor-promoting functions of B2M and suggest that targeting B2M or its downstream axis may provide an effective approach for treating GBM.

Key Words： Tumor-immune microenvironment; Glioblastoma stem cell

90. The role of fatty acid desaturase 2 in multiple tumor types revealed by bulk and single-cell transcriptomes

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Background: Previous studies have demonstrated the important role of fatty acid desaturase 2 (FADS2) in governing tumorigenesis and tumor metastasis. Although FADS2 is an essential regulator of fatty acid metabolism, its prognostic and immunotherapeutic value remains uncertain.

Methods: The role of FADS2 was investigated across different types of tumors. Besides, the relationship between FADS2 and survival prognosis, clinicopathologic features, tumor-infiltrating immune cells, immunoregulatory genes, chemokines, chemokines receptor, tumor mutational burden (TMB), and microsatellite instability (MSI) was also explored. FADS2-related genes enrichment analysis was performed to further explore the molecular function of FADS2. Finally, the relationship between FADS2 expression and altered functional states in single-cell levels across different tumor cells was explored.

Results: FADS2 was increased in most tumor tissues. Elevated FADS2 expression was associated with a poor overall survival (OS) and disease-free survival (DFS). FADS2 amplification was germane to worse progress-free survival (PFS). In addition, FADS2 correlated with the majority of tumor-infiltrating immune cells, immunoregulatory genes, and chemokines. Especially, FADS2 expression positively correlated with cancer-associated fibroblast (CAFs) infiltration. Gene Ontology and KEGG analysis demonstrated that FADS2 was involved in the fatty acid metabolic process, arachidonic acid metabolism, RAS, PPAR, and VEGF pathway. FADS2 had a positive relationship with tumor biological behaviors such as inflammation, cell cycle, proliferation, DNA damage, and DNA repair response in single-cell levels.

Conclusions: FADS2 can serve as a potential prognostic and immunotherapeutic biomarker for multiple tumors, revealing new insights and evidence for cancer treatment.

Key Words： Biomarker; FADS2; Immunotherapy; Prognosis.

91. Polymorphism rs2327430 in TCF21 predicts the risk and prognosis of gastric cancer by affecting the binding between TFAP2A and TCF21

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Background: Single nuclear polymorphisms (SNPs) have been published to be correlated with multiple diseases. Transcription Factor 21 (TCF21) is a critical transcription factor involved in various types of cancers. However, the association of TCF21 genetic polymorphisms with gastric cancer (GC) susceptibility and prognosis remains unclear.

Methods: A case-control study comprising 890 patients diagnosed with GC and an equal number of cancer-free controls was conducted. After rigorous statistical analysis, molecular experiments were carried out to elucidate the functional significance of the SNPs in the context of GC.

Results: TCF21 rs2327430 (OR = 0.78, P = 0.026) and rs4896011 (OR = 1.39, P = 0.005) exhibit significant associations with GC risk. Furthermore, patients with the (TC + CC) genotype of rs2327430 demonstrate a relatively favorable prognosis (OR = 0.47, P = 0.012). Mechanistically, chromatin immunoprecipitation assay and luciferase reporter assay revealed that the C allele of rs2327430 disrupts the binding of Transcription Factor AP-2 Alpha (TFAP2A) to the promoter region of TCF21, resulting in increased expression of TCF21 and inhibition of malignant behaviors in GC cells.

Conclusion: Our findings highlight the significant role of TCF21 SNPs in both the risk and prognosis of GC and provide valuable insights into the underlying molecular mechanisms. Specifically, the disruptive effect of rs2327430 on TCF21 expression and its ability to modulate malignant cell behaviors suggest that rs2327430 may serve as a potential predictive marker for GC risk and prognosis.

Key Words： Gastric cancer, Single nucleotide polymorphism, Transcription Factor 21, Transcription Factor AP-2 Alpha

92. Prognostic model of patients with unresectable hepatocellular carcinoma treated with targeted therapy

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Background: Currently, there is no well-established prognostic model for patients with unresectable hepatocellular carcinoma (u-HCC) undergoing targeted therapy. Therefore, we attempted to create a simplified prognostic model.

Methods: We retrospectively analyzed data from patients with u-HCC who received targeted first-line therapy at three centers. Clinical data in two centers divided into a 7:3 ratio for training and internal validation sets, while the data in the third center served as the external validation set.

Variables associated with overall survival (OS) and progression-free survival (PFS) in the training set were used to develop the targeted therapy unresectable hepatocellular carcinoma prognosis (TUHP) model. The model was tested on the internal validation set and compared with other prognostic systems. It was also applied to the external validation cohort for further evaluation.

Results: In the training set, variables independently associated with OS/PFS in multivariable analysis were alpha-fetoprotein (AFP) >20 ng/ml and macrovascular invasion (MVI). The TUHP model demonstrated a significant association with OS and PFS in the training set, with a median OS of 30.75 months for TUHP low risk, 15.25 months for TUHP medium risk, and 4 months for TUHP high risk ($p < 0.001$). The median PFS was 18 months for TUHP low risk, 6 months for TUHP medium risk, and 3 months for TUHP high risk ($p < 0.001$). In the validation set, the TUHP model also showed a significant association with OS and PFS, and exhibited greater discriminative abilities compared to existing prognostic models.

Conclusion: The model presented in the work can be used to predict OS and PFS in patients with u-HCC who received first-line targeted therapy. By identifying patients who are more likely to benefit from targeted therapy, this model may help optimize treatment outcomes for patients with hepatocellular carcinoma (HCC).

Key Words： Unresectable hepatocellular carcinoma, Prognostic model, Targeted therapy, Macrovascular invasion.

93. 药物 FN-1501 通过诱导细胞周期阻滞和促进细胞凋亡在弥漫大 B 细胞淋巴瘤中发挥抗肿瘤作用

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目的：FN-1501 作为一种有效的 Fms 样受体酪氨酸激酶 3(Fms-like receptor tyrosine kinase 3, FLT3)和细胞周期蛋白依赖性激酶(Cyclin-dependent kinases, CDKs)抑制剂，在部分实体瘤和血液肿瘤中已被发现具有显著的抗肿瘤活性。本研究旨在探讨 FN-1501 对弥漫大 B 细胞

淋巴瘤(Diffuse large B-cell lymphoma, DLBCL)的抗肿瘤疗效及机制，为进一步探索该药的临床应用开辟重要的新途径。

材料与方法：首先，我们研究了 FN-1501 的抗肿瘤作用，在体外通过 CCK-8 法检测 FN-1501 在不同浓度梯度下对 DLBCL 细胞系(SU-DHL-4、Farage、OCI-LY1、NU-DUL-1、U2932)增殖的影响，采用流式细胞术检测细胞周期和细胞凋亡，Western Blot 检测细胞周期和凋亡相关蛋白水平，并构建裸鼠皮下瘤模型，体内实验进一步验证其疗效。随后，采用流式细胞术、Western Blot 等方法探索并验证其分子机制。

结果：1. 细胞增殖实验表明，FN-1501 对 DLBCL 细胞增殖有明显的抑制作用(SU-DHL-4, 24h-IC50: 0.236μM, 95%CI: 0.2171~0.2562 ； Farage, 24h-IC50: 0.1802μM, 95%CI: 0.1705~0.1903；OCI-LY1, 24h-IC50: 0.217μM, 95%CI: 0.2064~0.2280；NU-DUL-1, 24h-IC50: 0.2341μM, 95%CI: 0.2189~0.2501； U2932, 24h-IC50: 0.2743μM, 95%CI: 0.2438~0.3094)，无论是 GCB 亚型还是 ABC 亚型，且呈浓度依赖性。2. 细胞周期流式结果和周期相关蛋白的 WB 结果显示，FN-1501 不仅能显著诱导 G1/S 期阻滞，还能调节 G1/S 期相关蛋白的表达。3. 细胞凋亡流式结果显示，FN-1501 诱导 DLBCL 细胞早期凋亡和晚期凋亡细胞亚群呈浓度依赖性增加，凋亡相关蛋白的 WB 结果显示 cleaved caspase-3、cleaved caspase-7、cleaved PARP 的表达均升高。4. FN-1501 作用于 DLBCL 细胞后，PI3K/Akt/mTOR 和 MAPK 信号通路中相关蛋白的表达均下调，LY294002（PI3K/Akt 抑制剂）和 U0126（ERK 抑制剂）预处理后，相较于单独使用 FN-1501 时，可观察到细胞周期阻滞程度和细胞凋亡水平均显著增加。5. 在体内实验中，与对照组相比，FN-1501 可显著减少 DLBCL 的肿瘤体积和肿瘤重量。

结论：FN-1501 通过诱导周期阻滞和促进凋亡的方式在 DLBCL 的体内和体外均发挥抗肿瘤作用，可能为 DLBCL 患者的临床治疗提供新的选择。

关键字： 弥漫大 B 细胞淋巴瘤；FN-1501；细胞周期；细胞凋亡

94. The clinical prognostic risk stratification system for HIV infected hepatocellular carcinoma

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Background: Patients with human immunodeficiency virus (HIV) are more susceptible to liver cancer because of their compromised immune system. There is no specific prognostic model for HIV-infected hepatocellular carcinoma (HCC) patients.

Methods: Clinical data of 85 patients with HIV-infected HCC was divided into a 7:3 ratio for training and internal validation sets, while the data of 23 patients with HIV-infected HCC was served as the external validation set. Data of 275 HIV-negative HCC patients was considered as external HIV-negative validation set. Variables associated with overall survival (OS) in the training set were used to develop the HIV-infected HCC prognosis (HIHP) model. The model was tested in the internal and external validation sets. The predictive accuracy of the model was assessed with conventional HIV-negative HCC prognostic scoring systems.

Results: In the training set, variables independently associated with OS in multivariable analysis were organ involvement and tumor number. The HIHP model demonstrated a significant association with OS in the training set, with a median OS of 13 months for low risk, 7 months for medium risk, and 3 months for high risk ($p < 0.001$). The HIHP model showed a significant

association with OS, and exhibited greater discriminative abilities compared to conventional HIV-negative HCC prognostic models both in the internal and external validation sets. In the external HIV-negative validation set, the HIHP model did not show better discrimination than conventional HIV-negative HCC scores.

Conclusion: The new model presented in the work provided a more accurate prognostic prediction of OS in HIV-infected HCC patients. However, the model is not applicable to patients with HIV-negative HCC.

Key Words： human immunodeficiency virus-infected hepatocellular carcinoma, prognostic model, risk stratification, organ involvement, tumor number.

95. Integrating single-cell and bulk transcriptomic analyses to develop a cancer-associated fibroblast (CAF)-derived biomarker for predicting prognosis and therapeutic response in breast cancer

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Purpose: Cancer-associated fibroblasts (CAFs) contribute to the progression and therapeutics of breast cancer (BRCA), yet signatures and molecular targets based on CAFs are still limited. This study aims to uncover novel CAF-related biomarkers in BRCA, enabling the development of a risk signature and a comprehensive characterization of the prognostic and therapeutic profiles of patients.

Materials and Methods: CAF-related genes (CAFRGs) and a risk signature based on these genes were comprehensively analyzed using publicly available bulk and single-cell transcriptomic datasets. Modular genes identified from bulk sequencing data were intersected with CAF marker genes identified from single-cell analysis to obtain reliable CAFRGs. Signature CAFRGs were screened via Cox regression and least absolute shrinkage and selection operator (LASSO) analyses. Multiple patient cohorts were used to validate the prognosis and therapeutic responsiveness of

high-risk patients stratified based on the CAFRG-based signature. In addition, the relationship between the CAFRG-based signature and clinicopathological factors, tumor immune landscape, functional pathways, chemotherapy sensitivity and immunotherapy sensitivity was examined. External datasets were used and sample experiments were performed to examine the expression pattern of MFAP4, a key CAFRG, in BRCA.

Results: Integrated analyses of single-cell and bulk transcriptomic data as well as prognostic screening revealed a total of 43 prognostic CAFRGs; of which, 14 genes (TLN2, SGCE, SDC1, SAV1, RUNX1, PDLIM4, OSMR, NT5E, MFAP4, IGFBP6, CTSO, COL12A1, CCDC8 and C1S) were identified as signature CAFRGs. The CAFRG-based risk signature exhibited favorable efficiency and accuracy in predicting survival outcomes and clinicopathological progression in multiple BRCA cohorts. Functional enrichment analysis suggested the involvement of the immune system, and the immune infiltration landscape significantly differed between the risk groups. Patients with high CAF-related risk scores (CAFRSs) exhibited tumor immunosuppression, enhanced cancer hallmarks and hyposensitivity to chemotherapy and immunotherapy. Five compounds were identified as promising therapeutic agents for high-CAFRS BRCA. External datasets and sample experiments validated the downregulation of MFAP4 and its strong correlation with CAFs in BRCA.

Conclusions: A novel CAF-derived gene signature with favorable predictive performance was developed in this study. This signature may be used to assess prognosis and guide individualized treatment for patients with BRCA.

Key Words： Breast cancer; Cancer-associated fibroblast; Prognostic signature; scRNA-seq; Tumor microenvironment.

96. Promotion of metastasis of ERBB2-positive breast cancer by mesenchymal stem cells via exosomes-mediated activation of ERBB2/ERBB3→PI3K/Akt singaling pathway

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Objective: Elevated expression of ERBB3 receptor correlates with increased distant metastasis of breast cancers with amplification and/or overexpression of ERBB2 (HER2/neu), which the underlying molecular mechanism remains unclear. In recent years, cumulative studies have demonstrated that mesenchymal stem cells (MSCs), one of the important cellular components in tumor microenvironment, play important roles in multiple hallmarks of cancer including invasion and metastasis. However, its role in metastasis of ERBB2-positive breast cancer as well as the precise mechanisms are largely unrevealed.

Materials and methods: Exosomes were harvested with ultrafiltration centrifugation. Co-culture of ERBB2-positive breast cancer cells with MSCs or treatment with MSCs-derived exosomes was carried out and cell morphology changes were examined. Transwell assay was used to detect the migration and invasion of ERBB2-positive breast cancer cells. Western blot analyses were performed to determine the expression and activation of proteins. Lentiviral expression system was used to introduce overexpression of exogeneous genes or gene-targeting short hairpin RNAs (shRNAs). LipofectamineTM 3000 was used in transfection of ERBB2-positive breast cancer cells with miRNAs mimics or inhibitors and qRT-PCR was carried out to analyze the mRNAs and miRNAs expression levels.

Results: We found that co-culture with MSCs or treatment with exosomes derived from MSCs can significantly promote the epithelial-mesenchymal transition (EMT), migration and invasion of ERBB2-positive breast cancer cells. MSCs exhibited significantly higher expression of NRG-1, a known ligand of ERBB3, as compared with ERBB2-positive breast cancer cells. The presence of NRG-1 in exosomes derived from MSCs was also evidenced. Mechanistically, co-culture with

MSCs or treatment with exosomes derived from MSCs induced upregulation of ZEB1 and Slug via activation of downstream PI3K/Akt singaling to promote EMT of ERBB2-positive breast cancer cells. In addition, the expression of MMP2 was also upregulated by treatment with MSCs-derived exosomes, which enhanced the migration and invasion of ERBB2-positive breast cancer cells simultaneously. Interestingly, our study further demonstrated that treatment with MSCs-derived exosomes could significantly downregulate the expression of PTEN, the key negative regulator of PI3K/Akt singaling, via transferring three PTEN-targeting miRNAs (miR-21-5p, miR-23a-3p, and miR-148a-3p).

Conclusion: Taken together, we presented here that MSCs may, on the one hand, directly activate the ERBB2/ERBB3→PI3K/Akt signaling pathway in ERBB2-positive breast cancer cells through the expression and secretion of NRG-1 via exosomes. Meanwhile, miR-21-5p, miR-23a-3p, and miR-148a-3p targeted delivery by exosomes specifically downregulated the expression of PETN, thus reliefs the negative regulation of PI3K/Akt signaling in ERBB2-positive breast cancer cells. These effects of MSCs act in concert to promote the metastasis of ERBB2-positive breast cancer.

Key Words： Mesenchymal stem cells (MSCs), ERBB2/3, Metastasis

97. Risk Stratification Based on DNA Damage-repair-related Signature Reflects the Microenvironmental Feature, Metabolic Status and Therapeutic Response of Breast Cancer

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Purpose: DNA damage-repair machinery participates in maintaining genomic integrity and affects tumorigenesis, but reliable molecular signatures of breast cancer (BRCA) based on DNA damage-repair-related genes(DRGs) are still lacking. This study aims to establish a novel risk signature based on DRGs to comprehensively evaluate the prognosis, tumor immunometabolic profile and therapeutic responsiveness of BRCA patients.

Materials and Methods: The Cox regression and the least absolute shrinkage and selection operator (LASSO) regression analyses were conducted to identify prognostic DRGs. Clinicopathological relevance assessment was carried out, after which a nomogram was established. The features of the immune microenvironment, metabolic status, functional pathways, antitumor immunity, mutational landscape, checkpoint expression and tumor stemness were analyzed. Using multiple algorithms and real-world cohorts, we also compare the sensitivity of individuals to immunotherapy and chemotherapy for therapeutic guidance. Small molecule compounds promising to target high-risk tumors were also predicted. Tissue samples and cellular functional assays to investigate the expression of key DRGs and their impact on tumor biological behaviors and microenvironment.

Results: Integrating public datasets and bioinformatics algorithms, we developed a robust prognostic signature based on 27 DRGs. Multiple patient cohorts identified significant differences in various types of survival between high- and low-risk patients stratified by the signature. The signature correlated well with clinicopathological factors and could serve as an independent prognostic indicator for BRCA patients. Furthermore, low-risk tumors were characterized by more infiltrated CD8+ T cells, follicular helper T cells, M1 macrophages, activated NK cells and resting dendritic cells, and fewer M0 and M2 macrophages. The favorable immune infiltration patterns of low-risk tumors were also accompanied by specific metabolic profiles, decreased DNA replication, and enhanced antitumor immunity. Low-risk patients may respond better to immunotherapy, and experience improved outcomes with conventional chemotherapy or targeted medicine. Real-world immunotherapy and chemotherapy cohorts verified the predictive results. Additionally, five small molecule compounds promising to target high-risk tumors were predicted. In vitro experiments confirmed the high expression of GNPNAT1 and MORF4L2 in BRCA tissues and their association with immune cells, and the knockdown of these two DRGs suppressed the proliferation of human BRCA cells.

Conclusions: This study proposed a novel DNA damage repair-related gene signature that performs well in predicting patient prognosis, immunometabolic profiles, and therapeutic sensitivity, hopefully contributing to precision medicine and the discovery of new targets for BRCA.

Key Words： DNA damage; DNA repair; Prognostic signature; Immune microenvironment; Metabolic status; Breast cancer

98. FTO 泛素化降解介导的 m6A RNA 甲基化下调 EGFR 促进胶质母细胞瘤耐药的机制研究

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背景：胶质母细胞瘤（Glioblastoma, GBM）是人颅内恶性度最高的原发肿瘤，即使最大安全范围的手术切除后积极放化疗，其中位生存期也仅有 20.9 个月。虽然靶向治疗或免疫治疗取得了一定的进展，但多数患者术后短时间内便产生耐药和复发。因此，明确 GBM 耐药的关键分子调控机制和新的靶点，探索可行的靶向策略，是 GBM 耐药研究的热点问题。

表皮生长因子受体（EGFR）是受体酪氨酸激酶中的表皮生长因子受体（HER）家族中的一员，在细胞生理过程中发挥增殖和抗凋亡等重要作用。研究表明超过一半的 GBM 存在 EGFR 改变，主要包括扩增和突变。N6-methyladenosine (m6A)是 RNA 的一种保守、动态的内部修饰，影响 RNA 转录后的稳定性，从而调控几乎所有重要的生物学过程。我们已经构建的替莫唑胺(Temozolomide, TMZ)耐药组织中 m6A 去甲基化酶 FTO 表达降低，总体 m6A RNA 甲基化水平显著增高，EGFR 的 m6A 水平也显著增高，与其蛋白表达成反比。因此，明确 EGFR 低表达及 EGFR 影响化疗敏感性的机制对指导 GBM 逆转耐药具有重要意义。

方法：我们前期已发表的研究中构建了 GBM 替莫唑胺（TMZ）体内耐药模型，通过耐药组织与敏感组织的蛋白定量质谱检测、m6A-RIP 测序结果及 RMbase 网站预测，证明 EGFR m6A 变化介导的低表达在 GBM 化疗耐药中的关键作用。CPTAC 蛋白数据库相关性分析显示 GBM 中 FTO 与 EGFR 显著正相关，泛素化实验表明耐药细胞中 FTO 的泛素化修饰显著增加，应用 GSK-3β抑制剂能够显著促进耐药细胞中 FTO 蛋白的表达，但不影响 FTO 的 mRNA，证明 GSK-3β可促进 FTO 的泛素-蛋白酶体降解。

结果：在本研究中，我们发现 TMZ 耐药模型中，GSK-3β表达和活性增高，并且可以通过调控特定位点磷酸化引发 FTO 多泛素化降解，导致 TMZ 耐药组织和细胞中 FTO 表达降低，从而引起耐药组织和细胞中总体 m6A 水平上升，并且上调 EGFR 的 CDS 区域的 m6A

水平，影响 EGFR 稳定性及表达，导致其表达降低，而 EGFR 的低表达则促进 GSK-3β的进一步增高和活化，形成诱导耐药的正反馈调节环路。

结论：总而言之我们明确 GSK-3β/FTO 调控的 EGFR m6A 修饰是导致 EGFR 下调的关键因素，发现 EGFR/GSK3β/FTO/m6A 调控环路在 GBM 化疗耐药的治疗中发挥重要作用。

关键字： 胶质母细胞瘤；EGFR；FTO；m6A；替莫唑胺耐药

99. 利用单细胞测序技术分析结直肠癌肝转移的细胞和分子特征

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背景：结直肠癌（Colorectal cancer，CRC）是消化道肿瘤中最常见的肿瘤之一，肝脏是结直肠癌通过血行转移发生最重要的靶器官。结直肠癌肝转移（Colorectal cancer liver metastasis，CRCLM）患者预后较差，且大部分 CRCLM 患者对目前化疗耐药。目前研究提示，基于肿瘤微环境（Tumor microenvironment，TME）的治疗可能为 CRCLM 治疗提供新见解。基于此，本研究系统全面地阐明 TME 组成和细胞间通讯，以及巨噬细胞亚群间细胞通讯，以期望为 CRCLM 治疗提供潜在靶点。

方法：本研究运用单细胞 RNA 测序（Single-cell RNA sequencing，scRNA-seq）技术系统分析结肠癌 GSE178318 数据集中 3 对 CRC 和 CRCLM 测序数据，以阐明 TME 的细胞组成和细胞通讯，以及巨噬细胞的细胞亚型和细胞通讯。使用 TCGA-COAD 和 GEO 数据集 Bulk-RNA 测序数据分析 H-MARCO 和 L-MARCO 组 CRC 患者的免疫细胞浸润水平、肿瘤突变负荷（Tumor mutation burden，TMB）水平，和免疫检查点表达水平。此外，应用免疫组化（Immunohistochemistry，IHC）和多重免疫荧光（Multiplex immunofluorescence，mIF）染色验证相应结果。

结果：细胞通讯结果显示，巨噬细胞与其它类型细胞间存在大量细胞通讯。此外，生物信息学和实验验证结果均表明，TNF-TNFR 和 GRN-SORT1 分别是 CRC 和 CRCLM 相关信号网络中特异的“配体-受体”对。本研究共鉴定出 6 个巨噬细胞亚群，其中具有胶原结构的巨噬细胞受体（Macrophage Receptor With Collagenous Structure，MARCO）巨噬细胞在 CRC

和 CRCLM 之间差异最显著。功能富集结果显示，MARCO-巨噬细胞主要与“白细胞的趋化和迁移”有关。此外，利用 MARCO 巨噬细胞特征基因结合反卷积算法，将 CRC 患者分为 High-MARCO 巨噬细胞组和 Low-MARCO 巨噬细胞组。生物信息学结果提示，与 Low-MARCO 组相比，High-MARCO 组免疫细胞浸润程度升高、免疫检查点表达水水平升高、TMB 水平升高，免疫治疗应答率升高。

结论：本研究阐明了 MARCO 巨噬细胞在 CRC 肝转移中发挥重要作用，基于 MARCO-巨噬细胞的分子亚型可以有效预测 CRC 患者免疫治疗应答，从而为肿瘤免疫提供理论基础。

关键字： 结直肠癌肝转移、免疫疗法、具有胶原结构的巨噬细胞受体（MARCO）、单细胞 RNA 测序、肿瘤微环境

100. Development and evaluation of polygenic risk scores for cancer prediction in Chinese population: a pan-cancer analysis based on the China Kadoorie Biobank

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Background

Polygenic risk scores (PRSs) have been extensively developed and utilized for individual risk prediction for the majority of diseases in European populations. However, it remains unclear how to improve the predictive accuracy of PRS for cancer risk in non-European populations.

Methods

We constructed 93 PRSs for the 13 most common cancer types using three different approaches, and evaluated these PRSs in 100,219 participants from the China Kadoorie Biobank. The optimal PRSs with the highest discriminatory ability (Harrell's C-index) were used to define genetic risk. We assessed the site-specific and cross-cancer associations of the optimal PRSs using the Cox proportional hazards regression model. We modeled 10-year absolute risk trajectories for each cancer across risk strata defined by PRSs (high risk: the top quintile; medium: quintile 2-4, low risk: the bottom quintile) and modifiable risk profiles (elevated: above the median; reduced: below the median). We also quantified the added predictive value and the explained relative risk (ERR) of integrating PRSs with modifiable risk factors for different cancers.

Results

Over a median follow-up of 11.33 years (IQR 10.18-12.26), 5,236 incident cancer cases were identified. Approximately 60% (56/93) of the constructed PRSs demonstrated significant associations with the corresponding cancer outcomes ($P<0.05$). We derived optimal PRSs to define genetic risk for nine cancer types, including esophageal cancer, stomach cancer, colorectal cancer, pancreatic cancer, lung cancer, breast cancer, cervical cancer, ovarian cancer, and prostate cancer. Each standard deviation increase in the nine optimal PRSs was significantly associated with the risk of the corresponding cancers, with hazard ratios ranging from 1.20 to 1.76. Compared with participants at low genetic risk and reduced modifiable risk scores, those with high genetic risk and elevated modifiable lifestyle scores had the highest risk of incident cancer, with HRs ranging from 1.97 (95% CI: 1.11-3.48 for cervical cancer, $P=0.020$) to 8.26 (95% CI: 1.92-35.46 for prostate cancer, $P=0.005$). We observed nine significant cross-cancer associations for PRSs ($P<0.05$) and found that the integration of PRSs and cross-cancer PRSs significantly increased the prediction accuracy for most cancers. The PRSs contributed to 2.6% to 20.3% of ERR (i.e. 20.3% for prostate cancer), while modifiable risk factors explained 2.3% to 16.7% of ERR (i.e. 16.7% for esophageal cancer) in Chinese populations.

Interpretation

We provide an approach to constructing PRSs for common cancers in non-European populations by synthesizing available evidence. For the first time, we elucidate the contribution of genetic and modifiable risk factors for nine common cancers in Chinese populations.

Key Words： pan-cancer; polygenic risk score; risk prediction; modifiable risk factor

101. An Analysis of the Gene Expression Associated with Lymph Node Metastasis in Colorectal Cancer

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Objective: This study aimed to explore the genes regulating lymph node metastasis in colorectal cancer (CRC), and to clarify their relationship with tumor immune cell infiltration and patient prognoses.

Methods: The data sets of colorectal cancer patients were collected through the Cancer Gene Atlas (TCGA) database; the differentially expressed genes (DEGs) associated with CRC lymph node metastasis were screened; a protein-protein interaction (PPI) network was constructed; the top 20 hub genes were selected; the gene ontology (GO) functions and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were enriched and analyzed. The Lasso regression method was employed to further screen the characteristic genes associated with CRC lymph node metastasis in 20 hub genes, exploring the correlation between the characteristic genes and immune cell infiltration, conducting a univariate COX analysis on the characteristic genes, obtaining survival-related genes, constructing a risk score formula, conducting a Kaplan-Meier analysis based on the risk score formula, and performing a multivariate COX regression analysis on the clinical factors and risk scores.

Results: A total of 62 DEGs associated with CRC lymph node metastasis were obtained. Among the 20 hub genes identified via PPI, only CLCAI expression was down-regulated in lymph node metastasis, and the rest were up-regulated. A total of 9 characteristic genes associated with CRC lymph node metastasis (KIF1A, TMEM59L, CLCA1, COL9A3, GDF5, TUBB2B, STMN2, FOXN1, and SCN5A) were screened by means of the lasso regression method. The 9 characteristic genes were significantly related to different kinds of immune cell infiltration, from which three survival-related genes (TMEM59L, CLCA1, and TUBB2B) were screened. A multi-factor COX regression showed that the risk scores obtained from TMEM59L, CLCA1 and TUBB2B were independent prognostic factors. Immunohistochemical validation was performed in tissue samples from patients with rectal and colon cancer.

Conclusion: TMEM59L, CLCA1 and TUBB2B were independent prognostic factors associated with lymphatic metastasis of CRC.

Key Words ： Colorectal Cancer, Lymphatic Metastasis, TMEM59L, CLCA1, TUBB2B

102. Escherichia Eoli Outer Membrane Vesicles Carrying CD47 Nanobody Target Tumor Microenvironment to Activate Macrophage Phagocytosis for Improved Tumor Immunotherapy

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Objective： The highly immunosuppressive tumor microenvironment (TME) in solid tumors often reduces the effectiveness of immunotherapy. Previous studies have found that CD47 nanoantibody (CD47nb) fused to the surface of OMV (OMV-CD47NB) can not only induce M1 polarization, but also block the "don't eat me" signal and other pathways to activate the phagocytosis of TAM on tumor cells. But,CD47 is ubiquitously expressed on normal cells, such as red blood cells and platelets， The side effects can be reduced by adding a shielding peptide to prevent binding to normal cells

Methods： hypervesiculating Escherichia coli Nissle was induced to highly express bacterial exocrine vesicles by knocking out the nlpI gene.The fusion protein CD47nb-CERX was constructed by attaching a shielding peptide CERX to CD47 nanoantibody (CD47nb), which was fused to the surface of OMV (OMV-CD47NB-CERX). CERX was digested with tumor microenvironment specific hydrolases. ELISA was used to detect the binding of OMV-CD47nb-cerx to CT26 cells. Hemagglutination and hemolysis experiments were used to explore the toxic effects of OMV-CD47nb-cerx before and after hydrolysis, Primary mouse macrophages were isolated to study the effect of OMV-CD47nb on macrophages after hydrolysis.

Results： The nlpI gene was successfully knocked out in E. coli to produce high-exocrine vesicles. Omv-cd47nb-cerx was successfully constructed, and the shielding peptide could be digested by tumor-specific hydrolases without affecting the function of OMV-CD47nb. OMV-CD47nb-cerx can block the binding of CT26 cells, block the "don't eat me" signal from CD47, and reduce the side effects of binding to normal cells. The hydrolyzed OMV-CD47nb can induce the polarization of M2 macrophages to M1, reshape the tumor immune microenvironment, and enhance the anti-tumor therapeutic effect

Conclusion： OMV-CD47nb -cerx was successfully constructed, which can reduce side effects. The hydrolyzed OMV-CD47nb can not only induce M1 polarization, but also block the "don't eat me" signal and other ways to activate the phagocytosis of TAM on tumor cells.

Key Words： Bacterial extracellular vesicles;CD47;tumor-associated macrophages

103. An individualized stemness-related signature to predict prognosis and immunotherapy responses for gastric cancer using single-cell and bulk tissue transcriptomes

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Introduction: Currently, many stemness-related signatures have been developed for gastric cancer (GC) to predict prognosis and immunotherapy outcomes. However, due to batch effects, these

signatures cannot accurately analyze patients one by one, rendering them impractical in real clinical scenario. Therefore, weaimed to develop an individualized and clinically applicable signature based on GC stemness. lIn this study, We developed an individualized stemness-related signature, which can accurately predict the prognosis and efficacy of immunotherapy for each GC sample.

Methods: Malignant epithelial cells from single-cell RNA-seq data of GC were used to identify stemness-related signature genes based on the CytoTRACE score. Using two bulk tissue datasets as training data, the enrichment scores of the signature genes were applied to classify samples into two subtypes. Then, using the identified subtypes as criteria, we developed an individualized stemness-related signature based on the within sample relative expression orderings of genes.

Results: We identified 175 stemness-related signature genes, which exhibited significantly higher AUCell scores in poorly differentiated GCs compared to differentiated GCs. In training datasets, GC samples were classified into two subtypes with significantly different survival times and genomic characteristics. Utilizing the two subtypes, an individualized signature was constructed, containing 47 gene pairs (47-GPS). In four independent testing datasets, GC samples classified as high-risk exhibited significantly shorter survival times, higher infiltration of M2 macrophages, and lower immune responses compared to low-risk samples. Moreover, the potential therapeutic targets and corresponding drugs were identified for the high-risk group, such as CD248 targeted by Ontuxizumab.

Conclusions: Overall, by integrating single-cell RNA-seq data and bulk tissue data, we developed a qualitative stemness-related signature, 47-GPS, which can accurately predict patients' prognosis and immunotherapy responses at an individual-level. This makes it applicable to real clinical scenarios and assists doctors in formulating appropriate treatment plans for GC patients.

Key Words： Gastric cancer; Stemness; Individualized signature; Prognosis; Immunotherapy responses

104. Acoustic Printing of Patient-Derived Organoids That Preserve Tumor Microenvironment for Personalized Drug Screening

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Aim: The development of personalized precision therapy models for patients has been slow and expensive, in part due to the limitations of current drug screening models in vivo and in vitro. Traditional 2D cellular models do not fully encapsulate the true 3D tumor environment. However, PDX models are too slow to model and clinical trials are difficult to perform. The lack of an appropriate model for in vitro studies has hindered the development of effective therapeutic strategies for multiple types of cancer. These drawbacks can be overcome by supplementing current testing methods with 3D in vitro culture systems (e.g., cell spheroids, organoids, and micro-tissues). Several studies have shown that organoids have the ability to respond to medications and toxins in a manner nearly identical to that of actual patients; and therefore, could potentially provide an improved platform for drug screening applications. However, many of the organoids prepared by current methods lack the tumor microenvironment derived from tumor patient tissues, which results in a diminished resemblance between organoids and tissues; thus, affecting the effectiveness of the drug testing. Herein, a technique for acoustic-droplet-printing-of-patient-derived-organoids (ADPDOs) is reported, which allows for high-throughput, high-viability, rapid, and uniform printing preparation of patient-derived organoids.

Materials and methods: In this research, we fabricated a fast, accurate acoustic droplet printing platform and established a system for the derivation and long-term culture of bladder tumor organoids through the acoustic printing technology. This acoustic droplet printing platform is

composed of a surface acoustic wave Micro–Nano chip, a horizontal moving operating platform, an acoustic signal stimulation system, and a microscope observation system. The surface acoustic wave has the advantages of low energy, low damage, no contact, and easy operation. In addition, this developed surface acoustic wave Bio-MEMS chip is designed with an open cavity, which would not clog the nozzle even with high concentration of cells. It can be printed on demand without the introduction of oil phase and improve the survival rate of tissue-derived cells. Moreover, the volume of droplets printed by the acoustic droplet printing device is controlled from picoliters to nanoliters, which can realize micro-droplet printing, and the combination with hydrophobic substrate can form nearly spherical scaffold-free microspheres on the hydrophobic receiver plate, accelerating the aggregation of cells; and thus, achieving rapid tumor spheroids formation.

Results: The printing device can print hundreds of uniformly sized cell-laden droplets at a controlled speed of 1 s a drop, which can quickly generate large quantities of homogeneous cell spheroids, making it more convenient and suitable for later drug testing and reducing sample discrepancies due to uneven sizes. Moreover, each cell droplet contains only 37.5% of gel, and only <100 nL of gel is needed in each droplet, which improves drug penetration rate and eliminates the need to remove the surrounding matrix gel with enzymes, reducing the number of experimental steps and shortening the experimental process. A total of 23 bladder cancer tissues were obtained from 23 patients and 16 patient-derived organoids were successfully established. Among them, the failure of culture in three cases might have been due to tissue contamination, which is associated with the collection of materials, and the other four unsuccessful cases may have been related to the pathological characteristics of the patients or limitations of the current organoid culture technology.

Conclusion: Comprehensive characterization of ADPDOs confirmed that they recapitulated the characteristics of the corresponding parental tumors in morphological and histological architecture after culture in vitro. The ADPDOs therapeutic response test was completed in less than 2 weeks, suggesting that the model can generate therapeutic recommendations in a clinically meaningful timeframe.

Key Words： Acoustic Droplets, CAFs, Personalized Therapy, Tumor Organoids

105. Distinct prognostic values of adenosine deaminase isoenzymes-ADA1 and ADA2 in cancer

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Objective: Adenosine deaminase (ADA) play an important role in immune response, which includes two isoenzymes: ADA1 and ADA2. This study aim to explore the roles of ADA1 and ADA2 in cancers.

Methods: Enzyme assay was used to detected the ADA1 and ADA2 activities in serum from cancer patients. Kaplan-Meier (KM) plotter was used to analyze the prognostic value of ADA1 and ADA2. TIMER2.0 was used to explore how ADA1 and ADA2 correlating with immune infiltration and immune checkpoints.

Results： There were no significant change for serum ADA1 activities in most cancer, while serum ADA2 activities were increased in most cancer. For prognosis, high ADA1 was associated with the poor survival for several cancers, including ESCC, HNSC , KIRC, KIRP, LIHC, LUAD and UCEC. However, high ADA2 expression showed a favorable prognosis in BRCA, CESC, HNSC, KIRC, KIRP, LUAD, OV, PAAD, Sarcoma and THYM. ADA1 showed a moderately positive correlation with multiple infiltrating immune cells in most cancers. ADA2 was positive correlated with B cells, CD8 T cells, Monocyte/macrophage and DCs, and was strong negatively correlated with Myeloid-derived suppressor cells.

Conclusion： Although as the isoenzyme, ADA1 and ADA2 showed the opposite prognostic value and different correlative pattern with immune infiltrating. These data demonstrated the distinct roles of ADA1 and ADA2 in cancer development, and ADA2 might act as a protective factor.

Key Words： ADA1, ADA2, Cancer, Prognosis, Immune infiltration

106. Neovascularization directed by CAVIN1/CCBE1/VEGFC confers TMZresistance in glioblastoma

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Acquisition of resistance to temozolomide (TMZ) poses a significant challenge in glioblastoma (GBM) therapy. Neovascularization, a pivotal process in tumorigenesis and development, remains poorly understood in its contribution to chemoresistance in GBMs. This study unveils aberrant vascular networks within TMZ-resistant (TMZ-R) GBM tissues and identifies the extracellular matrix (ECM) protein CCBE1 as a potential mediator. Through in vivo and in vitro experiments involving gain and loss of function assessments, we demonstrate that high expression of CCBE1 promotes hyper-angiogenesis and orchestrates partial endothelial-to-mesenchymal transition (EndMT) in human microvascular endothelial cells (HCMEC/d3) within GBM. This is likely driven by VEGFC/Rho signaling. Intriguingly, CCBE1 overexpression substantially fails to promote tumor growth, but endows resistance to GBM cells in a vascular endothelial cell-dependent manner. Mechanically, the constitutive phosphorylation of SP1 at Ser101 drives the upregulation of CCBE1 transcription in TMZ resistant tumors, and the excretion of CCBE1 depends on caveolae associated protein 1 (CAVIN1) binding and assembling. Tumor cells derived CCBE1 promotes VEGFC maturation, activates VEGFR2/VEGFR3/Rho signaling in vascular endothelial cells, and ultimately results in hyper-angiogenesis in TMZ-R tumors. Collectively, the current study uncovers the cellular and molecular basis of abnormal angiogenesis in a chemo resistant microenvironment, implying that curbing CCBE1 is key to reversing TMZ resistance.

Key Words： Glioblastoma, TMZ resistance, CCBE1, Hyper-angiogenesis

107. A 2-gene signature within blood leukocytes as diagnostic biomarkers for early colorectal cancer

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Background & Aims: Colorectal cancer (CRC) is one of the most common and deadly cancers worldwide. Here we aim to identify and develop novel diagnostic biomarkers to detect early-stage CRC.

Methods: Candidate biomarkers were identified from RNA-seq, validated using RT-qPCR essays and developed through the bioinformatics pipeline using multivariate binary logistic regression and receiver operating characteristic curve analysis.

Results: We identified a novel 2-gene signature within blood leukocytes which could robustly discriminate CRC from healthy controls (HC). Using an RT-qPCR assay based on the 2-gene signature, we detected CRC samples from HC samples with a sensitivity of 80% and a specificity of 81% in a training retrospective cohort of 314 samples and derived a logistic equation to calculate CRC risk probability termed as HIR-CRC. In an independent cohort of 178 samples, we validated 2-gene test and detected CRC from HC with a sensitivity of 82% and a specificity of 78%. Importantly, the 2-gene test can detect early-stage CRC and CRC which are tested negative for carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) with 76-88% sensitivity which is significantly higher than that of either CEA (31-56%) or CA19-9 (9-44%).

Conclusion: The 2-gene signature described here can potentially fill an unmet clinical need for a robust screening assay to identify CRC patients at early stages when potentially curative treatment options are available.

Key Words： Blood, Immune signature, early diagnosis, CRC

108. CLOMB: a validated scoring model to predict the relapse in the central nervous system of pediatric acute B-cell lymphoblastic leukemia

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To create a central nervous system relapse (CNSR) predictive model and modify the risk stratification of pediatric acute B-cell lymphoblastic leukemia (pB-ALL). Clinical data of pB-ALL was downloaded from the TARGET and split into training and internal validation cohort in a 7:3 ratio. An external validation cohort was recruited from a single-center in China. 1795 patients from the TARGET and 654 patients from the single-center were collected. In training cohort, we constructed a model called CLOMB and presented it visually using Nomogram. The C-index of CLOMB was 0.748. The AUROC for training cohort were 0.774, 0.766, and 0.754 at 1, 3, and 5 years, respectively. The internal validation cohort had AUROC values of 0.784, 0.749, and 0.742, respectively. The external validation cohort had AUROC were 0.622, 0.590, and 0.623, respectively. By X-tile software, CLOMB classified the patients into high-risk (HR) and low-risk (LR) groups using a cut-off value of 0.76. The Kaplan-Meier curves indicated that patients' EFS in HR of training cohort had significantly lower than that in LR (87.60% vs 96.80%, P-value<0.001). The internal and external validation cohort both produced the same results (90.10% vs 96.00%, P-value=0.009 in internal, and 75.00% vs 96.00%, P-value<0.001 in external). In external validation cohort, the AUROC of CLOMB was 0.590, which was significantly higher than that of MRD on day 19 and 46 (AUROC=0.536, P-value=0.009 and AUROC=0.564, P-value=0.017, respectively). Furthermore, CLOMB has shown strong power and utility in CNSR prediction and risk stratification, which may help modify treatment options in clinical routine.

Key Words： acute lymphoblastic leukemia, risk stratification, central nervous system relapse, clinical decision-making tool

109. RNA N6-methyladenosine demethylase ALKBH5 promotes bladder cancer progression through inhibiting ITGB3

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Objective： In recent years, the incidence and mortality rates of bladder cancer in China have been steadily rising, posing a significant threat to the health of our residents. N6-methyladenosine is one of the most common mRNA modifications in eukaryotic cells, and methylation has a significant impact on tumor initiation and progression. ALKBH5 has been found to play a critical role in various cancers, but its reported functions in different types of tumors are inconsistent. There are literature reports about different roles for ALKBH5 in bladder cancer, but the underlying mechanisms are not fully understood. Therefore, it is necessary to conduct functional and mechanistic studies on how ALKBH5 regulates the molecular mechanisms of tumors in bladder cancer.

Methods： We studied the role of ALKBH5 in bladder cancer through functional experiments. Additionally, we investigated the genes and pathways regulated by ALKBH5 in bladder cancer using cell transcriptome sequencing and bioinformatics analysis methods, and conducted preliminary explorations into the regulatory mechanisms.

Results： ALKBH5 exhibits elevated expression in bladder cancer tumors. In in vivo experiments, ALKBH5 significantly facilitates tumor progression, proliferation, migration, and colony formation. GO enrichment analysis reveals a close association between genes regulated by m6A methylation and cancer. GSEA gene set enrichment analysis indicates a noteworthy enrichment of the PI3K/AKT pathway. Through RT-PCR and immune imprinting experiments, the integrin family gene ITGB3 is identified as a downstream target of ALKBH5-mediated m6A modification. Mechanistically, ALKBH5 enhances the stability of ITGB3 mRNA through m6A-dependent modification. In both in vivo and in vitro experiments, ITGB3 promotes bladder cancer proliferation. In in vivo experiments specifically, ITGB3 contributes to bladder cancer migration

and invasion. Silencing ITGB3 significantly mitigates ALKBH5-dependent tumor growth and metastasis in in vivo experiments.

Conclusion ： Our study elucidates the biological functions of ALKBH5 in bladder cancer, demonstrating that ALKBH5 promotes the migration and invasion of bladder cancer cells through the stabilization of ITGB3 mRNA in an m6A-dependent manner. These findings suggest that ALKBH5 could serve as a predictive biomarker and a potential target for anti-metastatic therapy in bladder cancer patients.

Key Words： bladder cancer, m6A, ALKBH5, iTGB3

110. The Efficacy of Neoadjuvant Immunotherapy and Lymphocyte Subset Predictors in Locally Advanced Esophageal Cancer: A Retrospective Study.

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Background: Despite the recognized therapeutic potential of Programmed cell death protein 1/Programmed Death-ligand 1 (PD-1/PD-L1) inhibitors in advanced esophageal cancer (EC), their role in neoadjuvant therapy and reliable efficacy biomarkers remain elusive.

Materials and Methods: We retrospectively analyzed locally advanced EC patients who underwent surgery following a 2-cycle platinum and paclitaxel-based treatment, with or without PD-1 inhibitors (January 2020-March 2023). We assessed peripheral blood indexes and tertiary lymphoid structures (TLS) density to evaluate their impact on pathological response and prognosis, leading to a clinical prediction model for treatment efficacy and survival.

Results: Of the 157 patients recruited, 106 received immunochemotherapy (ICT) and 51 received chemotherapy (CT) alone. The ICT group demonstrated a superior pathological response rate (PRR) (47.2% vs. 29.4%, p=0.034) with comparable adverse events and postoperative complications. The ICT group also showed a median disease-free survival (DFS) of 39.8 months,

unattained by the CT group. The 1-year DFS and overall survival (OS) rates were 73% and 91% for the ICT group, and 68% and 81% for the CT group, respectively.

We found higher baseline activated T cells, lower baseline Treg cells, and a decreased post-treatment total lymphocyte and CD4+/CD8+ ratio predicted an enhanced PRR. Reduced post-treatment CD4+/CD8+ ratio and increased NK cells were associated with prolonged survival, while higher TLS density indicated poorer prognosis. Among ICT group, a lower post-treatment CD4+/CD8+ ratio indicated longer DFS and reduced post-treatment B cells indicated longer OS. A nomogram integrating these predictors was developed to forecast treatment efficacy and survival.

Conclusion: The combination of PD-1 inhibitors and chemotherapy appears promising for locally advanced EC. Evaluating the differentiation status and dynamic changes of peripheral blood immune cells may provide valuable predictive insights into treatment efficacy and prognosis.

Key Words： esophageal squamous cell , immunology, neoadjuvant chemotherapy, nomogram, prognostic factor, biomarkers

111. Machine learning-based cellular senescence signatures for prognostic prediction and effective therapeutic guidance in hepatocellular carcinoma

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Background: The high heterogeneity of hepatocellular carcinoma (HCC) is closely related to its poor prognosis and ineffective therapy. Patients’ accurate classification and differentiated therapy is critical to solving these challenges. However, effective predictive biomarkers are still lacking. Cellular senescence (CS) has been demonstrated in HCC tumorigenesis and associated with its heterogeneity. Here, we aimed to identify key CS-related genes in HCC progression by multiple machine learning algorithms and established a risk score (RS) signature to predict the prognosis and guide effective therapeutic.

Methods: The HCC patients' transcriptome expression and corresponding clinical information were obtained from TCGA (TCGA-LIHC(N=368)) and GEO (GSE14520(N=242), GSE116174(N=64), and GSE76427(N=115)) databases. The CS-related genes were provided by the MSigDB database. Differential expression genes (DEGs) were analyzed by the "limma" package and protein-protein interaction (PPI) network. Ten machine learning (ML) methods (Lasso, Enet, plsRcox, CoxBoost, StepCox, GBM, Ridge, RSF, survival-SVM, and SuperPC.) with 110 algorithms analysis were utilized to calculate the CS-related signature. Genes with significant mutations were identified by the R package "maftools". The CNV segments with significant variation in HCC were evaluated by the GISTIC2.0 method. Waterfall plots showing significant CNV segments were drawn using the "Complex Heat Map" R package. The potential biological functions and signal pathways of CS-related RS signatures were analyzed by Gene set enrichment analysis (GSEA) and Gene set variation analysis (GSVA). The "pRRophetic", "ESTIMATE" R package and ImmPort database were used to predict the response to chemotherapy and immunotherapy prediction in HCC patients.

Results: CS-related genes were associated with pathogenesis, multi-omics changes, and prognostic value of HCC patients. Total of 57 intersected CS-related genes had pathogenesis-related and multi-omics changes in HCC, and seven CS-related genes were finally screened out and constructed a CS-related RS-signature by 110 ML algorithm combinations analysis based on ten ML methods. The Kaplan-Meier analysis results revealed that the CS-related signature could effectively divided HCC patients into two prognostic RS groups, and patients in low-RS groups had a significantly higher survival rate than those in high-RS groups. The mutated genes (SMG) analysis showed a higher occurrence of TP53 (54/106, 50.94%) and OBSCN (15/106, 14.15%) mutations in high-RS group. The mutational signatures analysis revealed that high-RS group possessed the unique characteristics of signature 30, signature 24, signature 5, and signature 15, and low-RS group was marked by signature 16, signature 6, and signature 4. The CNV alteration results showed that the overall burden of copy number gain and loss was the highest in high-RS group, including copy number amplifications (1q21.3 and 17q25.3) and deletions (17p13.1, 17p11.21, 13q14.2, and 4q35.1).The potential biological functions and signal pathways of CS-related RS signatures analysis demonstrate the nucleic acid-related pathways (DNA repair pathways) and PI3K/AKT/mTOR pathway were significantly activated in high-RS

group. Patients in high-RS group had lower IC50 responses to the three drugs in HCC: sorafenib, cisplatin, and paclitaxel, while low-RS group patients showed a potentially more effective benefit to immunotherapy through specific immune-related pathways.

Conclusions: In summary, we used multiple ML algorithms to construct a CS-related RS-signature, which could efficiently classify HCC patients into high- and low-RS groups, and could predict patient's prognosis, beyond the traditional clinicopathological risk factors. Moreover, the signature may provide a more appropriate and reliable chemotherapy/immunotherapy drugs for HCC patients, which can help clinical management and improve the prognosis of HCC patients. Our study further demonstrated the important value of CS in HCC heterogeneity and established an effective signature for predicting HCC patients' progression, prognosis, and therapy based on CS in hepatocarcinogenesis.

Key Words： Hepatocellular carcinoma; cellular senescence; machine learning; prognosis signature; chemotherapy; immunotherapy

112. 超级增强子驱动的 lncRNA-LINC00880 作为 CDK1 和 PRDX1 之间的支架，促进肺腺癌的恶性进展

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Super-enhancers (SEs) are regulatory element clusters related to cell identity and disease. While the studies illustrating the function of SE-associated long noncoding RNAs (lncRNAs) in lung adenocarcinoma (LUAD) remains few. In our research, a SE-driven lncRNA, LINC00880, was identified, which showed higher expression in LUAD compared to normal tissues and indicated worse outcomes in stage I LUADs. We found that the transcription factor (TF) FOXP3 could simultaneously occupy the promoter and SE regions of LINC00880 to promote its transcription. The oncogenic function of LINC00880 was validated both in vitro and in vivo. Mechanically, LINC00880 binds to the protein CDK1 to increase its kinase activity, which rely on the phosphorylation state of pT161 in CDK1. LINC00880 also promotes the interaction between CDK1 and PRDX1. Moreover, LINC00880 interacts with PRDX1, which indicates that

LINC00880 acts as a protein scaffold between CDK1 and PRDX1 to form a ternary complex, thereby resulting in the activation of PI3K/AKT to promote malignancy. Our results reveal that the SE-associated lncRNA LINC00880 regulates the CDK1/PRDX1 axis to sustain the malignancy of LUAD, providing a novel therapeutic target.

关键字： super-enhancer, LINC00880, LUAD, CDK1

113. Mitochondria-translocated ALDH1L1maintains mitochondrial redox homeostasis in cancer cells

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Background and Objectives: Abnormal elevation of reactive oxygen species (ROS) within mitochondria is a common characteristic of tumor cells, but mitochondria are still able to maintain a balance in redox reactions. Surprisingly, it was found that mitochondrial ROS significantly increased after the knockout of the transcription factor A mitochondrial (TFAM). However, the mechanism by which TFAM regulates mitochondrial redox homeostasis has not been reported. Moreover, it remains unaddressed whether TFAM fulfills its functions alone or whether its function depends on the interplay with other factors within a complex.

Methods: The study utilized techniques such as immunoprecipitation combined with mass spectrometry and immunofluorescence to screen and identify antioxidant proteins that were enriched near TFAM. To validate the role of ALDH1L1 mitochondrial translocation in regulating mitochondrial redox reactions, mouse models with liver- and intestine-specific ALDH1L1 gene knockout were created using the Cre-loxP system, and stable human liver cancer and colon cancer cell lines with ALDH1L1 point mutations were generated using lentiviral vectors.Using mitochondrial ROS inducers or inhibitors to regulate the mitochondrial translocation of ALDH1L1, investigating the specific molecular mechanisms mediating ALDH1L1 mitochondrial translocation. Explore the binding domain of ALDH1L1 and TFAM by truncation method, inhibit the interaction between mitochondrial ALDH1L1 and TFAM, observe the change of mitochondrial redox

homeostasis and the malignant phenotype of tumor cells, and evaluate the biological significance of ALDH1L1 mitochondrial translocation in tumor cells.

Results: Mass spectrometry identified antioxidant proteins that were enriched near TFAM, including cytoplasmic aldehyde dehydrogenase ALDH1L1, which was found to undergo mitochondrial translocation in tumor cells and interact with TFAM. Super-resolution results confirmed the co-localization of TFAM and ALDH1L1 in mitochondria across various tumor cell types. Significant positive correlations between TFAM and ALDH1L1 co-localization were observed in clinical samples of liver cancer and colon cancer. Knocking out ALDH1L1 in tumor cells and reintroducing point mutant ALDH1L1 protein resulted in a decrease in mitochondrial NADPH abundance by 11.3%, an approximately 1.8-fold increase in reactive oxygen levels, a nearly 4.7-fold increase in cell apoptosis levels, and significant effects on TFAM-mediated mtDNA replication. These findings suggest that ALDH1L1 in tumor cells can prevent oxidative stress-induced cell apoptosis through its binding to TFAM. Inducing or inhibiting mitochondrial ROS using mitoQ or mito-LND revealed that under higher superoxide state feedback, cytoplasmic ALDH1L1 binds to heat shock proteins and undergoes mitochondrial translocation. Furthermore, after interacting with ALDH1L1, TFAM acts as a protective scaffold protein that prevents the degradation of ALDH1L1 by mitochondrial proteases, thereby stabilizing its antioxidant function.

Conclusion: The mitochondrial translocation of ALDH1L1 in tumor cells and its interaction with TFAM play a crucial role in maintaining mitochondrial redox homeostasis. This discovery deepens our understanding of the mechanisms through which tumor cells resist oxidative damage and provides potential targets for the prevention and treatment of tumors.

Key Words： Cytoplasmic aldehyde dehydrogenase; mitochondrial transcription factor A; reactive oxygen species; redox homeostasis

114. 单细胞测序揭示了皮肤鳞癌微环境异质性

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研究目的：皮肤鳞状细胞癌（Cutaneous Squamous Cell Carcinoma ,CSCC）是一类起源于皮肤角质形成细胞的恶性肿瘤，是非黑素瘤皮肤癌中发病率第二高的肿瘤。本研究旨在单细胞水平探究 CSCC 肿瘤微环境及其异质性，为阐明 CSCC 发病机制及开发药物靶点提供新的方向。

研究方法：对 3 例 CSCC 癌和癌旁组织进行单细胞测序，利用 PCA 降维、UMAP 可视化等确定主要细胞簇，利用 GO 分析、KEGG 分析、通路富集分析、拟时序分析等探究 CSCC 的细胞亚群功能及其异质性，并通过免疫组化验证蛋白表达。

结果：聚类分析显示，CSCC 细胞可分为上皮细胞，内皮细胞，成纤维细胞等 11 个细胞亚群。通路富集分析提示与细胞增殖、癌症进展和转移密切相关的通路（NOTCH 信号通路、NF-κB 通路、P53 通路）在肿瘤上皮细胞中高度富集，而与免疫活化相关的通路（IFN-γ，IL-6, IL-2，炎症反应等）显著下调。肿瘤中浸润的中性粒细胞可能通过激活 IL-4, IL-10, IL-13 等 Th2 型细胞因子，发挥抑制肿瘤的作用。此外，T&NK 细胞可通过干扰素刺激通路，白介素通路，TCR 通路等参与肿瘤微环境重编程，而巨噬细胞和树突状细胞则可能通过三羧酸循环促进巨噬细胞向 M2 型极化，发挥促肿瘤作用。

结论：本研究刻画了 CSCC 肿瘤微环境的单细胞图谱，证明了 CSCC 细胞亚群组成的广泛异质性。研究发现的多种细胞亚群特异的差异表达基因和关键通路有助于进一步理解 CSCC 的发生机制，为开发新的免疫治疗靶点提供基础。

关键字：皮肤鳞癌，单细胞测序，肿瘤微环境

115. Anti-BIRC5 autoantibody serves as a valuable biomarker for diagnosing AFP-negative Hepatocellular carcinoma

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Background: Autoantibodies targeting tumor-associated antigens (TAAbs) have emerged as promising biomarkers for early cancer detection. This research aimed to assess the diagnostic capacity of anti-BIRC5 autoantibodies in detecting AFP-negative hepatocellular carcinoma (ANHCC).

Methods: This research was carried out in three stages (discovery phase, validation phase, and evaluation phase) and included a total of 849 participants. Firstly, the anti-BIRC5 autoantibody was discovered using protein microarray, exhibiting a higher positive rate in ANHCC samples (ANHCCs) compared to Normal Control samples (NCs). Secondly, the anti-BIRC5 autoantibody was validated through enzyme-linked immunosorbent assay (ELISA) in 85 ANHCCs and 85 NCs from two clinical centers (Zhengzhou and Nanchang). Lastly, the diagnostic usefulness of the anti-BIRC5 autoantibody for (hepatocellular carcinoma (HCC) was evaluated by ELISA in a cohort consisting of an additional 149 AFP-positive hepatocellular carcinoma samples (APHCCs), 95 ANHCCs and 244 NCs. The association of elevated autoantibody to high expression of BIRC5 in HCC was further explored by the database from prognosis, immune infiltration, DNA methylation, and gene mutation level.

Results: In the validation phase, the area under the ROC curve (AUC) of anti-BIRC5 autoantibody to distinguish ANHCCs from NCs in Zhengzhou and Nanchang centers was 0.733 and 0.745, respectively. In the evaluation phase, the AUCs of anti-BIRC5 autoantibody for identifying ANHCCs and HCCs from NCs were 0.738 and 0.726, respectively. Furthermore, when combined with AFP, the AUC for identifying HCCs from NCs increased to 0.914 with a sensitivity of 77.5% and specificity of 91.8%. High expression of BIRC5 gene is not only correlated with poor prognosis of HCCs, but also significantly associated with infiltration of immune cells, DNA methylation, and gene mutation.

Conclusion: The findings suggest that the anti-BIRC5 autoantibody could serve as a potential biomarker for ANHCC, in addition to its supplementary role alongside AFP in the diagnosis of HCC. Next, we can carry out specific verification and explore the function of anti-BIRC5 autoantibodiy in the occurrence and development of HCC.

Key Words： AFP-negative hepatocellular carcinoma, BIRC5, autoantibody diagnostic, tumor marker

116. 乳腺癌新辅助治疗前后生物标志物的变化及其临床意义

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目的：本研究的主要目的是探讨乳腺癌患者接受新辅助治疗前后生物标志物术的一致性/不一致率，并分析生物标志物变化对内在亚型的影响，探讨 HER2 低表达亚型的一致率分析。

方法：搜集河北医科大学第四医院 2015 年 6 月至 2017 年 12 月期间接受新辅助治疗后乳腺手术切除患者 473 例，其中 461 例乳腺癌患者在术前进行空芯针活检，406 例患者未获得 pCR。

结果：我们对 406 例未获得 pCR 患者进行新辅助治疗前后标志物的变化，总的来说，新辅助治疗后激素受体、HER2 和 Ki67 的变化均呈负向趋势改变，一致性分析结果显示，HER2 是最稳定的生物标志物（Kappa=0.925），而 Ki67 是最容易发生改变的（Kappa=0.176）。对于分子分型的变化，共有 135 例患者新辅助治疗后分子分型发生了变化，其中 Luminal B 型-HER2 阴性新辅助治疗术前术后的一致率最差（38.8%），表现为高度不稳定性。三阴性型乳腺癌分子分型相对稳定（93.9%）。新辅助治疗对 HER2 低表达的影响，结果显示，新辅助治疗后 HER2 低表达从原发乳腺癌到残余病灶表现出了高度不稳定性。对于新辅助治疗术后不同分子分型患者与临床病理特征的比较，5 种分子亚型组间患者的年龄，组织学类型，淋巴结转移情况，脉管瘤栓，神经受侵均无统计学差异（P＞0.05），结果表明，分子分型与临床病理特征无相关性。

结论：乳腺癌新辅助治疗前后 HER2 表达是最稳定的生物标志物，但 HER2 低表达表现为高度不稳定性，LuminalB 型-HER2 阴性患者表现为高度不稳定性。

关键字：乳腺癌，新辅助治疗，生物标志物，HER2

117. 基于转录组差异表达基因谱构建乳腺癌预后预测模型

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目的：尽管乳腺癌的预后有所改善，仍有部分患者肿瘤进展，此过程所涉及的分子机制目前尚不清楚，因此我们筛选癌症基因组图谱（TCGA）数据库中浸润性乳腺癌患者的转录组数据对其进行生物信息学分析，确定与乳腺癌进展相关的关键基因和信号通路，旨在开发一种基于转录组数据分析的乳腺癌预后模型。

方法：从 TCGA 数据库筛选并下载 1102 例乳腺癌肿瘤组织和 113 例癌旁正常组织的基因表达谱和临床数据，使用 R 语言确定差异表达基因（DEGs）。对 DEGs 进行 GO 富集分析和 KEGG 通路富集分析，深入挖掘差异基因的功能及所在的信号通路，筛选乳腺癌显著差异基因注释情况和通路富集情况并可视化。应用 Cox 比例风险回归进行生存分析，绘制列线图以预测患者预后。校准图检验列线图的一致性，C 指数和 Time-ROC 曲线检验列线图的区分度。

结果：1. 通过差异基因表达分析，基因的表达量以| log2FoldChange |≥2 和 P＜0.05 为截断值进行筛选后，确定 3373 个 DEGs，其中 2243 个基因上调，1230 个基因下调。2. GO 富集分析结果表明，在生物学过程中，DEGs 富集最多的是膜电位的调节；在细胞成分中，DEGs 富集最多的是含胶原蛋白的细胞外基质；在分子功能中，DEGs 富集最多的是信号受体活化因子活性。KEGG 富集通路分析，结果发现 DEGs 最显著富集的是神经活性配体受体相互作用通路。3. 进一步确定 7 个显著差异表达基因，其中包括 KIF4A、COL11A1、PKMYT1、LINC01614 4 个上调基因；FHL1、LYVE1、TNS1 3 个下调基因。4. Kaplan-Meier 分析证明，LYVE1 表达水平越低，患者 OS 率越高，预后越好；而随着临床分期越高，患者 OS 率越低，预后越差。5. 构建列线图预后模型，以预测乳腺癌患者的总生存率（OS）。预测 OS 率的校准图（95% CI：66.36−93.72；AUC：0.780）表明，列线图表现良好，具有较高的预测能力。

结论：差异表达基因参与的生物学过程涉及细胞外基质的调节、跨膜转运过程中膜电位的调节以及信号转导通路的调节，这些可能在乳腺癌发生发展中发挥着一定的作用。

关键字：乳腺浸润性癌，差异表达基因，癌症基因组图谱

118. 乳腺癌新辅助治疗后非pCR患者TILs与淋巴结的关系及其预后意义

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目的：乳腺癌新辅助治疗会影响肿瘤和肿瘤微环境。较高的治疗前肿瘤浸润淋巴细胞（TILs）与病理完全缓解（pCR）率增加和长期生存显著相关。而淋巴结状态对乳腺癌也具有重要的预后意义。因此，本研究探讨了新辅助治疗后非 pCR 患者 TILs 表达与淋巴结状态之间的关系及预后意义。

方法：回顾性分析 2009-2017 年河北医科大学第四医院经新辅助治疗后非 pCR 的 1048 例乳腺癌患者的临床病理资料，对治疗后的 TILs 进行了评估，Spearman 等级相关性分析评估了 TILs 与淋巴结状态、淋巴结转移个数以及淋巴结转移最大径之间的相关性，通过 COX 比例风险回归进行单、多因素分析进而确定与预后相关的因素，Kaplan-Meier 分析用于评估乳腺癌患者的无病生存期（DFS）和总生存期（OS）。 所有统计检验均为双侧，$P<0.05$ 具有统计学意义。

结果：本研究中乳腺癌新辅助治疗后非 pCR 患者均为女性，平均年龄 50±10.3 岁（24-77 岁）。新辅助治疗后 TILs 与淋巴结状态（r=-0.163）、淋巴结转移个数（r=-0.127）以及淋巴结转移最大径（r=-0.125）之间均呈显著负相关（$P<0.001$）。在单因素分析中，新辅助治疗后 TILs 水平，淋巴结状态，淋巴结转移个数以及淋巴结转移最大径是 DFS 和 OS 重要的预后因素（$P<0.05$）。在多因素分析中，新辅助治疗后 TILs 水平，淋巴结转移个数以及淋巴结转移最大径是 DFS 和 OS 的重要独立预后因素（$P<0.05$）。此外，还分析了不同 TILs 分组中淋巴结状态对预后的影响，结果表明高水平 TILs 分组中无淋巴结转移的非 pCR 患者总生存期长（P=0.041）。

结论：新辅助治疗后 TILs 高水平、淋巴结转移个数较少以及淋巴结转移最大径较小的非 pCR 患者复发转移风险低，总生存期长。

关键字：新辅助治疗，TILs，淋巴结状态，预后

119. 蓝激光成像技术联合碘染色在早期食管癌性病变中的应用

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摘 要:目的 探究内镜下蓝激光成像技术（Blue laser imaging, BLI）联合碘溶液染色在诊断食管早期癌性病变中的价值。

方法 选取 2020 年 9 月到 2022 年 6 月通过问卷调查筛查出食管早癌高危人群 120 例，通过随机数字表法分为四组:白光内镜(30 例)、蓝激光成像技术(30 例)、碘染色组(30 例)、BLI 联合碘染色组(30 例),以病检结果为诊断的金标准,应用 Kappa 一致性检验,评价四组内镜检查结果与病理结果的一致性。

结果 对于食管早期癌性病变的筛查,白光组、蓝激光成像技术组、碘染色组以及蓝激光成像联合碘染色组与病理诊断的总体符合率分别为:80.00%、83.33%、86.67%、93.33%,敏感度分别为: 75.00%、80.00%、81.82%、90.91%, 特异度分别为: 83.33%、85.00%、89.47%、94.74%,阳性预测值分别为:75.00%、72.73%、81.82%、90.91%,阴性预测值分别为:83.33%、89.47%、89.47%、94.74%,以及 Kappa 值分别为:0.583、0.634、0.713、0.856。蓝激光与碘染色联合组与病理诊断的总体符合率、敏感度、特异度、阳性预测值、阴性预测值、Kappa 值均高于白光内镜、蓝激光成像组及碘染组。

结论 蓝激光成像技术联合碘染色有助于内镜医生提高对食管早期癌性病变的检出率。

关键字：蓝激光成像技术； 碘染色； 食管癌性病变

120. 乳腺癌主要 SWI/SNF 复合物亚基突变/缺失与肿瘤免疫反应及预后的关系

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目的：SWI/SNF 复合物由 10-15 个亚基组成，参与多种肿瘤的发生、发展。20%以上的恶性肿瘤存在 SWI/SNF 复合物亚基基因突变。本文章旨在探讨乳腺癌中主要 SWI/SNF 复合物亚基突变/缺失在预后及肿瘤免疫反应中的意义。

方法：利用 cBioPortal、 UALCAN 及 TISIDB 数据集统计分析乳腺癌中主要 SWI/SNF 亚基突变 / 缺失情况，及其与临床预后、肿瘤突变负荷、免疫抑制分子表达及肿瘤浸润淋巴细胞的关系。

结果：乳腺癌中主要 SWI/SNF 亚基发生突变/缺失占比前 6 位的亚基为 ARID1A、ARID1B、SMARCA2、SMARCA4、ARID2、PBRM1，突变率分别为 5%、4%、3%、3%、2.3%、1.8%。其中伴有 ARID1B、SMARCA4 突变的患者无进展生存期明显降低（P＜0.05）。相对于正常乳腺组织，在乳腺浸润性癌中，ARID1A、ARID2、SMARCA4 呈明显高表达（P＜0.05）。而 ARID1B、PBRM1、SMARCA2 呈低表达（P＜0.05）。cBioPortal 数据库分析显示 ARID1A、ARID1B、SMARCA2、ARID2、PBRM1 与免疫抑制分子 CD274 mRNA 表达呈正相关，与 CTLA4 mRNA 表达呈负相关（P＜0.05）。

结论：乳腺癌中主要 SWI/SNF 复合物亚基突变 / 缺失参与乳腺癌的发生、发展，并作用于肿瘤免疫反应，可作为预测乳腺癌免疫疗法是否有效的标记。

关键字： 乳腺癌；SWI/SNF 复合物亚基；突变/缺失；肿瘤免疫

121. The clinical diagnostic value of the super-enhancer-associated long noncoding RNA RP11-803D5.4 and AC005592.2 in colorectal cancer

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Purpose： Super-enhancer-associated long noncoding RNAs (SE-lncRNAs) play crucial roles in the pathogenesis of CRC and hold promise as noninvasive biomarkers for CRC diagnosis. RP11-803D5.4 and AC005592.2 were identified as SE-lncRNAs of interest via SE-lncRNA microarray analysis, and our study aimed to evaluate the clinical value of these two SE-lncRNAs in CRC diagnosis and prognosis assessment.

Methods： Fluorescence quantitative real-time PCR (qRT－PCR) was used to measure the expression of RP11-803D5.4 and AC005592.2 in the tissues and serum of CRC patients. Receiver operating characteristic (ROC) curves were generated to determine the predictive value of the two SE-lncRNAs. Functional assays were applied to assess the ability of RP11-803D5.4 to promote the proliferation, migration, and invasion of CRC cells.

Results： The two SE-lncRNAs were significantly upregulated in CRC tissue and serum samples vs. corresponding controls. ROC curve analysis indicated that RP11-803D5.4 (AUC=0.842) and AC005592.2 (AUC=0.811) had high diagnostic performance for CRC. The combination of RP11-803D5.4, AC005592.2, and CEA had an AUC of 0.946 and distinguished CRC patients and healthy controls better than either SE-lncRNA alone. The serum levels of RP11-803D5.4 and AC005592.2 were strongly correlated with their tissue expression levels. The expression levels of the two SE-lncRNAs were significantly lower in postoperative samples than in preoperative samples. Furthermore, similar to the findings of previous studies on AC005592.2, high RP11-803D5.4 expression promoted the proliferation, invasion, and migration of CRC cells.

Conclusion： The findings suggested that RP11-803D5.4 and AC005592.2 are upregulated in CRC and that they act as crucial promoters of CRC progression and might serve as noninvasive biomarkers for diagnosing CRC.

Key Words：colorectal cancer, super-enhancer-associated long noncoding RNA, RP11-803D5.4, AC005592.2, biomarker

122. 肿瘤浸润淋巴细胞对乳腺导管原位癌的预后价值：系统回顾和 meta 分析

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目的：本研究旨在评估肿瘤浸润淋巴细胞（tumor-infiltrating lymphocytes，TILs）及其亚型的浸润程度对乳腺导管原位癌（ductal carcinoma in situ，DCIS）预后价值。

方法：在 PubMed、Web of Science、Cochrane Library 和 EMBASE 数据库进行系统检索，以确定 2023 年 10 月 15 日前发表的符合纳入条件的文献。研究筛选、数据提取和偏倚风险评估由两名独立的审稿人进行。所有统计计算均采用 StataSE14.0 版软件进行。

结果：根据预先确定的纳入和排除标准，8 项回顾性队列研究共 3199 例患者，被纳入本荟萃分析。汇总的数据显示，与低 TILs 水平的 DCIS 患者相比，高 TILs 水平的患者具有更短的无病生存期（disease-free interval，DFS）（HR=1.91，95%CI：1.40 - 2.60，P<0.0001）。然而，根据 TILs 浸润程度高低分层的患者同侧乳腺事件（ipsilateral breast event，IBE）的发生率无差异（HR=1.52，95%CI：0.78 - 2.96，P=0.22）。另外，TILs 对 IBE 的预测价值在 CD4 淋巴细胞亚组（HR=1.66，95%CI：1.07 - 2.58，P=0.02）中显著，具有高密度 CD4+TILs 的患者往往同侧复发的发生率较高。另外，FOXP3 也是 DCIS 的不良预后因素，FOXP3 高表达与较短的复发间隔相关（HR=1.85，95%CI：1.15 - 2.97，P=0.01）。在其他淋巴细胞亚群，如 CD8+TILs（HR=0.99，95%CI：0.65 - 1.51，P=0.97）和 CD20+TILs （HR=1.05，95%CI：0.71 - 1.57，P=0.80），并未发现它们和 IBE 的累积发病率之间的显著联系。

结论：本研究是第一个系统评估 TILs 与 DCIS 预后之间关系的荟萃分析，并比较了 TILs 不同亚型的预后预测作用。我们的研究表明，肿瘤微环境中 TILs 的浸润程度为 DCIS 患者的长期生存提供了必要的信息，高水平的 TILs 与更短的 DFS 具有显著相关性。另外，虽然总 TILs 水平与同侧复发无相关性，但部分 TILs 特异性表型（CD4+TILs 和 FOXP3+TILs）有影响复发的趋势。

关键字： 肿瘤浸润淋巴细胞，乳腺导管原位癌，预后，meta 分析

123. HR 阳性乳腺癌中 HER2 低表达与 HER2-0 临床病理特征对比研究

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目的：对比激素受体（Hormone receptors，HR）阳性乳腺癌中 HER2 低表达与 HER2-0 患者临床病理特征的差异。

方法：收集 2016 年 1 月-2018 年 1 月，河北医科大学第四医院收治的 HR 性乳腺癌患者共 2032 例，将患者分为三组，第一组为 HER2 免疫组化为 0 患者 424 例（20.9%），第二组为 HER2 免疫组化为 1+患者 579 例（28.5%），第三组为 HER2 免疫组化 2+，且经 FISH 检测结果为阴性患者 1029 例（50.6%）。对比三组患者临床病理特征的不同，如肿物大小、年龄、淋巴结转移、Ki67 表达、脉管瘤栓、神经侵犯等临床病理特征。

结果：HER2 结果为 0 与 1+患者对比，HER2 -0 组患者肿物大小较小、组织学分级较低、神经侵犯较少、Ki67 表达较低，差异有统计学意义（$p<0.05$）。HER2 结果为 0 与 2+且 FISH 阴性患者对比，HER2-0 组患者肿物大小较小、组织学分级较低、神经侵犯较少、Ki67 表达较低、淋巴结转移较少，差异有统计学意义（$p<0.05$）。

结论：HR 阳性性乳腺癌患者中 HER2 低表达可能提示乳腺癌患者较高的恶性程度，对于推测预后，指导临床治疗有一定的指导意义。

关键字： 激素受体；乳腺癌；HER2；低表达

124. Integrated analysis of FANCE expression and its regulatory role in the immune microenvironment of Oral Squamous Cell Carcinoma

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Objective: Oral squamous cell carcinoma (OSCC) presents a significant health challenge due to a complex aetiology and limited effects of treatment strategies. Despite its role in DNA repair, the

specific function of FANCE in OSCC pathophysiology remains unclear. We aimed to determine the prognostic significance of FANCE and its effects on the tumor microenvironment (TME) in patients with OSCC.

Methods: We comprehensively analysed TCGA database to correlate FANCE expression with clinical features of OSCC. The role of the FANCE gene was elucidated by analysing differential expression, survival, immune cell infiltration and unsupervised clustering. We determined FANCE expression in OSCC cell lines using qRT-PCR and effects in cell proliferation and migration in vitro after FANCE knockdown. Immune cell markers and FANCE were analyzed in OSCC tissues by immunohistochemical (IHC) staining.

Results: Abundant FANCE expression in patients with OSCC correlated with larger tumors, advanced clinical stage of the disease, and poor survival. Machine learning cluster analysis segregated OSCC into subgroups with distinct FANCE expression, which corresponded to differences in immune cell infiltration. Furthermore, FANCE expression negatively correlated with immune cell markers in tumor samples. Knockdown of FANCE inhibited OSCC cell proliferation and migration and its expression negatively correlated with immune cell markers in tissue samples.

Conclusions: FANCE is a potential oncogene, a biomarker of a poor prognosis, and a modulator of the OSCC tumor microenvironment.

Key Words ： oral squamous cell carcinoma, FANCE, biomarker, prognosis, tumor microenvironment

125. HER2 低表达乳腺化生性癌的临床病理特征及预后分析

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目的：探讨乳腺化生性癌（MBC）HER2 低表达患者的临床病理特征，分析其预后影响因素。

方法：收集河北医科大学第四医院病理科 2005 年 1 月-2022 年 1 月间诊断的 MBC 共 113 例，同期乳腺浸润性导管癌（IDC）673 例。应用免疫组织化学（IHC）方法进行 ER、PR、HER2、Ki67 染色，根据 HER2 表达情况将 MBC 患者分为 HER2-0 组（HER2 IHC 结果为 0）共 72 例，HER2 低表达组（HER2 IHC1+/IHC 2+且 FISH-）共 35 例，HER2 阳性组（HER2 IHC3+/IHC 2+且 FISH+）共 6 例。对比 MBC 患者 HER2-0 组与 HER2 低表达组患者临床病理特征及预后的差异，对比 MBC HER2 低表达患者及 IDC HER2 低表达患者临床病理特征及预后的差异。

结果：MBC 组患者的中位年龄 55 岁，肿物最大径 0.6~19 cm，中位数为 3.5 cm。MBC 患者 HER2 低表达组 Ki67 高表达率高于 HER2-0 组，差异有统计学意义（P<0.05）。MBC 患者 HER2 低表达组与 IDC 患者 HER2 低表达组相比，肿瘤大小，淋巴结转移、Ki67 表达、脉管瘤栓情况，差异有统计学意义（均 P<0.05）。

结论：MBC 在临床少见，与 IDC 相比，通常体积较大、淋巴结转移较少、Ki67 增殖指数较高。

关键字： 乳腺肿瘤；化生；HER2 低表达；临床病理；预后

126. 乳腺癌染色质调节因子特征和预后模型的建立

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目的：染色质调节因子（chromatin regulators,CRs）是一类具有特殊功能结构域的酶，能够形成和维持表观遗传状态。CRs 通常分为三大类：DNA 甲基化、组蛋白修饰和染色质重塑因子，CRs 的异常表达与炎症、细胞凋亡、自噬和增殖等多种生物学过程有关，这表明 CRs 的失调可能导致包括癌症在内的多种疾病的发展。本文通过生物信息学分析，重点研究了乳腺癌患者中 CRs 的表达谱和预后价值。

方法：从 FACER 数据库中(http://bio-bigdata.hrbmu.edu.cn/FACER/)中获得染色质调节因子（CRs）。从 TCGA 数据库下载乳腺癌 mRNA 表达数据和临床信息。进行 Cox 回归分析和 LASSO 回归分析以筛选相关预后基因并构建预测乳腺癌患者预后的模型。Kaplan-Meier 分析用于评估高风险组和低风险组之间的预后。并在 GEO 数据集中进行验证。研究还进行了功能富集分析和蛋白质-蛋白质相互作用分析，以探索 CRs 的潜在功能。

结果：研究成功构建并验证了基于 7 个基因（BRCA1、BRCA2、CHAF1B、EXOSC4、FTO、HMGA1、TDRKH）的风险模型，TCGA 数据集中基于 CRs 特征的乳腺癌基因预测准确性在 1 年、3 年、5 年时分别为 0.752、0.742、0.779。功能分析表明 CRs 主要富集于癌症相关的信号通路。基于 CRs 的模型也与免疫细胞浸润和免疫检查点相关。

结论：本研究为乳腺癌中 CRs 的功能提供了新的见解，确定了预测乳腺癌患者预后的潜在生物标志物。

关键字：染色质调节因子，乳腺癌，TCGA，预后

127. 肿瘤相关浸润免疫细胞及 PD-L1 表达在 HER2 过表达型乳腺癌中的预后价值

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目的：肿瘤浸润淋巴细胞（TIL）是乳腺癌特定亚型的重要预后因素。然而，迄今为止，在 HER2 阳性乳腺癌病例中，PDL1 表达和肿瘤浸润淋巴细胞（TIL）的报道很少。

方法：采用组织芯片技术对 156 例 HER2 过表达型浸润性乳腺癌患者进行 CD8、CD4 和 PD-L1（SP142）免疫组织化学检测。收集患者完整临床资料，全部病例随访资料完整（23 例复发，2 例死亡）。以 PD-L1 表达状态和 CD8/CD4+TILs 浸润程度为依据，分析不同肿瘤免疫微环境（TIME）与患者预后的关系。

结果：HER2 过表达型乳腺浸润性癌中，PD-L1 表达阳性率为 31.4%（49/156）。我们发现 PD-L1 表达与 DFS 之间无相关性（χ^2=0.383 ，P=0.563），肿瘤免疫微环境与 DFS 相关（χ^2= 32.454，48.339，P 均＜0.001）。

结论：TIME-CD4 和 TIME-CD8 淋巴细胞浸润与 HER2 阳性乳腺癌的 DFS 有关。基于 CD4+的 TIME 分组中，CD4-/PD-L1-组患者预后组好，基于 CD8+的 TIME 分组中，CD8+/PD-L1-组患者预后最好。

关键字： 乳腺癌，TILs，PD-L1，HER2 过表达

128. 高糖通过调节 TCF7L2 表达影响乳腺癌患者预后

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目的：研究表明糖尿病患者患乳腺癌的风险相对较高。高血糖和胰岛素抵抗可能促进乳腺癌的发展，影响乳腺癌的治疗结果和预后。接受乳腺癌治疗的糖尿病患者可能面临更高的手术风险、化疗副作用和复发率。但目前并不清楚糖尿病是如何影响乳腺癌的预后的。进一步的研究和探索将有助于更好地了解糖尿病和乳腺癌之间的关系，并为乳腺癌治疗提供新的策略和方法。

方法：使用 The Cancer Genome Atlas (TCGA)数据库下载临床和 RNA-seq 数据。采用单因素和多因素 Cox 分析筛选糖尿病相关差异基因，构建预测特征。采用风险评分法将所有患者分为高危组和低危组。采用 Kaplan-Meier 法分析两组患者的总生存期(OS)，验证其预测特征。对两组患者进行免疫功能、免疫浸润、免疫检查点分析。然后，我们使用单细胞分析来检测这些差异表达基因在乳腺癌细胞中的分布，并通过免疫组织化学验证它们，此外为了进行机制研究，我们使用高糖刺激乳腺癌 4T1 细胞，检测 4T1 细胞 TCF7L2 的表达情况，并通过 si-TCF7L2 对乳腺癌 4T1 细胞进行敲减，敲减后观察乳腺癌 4T1 细胞的迁移，侵袭以及增殖情况。

结果：选择 5 个与糖尿病表达相关的基因(TCF7L2、BGLAP、MGAM、FOXM1、TNFRSF1A)构建乳腺癌预后特征(图 1)。经验证，预测特征的 ROC 曲线的 AUC 值为 0.76，1 年、3 年、5 年的 AUC 值分别为 0.770、0.735、0.76(图 2)。将 TCGA 临床资料随机分为训练组和验证组。验证结果与预期一致。应用预后特征将乳腺癌患者分为高、低危组。随后的免疫分析显示，免疫浸润、免疫状态和免疫检查点在高危组和低危组之间存在显著差异。此外，我们进行了单细胞测序，结果显示 TCF7L2 在乳腺癌细胞中表达(图 3)。随后，我们进行免疫组化验证，结果显示乳腺癌合并糖尿病患者中 TCF7L2 表达显著升高。此外，高糖培养可以使乳腺癌 4T1 细胞的 TCF7L2 表达升高，且会增加乳腺癌 4T1 细胞的迁移，侵袭以及增殖情况。然而，干扰了 TCF7L2 后高糖的刺激无法影响乳腺癌 4T1 细胞的迁移，侵袭以及增殖情况。

结论：高血糖可影响乳腺癌患者 TCF7L2 的表达，进而影响肿瘤细胞的迁移侵袭以及增殖情况，从而影响患者预后。

关键字：糖尿病，TCF7L2，乳腺癌，预后，预测模型

129. 与乳腺癌预后不良相关的调控基因的生物信息学分析

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目的：筛选在乳腺癌中发挥调控作用的基因，并验证其在乳腺癌预后中的作用。

方法：从 Gene Expression Omnibus（GEO）数据库下载 GSE38959 微阵列数据集，用 GEO2R 工具筛选出在乳腺癌组织中表达上调的基因，筛选条件 logFC > 2，P < 0.05；从基因表达谱交互分析（Gene Expression Profiling Interactive Analysis, GEPIA）数据库中下载乳腺癌的数据集，筛选在乳腺癌组织中表达上调的基因，筛选条件：log2FC>2.5，P < 0.05；利用 Venn 图筛选在两个基因集合中均表达的差异基因，然后进行通路富集分析，最后，使用在线 Kaplan-Meier plotter 生存分析工具来评估调控基因在乳腺癌患者中的预后价值。

结果：共筛选出 8 个在两个基因集合中均存在的基因，分别为 PRR15、TFF3、FOXA1、GATA3、CA12、AGR3、TFF1 和 ESR1，这 8 个基因显著富集到 DNA 转录因子激活通路（DNA-binding transcription activator activity, RNA polymerase II-specific），此外，这 8 个基因的过表达与乳腺癌的不良预后有关。

结论：在乳腺癌组织中高表达的 8 个基因与乳腺癌的不良预后显著相关，可作为乳腺癌的治疗靶点进行进一步研究，为乳腺癌的治疗提供指导。

关键字： 乳腺癌，预后不良，生物信息学

130. HBV DNA 聚合酶通过 VHL-HIF1α-SLC1A1 轴影响肝细胞癌的肿瘤进展

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目的：Hepatitis B Virus（HBV）感染是肝细胞癌的最常见致病因素，HBV 基因组有 4 个开放读码框，其中 P 基因区是最大的一个开放读码框，目前已有研究发现 HBV-DNA 聚合酶（HBV-DNAP）通过基因突变达到免疫逃避及耐药的效果。由于 HBV-DNAP 对宿主基因组的作用机制尚不太清楚，本文主要来研究 HBV-DNAP 对肝癌细胞的功能学机制的影响。

方法：在肝癌细胞系 Huh7 和 HepG2 细胞中进行 RIP-seq 测序，筛选出与 HBV DNAP 特异性结合的 VHL 基因。检测 HBV-DNAP 对 VHL 的表达调控作用，利用放线菌素 D 来检测 HBV-DNAP 对 VHL mRNA 稳定性的影响。利用氯化钴构建细胞缺氧模型，泛素化实验验证 VHL 对缺氧诱导因子（HIF-1α）表达水平的影响。核浆分离实验以及免疫荧光实验检测 HIF-1α的细胞定位情况。构建 HIF-1α过表达以及敲降质粒，检测其在缺氧状态下对谷氨酸转运体（SLC1A1）表达水平的影响，确定其在转录水平上的调控作用。利用 JASPAR 网站预测 SLC1A1 与 HIF-1α可能的结合位点。双荧光素酶报告系统确定其转录因子结合位点。通过一系列挽救实验来验证各基因与肝癌进展的作用关系。

结果：通过细胞功能学实验表明 HBV-DNAP 能够促进肝癌细胞的增殖。RIP-seq 测序后综合 GO 注释及 KEGG 分析寻找到了与 HBV-DNAP 特异性结合的 mRNA VHL。从转录水平、翻译水平证明了 HBV-DNAP 能够下调 VHL 的表达。VHL 促进 HIF-1α的泛素化降解，抑制 HIF-1α表达并减少其细胞核定位。HIF-1α是 SLC1A1 的转录因子并确定了其转录结合位点。挽救实验证明了 HBV-DNAP 能够通过影响 VHL-HIF1α-SLC1A1 轴来实现对肝癌细胞恶性行为的调控。

结论：HBV-DNAP 通过影响 VHL-HIF1α-SLC1A1 轴实现对肝细胞癌肿瘤进展的促进作用，为进一步揭示研究肝癌发生发展中的分子机制提供了新的探究基础。

关键字： HBV-DNA 聚合酶，VHL HIF-1α，肝细胞癌

131. 卵巢癌 BRCA1/2 基因大片段重排的临床病理特征及研究进展

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目的：BRCA1/2 基因为抑癌基因，在调节细胞复制、修复 DNA 损伤等方面具有重要作用，研究表明，BRCA1 突变携带者，≤70 岁时罹患乳腺癌和卵巢癌的累积风险分别为 65%和 39%，BRCA2 则为 45%和 11%。然而，BRCA1/2 基因变异位点分布广泛，变异类型多样。除常见的点突变(SNV)、插入缺失（Indel）外，大片段重排（LGR）也会影响 BRCA1/2 蛋

白功能，是常见的致病性突变之一。BRCA1/2 基因的 LGR 具有什么样的特点，与何种临床病理特征相关，是否会影响患者的预后，并没有充分的相关研究进行阐述。

方法：本文纳入河北医科大学第四医院 2021 年 1 月-2023 年 1 月运用 NGS 技术进行 BRCA1/2 检测卵巢癌样本共 1259 例，其中运用多重连接探针扩增技术（MLPA）对 LGR 进行验证共 20 例，检出 LGR 共 14 例。

结果：在纳入 1259 例 BRCA1/2 检测的病例中，BRCA1/2 突变率为 25.8%（325/1259，25.8%），包括 BRCA1 突变 189 例（15.0%），BRCA2 突变 136 例（10.8%），LGR 占所有 BRCA1/2 变异的 4.3%（14/325,4.3%），且均为 BRCA1 基因的疑似有害变异（4 类），这高于欧美人群的突变率。BRCA1 最常见的 LRG 为 exon15 del（28.6%，4/14），其次为 exon1-3del（14.3%,2/14）。存在 LRG 突变的患者中，所有患者均为微卫星稳定状态，且 HER2 为阴性。存在 LRG 患者的平均肿瘤体积为 4.8cm，较无 LRG 组稍大（4.3cm，P=0.867）。LRG 多伴有 TP53 突变（78.6%vs50%，P<0.05）和较低的 PR 水平（4.3%vs14.2%，P<0.05），且有较高的 Ki67 比例（55.7%vs40%），ER 的表达水平也较低（41.7%vs40.7%）。根据 ER、PR 及 Ki67 的表达水平来看，可能伴有 LRG 的患者预后会较差，但是需要进行长时间的随访后方能得到确切结论。

结论：LRG 在不同人种中的突变频率不同，中国人群较欧美人群较高。中国人群中 BRCA1 基因的 LRG 远远高于 BRCA2 基因，其中 exon15 del 突变频率最高。发生 LRG 患者通常伴有 TP53 突变、较高的 Ki67 水平和较低的 ER 和 PR 表达水平。LRG 患者预后是否会更差，需要更多样本进行长时间随访统计。

关键字： BRCA1/2，LGR，NGS，MLPA，卵巢癌

132. MGP 基因在乳腺肿瘤中的表达及其预后意义

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目的：基质 Gla 蛋白（MGP）是一种细胞外基质蛋白，是维生素 k 依赖蛋白家族的成员，含有多个 g-羧化谷氨酸残基。它主要被认为是异位钙化的生理抑制剂和 Keutel 综合征的致病基因，Keutel 综合征是一种钙沉积异常的特征，主要发生在软骨和血管系统。然而，在过去的几年里，对该基因的研究已经获得了与肿瘤进展相关的额外相关性。关于其功能在

致癌，MGP 基因表达可能是肿瘤依赖因素，已被证明呈现负相关与肿瘤进展和转移的发病在一些肿瘤，如肾癌和前列腺癌，而在乳腺肿瘤中的研究较少。本研究旨在比较乳腺肿瘤及癌旁组织中 MGP 的表达状态。

方法：利用癌症基因组图谱（TCGA）数据库，比较 MGP 在乳腺肿瘤和邻近组织中的表达，Timer2.0 数据库分析 MGP 相关性免疫基因，Kaplan-Meier plot (KMP)数据库分析 MGP 表达与乳腺肿瘤患者预后的相关性。

结果：TCGA 数据库分析显示，MGP mRNA 在癌旁组织中的表达量高于癌组织；Timer2.0m 免疫分析显示 MGP 表达与 B 细胞、嗜酸性粒细胞、单核细胞及 NK 细胞呈正相关，与 CD4+T 细胞呈负相关；KMP 数据库分析显示 MGP 高表达在 LumA、LumB 及 HER2 过表达分子类型中呈预后良好状态，但在三阴性分子类型呈预后不良状态。

结论：MGP 水平的改变与乳腺肿瘤进展之间存在很强的相关性，这表明它可以用于补充目前的临床生物标志物检测，用于乳腺癌症诊断及预后判断。

关键字： TCGA，乳腺癌，Time2.0，KMP，MGP

133. 血清 NY-ESO-1 自身抗体和 MMP1 联合检测对食管鳞状细胞癌的诊断价值

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目的 探讨血清 MMP1（Matrix metalloproteinase-1）和 NY-ESO-1（New York esophageal squamous cell carcinoma 1）自身抗体联合检测在食管鳞状细胞癌中的诊断意义。

方法 应用酶联免疫吸附实验检测 120 例食管鳞状细胞癌患者和 120 例正常对照血清中 MMP1 和 NY-ESO-1 自身抗体的表达水平，采用受试者工作特征曲线（Receiver operating characteristic，ROC）评价诊断效能。

结果 血清 MMP1 和 NY-ESO-1 自身抗体在食管鳞状细胞癌患者中的表达均明显高于正常对照（8.070±5.738 vs 4.331±3.137 ng/ml，Z=6.214，P<0.001；0.463±0.571 vs 0.156±0.086，Z=5.210，P<0.001）。ROC 曲线显示，当血清 MMP1 为最佳诊断临界值 10.586 ng/ml 时，其在诊断食管鳞状细胞癌的曲线下面积（area under the ROC curve，AUC）为 0.732（95%CI：0.671～0.787），敏感度为 24.2%，特异度为 95.0%。NY-ESO-1 自身抗体诊断食管鳞状细胞

癌 AUC 为 0.695（95%CI：0.632～0.752），敏感度为 33.0%，特异度为 95.0%。MMP1 和 NY-ESO-1 自身抗体联合检测诊断食管鳞状细胞癌的 AUC 为 0.800（95%CI 为 0.744～0.849），敏感度 47.5%，特异度 95.0%。

结论 血清 MMP1 和 NY-ESO-1 自身抗体联合检测可能有助于提高食管鳞状细胞癌的诊断效能。

关键字： 基质金属蛋白酶-1；NY-ESO-1 自身抗体；食管鳞状细胞癌；诊断标志物

134. 肺浸润性粘液腺癌中 Claudin18.2、TTF1、MUC5AC 表达特征及预后分析

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目的：基于蛋白水平分析肺浸润性粘液腺癌中 Claudin18.2、TTF1、MUC5AC 的表达特征及预后。

方法：收集我院 2013-2021 年间手术后诊断为肺浸润性粘液腺癌的石蜡包埋组织 245 例，分别进行 Claudin18.2、TTF1、MUC5AC 免疫组化染色及随访，Claudin18.2 判读标准以≥10%中等或强阳性为阳性，<10%弱阳性为阴性。

结果：肺浸润性粘液腺癌中 Claudin18.2、TTF1、MUC5AC 阳性表达率分别为 59.2%、15.9%、54.7%。在临床病理特征中，Claudin18.2 在 N0 期、胸膜无受侵、EGFR 野生型、ALK 野生型中表达率较高（P<0.05）；TTF1 在 EGFR 突变型及 ALK 融合型中表达率较高（P<0.05）；MUC5AC 在 N0 期、胸膜无受侵、ALK 野生型中表达率较高（P<0.05）。通过 Spearman 相关性分析显示，肺浸润性粘液腺癌中 Claudin18.2 的表达与 TTF1 呈负相关（P<0.01），与 MUC5AC 呈正相关（P<0.01）。Kaplan-Meier 生存分析显示，尚未发现三者对患者总生存期限的影响（均 P>0.05）。

结论：肺浸润性粘液腺癌中 Claudin18.2、MUC5AC 表达呈正相关，具有相似的临床病理特征，与 TTF1 表达呈负相关，三者的表达可能对肺浸润性粘液腺癌预后影响不显著。

关键字： 浸润性粘液腺癌，肺癌，Claudin18.2，TTF1，MUC5AC

135. 转录组测序分析肺浸润性粘液腺癌中 CLDN18 的表达特征

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目的：基于 mRNA 水平探讨肺浸润性粘液腺癌中 CLDN18 的表达特征。

方法：收集我院新鲜肺浸润性粘液腺癌 12 例，癌旁对照组织 10 例进行转录组测序，采用免疫组化法检测 Claudin18.2 蛋白。

结果：依据 Claudin18.2 蛋白表达进行分组，以≥10%中等或强阳性为阳性，<10%弱阳性为阴性。肺浸润性粘液腺癌中，CLDN18 阳性组 mRNA 表达量明显高于 CLDN18 阴性组（P<0.01）；CLDN18 阳性及阴性浸润性粘液腺癌组 mRNA 表达量均明显高于癌旁正常对照组（P<0.05）。肺浸润性粘液腺癌中，CLDN18 阳性组与 CLDN18 阴性组间存在共表达基因 34629 个，差异表达基因 3662 个；具有统计学意义的差异上调基因 295 个，前十名包括 GKN1、RN7SKP54、ZNF511-PRAP1、BTNL3、MUC17、REG3A、DKK4、REG4、APOA4、SULT1C2P2；差异下调 98 个，基因前十名包括 CTNNA1-AS1、CCDC185、XAGE1B、KISS1R、PITX2、IGLV3-12、CYP24A1、IGHV3-11、CNTNAP2、JPH3。蛋白互作网络分析显示，CASR、CCK、NPSR 等可能在 CLDN18 阳性组与阴性组差异上调蛋白中具有重要作用，KISSIR、PITX2 等可能在 CLDN18 阳性组与阴性组差异下调蛋白中具有重要作用。差异基因功能注释及 GO 富集分析均显示，差异基因在细胞外基质、分子趋化诱导活性方面具有明显作用。

结论：CLDN18 的表达在肺浸润性粘液腺癌中具有一定分子特征，可成为肺浸润性粘液腺癌的重要标记物之一。

关键字： 浸润性粘液腺癌，肺癌，CLDN18，分子特征，基因变异

136. IRX5 在肺腺癌中的表达及意义

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目的：易洛魁族同源盒基因 5（Iroquois homeobox gene 5，IRX5）编码蛋白属于核转录因子，是易洛魁族同源盒基因家族的一个成员，该家族参与了几个胚胎发育过程。过表达 IRX5 可促进舌鳞状细胞癌的增殖、侵袭和迁移，敲低 IRX5 表达可抑制前列腺癌细胞活力、增加细胞凋亡，IRX5 在肺腺癌中的作用尚不明确，本研究旨在探究 IRX5 在肺腺癌中的表达及意义。

方法：使用基于 TCGA 数据库的门户网站 cBioPortal，GEPIA、Ualcan 等生物信息数据库分析 IRX5 在在肺腺癌中的表达及意义。

结果：cBioPortal 结果显示 566 例肺腺癌患者中，5 例发生 IRX5 的基因突变（发生频率为 0.9%），1 例拷贝数扩增（发生频率为 0.2%），1 例纯合缺失（发生频率为 0.2%）。Ualcan 结果显示在 59 例正常肺组织内 IRX5 的基因表达中位数为 8.582，515 例肺腺癌中 IRX5 的基因表达中位数为 9.118，差异有统计学意义（$p<0.01$），GEPIA 数据库进行预后分析发现 IRX5 高表达的肺腺癌患者总体生存期显著下降（$P=0.034$）。

结论：通过深入研究公共数据库中肺腺癌相关基因信息，提示 IRX5 的 mRNA 水平在肺腺癌中高表达，并与不良预后相关，这可能为部分患者提供新的治疗靶点。

关键字 ：肺腺癌，TCGA，IRX5，预后

137. ANLN 在膀胱尿路上皮癌中的表达及意义

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目的：ANLN 基因编码的肌动蛋白结合蛋白(Anillin) 在细胞生长、迁移中发挥作用，并在有丝分裂过程中起枢纽作用。近年来研究发现 Anillin 表达异常与肿瘤的发生及发展关系密切。但是，ANLN 在膀胱尿路上皮癌（BLCA）中的作用鲜有报道，本研究旨在探索 ANLN 在膀胱尿路上皮癌中的表达及意义。

方法：使用基于 TCGA 数据库的门户网站 GEPIA、Ualcan 等生物信息学数据库分析 ANLN 在膀胱尿路上皮癌组织中的表达及其与临床预后的关系。

结果： 利用 GEPIA 平台分析 TCGA 数据库中 ANLN 在 BLCA 中的差异表达情况，结果显示 ANLN 在 BLCA 中表达为正常组织表达的 10.86 倍（P<0.0001）。此外，ANLN 在 BLCA 中的表达与 EGFR 的表达呈正相关（P<0.0001）。在 GEPIA 平台进行预后分析发现 ANLN 高表达的 BLCA 患者总体生存期（P = 0.034）与无病生存期（P = 0.026）显著降低。进一步在 Ualcan 数据库中对预后进行了验证分析，结果发现 ANLN 高表达的 BLCA 患者（n＝102）与 ANLN 低表达的 BLCA 患者（n＝304）相比，预后较差（P = 0.047）。

结论：ANLN 的 mRNA 水平在膀胱尿路上皮癌组织中呈高表达，并与其预后不良相关，可能作为 BLCA 的潜在预后生物标志物，有望成为膀胱尿路上皮癌药物治疗的重要治疗靶点。

关键字 ：ANLN；膀胱尿路上皮癌；GEPIA；Ualcan；预后标志物

138. 四种 PD-L1 抗体在食管鳞状细胞癌中的表达及对预后的影响

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目的：分析食管鳞状细胞癌中程序性死亡配体 1（programmed death ligand-1，PD-L1）的表达与临床病理特征及预后的关系，比较 PD-L1 四种抗体（Ventana SP263、E1L3N、SP142 和 Dako 22C3）在食管癌中表达的一致性。

方法：随机抽取河北医科大学第四医院自 2008-2017 年间行食管鳞状细胞癌（squamous cell carcinoma，SCC）根治性切除术患者 226 例。使用四种 PD-L1 抗体进行免疫组化染色，检测食管癌组织中 PD-L1 的表达，并使用综合阳性分数（CPS），阈值为 10 进行阳性判读。统计学软件 SPSS 25.00 进行分析和处理， x 2 检验进行相关性及一致性分析；Kaplan-Meier 法及 Log-rank 检验进行单因素生存分析；Cox 回归模型进行多因素分析，P＜0.05 为差异具有统计学意义。

结果：PD-L1 的表达情况：抗体 SP263、22C3、E1L3N 和 SP142 的阳性率分别为 58.4%（132/226）、55.3%（125/226）、58.0%（113/226）、39.8%（90/226）；SP263、22C3、

E1L3N 的一致性均较高（Kappa＞0.937），与 SP142 的一致性较低（Kappa＜0.700）。使用抗体 SP263、22C3、E1L3N 时，PD-L1 的表达与淋巴结是否转移有关（P＜0.05），差异有统计学意义，而与性别、年龄、肿瘤长度、组织学分级、T 分期无关（P＞0.05）；使用抗体 SP142 时，PD-L1 的表达与病理参数均无关（P＞0.05）。SCC 的预后与 T 分期、淋巴结转移、组织学分级、PD-L1 的表达、治疗方式相关（P＜0.05），且治疗方式、淋巴结是否转移、PD-L1 的表达（Dako 22C3）是食管鳞状细胞癌的独立预后因素，PD-L1 阳性患者平均生存时间为 42 个月，阴性患者为 84 个月。

结论：PD-L1 抗体 SP263，22C3，E1L3N 有较高的一致性，而三种抗体与 SP142 的一致性都较低，抗体 22C3（CPS≥10）是食管鳞状细胞癌的独立预后因素，在使用 PD-L1 抗体 Dako 22C3，且 CPS≥10 时，患者的预后更差，PD-L1 的表达可能成为预测食管鳞状细胞癌的预后指标。

关键字： 食管鳞状细胞癌，PD-L1，CPS，预后

139. 在非小细胞肺癌中与预后和免疫治疗疗效相关的与巨噬细胞相关基因的鉴定

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背景：恶性肿瘤，特别是非小细胞肺癌（NSCLC），由于其流行率和致命性，对人类健康构成重大威胁。NSCLC 的治疗方法在个体间差异很大，因此识别预测性标志物至关重要。此外，在肿瘤的发生和进展过程中，肿瘤细胞可以释放信号分子，诱导巨噬细胞极化为更有利于肿瘤的 M2 表型，这可能促进肿瘤生长、转移和药物耐药性。

方法：我们采用了综合方法，结合了批量 RNA 测序和单细胞测序分析。

结果：在我们的研究中，我们利用批量 RNA 测序和单细胞测序方法分析了 NSCLC 和相邻组织中的差异细胞，寻找能够预测预后和药效的相关标记基因。我们仔细研究了与巨噬细胞相关基因的甲基化、拷贝数变异和选择性剪接等生物现象。此外，我们利用了免疫和肿瘤细胞的共培养技术，探索了这些基因在巨噬细胞极化中的作用。我们的发现揭示了癌组织和相邻组织之间巨噬细胞的明显差异。我们确定了 ANP32A、CCL20、ERAP2、MYD88、TMEM126B、TUBB6 和 ZNF655 等与 NSCLC 患者预后和免疫治疗疗效相关的巨噬细胞相

关基因。值得注意的是，ERAP2、TUBB6、CCL20 和 TMEM126B 可以诱导巨噬细胞 M0 向 M2 的极化，促进肿瘤增殖。

结论：这些发现极大地促进了我们对 NSCLC 肿瘤免疫微环境的理解。它们为进一步研究这些基因作为调控肿瘤发生和发展的靶点的潜力铺平了道路。

关键字： 巨噬细胞、非小细胞肺癌、单细胞 RNA 测序、bulk-RNA 测序、免疫微环境

140. 胰腺实性假乳头状瘤的临床病理特征：单中心研究

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目的：胰腺实性假乳头状瘤（Solid pseudopapillary neoplasm，SPN）是一种低度恶性肿瘤，主要发生在年轻女性，其发病率较低，占所有胰腺肿瘤的 1-2%。由于影像学检查的广泛普及，近年来 SPN 的发病率一直在上升，但其发病机制仍不确定。本研究的目的是分析 SPN 的临床病理特征、鉴别诊断和预后，提高对 SPN 的认识，避免误诊误治。

方法：回顾性分析河北医科大学第四医院 2010 年至 2020 年的 94 例 SPN 病例。收集所有患者的临床病理资料并进行随访。所有标本均石蜡包埋，进行 4μm 厚的连续切片，行 HE 染色和免疫组织化学染色，包括 Syn、CgA、CD56、CD10、PR、β-Cateinin、AE1/AE3、Vimentin、pan-TRK、LEF1、AR、LMO2 和 INI-1。其中 8 例进行了下一代测序（Next Generation Sequencing，NGS）检测。

结果：94 例 SPN 患者中，男性 13 例（13.8%），女性 81 例（86.2%），男女比例大于 1：6，以女性患者居多。年龄 10～65 岁，中位年龄 29 岁，平均年龄 33±15.33 岁。肿瘤最大直径 1.5～18cm，平均（6.6±3.45）cm。肿瘤位于胰头（25.5%；24/94）、颈部（2.1%；2/94）、体尾部（72.3%；68/71）。94 例患者中有 4 例发生远处转移，其中肝转移 3 例，脑转移 1 例。在组织学上，有多种组织学结构，肿瘤由囊性区、实性区、假乳头区、退变区等混合而成，实性区常被纤细小血管分隔。肿瘤细胞呈小梁状、腺泡状、巢状等形态排列，细胞大小较一致，核圆形或卵圆形，核仁不明显，核分裂像罕见。免疫组化检测 CD10、β-Cateinin、Syn、CgA、PR、LEF1、AR、LMO2 的阳性率分别为 96.8%、98.0%、76.6%、1.4%、98.0%，92.0%、3.4%、27.6%。NGS 检测显示：8 例患者中 6 例检测出体细胞突变，但仅有

1 例与靶向药物相关，突变基因主要集中在 RET、ROS1、EGFR、ERBB2 等。随访 85 例，中位时间 61 个月，仅 1 例术后 16 个月因复发转移死亡。

结论：SPN 是一种罕见的胰腺恶性肿瘤，最常见于年轻女性。结合组织学形态学和免疫组化，SPN 的诊断并不困难。基因检测没有特异性改变，只有少数患者具有靶向治疗相关突变。手术切除可获得良好的预后。

关键字： 胰腺实性假乳头状瘤，临床病理特征，鉴别诊断，预后

141. ARPC1B 对肿瘤预后和免疫微环境的影响

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目的：肌动蛋白相关蛋白 2/3 复合物（Arp2/3）被广泛认为是通过促进肌动蛋白聚合和随后的肌动蛋白网络分支，被认为是促进癌症侵袭和迁移的重要因素。ARPC1B 是 Arp2/3 的一个组成亚基之一，在各种生物过程中也被认为是一个重要的分子。然而，迄今为止，还没有关于 ARPC1B 在泛癌预后和免疫微环境中的作用的综合研究。为了填补这一重要空白，我们的研究详细研究了 ARPC1B 对泛癌的影响。

方法：本研究在癌症基因组图谱（TCGA）数据库中研究了泛癌组织和相应的正常组织之间的表达差异。随后，我们应用了一系列的分析来探索 ARPC1B 在各种癌症中的预后影响、免疫相关性和基因改变。利用 Timer、TCGA、HPA 等公共数据库的数据分析 ARPC1B 的表达分布。此外，我们还利用 cBioPortal 和 UALCAN 数据库分析了 ARPC1B 的甲基化和基因突变及其对癌症的影响。使用 R 软件分析原始数据。基于 TCGA 肾透明细胞癌 FPKM 数据和免疫相关调控基因，建立了肾透明细胞癌的重要预测模型。证实了 ARPC1B 对表达、预后、突变和免疫的意义。先前的生物信息学分析的结果通过基础实验和临床样本进一步验证。

结果：ARPC1B 的表达分析显示，ARPC1B 的表达在不同类型的癌症中存在显著差异。除肾嫌色细胞癌（KICH）、肺鳞状细胞癌（LUSC）和前列腺腺癌（PRAD）外，大多数癌症组织中发病率普遍较高。在一些癌症中，ARPC1B 的过表达与不良预后密切相关，特别是在肾透明细胞癌（KIRC）中。有趣的是，我们发现 ARPC1B 与几个免疫指标基因、肿瘤突变负荷（TMB）和微卫星不稳定性（MSI）呈正相关，这可能是预测肿瘤治疗效果的间接因

素。基因突变的分析负责检测癌症中靶向 ARPC1B 突变的特定位置。KIRC 中 ARPC1B 及相关免疫基因的风险模型可能是预测 KIRC 患者生存的重要指标。风险模型的 ROC 曲线证实了其预测的准确性，1 年、3 年和 5 年的 AUC 值分别为 0.720、0.700 和 0.630。ARPC1B 的富集途径表明，ARPC1B 在肿瘤中起着重要作用。

结论 ：ARPC1B 已被确定为泛癌的生物标志物，特别是肾透明细胞癌，对临床患者和科学发展都有意义。

关键字： ARPC1B；泛癌；肾透明细胞癌；预后

142. Hsa_circ_0007990 promotes breast cancer growth via inhibiting YBX1 protein degradation to activate E2F1 transcription

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Objective: Breast cancer (BC) is the most common diagnosed malignant tumor and the leading cause of cancer in females worldwide. Although remarkable advances in early detection and treatment strategy lead to the steadily declined mortality, recurrence and metastasis still occurred frequently and remained the major reasons for cancer deaths in BC patients. Circular RNA (circRNA) is generated by special alternative splicing, with the properties of stability, high conserved and tissue, temporal and disease specificity. Increasing evidence has demonstrated that Circular RNA (circRNA) exerts critical functions in cancer progression. However, the detailed biological functions and molecular mechanisms of circRNAs in BC remain far from understood. This study aimed to investigate the possible role of circRNA in the progression of BC.

Methods: Differentially expressed circRNAs in BC were filtered by integrating breast tumor-associated somatic CNV data and circRNA high-throughput sequencing. Aberrant hsa_circ_0007990 expression and its host gene copy number were detected in BC cell lines with quantitative polymerase chain reaction (qPCR). The expression level of hsa_circ_0007990 in BC tissues was validated by situ hybridization (ISH). Sanger sequencing was used to identify the

head-to-tail splicing site of hsa_circ_0007990. Loss- and gain-of-function experiments in vitro and in vivo were performed respectively to explore the potential biological function of hsa_circ_0007990 in BC. The underlying mechanisms of hsa_circ_0007990 were investigated through MS2 RNA pull-down, mass spectrometry, RNA immunoprecipitation, RNA fluorescence in situ hybridization and immunofluorescence experiments, chromatin immunoprecipitation and luciferase reporter assay.

Results: The levels of hsa_circ_0007990 were elevated in BC tissues and cell lines, which was partly due to host gene copy number gains. Functional assays showed that hsa_circ_0007990 promoted BC cells growth. Mechanistically, hsa_circ_0007990 could bind to YBX1 and inhibit its degradation by preventing ubiquitin/proteasome-dependent manner, thus enhancing the expression of cell cycle-associated gene E2F1. Rescue experiments suggested that hsa_circ_0007990 invoked BC progression through YBX1.

Discussion: In general, our study identified and characterized a novel circRNA hsa_circ_0007990, that was upregulated in BC cells partially due to amplification of host gene PGAP3. The results also showed that hsa_circ_0007990 was overexpressed in BC tissues and associated with malignant progression in BC patients although there was no significant difference due to the small sample size. Functionally, hsa_circ_0007990 could promote proliferation and tumorigenesis of BC in vitro and vivo. Mechanistically, hsa_circ_0007990 interacted with YBX1 and inhibited its ubiquitination and degradation, subsequently promoted E2F1 transcription. Our investigation illustrated the possible role of hsa_circ_0007990 in BC and provided a promising therapeutic target for the treatment of BC.

Key Words： Breast cancer; CircRNA; YBX1; E2F1; Cell growth

143. Extended Enrichment for Ultrasensitive Detection of Low Frequency Mutations by Long Blocker Displacement Amplification

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Detecting low-frequency DNA mutations hotspots cluster is critical for cancer diagnosis but remains challenging. Quantitative PCR (qPCR) is constrained by sensitivity, and allele-specific PCR is restricted by throughput. Here we develop a long blocker displacement amplification (LBDA) coupled with qPCR for ultrasensitive and multiplexed variants detection. By designing long blocker oligos to perfectly match wildtype sequences while mispairing with mutants, long blockers enable 14-44 nt enrichment regions which is 2-fold longer than normal BDA in the experiments. For wild template with a specific nucleotide, LBDA can detect different mutation types down to 0.5% variant allele frequency (VAF) in one reaction, with median enrichment fold of 1,000 on 21 mutant DNA templates compared to the wild type. We applied LBDA-qPCR to detect KRAS and NRAS mutation hotspots, utilizing a single plex assay capable of covering 81 mutations and tested in synthetic templates and colorectal cancer tissue samples. Moreover, the mutation types were verified through Sanger sequencing, demonstrating concordance with results obtained from next-generation sequencing. Overall, LBDA-qPCR provides a simple yet ultrasensitive approach for multiplexed detection of low VAF mutation hotspots, presenting a powerful tool for cancer diagnosis and monitoring.

Key Words： long blocker displacement amplification, colorectal cancer, mutation hotspots, tumor heterogeneity

144. SRSF1 介导 LINC00525 调控 DKC1 mRNA 稳定性参与结直肠癌进展的机制研究

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目的与背景：结直肠癌（colorectal cancer，CRC）是全球范围内最常见的恶性肿瘤之一，预计到 2030 年，全球 CRC 新增病例将超过 220 万例，死亡超 110 万例，严重威胁人类健康。我国 CRC 的预防与诊治形势十分严峻，已成为严重危害中国人民健康及中国社会发展的重大公共卫生问题。越来越多的研究表明，长链非编码 RNA 在肿瘤的进展中发挥重要作用，我们通过分析结直肠癌组织的高通量转录组数据鉴定出在结直肠癌中异常表达的 lncRNA 谱，选择显著高表达的 LINC00525 进行初步探讨，并对其生物学功能及调控机制进行探讨，旨在为结直肠癌的诊治提供新的潜在标志物和治疗靶点。

方法：1. 通过分析癌症基因图谱（TCGA）数据库中结直肠癌及癌旁组织的转录组测序数据，得出在结直肠癌中表达异常的长链非编码 RNA，并筛选出显著高表达的 LINC00525 进一步研究。通过逆转录定量 PCR（qRT-PCR）和 RNA 原位杂交（ISH）验证 LINC00525 在结直肠组织及细胞株中的表达情况，利用组织芯片分析结直肠癌组织中 LINC00525 的表达并分析其与结直肠癌患者临床特征及预后之间的关系。

2. 克隆形成实验、CCK8 实验、EdU 实验、流式细胞周期实验、Transwell 实验及 Western blotting 检测 LINC00525 体外对结直肠癌细胞生物学功能的影响；利用裸鼠移植瘤模型及尾静脉肿瘤细胞转移模型分析 LINC00525 体内影响结直肠癌细胞的增殖及转移能力。

3. 通过转录组测序筛选 SNHG3 的靶基因，核质分离实验、RNA pull down 实验、ChIP、RNA 免疫共沉淀实验（RIP）等探究 LINC00525 调控靶基因的作用机制，并通过挽救实验进行验证。

4. 通过 JSPAR 软件预测调控 LINC00525 基因表达的转录结合因子，染色质免疫沉淀实验（ChIP）和荧光素酶报告基因明确其结合水平和结合区域；敲降和过表达该转录结合因子验证其与 LINC00525 表达之间的关系。

结果：1. 我们首先通过分析 TCGA 数据库的测序数据发现 LINC00525 在结直肠癌组织中表达显著升高；使用 qRT-PCR 和 ISH 实验证实结直肠癌细胞和组织中的 LINC00525 表达

显著增高。并通过组织芯片和患者的临床特征分析结果发现 LINC00525 表达水平越高患者预后越差。

2. LINC00525 可能通过促进 DKC1 的表达水平进而促进结直肠癌的生长，在结直肠癌细胞中敲降和过表达 DKC1 会导致 LINC00525 表达显著下调或升高。

3. 细胞功能实验、裸鼠移植瘤和小鼠尾静脉注射肿瘤细胞肺转移模型结果均表明敲降 LINC00525 后，体内、外结直肠癌细胞的增殖、迁移和侵袭能力显著降低，Western blotting 结果表明敲降 LINC00525 后结直肠癌细胞的生长及转移相关蛋白发生显著改变。

4. 核质分离实验发现 LINC00525 在结直肠癌细胞的胞质和胞核中均有分布，以细胞核中为主。通过 RNA pulldown 与蛋白质谱筛选出与 LINC00525 相结合的 SRSF1，随后通过免疫共沉淀进一步发现 DKC1 mRNA 异常富集。体外实验沉默或过表达结直肠癌细胞内的 LINC00525 或 SRSF1。结果发现 LINC00525 通过结合 SRSF1 维持 DKC1 的 mRNA 稳定性，进而促进 EMT。

5. 通过 JSPAR 软件预测调控 LINC00525 基因表达的转录结合因子 EF2A，利用染色质免疫沉淀实验（ChIP）和荧光素酶报告基因提示 EF2A 在 LINC00525 启动子 E6 区结合；敲降和过表达 EF2A 进一步验证 EF2A 与 LINC00525 表达之间的关系。

结论：本研究揭示了 LINC00525 在结直肠癌中表达上调且与结直肠癌预后较差相关；LINC00525 在结直肠癌细胞中的高表达受转录因子 EF2A 调节；并可通过结合 SRSF1 维持 DKC1 的 mRNA 稳定性，从而促进结直肠癌细胞的增殖和转移。提示 LINC00525 可作为结直肠癌诊治的潜在标志物和靶点。

关键字： LINC00525；SRSF1；DKC1；结直肠癌

145. Dihydroartemisinin Enhances Paclitaxel Sensitivity in Esophageal Squamous Cell Carcinoma by Targeting WTAP

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Esophageal squamous cell carcinoma (ESCC) is among the high-morbidity malignant tumors worldwide. In recent years, the medical community has made important progress in improving the diagnosis and treatment ability of ESCC, but the prognosis of patients is still poor and the

mortality rate remains high. The most important reason is that the pathogenesis of ESCC is still unclear. Thus, it is imperative to increase the quality of life and decrease the mortality of patients with ESCC by further clarifying the pathogenic mechanism of ESCC and exploring new diagnosis and treatment approaches. This study preliminarily explored the effect of dihydroartemisinin (DHA) on WTAP protein and ESCC, and its anti-ESCC effect in combination with paclitaxel (PTX). DHA could significantly decrease the m6A modification level of total RNA and WTAP protein expression yield in ESCC cells, and cellular autophagy was involved in the degradation process of DHA on WTAP protein. Molecular docking experiments and drug affinity responsive target stability assay confirmed that DHA can directly bind to WTAP protein. Functional studies revealed that DHA could reverse the promotion effect of WTAP on ESCC cell proliferation. Therefore, DHA is a potential small-molecule inhibitor of WTAP protein with anti-ESCC efficacy. Further studies confirmed that PTX was directly bound to WTAP protein in the spatial structure and promoted its expression. However, overexpression of WTAP reduced the sensitivity of ESCC cells to PTX chemotherapy. Therefore, WTAP was involved in the chemotherapy process of PTX. Compared with the single administration, the combination of DHA and PTX can more effectively inhibit the proliferation of ESCC cells. Thus, the combination of DHA and PTX may be a potential therapeutic modality for ESCC. In conclusion, DHA and PTX are potential small molecule regulators of WTAP protein, and the combination of the two drugs will contribute to the treatment of ESCC.

Key Words： Esophageal squamous cell carcinoma; WTAP; Dihydroartemisinin; Paclitaxel

146. Meta polygenic risk score and lung cancer risk prediction: two prospective cohort studies

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Background: Although several polygenic risk scores (PRSs) have been developed for lung cancer, their predictive power has been limited due to the low heritability explained by known susceptibility loci and the heterogeneity of histopathological subtypes. Recent advancements in

analysis techniques have allowed for the development of more powerful PRSs, such as the meta-score (metaPRS), which incorporates genetic information from the disease, its subtypes, and related risk factors. This innovative approach has shown promising results in predicting stroke and coronary artery disease. However, there were no studies investigating the use of this method to create a PRS for lung cancer and assess its impact on prediction accuracy and lung cancer screening. Hence, we aimed to construct a meta polygenic risk score (metaPRS) based on PRS of lung cancer and related phenotypes. We also aimed to assess its prediction of lung cancer risk and implication for screening.

Methods: First, we evaluated the performance of 9 lung cancer related PRSs based on the UKB, and the optimal PRS was used for further construction of the metaPRS. Second, we also included 12 SNPs to construct a PRS for lung adenocarcinoma (LUAD), 9 SNPs to construct a PRS for squamous cell lung carcinoma (LUSC), and 2 SNPs to construct a PRS for small cell lung carcinoma respectively, according to the largest GWASs of lung cancer in Europeans. Third, 17 potential lung cancer-related traits, including 5 smoking-related traits, 4 lung function-related traits, 4 chronic lung diseases, body mass index, height, family history of lung cancer, and education were used to construct the metaPRS. Each PRS was Z-score normalized to conduct an elastic-net Cox regression model. We used a 10-fold cross-validation method to determine the optimal model. Then, the metaPRS was calculated using the sum of weighted PRS, we developed a metaPRS by incorporating 10 lung cancer-related traits consisting of 753 genetic variants in the UK Biobank training set (n=442,508) for lung cancer and evaluated it in the PLCO validation set (n= 108,665).

Results: The metaPRS had the highest C-index compared with the previously reported 9 PRSs, increasing the C-index [C-index=0.590] by 0.025-0.059 over the previously reported LC PRSs [C-index=0.531-0.565] in the UK Biobank training set. Similarly, the metaPRS increased 0.016-0.067 over the previous PRS [C-index=0.580 vs C-index=0.513-0.564] in the PLCO validation set. Higher metaPRS was significantly associated with younger age at lung cancer diagnosis and shorter survival time since diagnosis. In the PLCO, we further assessed the interplay of the metaPRS and the predicted risk of lung cancer from the PLCOm2014. We observed significant gradients in the 6-year absolute risk of incident lung cancer across metaPRS categories within different risk categories predicted by the PLCOm2014 (Figure 4). For example, among

individuals predicted as high risk (≥ 1.51% in 6 years defined by PLCO m2014), the 6-year average absolute lung cancer risk varied from 3.68% for those with a low genetic risk to 5.19% for those with a high genetic risk. More interestingly, individuals at intermediate predicted risk (1.34%-1.51% in 6 years) in the intermediate-high genetic risk groups had a higher 6-year absolute risk>1.51%, which indicated these individuals should also be taken as high-risk populations of lung cancer in clinical practice. The addition of metaPRS to the PLCOm2014 model showed no significant improvement in C-index (0.01%) but continuous net reclassification improvement (continuous NRI=6.50%) in the PLCO cohort.

Conclusions: This study successfully constructed an optimized genetic indicator metaPRS for lung cancer. We demonstrated that the metaPRS can be used in conjunction with the lung cancer risk model PLCOm2014 to identify high-risk populations for screening. Additionally, we found that the metaPRS was significantly associated with the age of onset for incident lung cancer cases. Incorporating the metaPRS into a new risk model allowed for the identification of more high-risk groups. These findings suggest that integrating genetic risk assessment with lung cancer screening has the potential to enhance the benefits of screening.

Key Words： Lung cancer; Polygenic risk score; risk prediction; Lung cancer screening

147. Dihydroartemisinin inhibited stem cell-like properties and enhanced oxaliplatin sensitivity of colorectal cancer via AKT/mTOR signaling

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Colorectal cancer (CRC) is a common tumor with high morbidity and mortality. The use of oxaliplatin (L-OHP) as a first-line treatment for CRC is limited due to chemoresistance. Growing evidences have revealed that the existence of cancer stem-like cells (CSLCs) is one of the important reasons for drug resistance and recurrence of cancers. Dihydroartemisinin (DHA), a derivative of artemisinin, has showed anticancer effects on a variety of malignancies, in addition to its antimalarial effects. However, the effect and mechanism of DHA on CSLCs and chemosensitivity in CRC cells remains unclear. In this study, we found that DHA inhibited cell viability in HCT116 and SW620 cells. Moreover, DHA decreased cell clonogenicity, and improved L-OHP sensitivity. Furthermore, DHA treatment attenuated tumor sphere formation, and the expressions of stem cell surface marker (CD133 and CD44) and stemness-associated transcription factor (Nanog, c-Myc and OCT4). Mechanistically, the present findings showed that DHA inhibited of AKT/mTOR signaling pathway. The activation of AKT/mTOR signaling reversed DHA-decreased cell viability, clonogenicity, L-OHP resistance, tumor sphere, and expressions of stemness-associated protein in CRC. The inhibitory effect of DHA on tumorigenicity of CRC cells has also been demonstrated in BALB/c nude mice. In conclusion, this study revealed that DHA inhibited CSLCs properties in CRC via AKT/mTOR signaling, suggesting that DHA may be used as a potential therapeutic agent for CRC.

Key Words： dihydroartemisinin; cancer stem-like cells; resistance; AKT/mTOR signaling; colorectal cancer;

148. CTSL, a prognostic marker of breast cancer, that promotes proliferation, migration, and invasion in cells in triple-negative breast cancer

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Introduction: In the world, the incidence of breast cancer has surpassed that of lung cancer, and it has become the first malignant tumor among women. Triple_x0002_negative breast cancer (TNBC) shows an extremely heterogeneous malignancy toward high recurrence, metastasis, and mortality, but there is a lack of effective targeted therapy. It is urgent to develop novel molecular targets in the occurrence and therapeutics for TNBC, and novel therapeutic strategies to block the recurrence and metastasis of TNBC.

Methods: In this study, CTSL (cathepsin L) expression in tissues and adjacent tissues of TNBC patients was monitored by immunohistochemistry and western blots. The correlations between CTSL expressions and clinicopathological characteristics in the patient tissues for TNBC were analyzed. Cell proliferation, migration, and invasion assay were also performed when over-expressed or knocked-down CTSL.

Results: We found that the level of CTSL in TNBC is significantly higher than that in the matched adjacent tissues, and associated with differentiated degree, TNM Stage, tumor size, and lymph node metastatic status in TNBC patients. The high level of CTSL was correlated with a short RFS ($p<0.001$), OS ($p<0.001$), DMFS ($p<0.001$), PPS ($p= 0.0025$) in breast cancer from online

databases; while in breast cancer with lymph node-positive, high level of CTSL was correlated with a short DMFS ($p<0.001$) and RFS ($p<0.001$). Moreover, in vitro experiments showed that CTSL overexpression promotes the abilities for proliferation, migration, and invasion in MCF-7 and MDA-MB-231 cell lines, while knocking-down CTSL decreases its characteristics in MDA-MB-231 cell lines.

Conclusion: CTSL might involve into the regulation of the proliferation, invasion, and metastasis of TNBC. Thus, CTSL would be a novel, potential therapeutic, and prognostic target of TNBC.

Key Words： CTSL, triple-negative breast cancer (TNBC), prognostics, cell proliferation, migration, invasion

149. 氯喹增强食管癌细胞对紫杉醇敏感性的作用机制研究

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背景： 在我国，食管癌死亡人数居肿瘤死亡人数第五名。紫杉醇是应用最广泛的天然抗癌药物之一，临床上通常用于晚期以及转移性食管癌的化疗。肿瘤对化疗药物的化疗抵抗是造成食管癌患者疗效差、死亡率居高不下的主要原因。因此，如何有效提高食管癌的化疗效果在食管癌治疗中的地位不言而喻。

目的：明确紫杉醇抑制食管癌细胞生长的作用以及探索紫杉醇与氯喹联合应用对食管癌细胞的作用。

方法：用紫杉醇处理食管癌 KYSE150 和 KYSE410 细胞后，用 CCK8、平板克隆实验、Transwell 以及划痕实验检测药物处理后食管癌增殖、迁移能力变化。流式细胞术检测紫杉醇对细胞凋亡的影响， Western blot 实验检测细胞凋亡相关蛋白的变化。用葡萄糖、乳酸检测试剂盒检测紫杉醇处理后食管癌细胞葡萄糖的消耗以及乳酸的生成量，以及 Western blot 实验检测紫杉醇处理后对糖酵解相关蛋白的变化，利用分子对接以及药物亲和靶点稳定性实验分析紫杉醇与 GLUT1 的结合作用。同时，检测氯喹与紫杉醇联合用药对食管癌的作用。

结果：紫杉醇可以抑制食管癌细胞的增殖、迁移能力，紫杉醇处理后细胞凋亡率增加并且凋亡关键蛋白（PARP、C-PARP、Caspase-3、C-caspase-3）的表达升高。紫杉醇抑制了食管癌细胞葡萄糖的消耗、乳酸的生成，以及糖酵解的关键蛋白（GLUT1、PKM2、LDH）表达，紫杉醇在食管癌细胞内可能直接靶向 GLUT1 蛋白。紫杉醇与氯喹联合用药后对食管癌细胞活力以及糖酵解的抑制作用明显强于单独使用紫杉醇，并且两者联合用药为协同作用。DAPI 染色后发现药物作用后食管癌细胞染色质出现凝缩和断裂，细胞膜皱缩发泡，凋亡小体形成，联合用药组凋亡小体数量显著增多，凋亡率增加。

结论：紫杉醇在体外可显著抑制食管癌细胞生长并诱导细胞凋亡。紫杉醇可能通过下调 GLUT1 抑制食管癌细胞的糖酵解，从而抑制食管癌细胞的生长。 氯喹通过影响食管癌细胞糖酵解增强食管癌细胞对紫杉醇的化疗敏感性。

关键字： 食管鳞状细胞癌；紫杉醇；糖酵解；氯喹

150. 基于孟德尔随机化分析的肠道菌群与非小细胞肺癌预后之间的因果关联研究

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Background

Accumulating evidence suggests that gut microbiota is associated with the prognosis of patients with Non-Small Cell Lung Cancer (NSCLC). However, the causal inference between them remains unclear. This study aimed to explore the causal relationship between gut microbiota and the prognosis of patients with NSCLC.

Methods

We performed a Mendelian randomization study using the publicly available microbiome GWAS database from MiBioGen (N = 18,040). For outcomes, the meta GWAS pertinent to the prognosis of NSCLC was undertaken within the PLCO (N = 1,033) and TCGA (N = 745) NSCLC cohort. The major estimates were obtained via inverse variance weighting (IVW) meta-analysis, supplemented with additional sensitivity analyses encompassing MR-Egger, weighted median, weighted mode, and MR pleiotropy residual sum and outlier (MR-PRESSO) methods.

Results

The IVW method implicated seven bacterial genera to be associated with the prognosis of patients with NSCLC. Among these, Intestinimonas (OR = 1.85, 95%CI = 1.15-2.99, P = 0.012), Haemophilus (OR = 1.77, 95%CI = 1.10-2.84, P = 0.018), and RikenellaceaeRC9gutgroup (OR = 1.36, 95%CI = 1.01-1.83, P = 0.045) were risk factors for prognosis, while Paraprevotella (OR = 0.54, 95%CI = 0.36-0.80, P = 2.22E-03), Howardella (OR = 0.67, 95%CI = 0.51-0.89, P = 6.31E-03), RuminococcaceaeUCG003 (OR = 0.54, 95%CI = 0.32-0.99, P = 0.046), and Ruminococcusgnavusgroup (OR = 0.64, 95%CI = 0.41-1.00, P = 0.049) were protective factors. Sensitivity analyses did not reveal any heterogeneity or horizontal pleiotropy (P > 0.05).

Conclusions

The present study provides robust evidence that the gut microbiota was causally associated with prognosis of patients with NSCLC. These findings have implications for the treatment of NSCLC patients.

关键字 ： Gut microbiota, NSCLC, Prognosis, Mendelian randomization

151. 基质辅助激光解吸/电离飞行时间质谱法(MALDI-TOF-MS)在卵巢癌中的诊断效能

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研究目的：目前临床中缺少卵巢癌诊断有效的生物标志物，随着质谱技术的不断发展，其在肿瘤诊疗领域的研究和临床应用也逐渐深入。本研究旨在评估基质辅助激光解吸/电离飞行时间质谱法(MALDI-TOF-MS)检测对卵巢癌早期诊断的诊断效能，为质谱应用于卵巢癌的早期诊断提供新的理论基础。

研究方法：在 PubMed、Web of Science 和 Embase(直到 2018 年 11 月)进行了一项深入的研究，以确定评估 MALDI-TOF-MS 对卵巢癌准确性的研究。使用 MetaDisc1.4、Review Manager 5.3 和 Stata 15.1 软件对合并结果进行分析:敏感性、特异性、阳性似然比(PLR)、阴性似然比(NLR)、诊断优势比(DOR)和 95%置信区间(CI)。接收者工作特征曲线(SROC)和曲线下面积(AUC)显示了 MALDI-TOF-MS 的整体性能。

研究结果：18 项研究被纳入 meta 分析。纳入研究的方法学质量分析显示，这些文章的偏倚风险较低，总体上存在适用性问题。诊断参数的总结估计如下：敏感性为 0.77 (95% CI: 0.73-0.80)、特异性为 0.72 (95% CI: 0.70-0.74)、 PLR 为 2.80 (95% CI: 2.41-3.24)、NLR 为 0.30 (95% CI: 0.22-0.40)、DOR 为 10.71 (95% CI: 7.81-14.68)。综合以上分析 AUC 为 0.8336。Egger’s 检验显示本荟萃分析没有显著的发表偏倚。

研究结论：MALDI-TOF-MS 对卵巢癌具有较强的诊断效能，可提高卵巢癌早期诊断的灵敏度和特异度。后续进一步分析并鉴定卵巢癌发生发展相关的特异性蛋白片段将为卵巢癌的诊疗提供新的方案。此外，采用 MALDI-TOF-MS 诊断卵巢癌，进一步评估和优化标准化程序也是十分有必要的。

关键字：卵巢癌，质谱

152. The panoramic map of breast fat secretion and the occurrence of breast cancer

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Nowadays, breast cancer is the most common female malignancy all over the word, at a risen rate of over 1.7 million cases per year globally. Accumulating epidemiological evidence indicates that abnormal fat status such as obesity is an important risk and poor prognostic factor for breast cancer. In obesity, adipose tissue becomes dysfunctional, which results in disorder of metabolic microenvironment. Emerging data suggest that breast cancer development and progression is closely correlated with tumor microenvironment. Adipose, a significant component of the stromal tissues, also a type of metabolically active endocrine organ, is the most abundant stromal constituent in the mammary gland surrounding breast cancer. In addition, a growing number of studies have confirmed that adipocytes adjacent to invasive cancer cells, known as cancer-associated adipocytes (CAAs), participate in the regulation of breast cancer progression. Breast tumor adjacent adipocytes have the potential to drive the malignancy of tumor cells by secreting hormones, proinflammatory cytokines, and accelerating tumor metabolic

reprogramming. Despite of the diversity effects of adipokines on breast cancer, adipocytes secreted protein derived peptidome remains a black hole to our knowledge, since degradome has been expanding its roles in biology and pathology. In addition to glucose and lipid metabolic products, the fragments/peptides, which cleaved from extracellular matrix and membrane proteins degradation by proteinase or hydrolase at the level of cancer-tissue microenvironment, are supposed to carry cancer-specific information and further reveal the reciprocal interconnected network of tumor and surrounding stroma tissues. In this study, we aim to assess the biological effects of breast tumor adjacent adipocyte secreted protein derived peptides on breast cancer cells from multiple angles, and systematically analyze the degradome characters, expecting to realize a basic understanding of its role in the development and progression of breast cancer, which is of great significance for exploring new targets for breast cancer. In order to explore the underlying mechanism of communication between breast cancer and adipose tissue, we isolated adipocytes from adipose tissues adjacent to breast tumor (TAA) and breast benign lesions (BAA), and co-culture them with MCF-7 cells, respectively, followed by cell function tests. Furthermore, in order to assess the effects of adipose-derived peptides on breast cancer cells, we collected the supernatant of adipocytes cell culture, then treat MCF-7 cells with TAA and BAA-derived peptides respectively, and estimate the functional difference in terms of breast cancer cell malignancy. Before deciphering the mechanism of peptides on breast cancer malignancy, it’s of great necessity to detect the presence and the identity of the secreted peptides in advance. We examined the sequences of adipocyte secreted degradome using LC-MS/MS and compared the general physicochemical properties of the differentially secreted peptides between TAA and BAA. Moreover, we matched the peptide sequences to their precursor proteins by PEAKs software to explore the functional roles of these differentially secreted peptides in breast cancer development. The potential roles of these peptides played in regulating tumor behtavior is then predicted by their precursor proteins through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. To further screen functional peptides, Chemical property and structure analysis were performed to excavate peptides which might be easily captured by tumor cells. Through a series of biological experiments, the results showed that peptides collected from culture medium of tumor adjacent adipocytes have the potential to increase MCF-7 cell

proliferation, migration, and invasion dominantly. Simultaneously, LC-MS/MS data showed that there are about 100 identified peptides, which are of significant difference, might have a relationship with breast tumor development. Bioinformatic analysis showed that the MW of these differentially secreted peptides concentrated in the range 500~1200 Da. Due to low MW, peptides are more likely to be easily absorbed and re-used, which means that these differentially secreted peptides might be potential targets for breast cancer diagnosis and treatment. What ' s more, unlike the peptides of tumor, the majority precursor of adipocytes derived peptides are enzymes that participate in post-translational modification, cell-cell signaling, and receptor mediated cascade signaling pathway, indicating cleavage peptides information will help understanding the reciprocal interconnected network of tumor and surrounding stroma tissues. Bioinformatics analysis results demonstrated that these peptides could contribute to aberrant cell adhesion of tumor cells through regulating focal adhesion and pathways in cancer. Sparklingly, through Bioware and Protparam screening and analyzing, 2 lipophilic peptides are identified to be stable in adipocyte secretion degradome, which may create sustained effect on tumor cells. In conclusion, our results confirmed that mammary gland surrounding adipocytes induce malignancy phenotype of breast tumor cells, and delineated the interaction network between secreted degradome of breast tumor adjacent adipocyte and tumor cells. These differentially secreted peptides may shed light onto the mechanism of TAA facilitated breast cancer progression, and extrinsic peptides couple potentially be individual bio-markers for diagnosis or therapeutic targets for breast cancer treatment, which are believed to afford novel insights into breast cancer therapy and give support to the design of targeted therapy.

Key Words： breast cancer, adipocyte, degradome, tumor microenvironment

153. Exploring gut microbiome markers in predicting efficacy of immunotherapy against lung cancer

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Background: Immunotherapy has profoundly changed the treatment landscape for lung cancer (LC) due to its tolerable safety profile and longer sustained therapeutic response. However, only acout 20% of patients with locally advanced and metastatic disease can derive long-term clinical benefit from ICIs. Previous studies have suggested that the microbiome is involved in the development of LC in some way. We aimed to use the gut microbiome (GM) to model the benefit of immunotherapy and to mine the biomarkers with a global impact on immune response.

Methods: We performed human gut metagenomic analysis on the responder patients and non-responder patients with immunotherapy. A total of 296 fecal samples, including baseline samples (71 responders , 98 non-responders and 72 healthy controls), and 55 samples during treatment were enrolled in our study, the taxonomic and functional features of these samples also were excavated. A machine-learning model was developed to identify responders and non-responders. At the same time, we also explored the influence of antibiotic use on the above results.

Results: Specific species, Bacteroides caccae and Bacteroides uniformis, were positively correlated with responders. In non-responders, Prevotella copri was the main enrichment species. The α diversity of microbiota in responding patients was significantly higher than that in non-responding groups, and antibiotic use increased this trend. There was no significant difference in β diversity between the two groups, but LEFSE analysis also could obtain biomarkers of biological significance between the two groups. We used the biomarkers from the above analysis to construct a random forest model, and the area under the receiver operating characteristic curve (AUC) (species level: 82.10%; genus level: 79.4%). In addition, our studies suggested that metabolism such as amino acid metabolism, valine, leucine might be important in regulating the immunotherapy response that warrants further investigation.

Conclusions: Overall, our study explored the relationship between microbial composition and immunotherapy efficacy in LC patients and mined relevant markers, and further research is needed to investigate the mechanisms of action of these key strains in influencing immunotherapy in the future.

Key Words：metagenome；immunotherapy；lung cancer；microbiota；machine learning

154. Cisplatin synergizes immune checkpoint blocking through RNFT1 mediated PD-L1 recycling in Triple Negative Breast Cancer

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Since chemotherapy showed synergies with PD-1/PD-L1 blockage therapy in solid tumors, the efficacy in triple negative breast cancer (TNBC) varies greatly and only a subset of patients achieves durable responses. To increase their clinical efficacy, it is important to explore the underlying mechanisms of immune checkpoint ligand PDL1. Here, we found cisplatin influences the controlled intracellular transport of PDL1 by inducing the RNFT1-mediated endoplasmic reticulum autophagy. Overexpression of RNFT1 increases the endocytosis-recycling rate of the plasm membrane PDL1, which is regulated by K63-polyubiquitination and endoplasmic reticulum autophagy degradation of PDL1, thereby having negative impact on Antitumor immunotherapy, such as reduced effective drug concentration and avoiding immune surveillance. Genetically or pharmacologically modulating RNFT1-induced K63 polyubiquitination blocks endocytosis of PDL1, consequently enhances the antitumor response to PD-1 blockade. Thus, our results suggest that cisplatin treatment is involved in RNFT1-induced K63 polyubiquitination of PD-L1 endocytosis-recycling pathway that governs immune response, and blocking RNFT1 might enhance the efficacy of PD-1/PD-L1 blockade. These studies have high application and translational potential in Triple-negative breast cancer.

Key Words：ICI, RNFT1, Endocytosis-recycling pathway, K63 ubiquitination

155. 结直肠癌　腹膜癌患者错配修复蛋白的临床病理特征及与预后的关系

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目的：检测 DNA 错配修复（mismatch repair, MMR）主要蛋白（MLH1、MSH2、MSH6 和 PMS2）在人结直肠癌腹膜癌（peritoneal carcinomatosis from colorectal cancer, CRC PC）组织中的表达，并分析错配修复缺陷（defective mismatch repair, dMMR）与 CRC PC 临床病理因素及预后的关系。

方法：采用免疫组织化学染色法检测 4 种 MMR 蛋白（MLH1、MSH2、MSH6 和 PMS2）在 152 例人 CRC PC 组织中的表达，根据 dMMR 确定微卫星不稳定性（microsatellite instability, MSI）的结果，分析 MSI 与 CRC PC 临床病理特征的关系，利用 Kaplan-Meier 法构建生存曲线分析其与预后的关系。

结果：免疫组化结果显示在 152 例 CRC PC 组织中，MMR 蛋白表达正常（pMMR）组 136 例（89.5%），MMR 蛋白表达缺失（dMMR）组 16 例（10.5%），其中 MLH1 缺失 10 例（6.6%），MSH2 缺失 3 例（2%），MSH6 缺失 4 例（2.6%），PMS2 缺失 9 例（5.9%），MLH1 和 PMS2 共同缺失 6 例（4.0%），MSH2 和 MSH6 共同缺失 2 例（1.3%）。统计分析结果显示，MSI-H 与 CRC PC 患者年龄（p= 0.777）、性别（p= 0.170）、原发肿瘤部位（p= 0.071）、病理类型（p= 0.775）、有无脉管瘤栓（p= 0.357）、淋巴结有无转移（p= 0.093）及 Ki-67 水平（p= 0.247）无关。Kaplan-Meier 生存分析结果显示 MSI-H 型 CRC PC 患者预后较好，差异具有统计学意义（p= 0.043）。

结论：152 例 CRC PC 患者汇总 MSI/dMMR 型占比为 10.5%（16/152），结果显示 MSI-H 型 CRC PC 具有预后更好的趋势，与 MSS 间差异具有统计学意义。MSI 状态与 CRC PC 预后的关系尚需进一步深入研究和大样本数据的验证。

关键字：结直肠癌腹膜癌；错配修复蛋白；微卫星不稳定；预后

156. III/IV 期非小细胞肺癌免疫治疗疗效的预后模型：一项回顾性真实世界研究

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目的：免疫检查点抑制剂（immune checkpoint inhibitors, ICIs）具有延迟效应，包括假性进展和进展后的长期生存，因此评估 ICIs 的生存获益是一项艰巨的挑战。根据本中心全面的真实世界数据，本研究为接受 ICIs 治疗的非小细胞肺癌（non-small cell lung cancer, NSCLC）患者开发了预后模型，并进行了内部验证。

材料与方法：本研究是一项回顾性真实世界研究（ClinicalTrials.gov 识别号：NCT05719324），共纳入 394 名连续接受免疫治疗至少 2 周期的 III/IV 期 NSCLC 患者。主要终点是无进展生存期（progression-free survival, PFS），次要终点包括总生存期（overall survival, OS）、客观反应率（objective response rate, ORR）、疾病控制率（disease control rate, DCR）和免疫治疗相关不良反应（immune-related adverse events, irAEs）。通过单因素和多因素 Cox 比例风险分析来确定纳入模型的变量，通过受试者工作特征曲线下面积（the area under the receiver operating characteristic curve, AUC）、校准曲线和决策曲线下的面积评估模型性能。

结果：低水平的纤维蛋白原（fibrinogen, FIB）被证明与生存获益显著相关。PFS 预测因子的最佳组合包括对侧肺转移、胸膜转移、肝转移、东部肿瘤协作组体能状态（Eastern Cooperative Oncology Group performance status, ECOG PS）、用药线数、FIB 和血小板与淋巴细胞比率。OS 预测因子的最佳组合包括临床分期、ECOG PS、绝对淋巴细胞计数和 FIB。PFS 预后模型的 AUC 为 0.79，OS 预后模型的 AUC 为 0.74。此外，200 次的五折交叉验证进一步显示出了它们良好的区分度。多因素逻辑回归分析表明，乳酸脱氢酶和慢性阻塞性肺疾病（chronic obstructive pulmonary disease, COPD）是 ORR 的独立预测因子，而临床分期和 FIB 是 DCR 的独立预测因子。关于安全性预测，更多的区域淋巴结受累和患有 COPD 的患者发生 irAEs 的风险更高，而肾上腺转移的患者易发生多系统 irAEs。关于 irAEs 与疗效的关系，与没有发生 irAEs 的患者相比，发生轻度 irAEs 的患者往往长期生存获益，而发生重度 irAEs 的患者预后最差。从 ICIs 治疗开始至第一次 irAE 发生的时间间隔越长，患者的生存结果越好。

结论：本研究首次强调了低水平 FIB 是接受 ICIs 的 III/IV 期 NSCLC 患者生存获益的独立预测因素。第一次分别展示了针对 PFS 和 OS 的 NSCLC-ICI 个性化列线图，并提供了用户友好的网页界面以帮助识别免疫治疗的受益人群。可视化的 PFS 列线图网址为 https://qiliang.shinyapps.io/nsclc_ici_pfs/ ，可视化的 OS 列线图网址为 https://qiliang.shinyapps.io/nsclc_ici_os/。此外，免疫治疗期间出现轻度 irAEs 的患者生存期更长，且迟发型 irAEs 的患者预后更好。

关键字：免疫检查点抑制剂；非小细胞肺癌；纤维蛋白原；列线图；预后模型。

157. REG4 通过去泛素化稳定 SOX9 调控肝外胆管癌细胞铁死亡中的作用及机制研究

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目的：研究 REG4 在肝外胆管癌（Extrahepatic cholangiocarcinoma，ECC）中的表达及其对 ECC 细胞增殖、迁移和铁死亡的影响及潜在的分子机制。

材料与方法：对 3 对肝外胆管癌肿瘤组织及癌旁组织进行转录组测序，分析筛选出上调最为显著的 REG4 基因。采用 qRT-PCR 和 western blot 方法检测 60 对 ECC 患者的肿瘤组织及配对癌旁组织中 REG4 的表达，并分析其表达与患者临床参数之间的相关性。之后，运用克隆形成实验、CCK8 实验、Transwell 实验、流式细胞术及裸鼠成瘤等实验，在体外和体内研究 REG4 对 ECC 细胞增殖、死亡、迁移、铁死亡及肿瘤生长的影响。接下来，采用免疫共沉淀、质谱分析和免疫荧光等技术，研究 REG4 下游靶基因及其对靶基因的调控机制。最后，采用异种移植肿瘤模型研究 REG4 及其下游靶基因对 ECC 肿瘤生长的影响。

结果：转录组测序结果显示，与癌旁组织相比，REG4 在 ECC 肿瘤组织中上调最为显著。60 对 ECC 患者的肿瘤组织检测也表明，REG4 在肿瘤组织中高表达，且 REG4 的表达与 ECC 患者的总生存期和无疾病进展期成反比，与 ECC 患者的淋巴结转移成正比。体内、外研究结果显示，下调 REG4 可有效抑制 ECC 细胞增殖、迁移及异种移植瘤的生长，并促进细胞铁死亡。免疫共沉淀及质谱分析显示，REG4 可与 SOX9 结合。进一步对其调控机制研究发现，REG4 可通过去泛素化促进 SOX9 的稳定性，进而上调 SOX9 的表达。最后，体内研究表明，下调 REG4 可以抑制 SOX9 表达并抑制 ECC 肿瘤的生长。

结论：REG4 通过促进 SOX9 的去泛素化介导其稳定性来发挥癌基因作用。下调 REG4 可以在体内、外抑制 ECC 肿瘤及细胞的生长，提示 REG4 极可能是 ECC 的潜在诊疗靶点。

关键字： 肝外胆管癌，REG4，SOX9，去泛素化，铁死亡

158. 食管鳞癌肿瘤组织菌群特征分析

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目的：中国是世界食管癌高发地区，因缺乏有效的预治手段，5 年生存率不足 30%。近年来，病原微生物感染及微生态紊乱成为肿瘤研究的热点。已有研究表明，菌群失调在各种疾病中发挥重要作用，但目前食管鳞癌患者食管菌群研究较少。本研究基于中国食管癌高发区，分析食管鳞癌患者癌组织及邻近癌旁组织菌群特征，筛选差异性物种。

方法：本研究采用回顾性病例对照研究，收集中国食管癌高发地区安阳肿瘤医院 2022 年 6 月至 2023 年 3 年期间进行上消化道内镜检查并经病理学确诊的 50 例原发性食管鳞癌患者的癌组织和癌旁配对组织，基于 Illumina NovaSeq 6000 平台，对 16S rRNA 基因上的五个区域（V2、V3、V5、V6、V8）进行多重 PCR 扩增和测序。采用 Wilcoxonz 秩和检验比较两组食管菌群 α 多样性差异，采用主坐标分析（PCoA）和非参数多元方差分析（Adonis）分析两组菌群构成差异，通过线性判别效应量分析（LEfSe）筛选两组差异物种。

结果：食管鳞癌组 Chao1 指数（138.36±35.95）和 Shannon 指数（4.52±0.64）显著高于癌旁对照组（105.02±42.53、4.00±1.09），差异具有统计学意义（P<0.05），表明食管鳞癌组 α 多样性高于癌旁对照组。PCoA 不能将食管鳞癌组及癌旁对照组菌群区分开，说明两组群落构成相似。和癌旁对照组相比，食管鳞癌组含有较高丰度的梭杆菌门（Fusobacteriota，8.8 % vs 4.0%）及螺旋菌门（Spirochaetes，2.2% vs 0.5%），较低丰度的放线菌门（Actinobacteriota，0.7% vs 1.9%），（P＜0.05）。属水平上，食管鳞癌组梭杆菌属（Fusobacterium）、嗜二氧化碳噬纤维菌属（Capnocytophaga）、卡氏菌属（Catonella）和密螺旋体属（Catonella）菌群丰度显著高于癌旁对照组，而葡萄球菌属（Staphylococcus）和假单胞菌属（Pseudomonas）丰度低于癌旁对照组(P＜0.05)。LEfSe 分析结果显示：具核梭杆菌（Fusobacterium_nucleatum）、牙周梭杆菌（Fusobacterium_periodonticum）、生痰二

氧化碳嗜纤维菌（Capnocytophaga_sputigena ）和牙龈卟啉单胞菌（Porphyromonas_gingivalis）在食管鳞癌组富集，是食管鳞癌的重要生物标志物。

异乳链球菌（Streptococcus_dysgalactiae）和鞘氨醇单胞菌（Sphingomonas_leidyi）在癌旁对照组富集，是癌旁对照组的重要生物标志物。

结论：食管鳞癌患者食管菌群发生改变，具核梭杆菌（Fusobacterium_nucleatum）和牙龈卟啉单胞菌（Porphyromonas_gingivalis）可作为潜在生物标志物。

关键字：食管鳞癌，食管菌群，16S rRNA，具核梭杆菌，牙龈卟啉单胞菌

159. A novel signature associated with Porphyromonas gingivalis and inflammatory response-related genes assists in prognosis for patients with esophageal squamous cell carcinoma

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Purpose: Esophageal cancer is a malignant tumor that has a significant incidence and mortality rate and its prognosis is very poor, with a 5-year survival rate of less than 20%. Our previous research showed that Porphyromonas gingivalis (P. gingivalis) infection can activate the inflammatory signaling pathway and promotes the malignancy development of esophageal squamous cell carcinoma (ESCC). However, the prognostic significance of inflammatory response-related genes (IRRGs) in P. gingivalis-infected ESCC requires further elucidation. The aim of this study is to construct a prognostic model based on P. gingivalis and IRRG to forecast the survival of patients with ESCC, which may provide insight into new treatment options for ESCC patients.

Methods: Firstly, differentially expressed genes (DEGs) were identified in P. gingivalis-infected and P. gingivalis-uninfected ESCC cells by RNA-seq. The expression profiles and clinical information of ESCC patients were downloaded from the TCGA and GEO cohort. Furthermore,

we performed an intersection analysis to identify genes that were common between the DEGs in the self-sequencing data, DEGs in the TCGA-ESCC dataset, and the set of IRRGs. Then, we screened out potential prognostic biomarkers and constructed a risk score model by using univariate Cox regression analysis, the Least absolute shrinkage and selection operator (LASSO) algorithm, and the multivariate Cox regression analysis. Subsequently, we validated its prognostic value using the GSE53622 dataset. Patients were consequently categorized into high-risk and low-risk groups according to the median value of risk. Kaplan-Meier analysis was carried out compare the overall survival (OS) between the two subgroups. Next, Clinical factors and risk scores were incorporated into univariate and multivariate Cox regression to screen independent prognostic factors, a nomogram for forecasting survival rates of patients with ESCC (1-, 2-, and 3-year survival rates) was created. Furthermore, single-sample gene set enrichment analysis (ssGSEA) was utilized to analyze the immune cell infiltration between the two subgroups. The Genomics of Drug Sensitivity in Cancer (GDSC) database was used to predict drug sensitivity.

Results: We identified 365 DEGs between the P. gingivalis-infected group and the P. gingivalis-uninfected group, including 217 up-regulated and 148 down-regulated genes. Moreover, within the TCGA-ESCC dataset, we found 9,817 DEGs between the tumor and normal samples. A total of 66 crossover genes were identified using a Venn map. Four prognostic genes including DKK1, ESRRB, EREG, and RELN were screened out to construct the a risk model of prognostic genes (P=0.012， C-index=0.73). In both the training and validation sets, patients had a considerably shorter OS in the high-risk group than those in the low-risk group (P <0.05). Thus, a nomogram was created according to risk score, gender and N stage can effectively predict the prognosis of patients (P=0.016， C-index=0.66). The high-risk group displayed lower immune infiltrating cells, such as activated dendritic cell, type 2 T helper cell, and neutrophil (P<0.05). There were 41 of drugs, including dactinomycin, luminespib, sepantronium bromide and so on, with a significant difference of IC50 between the two risk subgroups.

Conclusion: We demonstrated the potential of a novel signature constructed from four P. gingivalis – related IRRGs for prognostic prediction and immune status assessment in ESCC patients.

Key Words： Esophageal squamous cell carcinoma; Inflammatory response; Porphyromonas gingivalis；Prognosis; Immune microenvironment; signature

160. Plasma Metabolomic Signatures of H. pylori infection, Drinking, Smoking and Risk of Gastric Cancer

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Objective: Gastric cancer is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide. It is widely accepted that the environment factors contribute to the etiology of gastric cancer, especially smoking, drinking and Helicobacter pylori (H. pylori) infection. Identifying populations at high risk of gastric cancer is necessary for implementing efficient prevention and management strategies. However, biomarkers that can predict the development of gastric cancer were limited. Recently, a number of studies have shown that metabolic perturbation played an important role in the occurrence and development of gastric cancer. Therefore, the aim of this study was to identify novel biomarkers for gastric cancer using untargeted plasma metabolomics and to investigate the mediation effects of metabolic characteristics in order to elucidate the potential mechanisms underlying the development of gastric cancer.

Methods: Based on two prospective community-based cohorts in East China (Changzhou and Nantong), plasma untargeted metabolomics were measured using Metabolon Discovery HD4 platform in 1,800 participants. We conducted a 1:1 matched nested case-control study (326 gastric cases: 326 healthy controls) to assess the associations between plasma metabolites and gastric

cancer risk, and a cross-sectional study (1,800 participants) was also conducted to identify the plasma metabolites associated with the risk factors of gastric cancer. H. pylori infection status was assessed using plasma samples that were immediately stored at -80° C until measurement. Anti-H. pylori IgG antibody levels were measured using the direct enzyme-linked immunosorbent assay kit "Helicobacter pylori IgG ELISA Kit" (TECAN, German).

Linear regression models were used to assess the correlations of plasma metabolites with risk factors of gastric cancer, adjusted with age, gender, body mass index (BMI), H. pylori infection, pack-years of smoking, drinking status, diabetes, hypertension, dyslipidemia and region. All the associations were considered statistically significant when $P < 0.05$ and FDR < 0.2. Then, the Least Absolute Shrinkage and Selection Operator (LASSO) analysis was performed to select metabolites that were most informative of each environmental factor. The metabolomic signatures were calculated as the weighted sum of the selected metabolites with weights equal to coefficients from the LASSO regression. The metabolic pathway analyses were conducted to measure the significant enriched pathways for individual metabolites associated with environmental factors of gastric cancer, using R package (MetaboAnalystR). All the main pathways were considered significant when $P < 0.05$ and pathway impact > 0.2.

Logistic regression models were performed to evaluate the associations between metabolomic signatures or plasma metabolites and gastric cancer risk, adjusted with age, gender, BMI, H. pylori infection, pack-years of smoking, drinking status, diabetes, hypertension, dyslipidemia and region. For the robustness of the results, sensitivity analyses were performed after the exclusion of participants who was diagnosed with gastric cancer within the first two years of follow-up. Mediation analyses were applied to discover the causal relationships between metabolites, risk factors and gastric cancer. The total and direct effects were assessed through multivariable logistic regression, without and with the metabolomic signature or plasma metabolite as a covariate.

Results: In the cross-sectional study, we assessed the associations between plasma metabolites and risk factors of gastric cancer including H. pylori infection, drinking status and smoking status. Of the 1,800 participants, 1033 participants (57.39%) were H. pylori positive, 622 participants (34.56%) were drinkers and 715 participants (39.72%) were smokers. With multivariable linear regression models, 31, 172 and 152 metabolites were found to be associated with H. pylori infection, drinking status and smoking status, respectively. Using LASSO, 22 H. pylori

infection-related, 154 drinking status-related and 49 smoking status-related metabolites were identified as independent predictors of each environmental factor.

In the 1:1 matched nested case-control study, the multivariable analysis showed that per 1-SD increment of the H. pylori infection-related metabolomic signature was associated with a higher risk of gastric cancer (OR = 1.53, 95% CI: 1.25-1.90, P = 6.31 × 10-5). However, no significant associations were observed between the metabolomic signatures of drinking or smoking status and the risk of gastric cancer. Among these environmental related metabolites, 26 were associated with the risk of gastric cancer in the nested case-control study, encompassing lipids, amino acids, xenobiotics, nucleotides, and carbohydrates. In the sensitivity analysis, similar correlations between metabolomic signatures and gastric cancer risk were observed after excluding the participants diagnosed with gastric cancer within the first two years of follow-up.

To elucidate the effects of plasma metabolites and environmental factors on gastric cancer, we conducted mediation analyses. In the nested case-control study, H. pylori infection was associated with an increased risk of gastric cancer, with an OR of 1.97 (95% CI: 1.42 – 2.73, P = 4.62 × 10-4). When adding H. pylori infection related metabolomic signature into the model, the effect of H. pylori infection was attenuated to 1.71 (95% CI: 1.22 – 2.39, P = 0.002). Accordingly, the association between H. pylori infection and the risk of gastric cancer was partly mediated by the metabolomic signature (22.38%, 95% CI: 0.08-0.49, P = 0.002). In the metabolites related to H. pylori infection, similar effect was found in the adenine. When adding adenine into the model, the effect of H. pylori infection was attenuated to 1.81 (95% CI: 1.30 – 2.52, P = 4.58 × 10-4). Accordingly, the association between H. pylori infection and the risk of gastric cancer was partly mediated by adenine (13.93%, 95% CI: 0.05-0.32, P = 0.002).

Conclusion: Through untargeted plasma metabolomics, our study identified novel metabolomic signatures for H. pylori infection, drinking status and smoking status, along with 26 metabolites related to gastric cancer risk. The metabolomic signature for H. pylori infection emerges as potential biomarkers for classifying the high-risk population for gastric cancer. External validation and further research on the detailed biological mechanisms of these relationships are warranted.

Key Words ： plasma metabolomic, gastric cancer, H. pylori infection, adenine

161. APOC3 regulates lipid metabolism and inhibit the proliferation and metastasis of lung adenocarcinoma

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Background: Lung cancer (LC) is one of the malignant tumors with high morbidity and mortality. The number of LC new cases is second only to breast cancer, accounting for about one tenth (11.4%) of the confirmed cancer cases, while the number of deaths ranks first, accounting for nearly one fifth (18.0%) of the total cancer deaths. APOC3, called apolipoprotein C3, as the protein part of plasma lipoprotein, and is also an important component of very low density lipoprotein (VLDL). APOC3 could combine blood lipids and transport them to various tissues of the body for metabolism and utilization. At present, the research about APOC3 mainly focuses on the related aspects of cardiovascular diseases and hypertriglyceridemia, and there are few studies related to cancer, lung cancer is even rarer. Therefore, the role of APOC3 in the occurrence and development of LUAD and the relationship among APOC3, blood lipid and LUAD still need to be further explored and understood. This study aims to explore the effects of APOC3 on biological functions such as proliferation and migration of LUAD, and preliminarily explore the possible correlation between APOC3 levels, lipid levels, and the occurrence and development of LUAD based on the data of clinical patients' blood lipid, so as to provide a certain research basis for clinical search for seeking effective therapeutic targets for patients with LUAD.

Objective： The purpose of this research mainly included the following aspects. Firstly, In order to determine the expression difference of APOC3 in LUAD and normal tissue, two methods were performed for verification, namely extracting and analyzing literature data (tissue proteomic analysis) and Immunohistochemical (IHC).Secondly, we would like to construct a lentivirus-mediated stably transformed cells overexpressing APOC3 and explore whether APOC3 can inhibit the proliferation and migration of LUAD cells. Thirdly, we aimed to study the correlation between APOC3 and blood lipid.

Methods:1.Determination of APOC3 expression in lung adenocarcinoma tissue and normal tissue by immunohistochemical (IHC).

2.The detection of the expression of APOC3 in six LUAD cell lines and one normal lung epithelial cell line by Western blot analysis and construct a lentivirus-mediated stably transformed cells overexpressing APOC3.

3.Explore whether APOC3 can inhibit the proliferation and migration of LUAD cells by CCK8 cell proliferation experiment and transwell migration experiment.

4.The oil red O staining experiment was carried out to detect the effect of APOC3 on the triglyceride level in LUAD cells.

5.Statistical analysis

Image J software was used to quantify the results of CCK8 proliferation assay and Transwell-migration assay. Image Pro plus 6.0 was used to count the results of oil red O staining (percentage of lipid droplet area to total cell area). the experimental data were statistically analyzed and the results were visualized by using SPSS 26.0 and GraphPad Prism 8.0. The difference between the two groups of data was analyzed by Mann-Whitney U test. Two-sided test was used in all statistical analysis. When $P<0.05$, the difference was considered statistically significant.

Results: 1.The expression levels of APOC3 in tumor tissues and non-cancerous adjacent tissues (NATs) in literature were extracted, and it was found that APOC3 was significantly lower expressed in LUAD cancer tissues than NAT ($P<0.001$). The levels of APOC3 in tumor and NATs were further detected in tissue chips containing 92 LUAD patients (88 of which had paired NATs) showed low expression level of APOC3 in tumor tissues, while higher expression level of adjacent tissues.

2.Western blot analysis showed that the expression of APOC3 was low in all LUAD cells and normal lung epithelial cells, and the expression of APOC3 protein in A549 cells and H1975 cells was significantly lower than that in BEAS-2B cells. The stably transformed cells overexpressing APOC3 showed that compared with the control cells, the protein expression and mRNA expression of APOC3 in the transformed cells were significantly increased.

3.Overexpression of APOC3 can significantly inhibit the proliferation and migration ability of A549 cells and H1975 cells.

4.The oil red O staining experiment was carried out in LUAD cells, and the results showed that the level of triglyceride in A549 cells and H1975 cells overexpressing APOC3 was significantly increased.

5.The blood lipid levels of LUADs were all lower than those of NCs ($P<0.05$), and the plasma TC, HDL and LDL levels of BPNs were significantly lower than those of NCs ($P<0.05$).

Conclusion: In order to effectively reduce the mortality of LC, it is very important to improve the early diagnosis strategy of LUAD. However, the exploration of the occurrence and development mechanism of LUAD and the search for potential therapeutic targets are also top priorities. Our research shows that the plasma level of APOC3 is related to the level of triglycerides, the level of triglyceride in A549 cells and H1975 cells overexpressing APOC3 was significantly increased as well. The study found that overexpression of APOC3 can significantly inhibit the proliferation and migration ability of A549 cells and H1975 cells. Our results reveal that APOC3 may be a valid therapeutic targets for patients with LUAD.

Key Words ： LUAD, APOC3, Triglycerides, migration, proliferation

162. 基于深度学习的肺腺癌气腔播散病灶识别和半定量评估模型的构建

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Purpose: Since 2015, the World Health Organization classified Spread Through Air Space (STAS) as a new invasion mode of lung cancer. Medical researchers gradually realized that STAS has its ow potential value in clinical treatment decision making. The reported incidence of STAS in NSCIC varies from 16% to 60% in multiple studies conducted worldwide. The detection rate of STAS exhibits significant differences among doctors, primarily influenced by their experience.

Methods: 506 digital WSIs of 285 LUAD patients were collected. A STAS detection model, named STASNet, was constructed based on the MobileNetV3 model, calculating semi-quantitative parameters associated with the density and distance of STAS to predict patient recurrence. The

artificial intelligence (AI)-assistance workflow was established to assist the STAS detection and assessment of recurrence risk.

Results: The STASNet exhibited an accurate rate of 0.93 for STAS detection on the tiles level and had an AUC ranging from 0.72-0.78 for determining the STAS status across three datasets on the whole slide images (WSI) level. Among the semi-quantitative parameters, T10S, combined with spatial location information, which significantly stratified stage I LUAD patients on the disease-free survival (DFS). As for the lightweight architecture of MobileNetV3, we also deployed the STASNet into a real-time pathological diagnostic environment, which boosted the detection rate of STAS and identified three easily misidentified types of occult STAS.

Conclusion: he deep learning mode established in this study showed the ability of predicting STAS lesions on tumor boundary image and the WSI level image of lung cancer. The model can also help pathologists to focus on the high incidence area of STAS in WSIs of lung cancer, which can improve reading efficiency. At the same time, this model can reduce cross observer bias among clinical physicians and improve diagnostic consistency for STAS.

关键字： Deep learning, STAS, LUAD

163. A gastric cancer risk variant at 6p21.1 impairs APOBEC2 functions in hypoxia-induced mitochondrial mitophagy by inhibiting HIF-1 α/BNIP3 pathway

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Objective: Gastric cancer (GC) is one of the most commonly diagnosed malignancies around the world, especially in East Asia. Epidemiological evidence has demonstrated that several risk factors play a role in the initiation and development of GC, with an estimated 20% genetic heritability. Up to now, multiple genome-wide association studies (GWASs) have advanced our understanding of GC host genetics and about a dozen of independent single-nucleotide polymorphisms (SNPs) have been proven to be associated with GC risk in both Asian and European populations. The susceptibility locus at chromosome 6p21.1 is one such region, which has been confirmed that the intronic SNP rs2294693 in UNC5CL was significantly related to an increased risk of gastric non-cardia cancer. In our study, a fine-mapping analysis was performed to confirm the association of genetic variants at 6p21.1 with GC susceptibility based on six independent GWAS datasets with the largest samples of 10,254 GC cases and 10,914 controls. Therefore, the aim of this study was to identify the potential functional variant at 6p21.1 and elucidated the regulatory mechanisms influencing gastric tumorigenesis.

Methods: Risk associations for the 6p21.1 locus were based on six published GWAS datasets. Fine-mapping analysis was restricted to SNPs within 1Mb flanking regions of rs9381024 that has the strongest association with GC at 6p21.1. All genetic variants in high linkage disequilibrium (LD, r2 ≥ 0.8) within 1Mb flanking regions around rs9381024 were included to perform

functional annotation. To further evaluate the allele-specific promoter activity for SNPs, we carried out dual-luciferase reporter gene assay. The binding of transcription factors was confirmed by electrophoretic mobility shift assay (EMSA) and chromatin immunoprecipitation (ChIP) assay. For hypoxia treatment, the cells were cultured in a Three-Gas CO2 Incubator (Thermo Fisher Scientific, Waltham, MA, USA) containing 1% O2, 5% CO2 and 94% N2 for 24 hours. RNA interference, plasmid overexpression, and CRISPR/Cas9-mediated activation, as well as cell viability, proliferation, 5-ethynyl-2'-deoxyuridine (EdU) incorporation assays and apoptosis of flow cytometry, were used to evaluate the biological functions of APOBEC2 in GC cells. MitoTacker Green (MTR-G, Thermo Fisher Scientific) and Tetramethylrhodamine (TMRM, Thermo Fisher Scientific) were used to detect mitochondrial mass and membrane potential. Extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) were performed to evaluate aerobic glycolysis rates and mitochondrial oxidative phosphorylation. To determine whether mitochondrial degradation increased in cells overexpressing APOBEC2 during the phase of attenuated autophagy by double staining GC cells with LysoTracker Red and MitoTracker Green fluorescent dyes, respectively.

Results: Fine-mapping studies showed that rs9381024 was the most significant genetic variant and the T allele of rs9381024 was associated with an increased GC risk in the 6p21.1 region (OR = 1.14, 95%CI = 1.09-1.20, P = 4.06 × 10-8) and it was the only independent association signal associated with GC risk in this region. Comprehensive functional annotation showed that rs2235679, which was in strong LD with rs9381024 (r2 = 0.80), had the highest score of 6. Besides, rs2235679 was located in the promoter region of APOBEC2 and had a high signal of histone marks, suggesting that rs2235679 might be functional in this region. And rs2235679 genotypes were significantly correlated with the expression level of APOBEC2. Dual-luciferase reporter assay revealed that the T allele of rs2235679 might reduce the promoter activity. EMSA and ChIP assays suggested the T allele of rs2235679 might enhance the binding affinity of MZF1to the promoter of APOBEC2 as a transcriptional repressor. Intriguingly, inhibiting the expression of MZF1 with specific siRNAs resulted in an increased expression of APOBEC2 in both BGC823 and MKN1 cells.

Cell viability and proliferation assays showed that cell proliferation was decreased in APOBEC2 overexpressing GC cell lines established using the CRISPRa system under hypoxia but not

normoxia. In addition, APOBEC2 did not affect the apoptosis of GC cell lines under hypoxia. We also used small interference to knockdown APOBEC2 of BGC823 on the basis of overexpressing APOBEC2 and found that the cell proliferation ability was restored. Besides, while overexpression of APOBEC2 increased mitochondrial membrane potential and mass, the overall potential of these mitochondria did not increase as a consequence, suggesting dysfunctional mitochondria. ECAR and OCR results also showed that APOBEC2 could affect the glycolysis ability and mitochondrial function of GC cells under hypoxia.

Further mechanistic studies showed that APOBEC2 reduced colocalization of mitochondria with lysosomes and the conversion from LC3-I to LC3-II under hypoxia, which revealed that overexpression of APOBEC2 had a negative effect on autophagic flux in GC cells and blockage of mitophagy. At the same time, the induction of both HIF-1 α and BNIP3 proteins by hypoxia were less in cells overexpressing APOBEC2 than in control cells. Dimethyloxalylglycine (DMOG) is an inhibitor of HIF prolylhydroxylase, which stabilizes and accumulates HIF-1 α protein in the nucleus. In order to confirm the stability of the results, we used 500uM DMOG to treat GC cell lines for 24 hours under hypoxic conditions. Interestingly, despite the existence of DMOG, the expression of HIF-1 α and BNIP3 were significantly decreased by overexpression of APOBEC2 compared to controls. Furthermore, we overexpressed HIF-1 α in APOBEC2 overexpression BGC823 cells. The intensity and number of these puncta decreased in cells overexpressing APOBEC2. The above results indicated that APOBEC2 reduced HIF-1 α /BNIP3-mediated mitophagy induction under hypoxic conditions.

Conclusions: The T allele of functional variant rs2235679 reduced the promoter activity by enhancing the binding affinity of transcriptional repressor MZF1, leading to decreased expression of APOBEC2 in the 6p21.1 region. Under hypoxia, APOBEC2 reduces hypoxia-induced mitophagy by inhibiting the HIF-1 α /BNIP3 pathway, contributing to the accumulation of dysfunctional mitochondria and eventually affecting tumor cell growth.

Key Words ： Gastric cancer, susceptibility, 6p21.1, APOBEC2, mitophagy

164. Revealing Gastric Cancer Mechanisms through Genetic Regulation of Expression, Splicing, and Polyadenylation

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Objectives： Genome-wide association study (GWAS) identify multiple susceptibility loci for gastric cancer, however, associations between transcriptional regulatory changes and gastric cancer remain elusive. Quantitative trait loci (QTLs) have been demonstrated to contribute to disease etiology by regulating gene expression, alternative splicing (AS), and alternative polyadenylation (APA). Here, we attempted to uncover the connections and differences between expression quantitative trait loci (eQTLs), splicing quantitative trait loci (sQTLs), and alternative polyadenylation quantitative trait loci (apaQTLs), as well as providing new insights into associations between transcriptional regulation of gastric tissue and gastric cancer.

Methods： We performed genome-wide QTL study to identify genetic variants that affect gene expression, alternative splicing or alternative polyadenylation in gastric tissues from 262 individuals of Chinese ancestry. Age, sex, Helicobacter polyri (H.polyri) infection, the first five PCs inferred on the basis of genotype data, and the first PEER factors were adjusted as covariates. We then applied a false discovery rate (FDR) threshold of ≤ 0.05 to identify genes, splicing junctions or 3’ UTRs with a significant QTL, following the analysis workflow consistent with the Genotype-Tissue Expression (GTEx) project.

After functional annotating of eQTLs, sQTLs and apaQTLs under the instruction of VEP, we compared the distribution between different significant QTL SNPs by GREGOR (Genomic Regulatory Elements and Gwas Overlap algoRithm). To assess the relationships between eQTLs, sQTLs, and apaQTLs, we evaluated the overlap of significant genes for each QTL and examined

the relationships between lead SNPs within the overlapping genes. Moreover, we performed transcriptome-wide association study (TWAS) by predicting genetically regulated expression, splicing junction or 3'UTR length for the individuals from the gastric cancer GWAS dataset and performing association analyses between predicted values and gastric cancer status. Colocalization of QTL and GWAS associations was conducted using the coloc software, which has been incorporated into the TWAS/FUSION pipeline. We performed summary data-based Mendelian randomization (SMR) to identify gene-trait, junction- or 3'UTR- associations by integrating QTL and gastric cancer GWAS data, as a complementary approach to TWAS.

Results： We performed RNA sequencing of gastric tissues derived from 262 unrelated healthy donors of Chinese population from Yangzhou screening program, and measured genotypes using the Illumina Asian Screening array on venous blood samples. After quality control and normalization of gene expression, intron usage ratio, 3'UTR usage and genotypes, we obtained a dataset of 20,051 genes, 79,908 introns, 39,101 APA events and 6.8 million variants. Our findings showed that over 50% of sQTL or apaQTL are independent of eQTL, indicating that the need for further exploration of sQTL and apaQTL mapping in future research. Following the pipeline previously reported by GTEx, we found 4,636 eQTL-harboring genes (eGenes) with 621,451 significant eQTLs, as well as 1,422 sQTL-harboring genes (sGenes) with 571,034 significant sQTLs and 511 apaQTL-harboring genes (apaGenes) with 118,334 significant apaQTLs at false discovery rate (FDR) q value < 0.05.

After functional annotating of these variants under the instruction of VEP and comparing the distribution between different significant QTL SNPs, we found that sSNPs were more significantly enriched in splice region, while aSNPs were significantly enriched in 3’ UTR. We further annotated and compared significant QTL SNPs with non-significant QTL SNPs, and identified key transcription factors like YY1, MYC, as well as key RBPs like HNRNPU, UCHL5, which have been reported play important role in diseases susceptibility.

Among overlapped QTL-harboring genes, the majority of the identified SNPs were found to be distinct, as evidenced by the substantial distances observed between eSNPs and sSNPs, eSNPs and apaSNPs, as well as sSNPs and apaSNPs. Additionally, it was observed that less than half of the lead SNPs exhibited high linkage disequilibrium (LD) with an r2 > 0.5. Furthermore, by integrating each QTL with gastric cancer GWAS data, we found that all QTLs show significant

enrichment in potential risk loci of gastric cancer. Although the number of significant GWAS SNPs is highest in eQTLs, the proportion of significant GWAS SNPs is significantly higher in sQTLs and apaQTLs.

To systematically identify the susceptibility genes of gastric cancer, we conducted TWAS as well as splicing-TWAS (spTWAS) and alternative polyadenylation-TWAS (apaTWAS) following the TWAS/FUSION framework. Under the condition of p values for heritability < 0.05, a total of 4,924 genes, 7,018 splicing junctions and 2,263 APA events were retained for further analysis. We identified tens of unique genes at FDR < 0.1 whose imputed expression, intron usage ratio, and 3'UTR usage were significantly associated with gastric cancer risk. Among these, there were genes in known gastric cancer susceptibility loci including MUC1, PRKAA1, PSCA and PLCE1. Based on the results of colocalization analysis and SMR (Summary-data-based Mendelian Randomization) analysis, we have identified candidate causal events for gastric cancer.

Conclusions： In this study, we generated a comprehensive catalog of genetic variants associated with a broad spectrum of gene expression, AS, and APA in human gastric tissue, significantly expanding our understanding of the genetic control of transcriptional regulation. By comparing the lead SNPs of different QTLs, we discovered that genetic variants associated with different transcriptional regulatory mechanisms tend to be independent and are located at considerable genomic distances from each other. In addition to that, we also observed a significant enrichment of gastric cancer GWAS signals in sQTLs and apaQTLs, with a higher proportion of GWAS significant SNPs compared to eQTLs. These observations are consistent with the growing evidence that eQTL had limitations in excavating the biological mechanism of variants in regulating gene expressions, while sQTL and apaQTL analysis might provide more effective approach for further disease susceptibility investigation. Finally, through integrating QTL data and gastric cancer GWAS data, we identified several novel genes associated with gastric cancer susceptibility. We present compelling examples where genetic and biological evidence converge, supporting their potential implication in gastric cancer susceptibility. These findings provide novel avenues and valuable resources for a deeper understanding of the genetic foundations of gastric cancer.

Key Words ： alternative splicing; alternative polyadenylation; quantitative trait loci; transcriptome-wide association studies; gastric cancer

165. 多项检验指标联合检测在结直肠癌诊断中的价值

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目的： 分析研究多项检验指标联合检测在结直肠癌诊断中的价值。

方法： 回顾性选择 2018 年 1 月至 2023 年 3 月于福建省肿瘤医院病理诊断为结直肠癌的 211 例患者作为首诊结直肠癌患者组，并选择同期结直肠良性肿物患者 103 例与健康人群的 77 例作为对照组，比较不同人群一般资料及糖类抗原 19-9（CA19-9）、癌胚抗原（CEA）、血红蛋白（Hb）、血小板/淋巴细胞比值（PLR）、系统免疫性验证指数（SII）、红细胞体积分布宽度（RDW）、白蛋白（ALB）、总胆固醇（TC）等水平，分析各项检验指标单项检测及联合检测对结直肠癌的诊断价值，并构建 nomogram 预测诊断模型。

结果：年龄及 CA19-9、CEA、RDW、PLR、SII、Hb、ALB、TC 在首诊结直肠癌患者组与对照组间差异有统计学意义（P＜0.05），在性别方面差异无统计学意义（P＞0.05）。首诊结直肠癌患者组中年龄、CA19-9、CEA、RDW、PLR、SII 水平显著大于对照组，而 Hb、ALB、TC 水平表现相反。单项检测时，ALB 诊断 CRC 效能最高。早期结直肠癌组中 CA19-9、CEA、PLR、SII 水平显著小于晚期结直肠癌组（P＜0.05），其中 CEA 判断分期效能最高。CA19-9+CEA+Hb+SII+ALB+TC 的组合结果最佳（P＜0.001）。基于分析结果建立包含各项检验项目预测因子的模型，并以 nomogram 列线图形式呈现，该预测诊断模型与临床实际结果具有良好的一致性，在较大概率阈值内 nomogram 模型预测诊断 CRC，患者净收益大于 0。

结论：单项 CA19-9、CEA、RDW、PLR、SII、Hb、ALB 及 TC 实验室指标可用于诊断结直肠癌患者，其中 ALB 诊断效能最高。CA19-9、CEA、PLR 、SII 单项检测结果可用于判断结直肠癌分期，其中 CEA 判断分期效能最高。CA19-9、CEA、PLR、SII 水平随着结直肠癌患者 TNM 分期的增高而升高。CA19-9+CEA+Hb+PLR+ALB+TC 六者联合检测诊断效能高于各项实验室指标单项检测结果，可提高检测 CRC 的准确性。建立 nomogram 预测模型可为临床诊断 CRC 提供重要的理论依据。

关键字： 结直肠癌；检验指标；联合检测；诊断

166. NDUFAF5 介导线粒体功能重塑促进卵巢癌细胞铂类药物耐药的机制研究

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顺铂是卵巢癌化疗中的一线药物，卵巢癌获得性铂类耐药是导致晚期卵巢癌患者 5 年总生存率较低的主要原因。代谢重塑是卵巢癌耐药性发展的基础，是调控卵巢癌细胞获得化疗耐药性的重要潜在机制之一。

本课题通过应用 Mitotrack 染色、电镜、Mitosox 染色等方式探究卵巢癌顺铂耐药株（A2780CP）与亲本株(A2780S)间代谢表型差异。应用自主设计并合成的线粒体基因 CRISPR-SCREEN 敲除文库筛选出介导卵巢癌获得性耐药代谢重塑的关键机制--线粒体复合物 I（CI）。通过细胞周期、细胞凋亡及平板克隆等方式验证 CI 抑制剂对卵巢癌顺铂耐药性的调控作用。应用 Mitosox 染色检测 ROS 生成方式验证 CI 抑制剂提高卵巢癌顺铂药物敏感性的机制。通过 Seahorse 验证顺铂对电子传递链的作用位点。通过线粒体复合物 II 抑制剂验证电子传递在调控顺铂耐药性中的作用。最后通过验证筛选的线粒体复合物 I 亚基 NDUFAF5 在顺铂耐药株中表达情况，探究顺铂调控卵巢癌获得性耐药机制。

实验结果显示在基础代谢条件下 A2780CP 细胞系 ROS 产生率高于 A2780S，在顺铂处理情况下，顺铂可以诱导 A2780S 的 ROS 显著升高，而无法诱导 A2780CP 细胞系 ROS 显著升高。共聚焦染色显示，A2780S 细胞系线粒体形态相对 A2780CP 细胞系的线粒体形态更分散。基于以上代谢异质性表型，我们通过 CRISPR-SCREEN 技术筛选出线粒体复合物 I 是调控顺铂敏感性的中心机制。进一步实验验证线粒体复合物 I 抑制剂通过提高顺铂诱导的细胞凋亡及 G2 周期阻滞进而提高顺铂敏感性。同时线粒体复合物 I 抑制剂可以提高顺铂诱导的 ROS 生成。Seahorse 结果提示卵巢癌顺铂耐药株 CI 基础活性高于亲本株，顺铂作用两株细胞系后 CI 活性增高。并且抑制 CII 使电子优先通过 CI 可以提高顺铂耐药性。GEO 及 TCGA 数据库分析结果指出，卵巢癌顺铂耐药株中 NDUFAF5 表达增高，且与卵巢癌铂类化疗患者预后相关，顺铂诱导后 NDUFAF5 转录增高。

通过以上结果，推测线粒体复合物 I 功能重塑是卵巢获得性耐药过程的关键机制，顺铂通过诱导 NDUFAF5 转录增高提高线粒体复合物 I 活性，电子传递优先通过 CI 进而提高线粒体功能介导卵巢癌获得性耐药。通过抑制线粒体复合物 I 的活性,提高顺铂诱导的 ROS 生成导致细胞凋亡增加及更多细胞周期阻滞进而逆转卵巢癌获得性耐药。

关键字： 卵巢癌；顺铂；获得性耐药；线粒体复合物 I

167. Extracellular vesicles carrying miR-6836 derived from resistant tumor cells transfer cisplatin resistance of epithelial ovarian cancer via DLG2-YAP1 signaling pathway

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Background: Chemotherapy resistance is a significant cause for poor prognosis of epithelial ovarian cancer (EOC). However, the molecular mechanism of chemo-resistance remains unclear, and developing available therapies and effective biomarkers for resistant EOC is in urgent demand. Stemness of cancer cells directly results in chemo-resistance. Exosomal miRNAs rebuild tumor microenvironment (TME) and act as widely used clinical liquid biopsy markers.

Methods: In our study, high throughput screenings and comprehensive analysis were performed to screen for miRNAs, which were both up-regulated in resistant EOC tissues and related to stemness, and miR-6836 was identified accordingly.

Results: Clinically, high miR-6836 expression was closely correlated with poor chemotherapy response and survival for EOC patients. Functionally, miR-6836 promoted EOC cell cisplatin resistance by increasing stemness and suppressing apoptosis. Mechanistically, miR-6836 directly targeted DLG2 to enhance Yap1 nuclear translocation, and was regulated by TEAD1 forming the positive feedback loop: miR-6836-DLG2-Yap1-TEAD1. Furthermore, miR-6836 could be packaged into secreted exosomes in cisplatin-resistant EOC cells and exosomal miR-6836 was able to be delivered into cisplatin-sensitive EOC cells and reverse their cisplatin response.

Conclusion: Our study revealed the molecular mechanisms of chemotherapy resistance, and identified miR-6836 as the possible therapeutic target and effective biopsy marker for resistant EOC.

Key Words： Cisplatin resistance; DLG2; Extracellular vesicles; Ovarian cancer; TEAD1; YAP1; miR-6836.

168. Proanthocyanidins inhibited colorectal cancer stem cell characteristics through Wnt/β-catenin signaling

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Background: Cancer stem cells (CSCs) play a key role in tumor cell growth, drug resistance, recurrence and metastasis. Proanthocyanidins (PC) is widely existed in plants and endowed with powerful antioxidant and anti-aging effects. Interestingly, recent studies have found that PC exhibits the inhibitory effect on tumor growth. However, the role of PC in CSCs of colorectal cancer (CRC) and molecular mechanism remain unclear.

Methods: CCK-8, colony and tumorsphere formation assay were used to evaluate cancer cell viability and stemness, respectively. Western blotting was used to detect the protein expression.

Tumor xenograft experiments was employed to examine the tumorigenicity of CRC cells in nude mice.

Results: PC decreased the proliferation of CRC cells (HT29 and HCT-116), and improved the sensitivity of CRC cells to oxaliplatin (L-OHP), as well as inhibited tumor growth in nude mice. Further studies showed that PC also down-regulated CSCs surface molecular and stemness transcriptional factors, while suppressed the formations of tumorspheres and cell colony in CRC. In addition, PC impaired proteins expressions of p-GSK3 β , β -catenin and DVL1-3. LiCl, an activator of the Wnt/ β -catenin signaling, rescued PC-induced downregulation of CSCs markers, and reduction of tumorspheres and cell colony formation abilities in CRC cells. Furthermore, the effects of PC on inhibiting cell proliferation and enhancing L-OHP sensitivity were impaired by LiCl.

Conclusions: PC exerted an inhibitory effect on CSCs via Wnt/ β -catenin in CRC, and may be a potential new class of natural drug for CRC treatment.

Key Words： Colorectal cancer; Cancer stem cells; Proanthocyanidins; Wnt/ β -catenin; drug resistance

169. 红肉暴露相关毒物靶基因的结直肠癌预后模型研究

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目的：本研究通过红肉相关毒物信息筛选结直肠癌特征基因并构建预后模型，探究其对结直肠癌患者生存预后的预测作用与价值。

方法：基于比较毒性基因组学（CTD）数据库识别红肉相关毒物 N-亚硝基二甲胺（NDMA）和 N-亚硝基吡咯烷（NPYR）靶向作用基因；利用肿瘤与癌症基因组图谱（TCGA）数据库获取结直肠癌与癌旁组织的转录组数据及临床信息。采用 limma 算法筛选受红肉毒物诱导的差异表达基因；联合 Lasso 和 Cox 回归鉴定特征基因，构建预后模型及风险评分，并绘制列线图可视化。

结果：共筛选得到 238 个红肉毒物靶向影响的肿瘤差异基因；经联合回归分析候选 6 个结直肠癌预后相关基因（IGSF9、TIMP1、EREG、CXCL13、GLYATL1、FER1L6）。构

建风险评分，发现高分组预后显著低于低分组（P<0.001）,且具有独立预后效应。列线图指示其对患者预后评估拟合度较高（C-Index=0.790）。预后相关基因在高分组与低分组表达差异显著，主要富集于细胞周期调节、p53 等信号通路。

结论：红肉相关毒物与结直肠癌进展相关，基于预后相关基因构建的模型能够较好地预测结直肠癌患者预后，为改善结直肠癌患者预后状况提供参考依据。

关键字： 红肉；结直肠癌；预后模型；生物信息学分析

170. Discovery, validation, and application of DNA methylation markers for early detection of cardia gastric adenocarcinoma and esophageal squamous cell carcinoma

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Aim: Cardia gastric adenocarcinoma (CGA) and esophageal squamous cell carcinoma (ESCC) remain major health burdens in China. Most of cases are diagnosed at advanced stages and carry a dismal prognosis. However, biomarkers for early detection of CGA and ESCC are still lacking. Here, we aim to integrate methylome and transcriptome data and identify DNA methylation markers for early detection of CGA and ESCC.

Material and Method: Infinium MethylationEPIC array was performed on 36 paired CGA and non-tumor adjacent tissues (NAT) in the discovery stage and differentially methylated CpG sites (DMCs) were identified between CGA/ESCC and NAT by combined analyses of in-house data and public database. Targeted pyrosequencing and quantitative real-time RT-PCR were performed to validate the methylation levels of candidate markers and expression levels of targeted genes on paired tumor and NAT from 50 CGA and 50 ESCC patients from an independent validation cohort. An independent cohort of 438 CGA, ESCC, high- and low-grade dysplasia (HGD/LGD), and

normal control biopsies was tested for selected DMCs using pyrosequencing. For separate analysis of two disease entities, logistic regression was performed to assess the diagnostic performance of individual biomarkers and their combined discriminatory ability as a marker panel, respectively. For combined analysis of two disease entities, we randomly divided the subjects into training (80%) and test (20%) sets to test performance of a multivariable stepwise logistic regression model. These analyses were performed on “normal/LGD” versus “HGD/cancer”, because patients with HGD or cancer are recommended to receive endoscopic or surgical therapy. Model discrimination was assessed through ROC analysis and AUC.

Results: We identified and validated three CGA-specific, two ESCC-specific, and one tumor-shared DMCs, which were significantly hypermethylated with lower expression of their located genes in tumor compared with NAT samples. Using these DMCs, we developed a CGA-specific 4-marker panel (cg27284428, cg11798358, cg07880787, and cg00585116) achieving an AUC of 0.995 (95% CI: 0.982-1.000) and 0.962 (95% CI: 0.920-1.000) for early-stage and all-stage CGA, respectively, and an ESCC-specific 3-marker panel (cg14633892, cg04415798, and cg00585116) with an AUC of 0.970 (95%CI: 0.939-1.000) and 0.978 (95%CI: 0.958-0.999) for detecting early-stage and all-stage ESCC, respectively. We then evaluated the performance of DMCs for detecting cancerous and precancerous lesions, the CGA-specific 4-marker panel discriminated cardia HGD/CGA patients from cardia LGD/normal controls with the area under ROC curve (AUC) of 0.917, and the ESCC-specific 3-marker panel distinguished esophageal HGD/ESCC with AUC of 0.865. Integrating cg00585116, age, and alcohol drinking, the tumor-shared model showed good discrimination for two cancer/HGD in the training set with AUC of 0.740, which was confirmed in the test set with AUC of 0.841.

Conclusion: Collectively, novel DNA methylation markers could differentiate CGA/ESCC and HGD from LGD and normal controls with promising accuracy. Our findings pave the way for targeted DNA methylation assays in future minimally invasive cancer screening methods.

Key Words： cardia gastric adenocarcinoma, esophageal squamous cell carcinoma, high-grade dysplasia, DNA methylation markers, early detection

171. Kinectin 1 靶向趋化因子重塑三阴性乳腺癌免疫微环境的机制研究

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目的：研究 KTN1 重塑三阴性乳腺癌免疫微环境的分子机制；探讨 KTN1 纳米抗体联合免疫抑制剂靶向三阴性乳腺癌治疗的潜在价值，为三阴性乳腺癌患者的治疗提供新型治疗前景。

材料与方法：本研究采用单细胞转录组测序分析 KTN1 与三阴性乳腺癌不同免疫细胞亚群及趋化因子的表达相关性；采用流式细胞术进行 shKTN1 荷瘤小鼠肿瘤组织中免疫细胞浸润组分分析；开发 KTN1 靶向特异性纳米抗体；采用人源化免疫重塑小鼠模型，评估 KTN1 特异性纳米抗体联合免疫抑制剂治疗疗效；

结果：（1）KTN1 促进 TNBC 肿瘤免疫的细胞因子表达：收集 5 例 TNBC 组织样本，采用单细胞转录组测序分析筛选发现，在高表达 KTN1 肿瘤细胞群中，促肿瘤免疫的细胞因子 CXCL16、CSF1、CXCL1 及 CXCL2 高表达。qRT-PCR 验证了以上结果，且采用 TIMER 数据库分析 139 例 Basal-like 亚型患者中，KTN1 与以上细胞因子呈正相关。以上结果表明：KTN1 促进 TNBC 肿瘤免疫的细胞因子表达。（2）KTN1 促进 TNBC 免疫抑制微环境的发生：细胞因子通过受体-配体互作影响肿瘤免疫微环境，这些促肿瘤免疫的细胞因子受体（CXCR1/CXCR2-CXCL1/CXCL2/CXCL8）主要通过高度富集 MDSCs 与 DCs 细胞影响肿瘤血管生成；而 CXCR6-CXCL16 主要影响 T 细胞功能。通过免疫细胞分群我们发现，在 TNBC 患者肿瘤中，CXCR6 高度富集耗竭型 CD8+ T 细胞；而 CXCR1/CXCR2 主要高度富集 M2 型巨噬细胞及 MDSCs。部分结果提示：KTN1 促进 TNBC 免疫抑制微环境。（3）KTN1 缺失抑制髓系抑制性细胞（MDSCs）富集：采用 4T1 细胞建立 shKTN1 荷瘤小鼠模型，收集肿瘤组织，将其消化为单细胞悬液用相关抗体进行流式细胞术分析，结果所示，KTN1 缺失的小鼠肿瘤中，MDSCs 富集显著减少，部分结果提示：KTN1 缺失抑制 TNBC 肿瘤免疫抑制微环境的进程。

结论 ：KTN1 增强三阴性乳腺癌免疫抑制微环境的发生，开发 KTN1 纳米抗体，为逆转 TNBC 患者免疫抑制提供新的治疗策略及科学依据。

关键字： 三阴性乳腺癌；KTN1；MDSCs；免疫微环境；T 细胞

172. Reactivation of methylation-silenced PAX1 inhibits cervical cancer proliferation and migration via the WNT/TIMELESS pathway

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Objective: Although aberrant methylation of PAX1 is closely associated with cervical cancer (CC), PAX1 methylation (PAX1m) and its role in CC remain to be elucidated. Here, we clarified the biological function of PAX1 in CC.

Methods: First, PAX1m in ThinPrep cytologic test (TCT) samples was measured via quantitative methylation-specific PCR (QMSP). The methylation and tissue array data were extracted from public databases to investigate their clinical relevance within CC. The half-maximal inhibitory concentration (IC50) was generated by exposing CC cells to varying concentrations of cisplatin. Then, CRISPR-dCas9-Tet1 was constructed to screen the most effective CpG sites associated with PAX1 expression. Gain- and loss-of-function experiments were used to identify the role of PAX1 in CC. Moreover, the effects of PAX1 overexpression on the WNT/TIMELESS signaling pathway were evaluated through quantitative real-time PCR and western blotting in CC cells. Coimmunoprecipitation was performed to investigate the interaction between PAX1 and TCF7L2 in SiHa cells.

Results: PAX1 promoter methylation levels were significantly increased in CC patients ($P<0.001$) and were positively correlated with tumor purity but negatively correlated with immune infiltration. DNA methylation participates in the regulation of PAX1 expression, and PAX1 overexpression restrained proliferation and migration and improved cisplatin sensitivity by

interfering with the WNT/TIMELESS axis in CC cells. A rescue experiment showed that knocking out PAX1 expression could restore the development of CC. Additionally, coimmunoprecipitation confirmed the interaction between PAX1 and TCF7L2.

Conclusion: Our results suggested that a tumor suppressor role of PAX1 in CC and CRISPR-based PAX1 demethylation editing might be a promising therapeutic strategy for CC.

关键字： PAX1 methylation；Cervical Cancer；CRISPR

173. 泛癌分析表明 PRMT1 是一种有前景的多种癌症（包括 LIHC）的预后生物标志物

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背景：精氨酸甲基转移酶 1(PRMT1)是最先在哺乳动物中发现和鉴定的蛋白。它在多种癌症的发生、生长和预后中起着关键作用。然而，PRMT1 的生物学作用尚未在泛癌数据集中进行分析。因此，我们对泛癌数据集进行了全面的生物信息学分析，以探索 PRMT1 在多种癌症中的作用机制。

材料和方法：通过 PRMT1 相关基因的富集分析以确定 PRMT1 与 TP53 之间的相互作用。对泛癌患者的数据集进行分析，以确定 PRMT1 的差异表达以及 PRMT1 与各种癌症的病理分级、预后、基因改变及免疫功能之间的关系。通过 MTS、细胞集落形成、细胞划痕实验、Transwell、免疫荧光分析、流式细胞术和蛋白质组序列分析等体外实验，进一步证实 PRMT1 在肝癌细胞中的生物学功能。

结果：PRMT1 与 TP53 显著相关。GO 和 KEGG 富集分析表明，PRMT1 相关基因与肿瘤的转移、增殖和细胞周期有关。泛癌分析表明，与相应的正常组织相比，PRMT1 在几种实体瘤中表达上调，并且 PRMT1 的表达与肿瘤的病理分级、分期及预后密切相关。在几种癌症类型中检测到了 PRMT1 基因的基因改变，包括突变、重复和深度缺失。并且 PRMT1 可通过影响免疫细胞的免疫浸润来调节各种癌症的免疫微环境与肿瘤免疫。体外实验表明，PRMT1 在肝癌细胞中表达上调并在细胞核中表达。PRMT1 表达降低可抑制肝癌细胞的增殖、迁移和侵袭，影响细胞周期、促进细胞凋亡。蛋白质测序分析的结果与细胞实验结果一致。

结论：PRMT1 与 TP53 显著相关。此外，PRMT1 在泛癌中表达上调，并通过多种机制促进癌症(尤其是 LIHC)的发生和进展。同时，PRMT1 与肝癌的增殖、侵袭和凋亡密切相关。因此，我们的研究表明，PRMT1 是一个有前景的预后相关生物标志物，也是包括 LIHC 在内的几种恶性肿瘤免疫治疗的潜在靶点。

关键字 ：RMT1，泛癌，LIHC， TP53

174. 基线泛免疫炎症值(PIV)及 PILE 对原发性中枢神经系统淋巴瘤预后的预测价值

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目的：探索泛免疫炎症值(Pan-immune-inflammation value, PIV)和 PILE 评分(基于 PIV、乳酸脱氢酶(lactate dehydrogenase, LDH)和美国东部肿瘤协作组体能状况评分(Eastern Cooperative Oncology Group Performance Status, ECOG PS))与原发性中枢神经系统淋巴瘤(primary central nervous system lymphoma, PCNSL)患者预后的相关性。

方法：共纳入 109 例 PCNSL 患者。PIV=（中性粒细胞计数×血小板计数×单核细胞计数）/ 淋巴细胞计数。根据 PIV、LDH 水平和 ECOG PS 计算 PILE 评分，采用 Kaplan-Meier 曲线和 Cox 风险回归模型进行生存分析。

结果：基线高 PIV 在单因素(HR=3.990, 95%CI: 1.778-8.954, $p < 0.001$)及多因素 cox 分析(HR=3.047, 95%CI: 1.175-7.897, $p = 0.022$)中均与较差的总生存期(overall survival, OS)显著相关。在单因素分析中，高 PIV 也与较差的无进展生存期(progression-free survival, PFS)显著相关(HR=2.121, 95%CI: 1.075-4.186, $p = 0.030$)，但在多因素分析中无统计学意义。PIV 在预测预后方面的表现优于其他外周血炎症参数。高 PILE 组（PILE 评分 2-3）患者与低 PILE 组（PILE 评分 0-1）相比，表现出更差的 OS ($p = 0.008$)和 PFS ($p < 0.001$)。

结论：基线高 PIV 和 PILE 与 PCNSL 患者较差的临床预后相关，PIV 和 PILE 可能是 PCNSL 患者预后的潜在预测指标。

关键字 ：原发性中枢神经系统淋巴瘤；预后；外周血炎症指数

175. 中性粒细胞相关基因预测急性髓系白血病患者的预后和免疫相关性

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研究目的

探讨中性粒细胞相关基因对急性髓系白血病（AML）预后的影响。并进一步探讨中性粒细胞相关基因 CD37 与肿瘤微环境之间的关系，以确定潜在的免疫治疗反应指标和新的治疗靶点。

材料与方法

1.数据来源和处理

下载的临床信息和转录组数据来自 TCGA 的 AML 患者。GEO 和 OHSU 数据集中的 AML 患者作为外部验证集。从已发表的研究中检索了与中性粒细胞相关的基因。LI24、LSC17 为基于基因表达的预后模型。

2.风险模型的构建与验证

单变量 COX 回归分析构建预后模型，构建预后中性粒细胞相关基因的森林图。再进行 LASSO 回归分析，并建立 5 基因风险模型。验证风险模型的预后价值，评估模型敏感性和特异性。

3.绘制 nomogram 图。

4.生存分析　绘制 Kaplan-Meier 曲线。

5.差异表达基因的分析

p 值小于 0.05 且绝对值 log2 fold change（FC）≥1，选择差异基因。

6.通路富集分析　GO、KEGG 和 GSVA 通路分析。

7.免疫细胞浸润

使用 ESTIMATE 算法评估肿瘤样本，并通过 ssGSEA 获得 24 种肿瘤浸润免疫细胞的相对丰度。使用 GSEA 算法计算免疫细胞的富集情况。

8.免疫相关性

CD37 与免疫检查点、HLA 基因的关系。TIDE 证明 CD37 与 T 细胞功能紊乱的关系及免疫应答情况。

结果

建立了一个基于中性粒细胞的预后模型，整合了 5 个中性粒细胞相关基因（CSF3R、BRAF、FFAR2、CD300A 和 CD37），并验证了该模型的预测价值。单变量和多变量 Cox 回归分析进一步表明，该模型是总体生存率的独立预后因素，并构建了用于临床实践的列线图。此外，CD37 被确定为 AML 中与不良预后相关的关键中性粒细胞相关基因。当将 LI24 和 LSC17 分层的风险组应用于 TCGA 数据集，表明 CD37 可作为改进现有分类方案的良好候选者。CD37 的上调表明细胞增殖负调控、免疫抑制肿瘤环境以及免疫细胞功能状态的异常。CD37 的表达与大多数免疫检查点和人类白细胞抗原（HLA）分子的表达呈正相关。肿瘤免疫功能障碍和排斥（TIDE）显示 CD37 表达与 T 细胞功能紊乱呈正相关，对免疫治疗反应有意义。CD37 预测免疫治疗的作用，并与化疗敏感性密切相关。

结论

基于中性粒细胞相关基因表达水平开发了一种新的预后模型，CD37 可作为癌药物反应的有前途的生物标志物，有助于个性化预后预测，并可能有助于临床决策。

关键字： 急性髓系白血病　中性粒细胞　CD37　免疫检查点

176. HR+和 HER2-/HER2+早期乳腺癌患者的辅助治疗新手段

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摘要：乳腺癌（Breast carcinoma, BC）作为女性最常见的恶性肿瘤，发病具有遗传性，病因尚不明确。近年来乳腺癌死亡率日渐增高，已成为严重威胁女性生命的严重疾病之一。乳腺癌早期治疗率可达 80%-90%，但对于存在激素受体阳性（Hormone receptor-positive，HR 阳性）和人表皮生长因子受体 2（Human epidermal growth factor receptor 2，HER2）改变的早期乳腺癌（Early breast cancer，eBC）患者来说，他们的预后虽然已显著改善，但仍然存在复发及远处转移，这会严重影响患者的生活质量和生存率，因此寻找新的辅助治疗手段以改善预后非常重要。对于 HR+/HER2+ 且 1 年内完成曲妥珠单抗辅助治疗的 eBC 欧洲患者来说，可选择奈拉替尼（Neratinib）来改善预后。而国内患者是否适用，应该经过一系列

临床试验来验证。对于 HR+/HER2- eBC 患者，经典临床病理学参数和增殖因子 Ki-67 对于是否可以辅助化疗无法做出明确的诊断，因此使用基因表达检测，例如 Prosigna。Prosigna 测试已在绝经后患者中得到验证，但在绝经前患者中 Ki-67 和基于 Prosigna 的风险评估之间的风险组分层不完全一致。绝经前患有乳腺癌的亚洲女性具有独特的疾病特征，针对亚洲女性亚洲乳腺癌合作组（Asian Breast Cancer Cooperative Group，ABCCG）认为具有绝经前辅助卵巢功能抑制（Ovarian function suppression，OFS）的 HR+和 HER2- eBC 患者，中危病例首选他莫昔芬（Tamoxifen），高风险患者给予辅助化疗并芳香化酶抑制剂和 OFS，晚期疾病患者，在此基础上可给予促性腺激素释放激素（Gonadotropin-releasing hormone, GnRH）。EBC 患者的辅助治疗应遵循个性化原则，本篇摘要为 eBC 患者临床新疗法提供了一定的理论基础，但是否适用于临床还需要进一步研究。

关键字：早期乳腺癌；HR/HER2；辅助治疗

177. 浆细胞瘤变异体易位 1 和 MYC 基因在泛癌中的表达及生存期预测价值分析

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目的：探讨浆细胞瘤变异体易位 1 (plasmacytoma variant translocation 1，PVT1)和 MYC 基因在泛癌组织中的表达水平，及其对患者生存期的预测价值。

方法：从癌症基因组图谱(The Cancer Genome Atlas，TCGA)数据库获取 31 种共计 10 016 例癌症患者的临床资料以及转录组 RNA 测序数据，其中 23 种癌症组织标本有相应的癌旁正常组织对照。应用 t 检验比较 PVT1、MYC 基因在 23 种癌症组织与癌旁正常对照样本中的表达水平差异。采用 Spearman 相关性分析 PVT1 与 MYC 基因在 31 种癌症中表达的相关性。应用 Kaplan-Meier 方法和 Cox 比例风险模型，分别在 31 种癌症中分析 PVT1、MYC 基因的表达水平与患者总体生存期的关系。

结果：PVT1 的表达水平在 19 种癌症组织中显著增高(P<0.05)；在 2 种癌症组织中显著降低(P<0.05)。MYC 的表达水平在 7 种癌症组织中显著升高(P<0.05)；在 6 种癌症组织中降低(P<0.05)。相关性分析发现，在约 87% (27/31)的癌症类型中，PVT1 与 MYC 基因的表达水平呈正相关(Rho>0，P<0.01)。总体生存期分析表明，PVT1 相对高表达在膀胱尿路上皮细

胞癌、乳腺浸润癌、肾上腺皮质癌、肾透明细胞癌、乳头状肾细胞癌、低级别胶质瘤、前列腺癌、睾丸生殖细胞肿瘤以及葡萄膜黑色素瘤中与较短的总体生存期显著相关(log-rank P<0.05)；MYC 基因相对高表达在肾上腺皮质癌、膀胱尿路上皮细胞癌、宫颈鳞状细胞癌、头颈部鳞状细胞癌、乳头状肾细胞癌、卵巢浆液性囊腺癌、胰腺癌以及肉瘤中与较短的总体生存期显著相关(log-rank P<0.05)，而在低级别胶质瘤及直肠腺癌中，MYC 基因相对高表达组的总体生存期显著长于相对低表达组(log-rank P<0.05)。

结论：PVT1 在癌症组织中表达升高相比 MYC 基因而言更具有普遍性。在多种癌症中，PVT1 与 MYC 基因的表达相关，提示两者在功能调控中可能存在联系。此外，在 9 种癌症中，PVT1 相对高表达患者的总体生存期较短，而 MYC 基因的表达情况在不同癌症中对患者总体生存期的影响存在差异。

关键字：长链非编码 RNA；PVT1；肿瘤；临床意义

178. SEMA4A 作为直肠癌放疗抵抗和肿瘤侵袭性生物标志物的应用及相关机制

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背景：放射治疗在直肠癌治疗中扮演着重要角色，但是肿瘤放疗抵抗是由包括获得性肿瘤干细胞特性、肿瘤微环境中大量抑制性免疫细胞浸润在内的多种因素所致，这些因素是导致直肠癌放疗反应率低的主要原因。信号素 4A（Semaphorin 4A，SEMA4A）是编码可溶性和跨膜信号蛋白家族的一个成员，参与多种功能调节，包括轴突发育、肿瘤发生发展和免疫调节。

方法：通过 GEO、HPA、GEPIA 对 MRPS24 的表达进行可视化，使用 GSVA 对潜在机制进行筛选，使用质粒瞬转构建 SEMA4A 过表达放射治疗模型，通过平板克隆、EDU 实验、细胞划痕愈合、Transwell 迁移和侵袭、流式检测细胞凋亡等实验评估直肠癌细胞增殖转移效应，使用 western blot 检测相关通路标志物的表达变化。

结果：本研究从 5 个 GEO 数据集中观察到 SEMA4A 在肿瘤组织中的表达远低于正常组织，且在接受放射治疗发生抵抗的直肠癌患者中显著低表达。OCLR 算法计算肿瘤干细胞性发现放疗抵抗组的肿瘤干细胞性较放疗敏感组显著增加，运用 GSVA 算法发现 Hedgehog 通路活性在放疗抵抗组和 SEMA4A 下调组中均显著增加，且 Hedgehog 通路活性、SEMA4A 和肿瘤干细胞性两两之间均为负相关。免疫细胞浸润分析发现，SEMA4A 低表达组的淋巴细胞浸润显著减少，抑制性髓系细胞浸润增加，而 SEMA4A 高表达组 CD8+T 细胞、TH1 细胞记忆细胞以及巨噬细胞等免疫细胞的浸润程度显著增加。为了探究其中潜在的关联，在 SEMA4A 过表达模型中引入放疗干预，通过平板克隆、EDU 实验、细胞划痕愈合、Transwell 迁移和侵袭、流式检测细胞凋亡等实验评估直肠癌细胞增殖转移效应，使用 western blot 检测 Hedgehog 通路和肿瘤干细胞标志物的表达变化。

结论：低表达的 SEMA4A 可能通过上调 Hedgehog 信号通路活性导致的肿瘤干细胞活性增加，从而导致直肠癌患者转移风险增加和对放射治疗耐受。此外，SEMA4A 还有可能作为放射治疗和免疫治疗反应的预后生物标志物，有助于发展直肠癌患者的精准医学。

关键字： 直肠癌，放射治疗，机制

179. Global burden of gastric cancer attributable to high sodium intake from 1990 to 2019, and projections until 2050

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Objectives: The prevalence of gastric cancer (GC) is tightly linked to dietary patterns across various regions, particularly diets high in sodium. However, there remains ambiguity surrounding the worldwide epidemiological patterns of GC attributed to excessive sodium intake. In this study, we systematically analyzed the disease burden of GC caused by high sodium intake, globally and regionally.

Materials and methods: Data on the global burden of GC attributable to diet high in sodium were obtained from the Global Burden of Disease (GBD) 2019. GBD study provides scientific and comprehensive assessments of the disease burden for 369 diseases or injuries, 286 causes of death and 87 risk factors across various ages and genders in 204 countries and regions from 1990 to

2019. Population projections data were sourced from the 2019 revision of the United Nations (UN) World Population Prospects, while normalized population data spanning from 2000 to 2025 were obtained from a publicly accessible website of the World Health Organization (WHO). The 24-hour urine sodium collected from the GBD 2019 study was served as the fundamental metric for evaluating individual sodium intake levels. We utilized the age-standardized mortality rate (ASMR) and the age-standardized disability-adjusted life years (DALYs) rate (ASDR) to analyze the burden of GC attributed to high sodium intake across genders, age groups, social demographic indices (SDI; including low, low-middle, middle, high-middle, and high SDI), regions, and countries. To quantify the secular trends in ASMR and ASDR from 1990 to 2019, the estimated annual percentage change (EAPC) was computed. Furthermore, the Bayesian age-period-cohort (BAPC) model, integrated with nested Laplace approximations, was employed to forecast the disease burden over the next 31 years.

Results: Globally, the ASMR of GC attributable to high sodium intake has decreased by 42.04%, from 1.57 (95% UI: 0.05, 6.26) to 0.91 (95% UI: 0.03, 3.64) per 100,000 population. Meanwhile, the ASDR of GC has declined by 45.72%, from 38.52 (95% UI: 1.07, 152.39) to 20.91 (95% UI: 0.58, 82.11) per 100,000 population. All in all, the ASMR and ASDR attributable to high sodium intake both decreased, with EAPC of -1.83 (95% CI: -2.02, -1.65) and -2.09 (95% CI: -2.29, -1.90), respectively. For different genders, the ASMR of GC attributable to diet high in sodium dropped annually by -1.65 % (95% CI: -1.61, -4.80) for males and -2.26% (95% CI: -2.22, -6.54) for females, with corresponding declines for ASDR of -1.89% (95% CI: -1.84, -5.48) and -2.54 % (95% CI: -2.50, -7.33). Between 1990 and 2019, the number of deaths and DALYs decreased in the 25-59 year age bracket and increased in those aged 60 and above among males. Conversely, among females, the number of deaths and DALYs decreased in the 25-64 year age group and increased in those aged 65 and above during the same period. At the regions level, except Oceania, the ASMR and ASDR of the disease burden of GC caused by high sodium intake in the remaining 20 regions were in a downward trend between 1990 and 2019, and the top three regions with the largest percentage change in decline were: High-income Asia Pacific, Western Europe and Eastern Europe. At the national level, the ASMR of GC attributable to high sodium intake have increased in 10 of 204 (4.9%) countries and territories, ranging from 7.7 (95% CI: 0.6, 0.93) in the Dominican republic to 0.21

(95% CI: 0.12, 0.3) in Sao Tome and Principe. The top three countries possessing the highest ASMR of GC related to diet high in sodium were Mongolia [3.26 (95% UI: 0.09, 13.94)], Bolivia [2.69 (95% UI: 0.07, 11.29)], and Guatemala [2.18 (95% UI: 0.05, 8.91)] per 100,000 population in 2019. For ASDR, Mongolia and Bolivia still ranked among the top two positions, with 73.96 (95% UI: 1.97, 318.67) and 55.13 (95% UI: 1.37, 232.60) per 100,000 population respectively, followed by Korea with 51.04 (95% UI: 1.08, 195.08) per 100,000 population. The most conspicuous decrease were observed in high SDI region, with an EAPC of - 2.63 (95% CI: -2.69, -2.58) for ASMR and -3.17 (95% CI: -3.22, -3.11) for ASDR from 1990 to 2019. And the relationship between SDI and expected ASMR and ASDR of GC attributable to diet high in sodium was positive when SDI was lower than 0.52, but negative when SDI was above 0.70. Additionally, by utilizing the BAPC model, we found that the changing trends of age-standardized rate (ASR) in females were similar to those in males in the next 31 years: both manifest a gradually downward trend.

Conclusions: In conclusion, despite a global decrease in the ASMR and ASDR for the burden of GC attributed to high sodium intake between 1990 and 2019, and a projected decline over the next 31 years, the burden remains substantial in middle and high-middle SDI regions, particularly among the elderly. Consequently, targeted health policies and interventions remain crucial in the future to address this ongoing challenge.

Key Words： Gastric cancer, Diet high in sodium, Global disease burden, Prediction

180. 全基因组视角下的泌尿系统肿瘤遗传相关性分析

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背景： 泌尿系统肿瘤是全球性的重要健康问题，因其高发病率和对患者生存率和生活质量的严重影响而备受关注。这类肿瘤包括前列腺癌、肾癌、膀胱癌和睾丸癌，在全球范围内对患者造成了巨大负担。尽管这些肿瘤在临床特征、发病机制和治疗方法上有所不同，但最近的基因组研究发现它们可能存在潜在的共同遗传机制。

方法：我们从 PRACTICAL 联盟（79,148 例患者和 61,106 例对照）获得了大规模全基因组关联研究摘要数据，以及从 FinnGen 联盟 R9 发布数据（40,926 例患者和 274,069 例对照）获得了肾癌、膀胱癌和睾丸癌的数据。我们首先通过双向孟德尔随机化方法确定了遗传因果关系。并且使用连锁不平衡分数回归(LDSC)和遗传协方差分析探究了四种泌尿系统肿瘤之间的遗传相关性。我们还进行了局部遗传相关性分析(HESS），并利用基因组注释的多标记分析，探索了组织和细胞类型水平的单核苷酸多态性富集情况。跨性状 meta 分析通过 MTAG 和 CPASSOC 得出共享风险 SNP。我们进一步利用基 SMR 方法探究潜在的功能基因，并进一步检查了这些风险基因在组织中的表达特征。

结果：通过孟德尔随机化分析，我们首先确定了前列腺癌与膀胱癌(p=7.08E-5, beta=0.16)、前列腺癌与睾丸癌(p=4.82E-2, beta=0.16)、前列腺癌与肾癌(p=1.95E-2, beta=0.09)以及膀胱癌与睾丸癌(P=4.81E-2, beta=0.46)之间存在显著的因果关系。这些发现得到了 LDSC 分析的支持。通过 MAGMA 分析，我们观察到了组织特异性的单核苷酸多效性在前列腺、小脑等组织中富集。另外，通过跨性状 meta 分析，我们得到了肿瘤间的共有风险 SNP。通过共定位分析和 SMR 分析进一步揭示了疾病间的相关性，并揭示了共同的风险基因，如 CCHCR1、C4A 和 RGS17 等，并揭示基因在调节细胞信号传导途径中起到的重要作用，以及对肿瘤的发生和进展的影响。

结论：本研究揭示了泌尿肿瘤间的遗传因果及共患病的机制，通过对相关基因的深入研究，我们不仅加深了对这些疾病遗传机制的理解，还为进一步解析肿瘤发生发展的分子机制提供了方向。其中包括与 CCHCR1、C4A 和 RGS17 等基因相关的调控通路。同时，前列腺癌在共病中的重要性也为未来临床诊断和治疗提供了新的启示。通过这一多样泌尿系统肿瘤谱，我们有望对肿瘤治疗提出新的见解。

关键字： 泌尿 肿瘤 孟德尔随机化 基因 前列腺癌

181. Association between polymorphisms in DNA damage repair pathway genes and female breast cancer risk

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Objective: Breast cancer, a highly heterogeneous disease, has an increasing impact on health of women worldwide. Cancer heterogeneity can be driven by genomic instability, which ultimately promotes cancer development and progression. Breast cancer causes are complex, involving physiological, environmental and genetic factors, with polymorphisms of genes in a range of biological pathways as potential risks for breast cancer. Besides, the occurrence and development of cancer are largely related to the abnormal DNA damage repair function. This study aims to assess the relationship between single nucleotide polymorphisms (SNPs) in genes related to DNA damage repair and female breast cancer risk in Chinese population.

Methods: A case-control study containing 400 breast cancer patients and 400 healthy controls was conducted. Genotype was identified using the sequence MASSarray method and the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) in tumor tissues was analyzed by immunohistochemistry (IHC) assay. Patient characteristics were assessed using the t-test, fitted chi-squared ($\chi 2$) test and the Hardy-Weinberg equilibrium (HWE) in the healthy control group was calculated using the two-side $\chi 2$ test. The association between SNPs and the risk of developing breast cancer was evaluated by calculating the odds ratio (OR) and 95% confidence interval (CI) using logistic regression. Besides, adjusted odds ratio (AOR) of each measurement with age and/or menopausal state was provided.

Results: A total of 400 patients and the same number of healthy controls were included in our study, and there was no statistically significant difference in age. The genotypic distribution of all SNPs was not biased in HWE. Logistic regression revealed that the RAD21 rs16888927 CC genotype was associated with an increased breast cancer risk in all participants (CC vs. TT: adjusted OR=3.93, 95%CI: 1.08-14.27, p=0.038). Moreover, other SNPs did not show an association with the risk of breast cancer. In stratified analysis, ATR rs13091637 was related to

decreased breast cancer influenced by ER (CT/TT vs. CC: adjusted OR=1.54, 95%CI: 1.04-2.27, p=0.032), PR (CT/TT vs. CC: adjusted OR=1.63, 95%CI: 1.14-2.35, p=0.008) expression. Stratified analysis revealed that PALB2 rs16940342 increased breast cancer risk in response to menstrual status (AG vs. AA: adjusted OR=1.59, 95%CI: 1.03-2.48, p=0.038; AG/GG vs. AA: adjusted OR=1.72, 95%CI: 1.13-2.62, p=0.011) and age of menarche (AG/GG vs. AA: adjusted OR=1.54, 95%CI: 1.03-2.31, p=0.037), while ATM rs611646 and Ku70 rs132793 were associated to reduced breast cancer risk influenced by menarche (AT/TT vs. AA: adjusted OR=0.61, 95%CI: 0.40-0.94, p=0.026; GA/AA vs. GG: adjusted OR=0.50, 95%CI: 0.30-0.95, p=0.033). In a summary, we found that PALB2 rs16940432, ATR rs13091637, ATM rs611646 and Ku70 rs132793 were associated with breast cancer risk.

Discussion: Through a case-control study of 400 breast cancer patients and 400 healthy controls, we assessed the association between SNPs in genes related to DNA damage repair pathways and breast cancer risk. The results revealed that SNPs were associated with an increased risk of breast cancer as well as some protective factors against breast cancer. We assessed the association of SNPs in HR pathway genes with breast cancer susceptibility. According to ATR, a key kinase of DNA damage which response as a sensor of replication stress, our results revealed that ATR rs13091637 increased the risk of ER-negative, PR-negative or HER-2-negative breast cancer. ATR signaling facilitates the tolerance to DNA replication stress, SNPs in ATR may consequently allow for normal dysfunction and increased DNA damage. We also investigated ATM, a tumor suppressor involved in the repair of broken double strands of DNA, and ATM rs611646 was related to decreased risk of breast cancer in participants with menarche after 14 years old indicating that longer exposure to estrogen is a detrimental factor in breast cancer. PALB2 rs16940342 increased breast cancer risk in specific populations who were exposed to estrogen for long periods of time, which may affect the homologous recombination (HR) pathway leading to genomic instability and tumorigenesis. RAD21 is a crucial component of cohesin complex involved in the repair of DNA double-stranded breaks. Dysfunction of cohesin caused by RAD21 mutation can drive genomic instability, which eventually leads to cancer occurrence, previous studies have revealed that RAD21 rs16888927 has the potential to be a marker for breast cancer. Our results revealed that RAD21 SNPs was linked to an increased risk of breast cancer, however, due to the limited sample size the results obtained were not reliable and stable. It is necessary to

expand the sample for further analyzes. In non-homologous end joining (NHEJ) pathway, Ku70 is important f DNA damage repair. Ku70 rs132793 was associated with a reduced risk of breast cancer, however, previous studies have found that Ku70 promoter region polymorphisms may be a susceptibility factor. The inconsistency between these researches may be attributed to ethnic diversity and geographic influences as well as individual characteristics of patients such as estrogen expression and immune status.

Key Words： SNP, polymorphisms, DNA damage repair, breast cancer

182. A machine learning model based on three immune factors for diagnostic prediction of esophageal squamous cell carcinoma

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Background: Esophageal squamous cell carcinoma (ESCC) is one of the malignant diseases which poor prognosis when diagnosed at the late stage and brings much economic and psychological burden. The early diagnosis of ESCC seemed to be important. Immune factors have been confirmed to play a vital role in cancer development. Therefore, in this study, we will tried to build a machine learning model based on immune factors for diagnostic prediction of ESCC.

Methods: A three-stage study was conducted, including discovery, training, and validation stages. In the discovery stage, Human Cytokine Antibody Array and differential expression analysis were used to screened out significant cytokines in the sera of 20 ESCC patients and 20 normal controls (NC), which were age- and gender-match. Then, enzyme-linked immunosorbent assay (ELISA) was used to detected the serum immune factors in both training (201 ESCC patients and 104 NC; from Cancer Hospital of Shantou University Medical College) and validation groups (93 early-stage ESCC patients and 90 NC; from Sun Yat-sen University Cancer Hospital). The diagnostic models were built using seven machine learning algorithms, and the performances were evaluated and compared using the area under the receptor operator curve (AUC).

Results: In the discovery stage, 22 cytokines were found significantly up-regulated in sera of ESCC patients. Combined with public data, only three immune factors (CCL4, CXCL13 and MMP-1) showed the insistent results. ELISA showed that these three immune factors were all up-expressed in training and validation groups (all $P < 0.0001$). The AUCs of these three factors in diagnosing ESCC were 0.819, 0.759 and 0.707, respectively in the training group. In early-stage ESCC of training group and in the validation group (all ESCC patients were early-stage), the AUCs of these three factors ranged from 0.698 to 0.827, which exhibited the good performances in distinguishing ESCC from normal controls. Seven machine learning algorithms were applied to build the diagnostic model in the training group, including gradient boosting machine (GBM), support vector machine (SVM), regularized discriminant analysis (RDA), random forest (RF), neural network (NN), naive bayes (NB), and penalized logistic regression (PLR). RF and GBM models both showed the better performances (no significant differences between them), but GBM model exhibited the robust discrimination, with the AUC of 0.910 (95%CI: 0.878-0.941) and 0.857 (95%CI: 0.799-0.912) in the test and validation groups, respectively. For early-stage ESCC in the test groups, the GBM model achieved an AUC of 0.896 (95%CI: 0.853-0.940).

Conclusion: This study provides a promising diagnostic prediction model using three immune factors based on the machine learning algorithm for the diagnosis of ESCC, especially in the early stage.

Key Words：Esophageal squamous cell carcinoma; immune factors; machine learning model

183. piRNA, a promising biomarker in detection of gastrointestinal diseases

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Piwi-interacting RNA (piRNA) is a small non-coding RNA molecules expressed in animal cells. Interacting with piwi-subfamily Argonaute proteins, piRNA are known to regulate the epigenetic

and post-transcriptional silencing of transposable element and some genetic elements in germ line cells. Besides, in recent years, even the mechanism is ambiguous, piRNA is proposed to be a promising biomarker in detection of gastrointestinal diseases including colorectal cancer, with fair meaning on suggest diagnosis and prognosis. This article reviewed related piRNAs and their potential roles in neoplastic diseases, inflammatory diseases, functional diseases and other diseases in gastrointestinal system. Moreover, underlying value of piRNAs in pathogenesis and progression of gastrointestinal diseases were evaluated and summarized in this review.

Key Words： Piwi-interacting RNA；gastrointestinal diseases；biomarker

184. Polycyclic Aromatic Hydrocarbons Mediate the Risk Association of Red Meat Intake on Mortality

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The effect of red meat intake on health remains controversial, and its mechanism needs to be explored. In this study, we aimed to investigate the relationship among red meat, polycyclic aromatic hydrocarbons (PAHs), and mortality risk.

National Health and Nutrition Examination Survey (2007-2010) cohort, with a median follow-up time of 10.67 years, provided 3,140 adult participants with qualifying data of urinary PAHs and red meat intake. Mortality outcomes were obtained by linkage to National Death Index. Generalized linear model, Cox proportional hazards regression model, and mediation analysis were used to examine candidate associations.

During 32,093 person-years of follow-up, 484 deaths were documented. High red meat intake, especially high cured red meat intake was significantly associated with increased urinary OH-PAH levels. Notably, high urinary 2-hydroxynaphthalene concentration was significantly associated with an increased risk of all-cause mortality [hazard ratio (HR) = 1.012, 95% confidence interval (CI) = 1.003-1.022], particularly with malignancy-specific mortality. Bootstrap mediation analysis additionally indicated that 2-hydroxyfluorene partially mediated the relationship between cured red meat intake and all-cause mortality risk (HR = 1.001, 95% CI = 1.0001-1.0024).

This study proposed a possible pathway from red meat intake to mortality via PAHs, providing insights for mechanistic interpretation and precision population health.

Key Words： Red meat, Polycyclic Aromatic Hydrocarbons, Mortality

185. β-榄香烯通过靶向醛脱氢酶 ALDH3B2 而抑制非小细胞肺癌细胞的上皮-间质转化

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目的： 确定醛脱氢酶 ALDH3B2 对于非小细胞肺癌(NSCLC)发生上皮-间质转化(EMT)的促进作用，阐明β-榄香烯通过抑制 ALDH3B2 而抑制 NSCLC 的 EMT。

材料与方法：基于 BATMAN-TCM 数据库和 TCGA 数据库对β-榄香烯作用于非小细胞肺癌的靶基因进行筛选鉴定，鉴定 ALDH3B2 的表达与临床肺癌患者病情进展及预后的关系。通过慢病毒感染于 NCI-H1373 细胞中过表达 ALDH3B2 后，以及通过 siRNA 敲降于 PC-9 细胞中抑制 ALDH3B2 的表达后，与各自的对照组进行比较，并分别以不同浓度的β-榄香烯作用不同组别的细胞，通过划痕实验、transwell 侵袭实验、克隆形成率检测、Western-blot 检测 EMT 相关蛋白等实验确定 ALDH3B2 的表达水平对于 NSCLC 细胞 EMT 的影响。

结果：生物信息学分析结果显示，与正常或相应的邻近组织相比，ALDH3B2 在肺腺癌和肺鳞状细胞癌样本中均显著过表达。且 ALDH3B2 的表达升高与肺腺癌和肺鳞状细胞癌患者的不良预后特异性相关。同时，评估了不同非小细胞肺癌细胞系（A549、PC-9、NCI-H1373 和 HCC827）中 ALDH3B2 的表达，发现 ALDH3B2 表达水平与细胞对β-榄香烯的敏感性呈正相关。此外，β-榄香烯抑制 ALDH3B2 在 PC-9 和 NCI-H1373 细胞系中的 mRNA 转录和蛋白表达，并呈现剂量依赖性。ALDH3B2 在 NCI-H1373 细胞中的过表达后导致细胞显著的迁移、侵袭和的 EMT。在 PC-9 细胞系中敲降 ALDH3B2 后减弱了细胞的迁移、侵袭和 EMT。

在 NCI-H1373 中过表达 ALDH3B2 后，可部分回复β-榄香烯对于 NSCLC 细胞的迁移、侵袭及 EMT 的抑制作用。

结论：ALDH3B2 的高表达与临床肺癌患者的病情进展及预后不良密切相关。ALDH3B2 可以作为致癌蛋白发挥作用，促进 NSCLC 细胞的转移、侵袭及 EMT。同时，β-榄香烯可通过靶向 ALDH3B2 而抑制非小细胞肺癌细胞的上皮-间质转化。我们的研究揭示了 ALDH3B2 可作为非小细胞肺癌治疗的潜在靶点，并发现 ALDH3B2 可作为β-榄香烯的发挥药效的靶标分子，以上发现丰富了对传统抗肿瘤药物β-榄香烯的药理机制的理解，为未来开发针对 NSCLC 临床治疗的新的干预手段提供了实验依据。

关键字： 榄香烯、非小细胞肺癌、ALDH3B2、上皮-间质转化

186. Construction and validation of prognostic signature for transcription factors regulating T cell exhaustion in hepatocellular carcinoma

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Purpose： In the tumor microenvironment (TME), CD8+ T cells showed stage exhaustion due to the continuous stimulation of tumor antigens. To evaluate the status of CD8+ T cells and reverse the exhaustion is the key to evaluate the prognosis and therapeutic effect of tumor patients. The aim of this study was to establish a prognostic signature that could effectively predict prognosis and response to immunotherapy in patients with hepatocellular carcinoma (HCC).

Methods： We used univariate Cox analysis to obtain transcription factors associated with CD8+T cell exhaustion from the TCGA data set. Then, the prognostic signature for transcription factors (BATF, EOMES and TBX21) regulating T cell exhaustion was constructed using LASSO Cox regression. The relative expression levels of the mRNA of the three transcription factors were detected by RT-qPCR in 23 pairs of HCC and paracancer tissues, and verified internally in TCGA dataset and externally in ICGC dataset.

Results ：Cox Regression analysis showed that risk score was an independent prognostic variable. The overall survival (OS) of the high-risk group was significantly lower than that of the low-risk group. The low-risk group had higher immune scores, matrix scores and ESTIMATE scores, and significantly increased expression levels of most immune checkpoint genes in the low-risk group.

Conclusion： Therefore, patients with lower risk score benefit more from immunotherapy. The combination of the three transcription factors can evaluate the exhaustion state of CD8+T cells in the TME, laying a foundation for evaluating the TME and immunotherapy efficacy in patients with HCC.

Key Words ： T cell exhaustion, hepatocellular carcinoma, transcription factors, prognosis, tumor microenvironment

187. FZD3 regulates the growth and metastasis of gastric cancer via the Syntenin-1/TGF-β signaling pathway

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Background: The occurrence and development of gastric cancer is a multi-factor, multi-stage, multi-gene abnormal accumulation process. Frizzled Class Receptor 3 (FZD3), a member of the Frizzled family, is closely associated with tumor development. Yet the specific mechanisms underlying its involvement in gastric cancer growth remain largely unexplored.

Method: Bioinformatics methods, western blot, immunohistochemistry and RT-qPCR were used to analyse the expression differences of FZD3 in gastric cancer and its correlation with clinicopathological indexes of gastric cancer patients. CCK-8 assay, cell cycle, wound-healing and transwell migration assays were used to detect the effects of FZD3 on the biological effects of gastric cancer cells. The correlation between FZD3 and TGF- β signaling pathway was analysed by KEGG pathway enrichment, and the effects of FZD3 on the proliferation and migration ability of gastric cancer cells through TGF- β signaling pathway were detected by cell cycle and transwell migration assays. The protein interactions between FZD3 and Syntenin-1 were analysed by protein interaction and Co-IP. The expression of Syntenin-1 in gastric cancer and its effect on

the proliferation and migration ability of gastric cancer cells were observed by western blot, CCK-8 assay, wound-healing and transwell migration assay. Finally, the effects of overexpression of FZD3 and knockdown of Syntenin-1 on the growth and migration of gastric cancer were observed by in vivo and in vitro experiments.

Results: FZD3 was highly expressed in gastric cancer and positively correlated with the poor prognosis of gastric cancer patients, and FZD3 promoted the proliferation and migration ability of gastric cancer cells. KEGG pathway enrichment analysis showed that FZD3 was significantly enriched in the TGF-β signaling pathway. Treatment of gastric cancer cells with TGF-β1 and TGF-β1 inhibitor (SB431542) revealed that FZD3 regulated the proliferation and migration of gastric cancer cells through the TGF-β signaling pathway. The protein interaction and Co-IP confirmed that FZD3 interacted with Syntenin-1, and Syntenin-1 was differentially expressed in gastric cancer cells and promoted the proliferation and migration of gastric cancer cells. In vitro and in vivo experiments confirmed that FZD3 promoted the proliferation and migration of gastric cancer cells through the Syntenin-1/TGF-β signaling pathway.

Conclusion: FZD3 promoted the proliferation and migration ability of gastric cancer cells through Syntenin-1/TGF-β signaling pathway and may be a potential diagnostic and prognostic target.

Key Words： Gastric cancer，Frizzled Class Receptor 3，Syntenin-1，TGF-β signaling pathway

188. ALDH2 as a predictive biomarker for better prognosis in patients with breast cancer

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Purpose: The primary function of the ALDH2 is to detoxify acetaldehyde (ACE) to non-toxic acetate. While ALDH2 deficiency is linked to various diseases, the role of ALDH2 in tumor progression remains unclear. Studies suggest that ALDH2-mediated cancer mechanisms involve the removal of endogenous aldehydes produced by ROS-mediated peroxidation and the metabolism of exogenous aldehydes. The accumulation of acetaldehyde can lead to DNA damage, including mutations, interstrand crosslinks, single-strand breaks, and double-strand breaks, which

are associated with alcohol-related tumors. Lack of ALDH2 function impairs the beclin-1-dependent autophagy pathway, suggesting that autophagy is one of the mechanisms through which ALDH2 regulates tumorigenesis and progression. ALDH2 also indirectly regulates the immune system by metabolizing aldehydes and acetaldehyde adducts. Dysfunction in the immune system mediated by ALDH2 may contribute to cancer initiation and progression. However, the role of ALDH2 in breast cancer has not been previously reported.

Methods and Materials: In this study, we examined the prognostic significance of ALDH2 expression in breast cancer using data from The Cancer Genome Atlas (TCGA) database. We first screened for ALDH2 expression and used R software to compare its expression in breast cancer tissues and adjacent non-cancerous tissues. Logistic regression was then employed to investigate the correlation between ALDH2 expression and clinicopathological parameters. Subsequently, we performed Kaplan-Meier survival analysis and Cox proportional hazards regression to assess the relationship between ALDH2 expression and the survival of breast cancer patients. Finally, we identified key biological processes associated with ALDH2 using Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) gene enrichment analysis, and gene set enrichment analysis (GSEA).The study utilized MCF-7 and HS-578T cell lines to transfected the ALDH2 plasmid in two types of breast cancer cells. The proliferation, invasion, and migration abilities of breast cancer cells were detected through various assays including Cell Counting Kit-8, Matrigel invasion assay, wound healing assay, and colony formation assay. The expression levels were determined through real-time fluorescent quantitative PCR and Western blotting. The apoptotic rate of breast cancer cells was determined through terminal deoxynucleotide transfer-mediated dUTP nick end labeling (TUNEL) analysis. The western blotting technique was employed to examine the underlying mechanism of ALDH2. Moreover, the role of ALDH2 in the proliferation, invasion, and migration of MCF-7 cells was determined through the use of short hairpin RNA.

Results: The analysis of TCGA data revealed that low expression of ALDH2 is associated with poorer overall survival and progression-free survival in breast cancer patients. Univariate analysis suggests that ALDH2, age, and TNM stage may be associated with poor prognosis. Multivariate analysis confirmed that ALDH2 is an independent prognostic marker, with a hazard ratio of 0.744 (95% CI, 0.614-0.902; P = 0.003). Additionally, The study found that increasing the expression of ALDH2 inhibited the growth and movement of MCF-7 and HS-578T breast cancer cells, while

also promoting cell death. Gene set enrichment analysis (GSEA) showed that this overexpression activates the JAK/STAT1 signaling pathway. Western blot analysis confirmed that ALDH2 overexpression increased the expression of phosphorylated Jak1 and Stat1, decreased the expression of Bcl2, and increased the protein expression of caspase-3 in both cell lines.Further experiments have shown that overexpression of ALDH2 increases the apoptosis rate of MCF-7 cell. The knockdown of ALDH2 promotes the proliferation, invasion, and migration ability of MCF-7 cells. Using the inhibitor Fludarabine to block stat1 signaling and downregulate casepase3, increases the expression of bcl2 and weakens the changes of ALDH2 on these proteins. In addition, overexpression of ALDH2 promotes apoptosis of tumor cells. The use of inhibitors weakened the proapoptotic ability of ALDH2.

Conclusion: This study utilized bioinformatics analysis and in vitro experimental research to investigate the role of ALDH2 in breast cancer progression and its potential as a therapeutic target for breast cancer patients. The results showed that the expression of ALDH2 was downregulated in breast cancer and that low expression was significantly associated with T stage clinicopathological features and shorter overall survival (OS). These findings suggest that ALDH2 may be a promising target for the development of new breast cancer treatments.Our study found that ALDH2 is an independent prognostic factor in breast cancer. Overexpression of ALDH2 resulted in decreased proliferation, monoclonal formation, invasion and migration ability of MCF7 cells, and increased apoptosis rate. The findings suggest that ALDH2 may regulate the stat1 signaling pathway to promote cell proliferation and apoptosis. Our study provides evidence that ALDH2 may contribute to the malignant phenotype of breast cancer cells by regulating apoptosis, and could serve as a potential biomarker for clinical treatment of breast cancer.

Key Words ： ALDH2, Biomarker, Breast cancer, Prognosis, Target therapy

189. 基于样本内基因间相对表达秩序的分子标志构建与应用

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目的

样本内基因间相对表达秩序（relative expression orderings，REOs）是指在同一样本内不同基因间表达值的秩次关系。REOs 在相同表型样本中保持稳定，在不同表型中差异显著，有助于生物标志构建和差异基因（DEG）分析。然而 REOs 数量巨大，如何从高维基因对中筛选出分子标志存在挑战。我们旨在明确基于 REOs 的分子标志理论框架，开发基于 REO 的分子标志建模方法。应用于评估预后风险、药物响应、肿瘤进展、免疫检查点阻断（ICB，Immune Checkpoint Blockade）和区分亚群等方面研究。

材料与方法

将基因配对得到 REOs，通过基于 AUC 的爬山法对高维基因对进行特征筛选，并通过下采样的方式减小过拟合风险。包含随机抽样的下采样方式增大样本量和赋予样本权重的下采样方式减小样本量两步。对获得的特征使用随机森林和多数投票规则的分类模型进行预测。

在模型测试方面，收集具有高/低风险和肿瘤有/无进展信息的 108 例神经母细胞瘤数据作为训练集，收集包含 ICB 治疗响应信息的 7 套黑色素瘤数据作为验证集。数据预处理包含：1）训练集数据按照高风险且肿瘤有进展和低风险且肿瘤无进展分为两组。2）收集到 27 个免疫相关基因，将其中 6 个 ICB 相关基因与除自身外基因基于 REOs 组合基因对。

结果

我们将算法用于小样本量数据集中进行评估。使用包含肿瘤进展和预后信息的 108 例神经母细胞瘤数据作为训练集，筛选得到 15 对特征基因对。特征在训练集中的 AUC 为 0.94，在 7 套包含 ICB 治疗响应标签的验证集中 AUC 分别为 1.00、1.00、1.00、0.83、0.77、0.75 和 0.75，平均 AUC 为 0.87，表现出良好的分类性能。与已发表的 46 种 ICB 响应预测的评分系统相比，我们识别的分子标志在 MGH PRE data 数据集的 AUC 为 0.75，仅低于 EMT Stroma core signature（AUC = 0.82）；在 Snyder data 数据集的 AUC 为 0.75，仅低于 HLA DRA（AUC = 0.76）；在 Liu data 数据集的 AUC 为 0.62，仅低于 PASS ON（AUC = 0.63）和 TLS score ssGSEA（AUC = 0.65）；在 Riaz PRE data 数据集的 AUC 为 0.65，仅低于 CTLA4（AUC 为 0.67）和 PASS PRE（AUC 为 0.73），表现出优异的性能优势。

结论

该算法使用基于贪婪算法的爬山法进行训练。同时采用下采样的方式，减小贪婪算法造成的过拟合问题。目前算法在小样本量数据集中获得了良好的性能，能够为临床中数据量有限的分析提供思路和帮助。

关键字： 分子标志，样本内基因间相对表达秩序，免疫检查点阻断

190. 基于空间转录组学的造釉型颅咽管瘤异质性研究

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背景

造釉型颅咽管瘤（ACP）是一种好发于蝶鞍或鞍上区域的脑肿瘤，存在显著的个体间差异，肿瘤实性和囊性成分变化大，免疫浸润程度不同，对免疫调节治疗的响应也不同。本研究通过空间转录组学结合单细胞转录组学解析 ACP 肿瘤微环境，阐述异质性产生的机制。

材料和方法

采用 10x-Genomics 单细胞转录组测序技术对 12 例 ACP 新鲜冷冻标本进行单细胞转录组测序，并使用 10x Genomics Visium 空间转录组测序技术对其中 3 例石蜡包埋样本进行空间转录组测序。使用 CellRanger、SpaceRanger、ClusterProfiler 等软件包对单细胞转录谱、空间分辨转录谱进行分析，并结合苏木精伊红染色病理图片进行整合分析。

结果

研究发现 ACP 肿瘤上皮细胞中 WNT、MAPK、Hippo 等信号通路显著激活。基底细胞部分区域炎症相关信号通路显著激活。联合单细胞谱分析发现 3 个不同分子亚型的 ACP 样本细胞类型组成和细胞比例存在较大的差异，特别是肿瘤上皮细胞和免疫细胞。对典型的病理特征成分，包括漩涡状上皮簇，栅栏样上皮细胞、湿角蛋白和星状网的分子特征进行表征，发现栅栏样的上皮细胞存在显著的炎症特征：趋化因子配体 2（CXCL2），Ig 超家族蛋白（VSIG4）高表达；漩涡状上皮簇中存在表明 WNT 信号通路显著激活，WNT 信号通路相关基因：WNT-5A 蛋白（WNT5A）和 WNT 信号通路的负调控因子（DKK4）高表达；星状

网存在细胞凋亡特征：PLEKHN1 基因高表达；湿角蛋白中表现出成牙的特征：釉成熟蛋白（AMTN），牙成釉细胞相关蛋白（ODAM）高表达。

结论

研究揭示了 ACP 不同病理组织结构的分子表达模式存在显著差异。不同分子亚型的 ACP 细胞组成和比例存在较大差异。

关键字：造釉型颅咽管瘤，空间转录组，Wnt/β-catenin 信号通路，肿瘤免疫浸润

191. Diagnosis and function of autoantibodies against tumor associated antigens in lung cancer non-small cell lung

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Background

Lung cancer is the most prevalent malignant tumor worldwide, with lung cancer mortality consistently ranking highest among all malignancies in China. Research has demonstrated that the 5-year survival rate for patients with advanced lung cancer is below 20%. The elevated incidence and low survival rate of lung cancer are primarily attributed to inadequate prevention, and diagnostic deficiencies. In order to facilitate effective implementation of lung cancer screening programs, it is imperative to enhance the capability of detecting this disease through more accessible and noninvasive diagnostic tests. Given the highly vascularized nature of lungs and their immune response, it is plausible that viable immune markers for diagnosing cancer may exist within blood samples. Autoantibodies could be a viable source of such markers, and a panel of blood autoantibody biomarkers could represent a noninvasive, cost-effective tool for clinical screening.

Objective

The main objectives of this study are as follows: firstly, to utilize statistical methods to identify significant and highly expressed tumor-associated antigens based on human proteome microarray and tissue proteomics results; secondly, investigating the differences indicators between early NSCLC, BPN, and normal controls, and assess their diagnostic efficacy; thirdly, exploring

autoantibodies present in the blood and examine their role in the occurrence and development of lung cancer; ultimately aiming to provide a theoretical foundation for the clinical application of new molecular targeted therapy.

Methods

1. Screening of candidate tumor-associated antigens (TAAs) for lung cancer

Based on the human proteome chip, the plasma samples of 10 LC and 10 NC mixed samples were analyzed when P<0.05, FC>2; resulting in the screening of 83 TAAs. Based on the proteomics results in the literature, the proteomics results of lung adenocarcinoma and lung squamous cell carcinoma were analyzed by statistical analysis. When P<0.05, Log2 FC>2. Combining these two proteomic screens with microarray results, 13 TAAs were identified, and 6 TAAs were subsequently identified through literature reading.

2. Preliminary verification of differential expression indicators

In the small sample stage, 94 patients with early non-small cell lung cancer (NSCLC) and 94 normal controls (NC) matched 1∶1 in age and gender were selected from the plasma sample bank. The expression levels of tumor-associated autoantibodies (TAAbs) in plasma were detected by indirect ELISA. The TAAbs with significantly different expressions in early NSCLC and NC were further screened for subsequent analysis.

3. Large sample validation of candidate TAAbs

In this stage, 327 patients with NSCLC, 327 BPN, and 327 normal controls matched for age and gender were selected to detect the TAAbs by ELISA. The diagnostic value of the indicators can be evaluated and analyzed, and different clinical characteristics can be further analyzed and verified.

4. Exploration of the functional mechanisms of candidate autoantibodies

Firstly, the serum with a high content of specific antibodies was found according to the previous research content of this study, and the antibodies were extracted through antibody purification experiments. Subsequently, the purified antibodies were verified by Western blotting, and the binding ability and localization relationship between antibodies and antigens were explored through cell immunofluorescence experiments

5. Statistical analysis

Quantitative analysis of cell experiment results was performed using Image J 6.0 software. SPSS 26.0 and GraphPad Prism 8.0 software were used to analyze the experimental data and visualize

the results. A non-parametric test was used to analyze the difference of each index between the model groups by Mann-Whitney U test. The area under the ROC curve (AUC) and the specificity of each index or model in the differential diagnosis of lung cancer were considered statistically significant in all statistical analyses.

Results

1. Six markers (NACA, BASP1, NASP, SLC16A1, HSPD1, SMARCC1) differentially expressed between LC and NC were identified through microarray and tissue proteomics results.

2. The expression levels of 6 markers were verified. Six selected markers were detected by indirect ELISA. Four biomarkers (NACA, BASP1, SLC16A1, HSPD1) could differentiate LC from NC. The diagnostic ability of the four candidate markers was revalidated in a large sample cohort, and the results were consistent with those obtained from a small sample validation. The results showed that the efficacy of the four candidate markers (NACA, BASP1, SLC16A1, HSPD1) in the differential diagnosis of LC and NC was 0.574 (0.529-0.618), 0.702(0.662-0.742), and 0.564(0.520-0.608) and 0.545 (0.501-0.590). In addition, the anti-BASP1 autoantibody and three traditional markers (CEA, CA125, CA199) were analyzed by logistic regression, which were then combined to construct a differential diagnosis model. The model could effectively distinguish LC and BPN, NC with an AUC of 0.754, 0.786.

3. The anti-BASP1 autoantibody obtained in the final verification was used to explore the functional mechanism of screening a promising autoantibody. It was found that in vitro cell experiments, could promote cell proliferation, invasion, and migration.

Conclusions

The plasma levels of autoantibodies against NACA, BASP1, SLC16A1, and HSPD1 are elevated in patients with LC compared to NC, suggesting their potential as novel plasma markers for the differential diagnosis between LC and NC. A diagnostic model incorporating anti-BASP1, CEA, CA125, and CA199 had good diagnostic efficacy in differentiating LC from BPN, NC. The function of BASP1 autoantibody was investigated in vitro.

Key Words ： Plasma Lung Cancer Autoantibodies Diagnosis

192. 食管海绵细胞学在食管癌高发区县筛查中的应用研究

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目的：探讨食管海绵细胞学在食管癌高发区县筛查中应用的准确性和可行性。

方法：对 2021 年 5 月至 2022 年 06 月在我院就诊有食管癌高危因素、年龄 40-75 岁的人群进行食管癌机会性筛查。利用我国自主研发的新型食管细胞收集器进行食管海绵细胞学采样并进行细胞病理分析，非典型鳞状细胞或更严重的病变被定义为食管海绵细胞学阳性。与胃镜病理检查结果相比较，评估食管海绵细胞学检查的诊断效能、安全性与耐受性。

结果：共有 1590 名患者完成本研究。在食管海绵细胞学检查采样过程中，未见严重不良事件，其不良反应主要表现为采样过程中呕吐（5 人，0.30%）、采样过后喉咙痛（39 人，2.50%），均能自行缓解，无需进一步医疗干预。使用可视化模拟评分评估受试者对采样过程的耐受性，发现大部分受试者的耐受性良好，表示可以接受（1568 人，98.60%）。以内镜与活检病理诊断为标准，食管海绵细胞学阳性用于诊断食管癌及癌前病变（包括低级别上皮内瘤变、高级别上皮内瘤变、食管鳞癌、食管胃交界腺癌）的 ROC 曲线下面积为 0.890（95%CI:0.874-0.905），其诊断敏感度为 84.25%（95%CI:76.48%-89.89%）、特异度为 93.78%（95%CI:92.39%-94.94%）、阳性预测值为 54.04 %（95%CI:46.84%-61.08%）、阴性预测值为 98.56%（95%CI:97.75%-99.10%）；食管海绵细胞学阳性用于诊断食管上皮高级病变（包括高级别上皮内瘤变、食管鳞癌、食管胃交界腺癌）的 ROC 曲线下面积为 0.950（95%CI:0.939-0.961），其诊断敏感度为 98.57%（95%CI:91.23%-99.93%）、特异度为 91.51%（95%CI:89.97%-92.84%）、阳性预测值为 34.48%（95%CI:28.32%-41.98%）、阴性预测值为 99.93%（95%CI:99.53%-100%）。

结论：食管海绵细胞学对食管上皮高级病变的诊断效能较高，对食管癌高发地区而言，是一种简单方便、患者接受度较高、安全有效的食管癌筛查方法。

关键字：食管高级别上皮内瘤变；食管鳞状细胞癌；食管胃交界腺癌；筛查；食管海绵细胞学；诊断

193. 肺癌免疫应答特异菌群研究及模型搭建

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背景：近些年来，免疫治疗由于其较好的耐受性及安全性极大的改变了肺癌的治疗格局。然而，目前仅有 20%的局部转移或晚期患者能够获得免疫检查点药物所带来的长期获益。先前的研究已经表明，肠道菌群可调节机体的抗肿瘤免疫反应且应答菌群的移植同样可以显著改善非应答机体对免疫治疗药物额敏感性。基于此，我们拟荟萃来自全球多个国家和地区的肠道样本，试图挖掘适用范围更广稳健性更好的免疫应答标志物。

方法：我们对纳入的免疫治疗患者的基线肠道样本及治疗期间样本进行宏基因组测序。总共纳入了 296 份样本，其中基线样本（应答患者 71 份，非应答患者 98 份以及 72 份健康对照样本）和 55 份治疗阶段中的样本。基于原始的测序数据进行物种构成及功能预测等生物信息学分析。还利用随机森林算法搭建了用于预测免疫疗效的预测模型，以挖掘较为稳健的免疫应答标志物。

结果：应答患者肠道菌群中的物种丰富度始终高于非应答患者，这一趋势并不受抗生素的影响。在物种构成方面，s_Bacteroides caccae 和 s_ Bacteroides _uniformis 是应答组具有显著性差异的富集菌，s_Prevotella copri 则被筛选为非应答组的差异富集菌。我们基于 lefse 分析筛选出的标志物，在物种水平以及属水平建立了随机森林预测模型，AUC 值分别达 0.82 和 0.79。此外，我们的研究还表明，一些代谢过程如氨基酸代谢（缬氨酸、亮氨酸）可能参与了免疫治疗应答的调节过程。

结论：我们的研究对肺癌人群肠道内与免疫治疗应答有关的菌群进行了探索性研究，并且挖掘出一些较为稳定的标志物。同时基于这些标志物我们还在不同水平搭建了预测效能良好的机器学习模型。未来的研究需要更多的关注到这些特异菌在是如何在机体中参与调节免疫应答敏感性以及参与肺癌发生发展的机制谈探索。

关键字：肺癌；免疫治疗；肠道菌群；机器学习；荟萃分析

194. FOXA1-eRNA 在前列腺癌发生发展及 CRPC 进展中的作用及机制

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目的：FOXA1-eRNA 在前列腺癌发生发展及 CRPC 进展中的作用及机制

材料与方法：分析 NONCODE、LncExpDB 数据库非编码 RNA 与增强子关联，并结合 LNCaP-GRO-seq 测序数据，鉴定出 FOXA1-eRNA；检测不同前列腺癌组织及其他癌细胞中该 eRNA 的表达水平；对 CRPC 增强子相关基因 GO 通路富集分析并验证相关通路；FOXA1-eRNA 对前列腺癌细胞体外增殖、迁移和克隆形成等恶性生物学行为的影响；3C 实验验证该 eRNA 对 FOXA1 增强子-启动子（E-P）相互作用的影响；eRNA 对 FOXA1 和 AR 核转移、相互作用、与染色质结合能力及对下游基因（如 PSA 等）转录的影响；RNA pulldown 结合质谱筛选前列腺癌细胞中与该 eRNA 相互作用的蛋白；敲低 p68 检测 FOXA1 的表达水平及 3C 实验验证 eRNA 对 FOXA1 的 E-P 环相互作用影响；检测该 eRNA 对 p68 蛋白和 FOXA1 液相分离能力影响；

结果：分析数据库与测序数据发现 FOXA1-eRNA 在前列腺癌中表达高于正常组织，该 eRNA 在前列腺癌细胞中表达显著高于肾癌、肝癌和胰腺癌细胞。与 CSPC 细胞系 LNCaP 相比，其在 CRPC 细胞系（PC3 和 DU145 等）中表达明显升高。FOXA1 增强子信号在 CRPC 组织中显著高于启动子；GO 通路分析 CRPC 增强子相关基因在 AR 信号通路富集，3C 实验明确该 eRNA 促进 FOXA1 的 E-P 环形成。敲低 FOXA1-eRNA 后，FOXA1 和 AR 下游基因 PSA 及 KLK2 的 mRNA 水平下降；CCK8 实验检测细胞增殖能力减弱及对恩杂鲁胺的敏感性增加。WB 和 RIP 实验验证该 eRNA 与 p68 结合；FOXA1 和 p68 存在易发生相分离 IDR 序列；FOXA1 和 p68 内源性及外源性蛋白可以发生相分离且加入液相分离抑制剂 1,6-己二醇后液滴消失，提示 p68 驱动液相分离；敲低 FOXA1-eRNA 后，FOXA1 的 E-P 环相互作用频率及形成相分离的能力均下降提示该 eRNA 是驱动 FOXA1 和 p68 结合并形成相分离的关键因素。以上结果提示，FOXA1-eRNA 结合 p68 和 FOXA1 形成液相分离，促进 FOXA1 的 E-P 环互作和增强其转录并激活下游 AR 信号通路促进前列腺癌进展。

结论：FOXA1-eRNA 促进 p68 在 FOXA1 的 E-P 环局部形成液相凝集物，增强 FOXA1 转录，激活下游 AR 信号通路促进前列腺癌进展。

关键字： FOXA1-eRNA、前列腺癌、相分离、AR、p68

195. Pg 感染及 TFAM 表达对食管鳞癌患者预后的影响及机制研究

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目的：食管鳞癌（ESCC）病因不明、发病分子机制不清。研究表明，牙龈卟啉单胞菌（Pg）感染可促进 ESCC 演进。病原微生物可通过激活宿主细胞线粒体转录因子 A（TFAM），增强其线粒体氧化磷酸化（mtOXPHOS）功能，为其恶性增殖供能。本研究旨在探索 ESCC 中 Pg 感染及 TFAM 表达对患者生存预后的影响及及潜在生物学机制，为 ESCC 临床防治策略的制定提供新靶点。

材料与方法：常规培养人 ESCC 细胞系 KYSE450 及 KYSE150，建立 TFAM 稳定敲降的 KYSE450-shTFAM 及 KYSE150-shTFAM。将 KYSE450 及 KYSE150 分为对照组、Pg 感染组、TFAM 敲降组及 Pg 感染+TFAM 敲降组，通过 Western blot 及线粒体压力测试检测各组细胞中 TFAM 蛋白表达量及 mtOXPHOS 水平，采用 CCK8 法、平板克隆、划痕实验及 Transwell 实验检测各组细胞的体外增殖、迁移及侵袭能力。选择 384 例 ESCC 组织（来自 ESCC 高发区安阳市肿瘤医院）石蜡切片为研究对象，分别采用 RNAscope 及免疫组化法检测 ESCC 组织中 Pg 感染及 TFAM 蛋白表达情况。采用 Kaplan-Meier 生存分析比较 Pg 感染及 TFAM 表达与患者生存时间之间相关性；通过 COX 回归分析 Pg 感染及 TFAM 表达对 ESCC 预后的影响。

结果：与对照组相比，Pg 感染组细胞的 TFAM 蛋白表达量增高、mtOXPHOS 功能增强、体外增殖、迁移及侵袭能力均增强（均 $P<0.05$），提示 Pg 感染可诱导 ESCC 细胞中 TFAM 高表达、mtOXPHOS 增强、恶性生物学能力增强；TFAM 敲降组的上述指标均降低（$P<0.05$），提示 TFAM 在 ESCC 细胞 mtOXPHOS 功能及恶性生物学能力维持中发挥关键作用；Pg 感染+TFAM 敲降组的上述指标变化不显著，提示 TFAM 敲降后，Pg 感染无法增强 ESCC 细胞的上述功能，表明 TFAM 是 Pg 发挥促癌作用中的关键调控因子。ESCC 组织中 Pg 感染率

为 41.15%、TFAM 阳性率为 43.23%，两个指标一致性很强（P＜0.05）。两个指标阳性组患者中有吸烟史、有饮酒史、男性患者比例居多，肿瘤侵及纤维膜、有淋巴结转移及 TNM 分期 III/IV 期的患者比例居多（均 P＜0.05）。与 Pg 感染及 TFAM 表达阴性组患者相比，两个指标阳性组患者的 5 年生存率及中位生存时间均缩短，死亡风险均增加（P＜0.05）。

结论：Pg 感染可诱导 ESCC 细胞中 TFAM 高表达，增强其 mtOXPHOS 功能，促进其恶性增殖、迁移及侵袭，导致患者预后不良。

关键字： 食管鳞癌；牙龈卟啉单胞菌；线粒体转录因子 A；预后

196. 肿瘤相关的巨噬细胞分泌富含 circ-MALAT1 的外泌体促进前列腺癌进展

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目的：之前研究发现肿瘤相关的巨噬细胞（TAM）主要表现出 M2 型巨噬细胞的特征，转录因子 YY1 在 M2 型巨噬细胞极化中起重要作用，过表达 YY1 的 M2 型巨噬细胞分泌细胞因子促进前列腺癌细胞恶性进展。但加入细胞因子中和抗体不能完全阻断其促进前列腺癌细胞恶性进展，因此我们研究 M2 型巨噬细胞来源的外泌体对前列腺癌细胞恶性进展影响。

材料和方法：体外构建过表达 YY1 的 M2 型巨噬细胞模型。同时构建过表达 YY1 和野生型转基因小鼠，提取腹腔和骨髓来源的巨噬细胞，诱导成 M2 型巨噬细胞。提取其细胞培养上清（CM）、外泌体（exos）与去除外泌体 oe-YY1 M2 CM 与 LNCaP 或 RM-1 共培养。透射电镜，NTA，WB 分别鉴定外泌体，PKH67 染色示踪外泌体，细胞迁移、侵袭和划痕实验，探索过表达 YY1 的巨噬细胞分泌的外泌体对前列腺癌细胞影响。采用外泌体 circRNA 芯片发现 oe-YY1 M2 与 nc-YY1 M2 细胞分泌外泌体包含环状 RNA；定量 PCR，核质分离，RNA Fish，荧光素酶报告基因，RNA pulldown、细胞迁移、侵袭、划痕和尾静脉注射等实验证明 circ-MALAT1 功能及 circ-MALAT1 靶向下游靶基因（miR-338-3p 和 AR）。Chip-seq 和染色质构象铺获实验（3C）探索 YY1 对 circ-MALAT1 母体基因 MALAT1 转录的影响；定量 PCR、WB 等实验证明 YY1 对 RNA 剪切蛋白 QKI 的影响，探索 YY1 通过促进 QKI 表达影响 MALAT1 剪切 circ-MALAT1；Co-IP，泛素化等实验探索 YY1 通过 NUSAP1 影响 HIF-1a 泛素化，进而探索 YY1 对外泌体释放的影响。

结果：过表达 YY1 的 M2 型巨噬细胞分泌外泌体增加，该外泌体促进前列腺癌细胞增殖和迁移等恶性进展。分泌的外泌体富含 circ-MALAT1，其功能主要是通过竞争性结合 has-miR-339-3p 影响 AR 表达。YY1 可以结合在 MALAT1 的增强子-启动子（EP）上并促进与维持 EP 环形成，进而促进 MALAT1 转录。同时 YY1 可以促进 QKI 表达，QKI 可促进 MALAT1 剪切形成 circ-MALAT1。YY1 结合 NUSAP1 共同抑制 HIF-1a 的泛素化，HIF-1a 可促进外泌体的释放。

结论：高表达 YY1 的 M2 型巨噬细胞分泌的外泌体促进前列腺癌进展。

关键字： YY1、肿瘤相关巨噬细胞、外泌体、前列腺癌、环状 RNA

197. 肌少症通过抑制肿瘤免疫和效应 T 细胞浸润增加前列腺癌根治术后生化复发风险的研究

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目的：本研究旨在利用临床样本探究肌少症预测前列腺根治术后生化复发的预后价值，挖掘其中潜在生物学机制，为提高前列腺癌一线治疗疗效和改善术后患者预后提供理论依据。

材料与方法：本研究收集了 2014 至 2020 年于东南大学附属中大医院行腹腔镜或机器人腹腔镜前列腺根治性切除术的前列腺癌患者信息。使用限制性立方样条函数分析骨骼肌指数与生化复发相关性，采用 Kaplan-Meier 分析倾向性评分匹配前后肌少症对前列腺根治术后生化复发的影响；收集临床前列腺癌组织样本进行转录组测序，利用 TCGA-PRAD 队列筛选出肌少症相关基因中的生化复发危险因素，通路富集分析预测其生物功能；利用 ESTIMATE 和 CIBERSORT 分析肌少症相关基因与免疫细胞浸润相关性，免疫荧光实验验证；构建多变量列线图模型应用于预测根治术后前列腺生化复发，ROC 曲线评价其诊断效力。

结果：肌少症是前列腺癌患者根治术后生化复发独立危险因素。肌少症相关基因 PPP1R14B、RAB26 和 TEDC2 是前列腺癌恶性进展的危险因素，它们的异常高表达可抑制 T 细胞受体和干扰素 γ 抗肿瘤免疫信号通路，导致肿瘤 pT 分期、N 分期、Gleason 评分和生化复发风险的增高；三者的表达水平均与前列腺癌中抗肿瘤免疫细胞 CD4+记忆 T 细胞和 CD8+T 细胞浸润水平负相关，与 Tregs 浸润水平正相关。TEDC2 是前列腺根治术

后生化复发的独立危险因素，联合 TEDC2 提高了多变量列线图预后模型对术后 1 年、2 年、3 年无生化复发生存的预测效力。

结论：肌少症通过抑制前列腺癌中的 T 细胞相关抗肿瘤免疫增加根治术后生化复发的风险，预后相关临床指标联合肌少症相关的基因 TEDC2 可有效预测术后生化复发。

关键字： 前列腺癌；肌少症；前列腺根治性切除术；生化复发；免疫微环境

198. Hypoxia-induced phase separation of YY1 and HIF-1α in macrophages suppresses prostate cancer tumor immune response

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Aggregation of tumor-associated macrophages (TAMs) and lack of T cells constitute the immunosuppressive tumor microenvironment (TME) of prostate cancer (PCa), with TAMs are highly expressed in hypoxic areas of the tumor. However, the potential mechanism that hypoxia orchestrated macrophages in the TME remains unclear. We discovered that YY1+ macrophages aggregated in hypoxic tumor tissues and expressed high levels of PD-L1. Mechanistically, hypoxia promotes phase separation of YY1 in the nucleus by upregulating tyrosine phosphorylation of YY1 in macrophages. Furthermore, YY1 can bind to NUSAP1 to inhibit the ubiquitination degradation of HIF-1 α , while NUSAP1-mediated SUMOylation promotes the phase separation of HIF-1 α , stabilizing HIF-1 α expression and thereby enhancing the expression of PD-L1. Additionally, we found that the small molecule inhibitor Tenapanor, targeting the YY1-NUSAP1-HIF-1 α linkage, can inhibit the progression of PCa. Moreover, we constructed a proteolysis-targeting chimera (YY1-DbTAC@jetPEI) targeting the degradation of YY1, and YY1-DbTAC@jetPEI exhibited excellent in vivo anti-tumor effects. In conclusion, we identified that YY1 plays a critical role in the hypoxia/HIF-1 α pathway in macrophages, thereby inhibiting PCa tumor immune response. Immunotherapy targeting macrophage YY1 holds promising clinical application

Key Words： YY1/tumor-associated macrophages/HIF-1 α /prostate cancer/NUSAP1

199. βIII 微管蛋白---子宫内膜癌的预后生物标志物和潜在的基因治疗靶点

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目的：探索βIII微管蛋白（betaIII-Tubulin, TUBB3）对子宫内膜癌（endometrial cancer, EC）细胞株增殖、迁移、侵袭及上皮-间质转化（epithelial-mesenchymal transition, EMT）的影响，并探究 TUBB3 基因在 EC 中的分子机制。

方法：从 TCGA、GEO、HPA 数据库分析比较 TUBB3 在子宫内膜癌及正常组织中的差异表达情况，并进行临床相关性分析。通过 qRT-PCR、Western blot 和免疫组织化学技术进一步验证 TUBB3 在 EC 患者癌组织及对应正常内膜组织中的表达情况，并分析其临床特征。在子宫内膜癌 Ishikawa 细胞中分别转染 TUBB3 敲减/过表达质粒，通过 qRT-PCR 和 Western blot 检测其敲减/过表达效率；通过体外实验探究 TUBB3 对 Ishikawa 细胞增殖、迁移和侵袭的影响。采用 Western blot 进一步检测 TUBB3 对 EMT 相关标志物的影响及其分子机制。

结果：生物信息学分析比较差异表达基因，并结合免疫组化结果发现 TUBB3 在 EC 中表达显著高于癌旁正常组织，其表达与肿瘤大小、组织学类型、FIGO 分期及 TP53 突变呈正相关，且 TUBB3 高表达与患者不良预后关系密切。与对照组相比，敲减 TUBB3 明显抑制肿瘤细胞的增殖、迁移和侵袭；反之，过表达 TUBB3 使肿瘤细胞的增殖、侵袭和迁移能力明显增强。RT-qPCR 和 Western blot 结果显示 TUBB3、间质细胞标志物（N-cadherin、Vimentin）在子宫内膜样腺癌组织中表达显著高于其癌旁组织，而上皮细胞标志物（E-cadherin）在癌组织中表达较癌旁组织明显降低。同时，转染 TUBB3 敲减质粒后，能显著抑制肿瘤细胞中 N-cadherin、Vimentin 表达，并促进 E-cadherin 表达。而过表达 TUBB3 通过上调 N-cadherin、Vimentin 表达，并下调 E-cadherin 表达，进而促进内膜癌的 EMT 进程。机制上，TUBB3 通过 PI3K/AKT/mTOR 信号通路介导内膜癌细胞增殖、侵袭、迁移及上皮-间质转化。

结论：TUBB3 通过激活 PI3K/AKT 信号通路，促进子宫内膜细胞的增殖、迁移和侵袭，加速上皮-间质转化的进程。为子宫内膜患者早期诊断和治疗提供了新的靶点。

关键字： β III 微管蛋白、子宫内膜癌、上皮间质转化

200. Hypoxia-induced Upregulation of POSTN in Cancer-associated Fibroblasts Promotes Progression of Colorectal Cancer

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Background: Hypoxia is a typical marker of solid tumors and plays an important role in the progression of colorectal cancer (CRC). Cancer-associated fibroblasts (CAFs) influence tumor microenvironment and tumor growth. However, the role of hypoxia induced CAFs in the development of colorectal cancer (CRC) is not fully understood.

Methods: Bulk RNA-seq data and microarray data of CRC were obtained from the TCGA and GEO databases. The signal-cell RNA sequencing (scRNA-seq) data was obtained from the GEO database. CAFs and NFs were obtained from fresh CRC and adjacent normal tissues. POSTN+CAFs were purified by flow cytometry. The conditioned medium of POSTN+CAFs (CAF-CM) from was used to culture cell lines of CRC. RNA sequencing was used to explore the specific targets of POSTN+CAFs on CRC cells. Western blot, quantitative real-time polymerase chain reaction (qRT-PCR) or immunofluorescence staining were used to detect the activation of POSTN+CAFs. The regulation of transcriptional HIF1 α on POSTN was studied by chromatin immunoprecipitation quantitative real-time PCR (CHIP-qPCR).

Results: The prognosis analysis showed that hypoxia was a poor prognostic factor in CRC patients. By single-cell transcriptomic analysis of 10,108,819 cells from 46 CRC samples, POSTN+CAFs was the most significantly enriched subgroup of CAFs in hypoxia. Compared with the adjacent normal tissues, POSTN expression was upregulated in the hypoxia region of colorectal cancer tissues. Upregulation of POSTN in CAFs, which was induced by HIF-1 α

-mediated transcriptional activation, facilitated the proliferation and metastasis of CRC cells both in vivo and in vitro.

Conclusion: Altogether our work demonstrates a critical role of POSTN activation in CAFs in CRC development.

Key Words： Colorectal cancer (CRC); Hypoxia; Cancer-associated fibroblasts (CAFs); POSTN.

201. COL11A1+Cancer-associated Fibroblasts Promote Cancer Metastasis in Colorectal Cancer via the Wnt/β-catenin Pathway

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Background: Metastasis is the main cause of death in patients with colorectal cancer (CRC). Cancer-associated fibroblasts (CAFs) play a role in cancer treatment response and patient prognosis. CAFs exhibit phenotypic and functional heterogeneity and widely in tumors of different tissue origins. However, the role of different CAFs subpopulations in CRC metastasis remains unknow.

Methods: To elucidate the causes of CRC metastasis, we analyzed single-cell sequencing data from 169 CRC patients and spatial transcriptome data from 4 CRC patients. The co-culture system of patient-derived organoids and CAFs was established. RNA sequencing was performed on purified CAFs sorted by fluorescently activated cells to identify potential therapeutic targets in CAFs. To investigate the prognostic significance of metastasis associated CAFs, we used RNA sequencing data and tissue chips from CRC patients. CRC organoids and CAFs were injected together into the spleen of nude mice to evaluate the mechanisms involved in colorectal cancer metastasis.

Results: We identified COL11A1 as a CAF-specific gene involved in CRC metastasis. Functionally, we found that abnormally activated transcription factor LEF1 in COL11A1+CAFs induced increased secretion of COL11A1 and remodeled extracellular matrix remodeling. Mechanistically, COL11A1 induced the increase of LAMC2 expression in colorectal cancer cells

by binding to the receptor Integrin α2β1 on the surface of colorectal cancer cells, activated the EMT and wnt/β-catenin signaling pathway of colorectal cancer cells, and promoted the metastasis of colorectal cancer cells. COL11A1+CAFs promoted M2-type polarization of macrophages through LGALS9-CD44 ligand pathway and induced tumor immunosuppressive microenvironment. CRC cells and COL11A1+CAFs promoted the formation of COL11A1+CAFs subtype through the release of TGFβ

Conclusion: In conclusion, this study described the mechanism by which COL11A1+CAFs regulate colorectal cancer metastasis, thus providing a new target for colorectal cancer metastasis intervention.

Key Words： Colorectal cancer (CRC); Metastasis; single-cell; Cancer-associated fibroblasts (CAFs); COL11A1.

202. IDO 对甲状腺乳头状癌局部淋巴结转移的影响及其机制

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目的：甲状腺癌是最常见的头颈部恶性肿瘤，主要病理类型为甲状腺乳头状癌（PTC）。PTC 预后较好，但易发生颈部淋巴结转移，复发风险高。研究表明，免疫检查点分子吲哚胺 2,3-双加氧酶（IDO）可催化 T 细胞增殖所需的色氨酸耗竭，抑制 T 细胞的杀伤能力，引起肿瘤免疫逃逸。本研究旨在探索 PTC 中 IDO 高表达对局部淋巴结转移的影响及潜在生物学机制，为 PTC 临床治疗提供新思路。

材料与方法：选择有局部淋巴结转移及无局部淋巴结转移的 PTC 患者各 100 例为研究对象。采用免疫组化法检测两组患者癌组织石蜡切片中 IDO 表达情况及 CD8+T 细胞浸润情况。建立人甲状腺癌细胞（KTC-1 及 TPC-1）与人 CD8+T 细胞体外共培养体系，将各共培养体系分为对照组及 IDO 抑制剂组，通过流式细胞术检测各共培养体系中 CD8+T 细胞的增殖情况。建立 NSG 鼠荷瘤模型，分别将 KTC-1 及 TPC-1 细胞接种于 NSG 鼠皮下，并于每只 NSG 鼠尾静脉接种人 CD8+T 细胞，实验分为对照组及 IDO 抑制剂组。期间记录各组肿

瘤体积变化，结束后测量肿瘤重量，并通过免疫组化法检测各组 NSG 鼠瘤体内 CD8+T 细胞浸润情况。采用卡方检验分析 IDO 表达及 CD8+T 细胞浸润与 PTC 患者淋巴结转移之间的相关性；采用 t 检验比较对照组及 IDO 抑制剂组中 CD8+T 细胞增殖率与百分比差异、NSG 鼠肿瘤体积与重量差异。

结果：有淋巴结转移患者的癌组织中 IDO 表达量显著高于无转移患者（P<0.05），而 CD8+T 细胞浸润阳性率显著低于无转移患者（P<0.05），表明有淋巴结转移的 PTC 患者癌组织中 IDO 高度激活，而微环境中 CD8+T 细胞浸润较少。体外共培养模型结果显示，与对照组相比，IDO 抑制剂组 CD8+T 细胞的增殖率增高（P<0.05），表明抑制 IDO 的活性可有效刺激 CD8+T 细胞增殖。NSG 鼠模型结果显示，与对照组相比，IDO 抑制剂组 NSG 鼠肿瘤体积及重量均减少（P<0.05），且瘤体内浸润的 CD8+T 细胞比例增加（P<0.05），表明抑制 IDO 活性，可促进 CD8+T 细胞瘤内富集，抑制癌细胞的恶性增殖。

结论：PTC 中 IDO 高表达可抑制免疫微环境中 CD8+T 细胞增殖，削弱其杀伤能力，导致癌细胞逃避免疫监视，易发生局部转移。

关键字： 甲状腺乳头状癌；吲哚胺 2,3-双加氧酶；CD8+T 细胞；局部淋巴结转移

203. 基于转录组的结肠癌远处转移预测模型

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目的：结肠癌是最常见的消化道肿瘤之一。远处转移是造成结直肠癌患者死亡的最重要原因。因此预测是否会发生远处转移对评价患者预后和制定治疗策略至关重要。本研究拟利用肿瘤转录组信息以构建远处转移相关模型，预测结肠癌患者的转移风险。

材料与方法：使用 R 语言 GEOquery 包下载 GEO 数据集（GSE41258 和 GSE18105），使用 TCGAbiolinks 包下载 TCGA 结肠癌数据集（TCGA-COAD）。以 GSE41258 数据集作为训练集，用 limma 包筛选有远处转移和无远处转移患者肿瘤组织的差异基因。去掉高相关性基因后用 LASSO 回归和逐步回归进行特征筛选，最后采用 logistic 回归进行模型构建。在 TCGA-COAD 和 GSE18105 数据集中对模型进行验证。使用准确性、灵敏度、特异度及受试者工作特征曲线的曲线下面积（area under the curve，AUC）对模型效能进行评价。

结果：GSE41258 数据集包含 168 名 I-IV 期结肠癌患者肿瘤组织的转录组数据，有 77 个基因在 IV 期和 I-III 期的肿瘤组织中差异表达。随后筛选出 11 个有预测潜能的基因（MTUS1、PIR、IRF8、CXCL1、TRIP6、PSPH、GPC1、MAGEA6、BEX4、HOXC6 和 MTMR1）并构建 logistic 回归模型，该模型诊断远处转移的准确性、灵敏度、特异度分别为 0.869、0.849、0.878，AUC 为 0.938。该模型对 TCGA-COAD 数据集中 IV 期患者的诊断准确性、灵敏度、特异度分别为 0.705、0.730、0.700，AUC 为 0.743。GSE18105 数据集中包括 70 名 II-III 期患者，其中 14 名患者在随访过程中发生远处转移。研究发现该模型预测这些远处转移患者的准确性、灵敏度、特异度分别为 0.786、0.857、0.768，AUC 为 0.804。

结论：本研究构建了一个由 11 基因组成的结肠癌远处转移预测模型，具有良好的预测效能，有助于指导结肠癌患者的个体化治疗及随访，具有一定的临床应用价值。

关键字： 结肠癌 远处转移 生物标志物

204. 癌组织驻留肥大细胞通过 TLR4 活化及 CXCL8、CCL19 分泌诱导纤维化的研究

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目的：肿瘤微环境中浸润的免疫细胞对癌症发生发展和预后的影响极为重要。肥大细胞是其中长寿命的免疫细胞，但其对癌细胞特征和侵袭性的相关研究少。本研究通过分析癌组织中肥大细胞分布及趋化因子表达等，旨在为恶性肿瘤预后提供潜在预测指标。

方法：通过生信分析、组织芯片、免疫荧光染色、体外实验等方法，分析癌组织中驻留肥大细胞与组织纤维化等肿瘤病理特征之间的关系及相关机制。

结果：TCGA 数据库中，通过肥大细胞标志基因 KIT 的表达分析，与正常组织相比，肥大细胞在包括乳腺癌、肺癌、食管癌在内的多种恶性肿瘤组织中出现数量变化。其中，肥大细胞在食管腺癌和食管鳞癌组织中较正常食管组织显著下降，但食管腺癌和食管鳞癌间的差异无统计学意义。同时，通过肥大细胞活化标志基因 FCER1A 的表达发现，肥大细胞在食管腺癌和食管鳞癌组织中较正常食管组织显著下降。食管腺癌和食管鳞癌总生存差异无统计学差异。通过 KIT 和 FCER1A 不同程度表达交叉富集，寻找出食管癌肥大细胞交叉基因 87 个。通过 GO 富集分析对 87 个交叉基因进行功能分类，发现这写交叉基因的主要功能是

调节细胞外基质。进而通过 KEGG 富集分析对 87 个交叉基因进行功能分类，发现这写交叉基因的主要功能是影响血管平滑肌收缩。食管癌患者组织芯片 HE 及免疫荧光染色发现，食管癌组织中表达细菌内毒素脂多糖（LPS）；对比显示，LPS 影响癌组织中的肥大细胞数量，且 LPS 阴性患者中总生存时间更长。此外，食管癌组织呈现不同程度的纤维化和结缔组织反应性增生，组织纤维化弱或结缔组织反应性增生的患者中总生存期更长。体外实验发现，LPS 可以活化肥大细胞株 HMC-1，活化的 HMC-1 对趋化因子 CXCL8 和 CCL19 的分泌显著增加。

结论：癌组织驻留肥大细胞促进肿瘤组织纤维化，这一作用可能通过其 TLR4 信号活化及 CXCL8、CCL19 分泌诱导产生。

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关键字： 组织驻留肥大细胞，TLR4, CXCL8, CCL19，癌组织纤维化

205. Histopathology images-based deep learning prediction of prognosis and therapeutic response in small cell lung cancer

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Background： Small cell lung cancer (SCLC) is a highly aggressive subtype of lung cancer characterized by rapid tumor growth and early metastasis. Accurate prediction of prognosis and therapeutic response is crucial for optimizing treatment strategies and improving patient outcomes.

Materials and Methods： We retrospectively collected 380 surgically resected and pathologically confirmed specimens of SCLC from two independent medical centers, including 286 patients from the Cancer Hospital, Chinese Academy of Medical Science (CHCAMS cohort), spanning the

period from January 2005 to December 2016, and 94 patients from the Peking University Cancer Hospital between January 2010 and April 2023 (PUCH cohort). We proposed a self-supervised deep learning framework called DL-CC to extract histomorphological features from histopathological images and identified 50 intricate histomorphological phenotype clusters (HPCs) as pathomic features. We identified two of 50 HPCs with significant prognostic value and then integrated them into a pathomics signature (PathoSig) using the Cox regression model.

Results： PathoSig showed significant risk stratification for overall survival and disease-free survival and successfully identified patients who may benefit from postoperative or preoperative chemoradiotherapy. The predictive power of PathoSig was validated in independent multicenter cohorts. Furthermore, PathoSig can provide comprehensive prognostic information beyond the current TNM staging system and molecular subtyping.

Conclusion： Our study highlights the potential of utilizing histopathology images-based deep learning to improve prognostic predictions and therapeutic response evaluation in SCLC. The PathoSig we developed, validated through extensive analysis of multicenter retrospective datasets, demonstrates remarkable predictive performance, robustness and generalizability, offering clinicians valuable insights for making informed treatment decisions.

Key Words ： small cell lung cancer, prognosis, therapeutic response, histopathological images, deep learning

206. M6A 修饰的 circRNA SPECC1 通过编码一种新多肽 SPECC1-415aa 调控胶质母细胞瘤对替莫唑胺的敏感性

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目的：探究 m6A 修饰的环状 RNA (circular RNA) SPECC1 通过编码一种新多肽 SPECC1-415aa 调控胶质母细胞瘤对 TMZ 敏感性的分子机制。

内容：研究胶质母细胞瘤的 circRNA 微阵列表达谱。探究 circSPECC1 对胶质母细胞瘤细胞恶性表型的影响。研究 circSPECC1 通过编码新多肽 SPECC1-415aa 竞争性结合 ANXA2，抑制 ANXA2 与其靶蛋白 EGFR 的结合，抑制 EGFR 和其下游通路 AKT 的磷酸化激活，从而调控胶质母细胞瘤细胞对 TMZ 敏感性的分子机制。

方法：收集 4 例原发和 4 例复发胶质母细胞瘤患者组织样本，利用 circRNA 微阵列测序，筛选差异表达的 circRNA。利用 circBank 、circRNADb 和 TransCirc 数据库分析具有潜在翻译功能的 circRNA。同时分析 circRNA 的 IRES 中 18S rRNA 和 SuRE 结构元件。通过实时荧光定量聚合酶链式反应（RT-qPCR）、琼脂糖凝胶电泳、Sanger 测序、RNase R 以及放线菌素 D 实验 (Act D)来验证 circSPECC1 的环状结构。核浆 RNA RT-qPCR 和 RNA 原位杂交 (FISH)验证 circSPEC1 的亚细胞定位。通过 CCK-8、划痕实验、Transwell 实验和集落形成实验验证 circSPECC1 对胶质瘤细胞增殖、迁移、侵袭和集落形成能力的影响。经过免疫荧光实验和彗星实验验证 circSPECC1 对胶质瘤细胞 TMZ 敏感性的影响。通过 meRIP、RNA 免疫共沉淀 (RIP)和免疫荧光等试验验证 circSPECC1 受到 m6A reader IGF2BP1 的调控。基于蛋白印迹 (WB)、免疫沉淀实验 (IP)联合质谱分析(LC-MS)，检测 circSPECC1 编码的多肽，并且通过 IP-MS 筛选多肽 SPECC1-415aa 的结合蛋白。进一步通过 IP 实验、免疫荧光实验和蛋白印迹实验验证 circSPECC1 通过编码新多肽 SPECC1-415aa 竞争性结合 ANXA2，抑制 ANXA2 与其靶蛋白 EGFR 的结合，抑制 EGFR 和其下游通路 AKT 的磷酸化激活。通过 EdU、TUNEL 实验、免疫荧光实验和彗星实验验证 SPECC1-415aa 通过下游 EGFR-AKT 信号通路调控胶质瘤的生物学功能和胶质瘤细胞对 TMZ 的敏感性。最后，通过原位异种移植瘤模型，在体内进一步验证 circSPECC1 过表达联合 TMZ 干预治疗 TMZ 抵抗的胶质母细胞瘤，能恢复 TMZ 抵抗的胶质母细胞瘤对 TMZ 的敏感性。

结果：通过微列阵分析发现，与原发胶质母细胞瘤样本相比，在复发胶质母细胞瘤样本中有 412 个 circRNA 上调和 173 circRNA 下调。基于 circRNADb、circbank 和 TransCirc 数据库分析、circRNA 的 IRES 序列分析和蛋白印迹实验的编码潜力验证发现 circ_0000745 和 circ_0007940 均具有编码能力，进一步通过 GEO 数据库分析和 RT-qPCR 筛选出了 circ_0000745 (circSPECC1)作为研究对象。进一步表征了 circSPECC1 的环状结构和稳定性，并发现 circSPECC1 主要位于细胞质。表型实验表明 circSPECC1 可以抑制胶质瘤细胞的增殖、迁移、侵袭和克隆形成能力。IP-MS 和蛋白印迹实验表明 circSPECC1 能编码一个新多肽 SPECC1-415aa。并且 circSPECC1 能通过编码多肽 SPECC1-415aa 调控胶质瘤细胞生物学功能以及对 TMZ 的敏感性。CircSPECC1 受到 m6A reader IGF2BP1 的调控。IP-MS 和蛋白

印迹等实验表明 SPECC1-415aa 与 ANXA2 结合，抑制 ANXA2 与 EGFR 的结合，从而导致 EGFR (Tyr845)和下游 AKT (Ser473)的磷酸化激活抑制，从而调控胶质瘤的生物学功能和胶质瘤细胞对 TMZ 的敏感性。体内实验表明过表达 circSPECC1 可联合 TMZ 干预治疗 TMZ 抵抗的胶质瘤，从而恢复 TMZ 抵抗的胶质瘤对 TMZ 的敏感性。

结论：在复发胶质母细胞瘤中低表达的 circSPECC1 受到 IGF2BP1 的调控。circSPECC1 可以通过编码多肽 SPECC1-415aa，竞争性结合 ANXA2，阻碍 ANXA2 与 EGFR 结合，抑制 EGFR 和 AKT 磷酸化激活，从而恢复耐 TMZ 胶质瘤细胞对 TMZ 的敏感性。

关键字： circSPECC1 SPECC1-415aa 胶质瘤 ANXA2 EGFR TMZ 敏感性

207. tRF-29-79 通过抑制谷氨酰胺转运体 SLC1A5 生成调节肺腺癌恶性进展

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背景：肺癌是全球发病率及死亡率最高的恶性肿瘤，严重影响着人类的健康。近年来，肺癌发病率最高的病理类型已由肺鳞癌（squamous cell carcinoma，LUSC）向肺腺癌（lung adenocarcinoma，LUAD）转变，LUAD 成为肺癌中发病率最高的类型，约占肺癌的 2/3。对 LUAD 癌变和转移的分子机制进行了广泛的研究。近年来，高通量技术和微阵列技术的进步使研究人员得以探索新型肿瘤靶点。在这些靶标中，tRNA 衍生的小非编码 RNA (tRFs 和 tiRNAs)已成为肿瘤研究的重要焦点。tiRNAs 包括 5' tiRNAs 和 3' tiRNAs ，它们是由特异性的 tRNA 切割产生的。tRNA 相关片段(tRFs)根据其产生位置可以进一步分为 5'-tRF、3'-tRF、5'-half、3'-half 和 i-tRF 五种类型。大量研究表明，tRFs 和 tiRNAs 可以通过直接结合 RNA 或蛋白质发挥作用，广泛参与各种癌症的进展。尽管已经在各种实体肿瘤中有了对 tRFs 的大量研究，但对其在 LUAD 中的作用的研究仍然有限。本研究通过阐述与 LUAD 分期和预后密切相关 tRF-29-79 在肺腺癌的恶性进展中的生物学功能及作用机制，为肺癌诊疗提供新思路。

方法：本研究通过分析三对 LUAD 组织中 tRFs 的表达量进行高通量测序（tRF&tiRNA seq），同时根据候选 tRFs 在肺腺癌肿瘤组织和邻近正常组织之间差异表达情况，筛选出本研究的目标：tRNAGlyGCC 衍生的 5'-tRFs tRF-29-79。我们发现 tRF-29-79 在 LUAD 中下调，

且 tRF-29-79 的下调与较差的分期和预后相关。之后在肺腺癌细胞系中过表达或沉默 tRF-29-79，通过 CCK8，EdU，Transwell 等体外功能实验和小鼠皮下荷瘤实验分析 tRF-29-79 在肺腺癌恶性进展中的功能。通过 RNA-pulldown、RIP 实验等确定可以被 tRF-29-79 所吸附的 RBP（PTBP1）。并通过 miRNA-pulldown 及 RNA 原位杂交确认 tRF-29-79 与该蛋白的定位情况。进一步通过 RNA-seq、GO 功能富集分析、实时荧光定量 PCR 及双荧光素酶实验确认 tRF-29-79 的下游 SLC1A5。最后通过依赖性及挽救实验验证 tRF-29-79 通过 SLC1A5 抑制肺腺癌的恶性表型。

结果：tRF&tiRNA 高通量测序分析提示， tRFs tRF-29-79 在肺腺癌中特异性低表达。肺腺癌肿瘤组织和邻近正常组织之间差异表达情况进一步确认 tRF-29-79 在肿瘤组织中低表达，提示可能与癌症的恶性表型相关。进一步应用附有完善随访资料的 84 例肺腺癌组织芯片进行 tsRNA 表达与肺腺癌临床病理特征及预后的相关性分析，提示 tRF-29-79 表达与更好的临床病理特征和更好预后相关，可能是肺腺癌患者的独立危险因素。之后的功能实验表明，肺腺癌细胞系中过表达或沉默 tRF-29-79 分别抑制了或促进了肿瘤细胞的增殖与侵袭。机制探索确认了 tRF-29-79 可以特异性结合可变剪切因子 PTBP1。而 PTBP1 可以特异性调控谷氨酰胺代谢的关键转运体 SLC1A5 的可变剪切。依赖性及挽救实验验证 tRF-29-79 通过抑制 PTBP1 的入核，抑制了 SLC1A5 的可变剪切，从而导致肺腺癌细胞的谷氨酰胺代谢能力下降，从而抑制肺腺癌的恶性进展。

结论：本研究根据 tRF&tiRNA 高通量测序结果结合肺腺癌肿瘤组织和邻近正常组织之间差异表达情况筛选出在肺腺癌中特异性低表达的 5'-tRFs tRF-29-79。tRF-29-79 可以特异性结合可变剪切因子 PTBP1，进而抑制谷氨酰胺代谢的关键转运体 SLC1A5 的表达，并抑制了肺腺癌中谷氨酰胺代谢的能力以及肺腺癌的恶性进展。本研究从肺腺癌病理分期和预后相关的 tRFs 的角度研究了 tRF-29-79 在 LUAD 中发挥生物学功能的分子机制，拓展了 tRFs 与谷氨酰胺代谢的调控关系。本研究也为从 tRFs 角度靶向调控成肺腺癌恶性进展提供新思路。

关键字： 肺腺癌，tRFs，tRF-29-79， PTBP1，SLC1A5，谷氨酰胺代谢

208. IFIH1 regulates the expression of PD-L1 in breast cancer through TBK1/IRF3 pathway

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Purpose: As an intracellular RNA sensor, the innate immune receptor interferon-induced helicase 1 (IFIH1)regulates crucial biological processes associated with the onset and progression of cancer. It has been extensively demonstrated to play a significant role in various types of cancers. However, the potential functions and mechanisms of IFIH1 and its related pathways in breast cancer progression and tumor immunology have not been well studied.

Methods: The transcriptome expression data of IFIH1 were obtained from TCGA database and the related differential genes were screened. Gene concentration analysis (GSEA) and protein-protein interaction network (PPI) were used to study the signal transduction pathway of IFIH1 involved in Breast Cancer (BC).The function and regulatory pathway of IFIH1 were verified through various methods including immunohistochemical analysis, quantitative reverse transcriptase polymerase chain reaction (RT-qPCR), cell counting kit-8 (CCK-8) analysis, clone formation test and Western blotting analysis.

Results: The expression of IFIH1 is markedly up-regulated in variety tumors, including breast cancer. The immunohistochemical results of 39 breast cancer patients revealed that IFIH1 was specifically located in the cytoplasm and cell membrane of cancer tissues. Moreover, it was found to have a significant correlation with the expression of PD-L1. GSEA analysis showed that the genes co-expressed with IFIH1 were involved in tumor immune-related pathways and apoptosis. In conclusion, the knockdown of IFIH1 in MDA-MB-231 and BT-549 cell lines resulted in significantly increased cell proliferation and clone creation capabilities, as demonstrated by CCK8 and clonal formation assays.The Western blot analysis revealed that along with the alterations in apoptosis-pathway related proteins, there was a significant decrease in phosphorylated tank-bound kinase 1 (p-TBK1) and phosphorylated interferon regulatory factor 3 (p-IRF3) in cells following

IFIH1 knockdown. Additionally, the expression of PD-L1 was also significantly down-regulated ($p<0.05$).Furthermore, we also demonstrated the existence of binding sites between IRF3 and PD-L1 promotors, This finding provides additional evidence supporting the correlation between IFIH1 expression and downstream apoptotic pathway as well as the expression of immune checkpoint gene PD-L1 expression.

Conclusions: In summary, IFIH1 is an crucial regulatory gene involved in the occurrence and development of breast cancer and controls theexpression of PD-L1. Consequently, we anticipate that IFIH1 and associated pathways may emerge as a novel therapeutic target for stimulating apoptosis of breast cancer cells and tumor immunotherapy.

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Key Words ： IFIH1,BC,PD-L1,Tumor immunotherapy

209. 肝星状细胞在慢性肝损伤中的异质性研究

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目的：慢性肝病是全球主要的疾病负担之一，严重影响患者生活质量、增加并发症和死亡率。而持续的肝脏炎症是慢性肝脏疾病进展的一个重要因素。Mallory-Denk bodies（马洛里小体，MDBs）是发生在慢性肝细胞损伤中的一种炎症聚集物。肝脏慢性炎症刺激肝星状细胞（HSC）活化，活化的肝星状细胞（aHSC）通过肝肿瘤微环境（TME）中的旁分泌串扰和基质细胞蛋白会促进肝细胞损伤，引起 MDBs 病理性形成。本文通过构建小鼠慢性肝损伤模型，运用单细胞测序探讨 HSC 在 MDBs 病理形成中的异质性和分子机制，为慢性肝病的发病机制和防治提供新思路。

方法：通过饲喂小鼠 0.1%的 1,4-二氢-2,4,6-三甲基-3,5-吡啶脱甲酸二乙酯（DDC）10 周构建慢性肝损伤模型，之后撤去 DDC1 月，再重新饲喂 1 周。运用单细胞核 RNA 测序对已形成 MDBs 的小鼠模型进行测序，分析 HSC 在 MDBs 病理性形成过程中的分子机制。之后通过运用生物信息学和分子生物学方法分析 HSC 在 MDBs 形成及慢性肝损伤中的异质性，最后通过体内外实验验证亚群中关键分子可能对慢性肝损伤产生的作用。

结果：为了探索肝脏 MDBs 病理形成机制，我们分析了动物模型，通过单细胞核测序结果显示，HSC 细胞在 4 组样本中共有 2792 个细胞，通过 t-SNE 识别成 4 个不同的细胞簇，依据细胞簇自身的特征命名为 aHSC、qHSC、Mmp14-Bmp2+和 Mmp14-IL7r+。根据 t-SNE 图得出 aHSC 和 Mmp14-IL7r+亚群在喂药后细胞明显增多，之后对亚群特异性基因进行分析，并通过 GO 分析表明含胶原的细胞外基质（ECM）明显增多，而 aHSC 亚群中的特异性基因 Itgbl1 上调暗示其与 ECM 形成密切相关。随后通过 KEGG 分析表明 PI3K-AKT 炎症信号通路在 aHSC 中富集增多。Western Blot 结果表明在小鼠四组样本中 AKT 和 I κ B 在喂药后都显著上调，证明 PI3K-AKT 炎症信号通路在慢性肝损伤后被激活。

结论：本文首次报道了 HSC 在 MDBs 形成过程中发现了新的亚群 aHSC，并且发生了功能重塑。单细胞测序结果 KEGG 和 GO 分析显示在新发现的亚群中可能有重要蛋白和关键 PI3K-AKT 炎症信号通路调控 MDBs 病理性形成。这一发现阐明了 HSC 在肝脏 MDBs 与肝脏炎症形成的新机制，可能成为后续慢性肝损伤发病机制的新靶点，为慢性肝病的防治提供新思路。

关键字： 慢性肝病；肝星状细胞；马洛里小体；炎症；

210. TGF-β/TGF-βRⅡ轴通过调控 c-JUN 激活在慢性肝损伤中的作用研究

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目的：作为危害人类健康的主要病因之一，慢性肝病的发病机制一直是肝脏病因学研究的难点。肝脏马洛里小体（Mallory-Denk Bodies，MDBs）作为慢性肝损伤中与炎症相关的肝脏蛋白聚集体，存在于各种慢性肝脏疾病包括肝癌中。因此研究 MDBs 发生机制对于慢性肝病发病机制与防治具有重要意义。转化生长因子β（TGF-β）作为一种强大的炎症免疫反应调节器，在炎症过程中可以诱导肝巨噬细胞释放不同的生长因子和炎症介质，起到推动炎症反应级联放大的作用。本文通过构建二乙基-1,4-二氢-2,4,6-三甲基-3,5-吡啶二羧酸酯（DDC）诱导小鼠肝脏 MDBs 形成的病理模型以探究 TGF-β介导的信号在 MDBs 形成中的作用，为慢性肝脏疾病治疗和防治提供新的药物靶点和理论依据。

方法：实验小鼠通过 0.1%DDC 诱导小鼠约 10 周形成 MDBs 基础上（DDC-Fed），后撤药 1 月（DDC-Withdrawn）， MDBs 消失，再重新喂药 6 到 10 天， MDBs 快速形成（DDC-Refed）。同时，对照小鼠喂养正常饮食。进一步我们将上述四组小鼠肝脏取材、制备成单细胞悬液进行单细胞核测序和生物信息学分析，随后利用小鼠组织和血清进行 ELISA、Wetern Blot 等体内外实验进行验证。

结果：单细胞测序数据分析表明，在 MDBs 形成过程中，肝细胞-巨噬细胞配受体对 TGF-β/TGF-βRⅡ轴在 DDC-Fed、DDC-Refed 组中显著富集，且 GSVA 分析显示 TGF-β信号通路在喂药组中也明显激活。转录因子分析结果显示 c-JUN 在 DDC-Fed 与 DDC-Refed 组中明显上调。由于 UbD 是 MDBs 形成的关键驱动因子，我们也预测到在 UbD 的启动子序列上存在多个 c-JUN 的结合位点，暗示 c-JUN 激活可以调节 UbD 的表达，促进 MDBs 的形成。体外实验结果表明，DDC 喂养 10w 后的小鼠血清中 TGF-β1 分泌明显增多。Western blot 结果表明，与对照组相比，在形成 MDBs 后的小鼠 DDC-Fed、DDC-Refed 肝脏组织中，TGF-βRⅡ受体显著激活，而且 c-JUN 的蛋白水平同步上调。

结论：本文首次报道肝脏 MDB 形成过程与 TGF-β/TGF-βRⅡ轴信号通路调控的紧密关系，且 TGF-β信号通路及下游分子在 DDC 诱导的肝脏 MDBs 形成过程中明显激活。同时，启动子结合位点预测表明 c-JUN 多个位点可以结合在 UbD 的启动子区域参与调控 UbD 的活化。这对进一步探索肝脏 MDB 形成慢性肝病发病机制与防治具有重要意义。

关键字： TGF-β；慢性肝损伤；MDBs；c-JUN

211. 基于 PANDORA-seq Small RNA 测序探究绞股蓝皂苷 L 介导 PIWI/piRNA 对卵巢癌的影响及机制

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摘要：目的 本课题前期运用网络药理学策略及以及分子对接技术探究绞股蓝中关键有效成分防治卵巢癌的潜在靶点，并通过一系列细胞实验验证证实，绞股蓝关键有效成分通过多靶点对卵巢癌的发生与发展产生重要影响。PIWI 蛋白和与 PIWI 相互作用 pi RNA 形成的 PIWI/piRNA 分子机制在诸如胃癌、乳腺癌、肠癌等多种肿瘤疾病中异常表达，起到重要的调控作用，其在卵巢癌中发挥的相关调控作用也被证实。绞股蓝皂苷 L 是课题组前期筛选

出的绞股蓝中关键有效成分之一，基于上述研究基础，本课题主要目的是探讨绞股蓝皂苷 L（Gps-L）通过 PIWI/piRNA 通路对卵巢癌细胞的影响。方法 首先通过分子对接技术评价绞股蓝皂苷 L 药物成分与 PIWI 蛋白靶点间结合活性；其次选取两株卵巢癌细胞系 OVCAR3 与 SKOV3 进行绞股蓝皂苷 L 给药干预，采用 CCK-8 法分别筛出选两株细胞最佳作用浓度然后将细胞分为 OVCAR3 组、OVCAR3+Gps-L 组；SKOV3 组、SKOV3+Gps-L 组；平板克隆实验检测各组细胞的增殖能力，划痕实验检测各组细胞的迁移能力；通过对卵巢癌细胞 OVCAR3 进行 PANDORA-seq Small RNA 测序筛选出 piR-hsa-2804461、piR-hsa-2685992、piR-hsa-2812571、piR-hsa-5936331、piR-hsa-3098695、piR-hsa-322375、piR-hsa-3845023、piR-hsa-2659228、piR-hsa-3143510 九个 piRNA；将卵巢癌组织分为癌旁组与卵巢癌组，Western blot 检测各组卵巢癌组织中 PIWIL1、PIWIL2、PIWIL3、PIWIL4 的表达水平 ；qRT-PCR 检测各组卵巢癌组织中上述 9 个 piRNA 的表达水平；Western blot 检测各组细胞中 PIWIL1、PIWIL2、PIWIL3、PIWIL4 的表达水平 ；qRT-PCR 检测各组细胞中上述 9 个 piRNA 的表达水平。结果 平板克隆实验及划痕实验结果表明，分别与 OVCAR3 组和 SKOV3 组细胞相比，OVCAR3+Gps-L 组、SKOV3+Gps-L 组的细胞克隆形成率降低（P<0.05），细胞迁移率降低（P<0.05），绞股蓝皂苷 L 可抑制 OVCAR3 及 SKOV3 细胞的增殖及迁移能力；Western blot 结果显示，与癌旁组相比，卵巢癌组 PIWIL1、PIWIL2、PIWIL3、PIWIL4 的表达下调（P<0.05）；qRT-PCR 检测显示，与癌旁组相比，卵巢癌组上述 9 个 piRNA 表达水平下调（P<0.05）。Western blot 结果显示给药干预后两株卵巢癌细胞中 PIWIL1、PIWIL2、PIWIL3、PIWIL4 的表达下调（P<0.05）；qRT-PCR 检测给药干预后两株卵巢癌细胞中上述 9 个 piRNA 表达水平下调（P<0.05）。结论 绞股蓝皂苷 L 可抑制卵巢癌细胞增殖与迁移，其作用机制可能与 PIWI/piRNA 通路有关。

关键字： 绞股蓝皂苷 L；卵巢癌；PIWI 蛋白；piRNA

212. HNF4α在肝癌进展过程中的作用

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肝癌是全球癌症死亡的第二大原因， 80%以上的肝细胞癌发生于肝纤维化或肝硬变，提示肝纤维化在肝脏癌前环境中起重要作用。肝细胞核因子 4a（Hepatocyte nuclear factor 4 α ,HNF4a）属于肝细胞核因子（HNF）家族，在多种方面都是一种独特的核受体。HNF4 α 在多种内胚层来源的组织中都有表达，但最为人熟知的是它在肝脏内稳态和功能中的核心作用，它不仅是肝脏器官发生的主要调节因子，也是肝脏中的肿瘤抑制因子。

HNF4 α 的功能变化是反映肝病进展的重要参数，其表达和功能的丧失与慢性肝病的进展相关。随着肝病从脂肪变性到非酒精性脂肪性肝炎到肝纤维化、再到肝硬变，HNF4 α 的功能逐渐下降，最终导致肝细胞癌（Hepatocellular Carcinoma，HCC）。众所周知，HNF4a 在调节肝脏谱系分化和维持肝功能方面发挥着不可或缺的作用。在正常肝脏中，HNF4 α 在调节分化的同时，抑制与增殖相关的促有丝分裂基因的表达来维持成人正常的肝功能。在肝纤维化中，坏死的肝细胞释放损伤相关模式分子（Damage-associated molecular patterns，DAMPs）与 Kuffer 细胞表面受体结合，从而激活 Kuffer 细胞释放细胞因子，导致 HNF4a 的表达水平下降。HNF4a 的下调导致与细胞增殖和细胞周期进程有关的基因上调，如 Ki-67、细胞周期蛋白(A2、B1、B2)、Egr1、Ect2 和 c-MYC 等，促进了肝细胞增殖，抑制了肝细胞恢复正常功能，最终导致癌症。HNF4 α 的缺失还可引起显著的肝癌进展，如肿瘤大小和数量增加，肝脏与体重比增加一倍。人肝癌标本中 HNF4 α 的表达显著降低，容易导致疾病预后不良。

HNF4 α 在 HCC 中充当肿瘤抑制因子，它在 HCC 中的高表达可能意味着更好的预后，对未来治疗 HCC 是个潜在的靶点。

关键字 ： HNF4 α 、肝癌、肝纤维化

213. BTF3 Potentiates the Malignancy of Esophageal Squamous Cell Carcinoma via Modulating Snail

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Background: Esophageal cancer(EC) was one of the most common malignancies with a high mortality. Basic transcription factor 3 (BTF3) participating in the development of many kinds of tumors. However, the role and mechanism of BTF3 in esophageal squamous cell carcinoma (ESCC), which was the main prevalent histological type of EC in east Asian, are far from clear. This study aimed to analyze the expression of BTF3 and investigate the mechanism as well as the impact of BTF3 expression on clinical prognosis in ESCC.

Methods: Immunohistochemistry (IHC) was used to examine the expression of BTF3 in clinical samples. QRT-PCR was performed to detect the expression of BTF3 in ESCC cell lines. Expression of BTF3 and EMT related proteins were detected by western blot. Meanwhile, cell proliferation, colony formation and transwell were performed after shBTF3 lentivirus or Snail overexpression lentivirus transfected into ESCC cells. Furthermore, to constructed the xenografted mice model, KYSE150 cells which infected with shBTF3 lentivirus were subcutaneously injected into nude mice.

Results: It was discovered that BTF3 is overexpressed in ESCC samples and is an independent risk factor for overall survival of ESCC. Silencing of BTF3 can lead to the marked suppression of cell proliferation, migration and invasion of ESCC cells. Mechanistically, EMT progression was repressed when BTF3 was knocked down, and up-regulation of Snail can partially rescue the effect of BTF3 silencing. The xenografted mice model also proved the significantly decrease in BTF3 and Snail expression in the tumor tissue after BTF3 silencing.

Conclusions: BTF3 can serve as a potential predictive biomarker for prognosis of ESCC and provide novel insights into the regulation of BTF3 as an oncogenic transcription factor in ESCC.

Key Words ： Esophageal squamous cell carcinoma, BTF3, EMT, Snail, Prognosis

214. 肝癌标志物 AFP 在肝再生中临床价值研究

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目的：甲胎蛋白（alpha-fetoprotein，AFP）作为肝细胞癌诊断和预后的标志物，在不少肝衰竭患者中水平较高，随着病情好转，AFP 水平逐渐下降，这在一定程度上提示 AFP 的肝脏修复及再生标志作用。本文探讨 AFP 在肝再生中的临床价值。

方法： 纳入 2012 年 3 月至 2023 年 5 月期间入住西部战区总医院消化内科的乙肝相关慢加急性肝衰竭（hepatitis B virus- related acute - on - chronic liver failure, HBV - ACLF）患者。记录一般人口统计学资料及临床指标。采用 CTP、MELD 和 CLIF 系列等评分系统判断患者病情。随访时间为发生 ACLF 后 28 天、90 天，随访终点为死亡或接受肝移植。

结果：1. 在 2012 年 3 月至 2015 年 12 月期间入住我院的 92 例 HBV - ACLF 患者的 180 天内总存活率为 43.48%，年龄(HR 1.041)、TBil (HR 1.004)、log10AFP (HR 2.155)和 INR(HR 1.446)是这些患者生存的危险因素，且 log10AFP ≥ 2.04 的 HBV - ACLF 患者预后较好（特异度为 76.9%，敏感度为 62.5%）。建立了预后模型 TACIA 评分= 0.028 × 年龄(岁) + 0.003 × 总胆红素(μ mol/L) + 0.004 × 肌酐(μ mol/L) - 0.071 × 白蛋白(g/L) + 0.089× 中性粒细胞计数(×109/L) + 0.363 × INR - 0.001 × 甲胎蛋白(ng/mL)。该模型预测患者 90 天预后的 ROC 曲线下面积（AUROC）在建模组和测试组中分别为 0.822 和 0.842，该评分较低(< 4.34)的患者生存时间较长(P < 0.001)，能有效地预测 HBV - ACLF 患者的短期生存。

2. 在 2015 年 1 月至 2017 年 12 月期间，HBV-ACLF 患者人工肝术后 30 天(P = 0.01)、90 天 (P = 0.04)、180 天(P = 0.03)高 AFP 组（≥ 110 ng/mL）患者生存时间显著高于低 AFP 组（＜110 ng/mL），由此建立包含 AFP 的改良 iMELD 评分模型即 iMELD-AFP 评分模型。该模型预测 180 天生存情况的 ROC 曲线下面积为 0.989，高于单一 AFP 水平（0.64）、MELD（0.727）、MELD-Na（0.725）、iMELD（0.745）评分模型。

3. 在 2012 年 3 月至 2017 年 7 月期间入住我院的晚期 ACLF 患者中，4 周生存组年龄较小（P＜0.001）、血清 AFP（P=0.039）和 ALT（P=0.040）水平较高。

4. 在 2015 年 1 月到 2023 年 5 月入院一周内 MELD 评分恶化的 HBV-ACLF 患者 90 天生存组的基线 AFP 值 63.52(12.98,174.02)较死亡组 AFP 值 11.39（3.93，27.10）高。

结论：1. AFP 是 HBV-ACLF 短期预后的独立影响因素，AFP 水平较高的患者其不良结局发生率更低。HBV-ACLF 的预后评估模型（TACIA 评分）稳健性及预测效能较好，有利于为患者提供更有效的治疗策略，优化患者的临床管理。

2. 血清 AFP 水平可作为 HBV-ACLF 患者人工肝血浆置换治疗后生存情况的初步预测因子。iMELD-AFP 评分模型能有效预测患者人工肝血浆置换治疗后的生存情况。

3. 晚期 ACLF 患者中，血清 AFP 和 ALT 水平较高、年龄较小的患者的肝脏再生能力强，经有效的内科治疗后，病情有望逆转。

4. AFP 是预测早期 MELD 评分恶化 ACLF 患者预后的有价值指标。

5. 肝癌标记物 AFP 可作为 HBV-ACLF 患者肝脏再生的血清标志物，是 ACLF 患者良好生存预后的重要指标。

关键字 ：肝癌标志物、甲胎蛋白、肝再生

215. Causal Association Between Modifiable Risk Factors and Esophageal Cancer: A Mendelian Randomization Study

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Bcakground: Esophageal cancer (ESCA), recognized for its aggressive nature, ranks as the sixth leading cause of cancer-associated mortality globally. The incidence of ESCA has been suggested to link with lifestyle, obesity, and glycemic traits; however, the causality of this association re-mains uncertain. Consequently, our study aims to elucidate the causal connections between modi-fiable risk factors and ESCA.

Method: We adopted single nucleotide polymorphisms (SNPs) as genetic instrumental variables and conducted a two-sample Mendelian randomization (MR) analysis to estimate the causal in-fluence of 14 amendable risk factors on ESCA, incorporating 740 cases and 372,016 controls.

Results: The data revealed a significant association of coffee intake (OR=1.003, P=0.046), smoking (OR=1.008, P=0.001), and Body Mass Index (BMI) (OR=1.001, P=0.002) with an increased risk of ESCA. Conversely, type 2 diabetes (OR=0.999, P=0.003), education duration (OR=0.999, P=0.012), and Low-Density Lipoprotein Cholesterol (LDL-C) (OR=0.999, P=0.011) were correlated with a reduced risk of ESCA.

Conclusions: Our findings suggest that coffee intake, smoking, and BMI potentially contribute as risk factors in the pathogenesis of ESCA, whereas type 2 diabetes, duration of education, and LDL-C may function as protective elements against the development of this malignancy.

Key Words： ESCA、Mendelian Randomization、Modifiable Risk Factors.

216. 母细胞性浆细胞样树突细胞肿瘤 1 例临床病理学分析

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目的：探讨母细胞性浆细胞样树突细胞肿瘤 (BPDCN) 的临床病理学特点及免疫表型。

方法：选取郑州大学第一附属医院 1 例老年男性患者的临床病理资料，结合文献讨论该疾病的临床表现、组织学形态、免疫表型以及预后。

结果：患者男，70 岁，因“头部肿块 1 月余，全身暗红色丘疹结节半月”入院。体格检查显示枕部可见一鹌鹑蛋大小红色肿块，表面光滑，边界不清，无压痛。额部、前胸、后背、双下肢对称密集分布暗红色丘疹、结节，黄豆至花生米大小，边界清楚，表面光滑，无破溃。组织学上，真皮层见大量中等大小的类似淋巴母细胞或髓母细胞的母细胞弥漫性浸润，与表皮有一定的距离并浸润皮下脂肪，肿瘤细胞胞质少，嗜碱性，无颗粒。细胞核形不规则，染色质细腻，可见一至数个小核仁。核分裂象容易看到，很少有血管侵犯和凝固性坏死。骨髓流式提示肿瘤侵犯骨髓。免疫表型上，CD4、CD123、CD56 阳性，不表达 B 系、 T 系淋巴细胞及髓系标志物，，Ki-67 阳性指数约 90%。随后患者积极化疗，确诊后 6 月，患者死亡。

结论：BPDCN 是一种来源于 PDC 前体细胞的血液系统恶性肿瘤，具有高度侵袭性、预后差、易累犯皮肤的特点，BPDCN 的发病率极低，在血液恶性肿瘤中约占 0.44%，在皮

肤造血系统肿瘤中约占 0.7%，主要发生于老年男性病人，可累及全身多个部位。其诊断需结合临床表现、组织学形态及免疫表型综合分析。

关键字： 母细胞性浆细胞样树突细胞肿瘤 临床病理 免疫 预后

217. PSMA 在食管鳞状细胞癌中的表达及意义

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目的：探讨 PSMA 在食管鳞状细胞癌中的表达及对微血管密度标记的意义，并分析其与临床病理学特征及预后的相关性。

方法：采用免疫组化 EnVision 法检测 60 例食管鳞状细胞癌中 PSMA 的表达情况，整理临床相关信息，分析 PSMA 与临床病理特征及预后的相关性。

结果：2/3 病例的肿瘤组织中新生的血管表达 PSMA，在食管组织的正常血管内皮未见其表达，肿瘤细胞未见 PSMA 表达；PSMA 标记的微血管密度平均值为 30，其在肿瘤组织及正常对照组织中的表达差异有统计学意义($P< 0.05$)；PSMA 标记的微血管密度与食管鳞状细胞癌病理分级($P< 0.05$)和淋巴结转移($P< 0.05$)相关，与患者的预后呈正相关($P< 0.05$)。

结论： PSMA 高表达于食管鳞状细胞癌血管内皮，且与病理分级、淋巴结转移显著相关，提示 PSMA 可能作为食管鳞状细胞癌血管靶向治疗的新靶点，为 PSMA 用于食管鳞状细胞癌的靶向治疗提供理论依据。

关键字： PSMA，食管鳞状细胞癌，微血管密度

218. 生物信息学分析 CD36 在肝细胞癌中的表达及临床意义

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目的：肝细胞癌在中国乃至世界有较高的发病率与死亡率，且一线常规疗法的疗效较差，而免疫疗法在肝细胞癌患者中的疗效又会因为肝组织自身的免疫抑制作用而减弱甚至无效。

CD36 因其在各类肿瘤类型中观察到的多种功能，被认为是癌症的潜在生物标志物和治疗靶点，但其在肝细胞癌中作为预后生物标志物的可能性尚未得到确认。

方法：在以 TCGA、IMMUcan scDB 等多个公开生物数据库中评估 CD36 的表达及其临床特征与生存情况的相关性，通过 Timer2.0 以不同的免疫浸润评分算法评估样本免疫浸润程度，探索肝细胞癌中 CD36 与免疫浸润及肿瘤相关免疫细胞的基因标志物之间的关联。

结果：我们发现 CD36 主要分布在内皮与髓系细胞中，且相对正常组织，肝细胞癌组织中的 CD36 表达水平更高，同时男性群体中较高的 CD36 表达与不良预后和总生存期缩短有关。进一步研究发现，CD36 的表达水平上调会通过阻止巨噬细胞的 M1 型转化，降低 T 细胞及 NK 细胞的表达，提高 Tregs 活性等途径影响肝细胞癌的肿瘤微环境。

结论：研究表明，CD36 的肝组织高水平表达对肝细胞癌预后的不良影响与其免疫浸润水平有关，CD36 通过对多种免疫相关细胞的表达调控影响肿瘤免疫微环境，最终使其向免疫抑制的方向发展。以上发现提示了 CD36 作为肝细胞癌预后生物标志物的潜力，也为后续找寻提高肝细胞癌免疫治疗疗效的靶点相关研究提供参考。

关键字： 肝细胞癌，CD36，预后，肿瘤微环境，生物标志物

219. Microbial Interaction Patterns and Macrophage Ferroptosis Implicated Tumor Microenvironment and Prognosis in Gastric Cancer

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Background: The interplay between gastric microbiota and the tumor microenvironment is increasingly recognized as a critical factor in gastric cancer (GC) progression. This study aims to elucidate the role of microbial interaction patterns in inducing macrophage ferroptosis, which subsequently alters the GC microenvironment and influences patient prognosis.

Methods: We performed a comparative analysis of microbial expression profiles in cancerous and adjacent non-cancerous tissues from GC patients. Utilizing bioinformatic tools, we constructed an interaction network to identify microbial disturbance patterns. Microbial disturbance patterns

analysis was conducted to identify genes influenced by microbial interactions, termed microbiome-mediated genes. Single-cell data analysis further localized these genes to macrophages, confirming their role as microbiome-mediated macrophage genes. A gene perturbation network was then established, stratifying GC into four subtypes (C1, C2, C3, and C4) based on these genes. Prognostic analysis revealed that C1 had the best prognosis, while C3 had the worst. To explore the underlying reasons for these prognostic outcomes, we conducted comprehensive analyses at the genomic (copy number variations and somatic mutations), transcriptomic, and drug sensitivity levels. Ten machine learning (ML) methods with 110 algorithms analysis were utilized to calculate the microbial-related prognostic signature.

Results: Patients which in C3 subtype had shorter survival times compared to those which in C1 subtype. The C3 subtype patients showed activation of the KRAS signature and G2M checkpoint pathway, while these pathways were suppressed in C1 subtype patients. The C3 subtype patients exhibited more copy number gains and losses, whereas the C1 subtype patients had more gene mutations associated with DNA repair. Our findings indicate that microbial disturbance patterns in the C3 subtype are associated with an increased expression of macrophage ferroptosis driver GABARAPL1, leading to a significant alteration in the immune microenvironment of GC. This change was found to be a key determinant of patient prognosis. Additionally, by applying ten machine learning models to the differential genes between C1 and C3 subtypes, we developed a microbial-related prognostic risk score that effectively predicts the survival outcomes of GC patients. Notably, the low-risk patients showed better responses to immunotherapy.

Conclusion: This study provides a novel perspective on the impact of gastric microbiota on macrophage ferroptosis and its subsequent effects on the tumor microenvironment and patient prognosis. The identification of microbial interaction patterns and their prognostic implications offers potential targets for therapeutic intervention and personalized treatment strategies in GC.

Key Words ： gastric cancer, microbiota, macrophage ferroptosis, tumor microenvironment, prognostic biomarkers

220. 肿瘤相关成纤维细胞的自噬通量与多发性骨髓瘤血管生成的关系及机制

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目的：多发性骨髓（MM）第二大常见的血液系统恶性肿瘤，其疾病的进展与血管生成密切相关。研究表明肿瘤微环境中的肿瘤相关成纤维细胞（CAF）与肿瘤的增殖、迁移、侵袭以及耐药密切相关。在前期研究的基础上，我们以 CAF 的自噬为切入点，进一步研究体内外条件下，抑制或激活 CAF 自噬与 MM 血管生成的关系及其可能机制，为临床通过阻断血管形成，进而治疗肿瘤提供新的理论依据。

材料与方法：1. 通过 Ficoll 密度梯度离心法从 MM 组织标本中分离、培养并鉴定 CAF；从营养不良性贫血患者骨髓活检组织标本中分离、培养并鉴定正常成纤维细胞（NF）；通过 Western blot、免疫荧光检测 CAF 标志蛋白α-SMA、FAP、FSP、Vimentin，对分离的 CAF 进行鉴定。2. 通过 Western blot、GFP-RFP-LC3 斑点化实验以及吖啶橙染色等实验方法，检测 NF 和 CAF 的自噬通量差异。3. 体外使用骨髓瘤上清诱导人脐静脉内皮细胞（HUVEC）为肿瘤相关内皮细胞（MMEC），并对其标志物以及增殖、迁移、侵袭、成管能力进行检测。4. 使用 3-甲基腺嘌呤或雷帕霉素，抑制或激活 CAF 的自噬，Western blot 检测各组 LC3B、Beclin1、BNIP3 及 CTSB 的表达；并收集 CAF 上清作为条件培养基培养 MMEC，鬼比环肽染色观察各组 MMEC 的细胞骨架以及侵袭性伪足的形态和数量；通过 CCK8 增殖实验、Transwell 侵袭实验、划痕实验、小管形成实验观察 CAF 上清对各组 MMEC 的增殖、迁移和成管能力的影响。4.Western blot 检测各组细胞中 AMPK 、p-AMPK、mTOR、p-mTOR、HIF-1α、VEGF-A 的表达。5.分组构建裸鼠 MM 移植瘤模型，应用免疫组织化学方法检测各组 MM 移植瘤组织中 CD34，标记血管内皮细胞，计算 MVD 值，观察 CAF 自噬体内对移植瘤血管形成的影响；通过 Western blot 检测移植瘤模型中 AMPK、p-AMPK、mTOR、p-mTOR、HIF-1α、VEGF-A 的表达 。

结果：1. MM 患者样本中的 CAF 比正常人 NF 的自噬通量更高，且 CAF 的高水平自噬可增强 MMEC 的增殖、迁移、侵袭和成管能力。2. 激活 CAF 自噬可进一步促进 MMEC 增殖、迁移、侵袭和成管能力；抑制 CAFs 自噬可降低 MMEC 增殖、迁移、侵袭和成管能力。3. 自噬通路的激活或抑制，会调控 HIF-1α、VEGFA 的表达。4. 体内激活 CAF 自噬可促进

裸鼠 MM 移植瘤组织中的血管生成加速肿瘤生长，而抑制 CAF 自噬可减少裸鼠 MM 移植瘤组织中的血管生成延缓肿瘤生长。

结论：1. 骨髓瘤相关成纤维细胞有更高的自噬通量，其高通量自噬可促进多发性骨髓瘤的血管生成。2. 激活骨髓瘤相关成纤维细胞的自噬可进一步促进骨髓瘤血管生成及肿瘤进展；抑制骨髓瘤相关成纤维细胞的自噬可减少骨髓瘤血管生成，延缓肿瘤进展。

关键字： 自噬、多发性骨髓、肿瘤相关成纤维细胞、血管生成、肿瘤微环境

221. HnRNPR-Mediated UPF3B mRNA Splicing Drives Hepatocellular Carcinoma Metastasis (Academic Poster)

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Introduction: Abnormal alternative splicing (AS) contributes to aggressive intrahepatic invasion and metastatic spread, leading to the high lethality of hepatocellular carcinoma (HCC).

Objectives: This study aims to investigate the functional implications of UPF3B-S (a truncated oncogenic splice variant) in HCC metastasis.

Methods: Basescope assay was performed to analyze the expression of UPF3B-S mRNA in tissues and cells. RNA immunoprecipitation, and in vitro and in vivo models were used to explore the role of UPF3B-S and the underlying mechanisms.

Results: We show that splicing factor HnRNPR binds to the pre-mRNA of UPF3B via its RRM2 domain to generate an exon 8 exclusion truncated splice variant UPF3B-S. High expression of UPF3B-S is correlated with tumor metastasis and unfavorable overall survival in patients with HCC. The knockdown of UPF3B-S markedly suppresses the invasive and migratory capacities of HCC cells in vitro and in vivo. Mechanistically, UPF3B-S protein targets the 3'-UTR of CDH1 mRNA to enhance the degradation of CDH1 mRNA, which results in the downregulation of E-cadherin and the activation of epithelial–mesenchymal transition. Overexpression of UPF3B-S enhances the dephosphorylation of LATS1 and the nuclear accumulation of YAP1 to trigger the Hippo signaling pathway.

Conclusion: Our findings suggest that HnRNPR-induced UPF3B-S promotes HCC invasion and metastasis by exhausting CDH1 mRNA and modulating YAP1-Hippo signaling. UPF3B-S could potentially serve as a promising biomarker for the clinical management of invasive HCC.

Key Words： Alternative Splicing; Hepatocellular Carcinoma; Invasion and Metastasis; UPF3B-S; HnRNPR.

222. 婴儿孤立性肥大细胞瘤 1 例

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目的：探讨婴儿孤立性肥大细胞瘤的临床病理特征及免疫表型。

方法：选取郑州大学第一附属医院 1 例足底肥大细胞瘤患儿的临床病理资料，结合文献讨论该疾病的临床表现、组织学形态、免疫表型以及预后。

结果：患儿男，4 月，出生 10 天家人无意中发现足底一小米大小肿物，后肿物逐渐增大，直径约 0.6cm，隆起于皮面，质韧，灰红色，内可见血丝并表面结痂，触之不痛，Darier 征阴性。随后对患儿进行了肿物切除术。组织学上，表皮萎缩变薄，鳞状上皮板层状角化过度及角化不全，真皮浅层可见大量巢团样分布的肥大细胞浸润生长，细胞异型性小，呈圆形，中等大小，胞浆丰富透亮或弱嗜碱性，细胞核略呈空泡状，核仁不明显，核分裂像罕见。免疫表型上，CD117、LCA、P16 阳性，CK、S-100、HMB45、Melan-A、CD163、ALK、CD30、CD3、CD20、CD207、MPO、CD1a 阴性，Ki-67 阳性指数约 10%。术后 2 个月回访，患儿后足底皮损恢复良好，未复发，未行药物治疗。

结论：肥大细胞增生症是一种异质性疾病，表现为肥大细胞数量的增加以及在某些器官的异常集聚，依据第 5 版 WHO 皮肤肿瘤分类可分为皮肤性肥大细胞增生症、全身性肥大细胞增生症及肥大细胞肉瘤。皮肤型肥大细胞增多症又分为色素性荨麻疹 、弥漫性皮肤型肥大细胞增生症、皮肤肥大细胞瘤三种亚型。当患者仅表现为单处皮肤损伤而没有系统性病变时称为孤立性肥大细胞瘤。肥大细胞增生症被美国国立卫生研究院罕见病办公室列为“罕见病”，肥大细胞瘤大约占所有皮肤肥大细胞增生症的 10%～15%，故更为罕见。肥大细胞瘤常发生在出生 3 个月内婴幼儿的肢体末端。在本病例中，患儿仅表现为足底无痛性肿物而无其他特定的临床表现，因此组织病理学诊断的作用十分必要。临床实践中对于婴幼儿四肢末

端的单发红褐色肿物，应考虑皮肤肥大细胞增生症的可能性，同时积极完善组织病理学及免疫组化检查，早期诊断，早期治疗。

关键字： 婴儿孤立性肥大细胞瘤 免疫表型

223. BMP4 通过外分泌途径促进胰腺癌肝转移的作用与机制研究

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研究目的：胰腺癌是恶性程度极高的消化系统肿瘤，因其恶性高、进展快和高转移的特点，患者的治疗效果与预后生存往往不理想。而造成这一事件结局的主要原因，是胰腺癌转移特性决定的。肝由于其特殊的解剖位置，毗邻胰腺，成为胰腺癌转移的首要脏器。故而在胰腺癌整体发展进程中，针对其肝转移环节，进行有效的干预或阻断，成为近年来研究的热点。基于“肿瘤微环境”这一概念的提出与近年来相关研究的补充完善，本研究意在寻找出促进胰腺癌肝转移前微环境形成因素并进行干预，为减缓胰腺癌肝转移的发生发展提供新手段。

研究方法：通过比对胰腺癌患者资料与血液样本，发现 BMP4 与胰腺癌的进展分期和患者预后生存相关。细胞实验表明，BMP4 可刺激促进肝脏星状细胞的活化，敲除/过表达胰腺癌细胞中的 BMP4 基因，可减轻/增加胰腺癌细胞自身的侵袭能力。动物实验表明，拮抗 BMP4 作用靶点，可通过改变胰腺癌肿瘤的微环境减少胰腺癌肝转移的发生。通过对胰腺癌小鼠的肝转移灶组织进行转录组测序技术，发现 BMP4 或通过作用于血小板衍生生长因子受体活化肝脏中星状细胞向肝周细胞转化，来促进胰腺癌肝转移前的微环境形成，从而促进胰腺癌细胞的肝脏转移。

研究结果：首先，我们在体外细胞实验，通过在人肝形状细胞中加入梯度浓度的 BMP4 重组蛋白细胞因子与 BMP4 受体结合抑制剂处理 24 小时，选取出适宜的刺激浓度。我们在体外设置 4 个处理组别，发现 BMP4 可以促进肝星状细胞的活化。接下来我们进行动物实验，通过经脾静脉注射方式构建小鼠肝转移模型，将小鼠分为三种不同的处理组，分别为：空白对照组、低剂量和高剂量。经过 3-4 周的处理，探查不同处理组小鼠肝脏中胰腺癌转移灶的数目与面积范围是否发生变化。结果所示，小鼠肝脏中的胰腺肿瘤的癌灶面积与抑制剂量呈负相关。最后，我们将每组小鼠的胰腺癌肝转移组织进行 RNA-seq 测序，测序数据分

析结果提示发现周细胞这一细胞群的变化。综上所述，我们发现了 BMP4 通过改变血管内皮，促使肝星状细胞向肝周细胞转化，增加肿瘤的血管侵袭能力，最终形成胰腺癌肝转移。

研究结论：本研究证实胰腺癌来源的 BMP4 通过外分泌途径影响肝周细胞的活化与聚集，从而促进胰腺癌肝转移这一进程的发展，为将来胰腺癌肝转移途径的干预手段，增加新的理论依据。

关键字： 胰腺癌肝转移；骨形态发生蛋白 4；肿瘤迁移与侵袭；肿瘤相关成纤维细胞；肝周细胞

224. 糠酸莫米松通过 PTPN11 调控头颈鳞癌进展的初步研究

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目的：通过体内外实验探究糠酸莫米松 (Mometasone furoate, MF) 对头颈鳞癌 (head and neck squamous cell carcinoma, HNSCC) 细胞增殖及凋亡的影响，并探究内在机制，为其成为治疗 HNSCC 有效化疗药物奠定基础。

材料与方法：使用不同浓度 MF 处理 CAL-27 细胞，在体外通过 CCK-8、克隆、流式细胞术检测 MF 对细胞增殖和凋亡的影响；体内通过异种移植瘤研究 MF 对肿瘤生成的影响。随后，使用 Pharmmapper, GeneCards 和 CTD 网站预测 MF 作用于 HNSCC 潜在靶点，并针对潜在靶点进行 KEGG 富集分析。通过 Cytoscape3.7.1 软件进行两步拓扑结构分析，得到 MF 作用于 HNSCC 的关键靶点。最后利用癌症基因组图谱 (The Cancer Genome Atlas, TCGA) 数据库分析，RT-PCR 分析和分子对接筛选 MF 最佳潜在靶点。

结果：MF 处理细胞后，CCK-8 和克隆实验结果表明 CAL-27 细胞增殖能力呈浓度依赖性减弱；流式细胞术分析可见 MF 处理后细胞周期阻滞于 S 期并且细胞凋亡率明显增加，同时体内异种移植瘤模型也表明 MF 处理后抑制了 HNSCC 进展。Pharmmapper，CTD 和 Genecards 网站预测交集共得到 168 个潜在靶点，KEGG 富集共 27 个潜在靶点富集在 Proteoglycans in cancer 通路；两步拓扑结构分析得到 10 个核心潜在靶点。最后利用 TCGA，RT-PCR 结果及分子对接表明，PTPN11 为 MF 最佳潜在靶点。

结论：MF 能够靶向 PTPN11 以促进细胞周期阻滞和细胞凋亡，进而抑制 HNSCC 的进展，提示其可能是临床 HNSCC 治疗的新型候选药物。

关键字： 头颈鳞癌，糠酸莫米松，细胞周期，细胞凋亡，药物靶点

225. H.pylori 感染相关性胃癌组织中炎症小体 NLRP3 表达与临床预后

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摘要：目的 探讨幽门螺杆菌（H.pylori）感染相关性胃癌组织中炎症小体的表达与临床预后的相关性。

方法： 运用 TCGA 及 GEO 公共数据库分析胃癌患者高通量基因测序及 RNA-seq 表达数据和临床信息资料，TIMER、UALCAN 及 Kaplan-Meier Plotter 数据库分别分析 NLRP3 mRNA 在各种肿瘤和正常组织中的差异表达、H.pylori 感染对胃癌基因表达的差异及胃癌患者 NLRP3 表达水平与临床生存预后的相关性。收集临床胃癌组织进行快速尿素酶试验检测是否感染 H.pylori，免疫组织化学（IHC）分析临床胃癌组织中 H.pylori 感染对 NLRP3 表达的影响。结果 TCGA 数据中显示 NLRP3 在胃癌及癌旁组织间表达有显著性差异，胃癌组织中表达升高（P＜0.05）；同时发现 H.pylori 感染的胃癌组织中 NLRP3 基因表达显著升高。NLRP3 mRNA 在肿瘤≥5 厘米、存在淋巴结转移、TNM 分期III/IV期、低分化或未分化患者癌组织中的相对表达水平显著高于肿瘤＜5 厘米、淋巴结未转移、TNM 分期I/II期、高分化、中分化患者，且 NLRP3 mRNA 在中分化患者中的表达水平也显著高于高分化患者（P＜0.05）。临床生存预后分析显示 NLRP3 高表达患者 10 年生存率降低（P =0.037）；结合临床收集的胃癌病例随访信息进行生存曲线分析，肿瘤大小，淋巴结转移，侵袭与远端转移与 NLRP3 高表达均为胃癌患者死亡高风险因素；在不同胃癌类型中，高表达的 NLRP3 跟年龄因素相仿，均预示着较短的生存周期（Long-Rank P＜0.01）。免疫组化分析显示 H.pylori 感染的胃癌组织中 NLRP3 表达量明显增高；根据 H.pylori 感染情况分组，H.pylori 感染阳性的胃癌组织中 NLRP3 表达情况较阴性者明显增高。

结论： H.pylori 感染可促进胃癌组织中 NLRP3 基因表达升高。NLRP3 高表达促进胃癌增殖，淋巴结转移、癌细胞低分化与 TNM 分期增高，直接导致胃癌患者预后不良，10 年生存率显著降低。

关键字： 胃癌，炎症小体，NLRP3，幽门螺杆菌，细胞焦亡，预后

226. PD-1/PD-L1 相关的免疫检查点抑制剂在结直肠癌治疗中的作用

常悦

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结直肠癌是消化系统中常见的恶性肿瘤，其发病率和死亡率分别位居常见恶性肿瘤的第 3 位和第 2 位，已成为癌症相关死亡的主要原因。多数患者确诊时已发展至中晚期，发生转移的人数较多，治疗和预后效果不佳。因此，积极研究其发病机制以及开展更为有效的治疗方式已经成为必须关注的问题。近年来许多研究证明，免疫微环境在肿瘤的发生发展中发挥了重要作用。肿瘤免疫微环境（TME）包括 T 细胞、B 细胞、肿瘤相关成纤维细胞(CAFs)、肿瘤相关巨噬细胞 (TAMs)等细胞以及它们所释放的相关因子等。其中，M2 型 TAMs 和 CAFs 是 TME 中具有免疫抑制功能的主要成分，有刺激血管生成的作用，还与免疫抑制、癌细胞的侵袭和转移有关。CAFs 还可诱导 M2 型 TAM 表达的程序性细胞死亡蛋白-1（PD-1）水平升高。PD-1 主要表达于免疫细胞上，与肿瘤细胞表面高表达的 PD-L1 结合后，抑制 T 细胞的激活和增殖，并诱导 T 细胞凋亡，实现免疫逃逸，在机体免疫耐受中起到重要作用。PD-1/PD-L1 信号通路是重要的免疫检查点，近年来，免疫治疗作为抗癌疗法的新热点，在结直肠癌的治疗上也取得了一定的成绩，PD-1 抑制剂通过阻断 PD-1 与 PD-L1 之间的结合增强抗肿瘤免疫应答，发挥抗肿瘤作用，例如帕博利珠单抗、纳武利尤单抗等。PD-1 抑制剂和 CTLA4 抑制剂的联合应用也明显提高了患者的免疫应答率和总生存期。PD-1 抑制剂与瑞戈非尼协同作用，还可以减少 TAMs 浸润，并调控 TAMs 向 M1 型 TAMs 极化，减少 M2 型 TAMs 的数量，有效抑制肠癌细胞的增殖，对抑癌起到重要作用。但 PD-1/PD-L1 抑制剂的疗效有限，对微卫星稳定和无 DNA 错配修复功能完整（pMMR）患者的治疗效果不佳，只适合微卫星高度不稳定性（MSI-H）和错配修复功能缺陷（dMMR）型的少数结直肠癌患

者。目前，抗 PD-1 治疗在淋巴瘤、黑色素瘤的治疗中效果良好，但是在结直肠癌患者中仍有局限性。因此，通过探索免疫微环境在肿瘤发展中的具体机制，探究结直肠癌患者免疫治疗抵抗的原因，提高 PD-1 抑制剂在结直肠癌患者中的治疗效果，或寻找新的免疫治疗靶点，来开发更多新的免疫治疗组合策略，为结直肠癌患者寻找到更精准的免疫治疗策略至关重要。

关键字 ： 结直肠癌　PD-1/PD-L1　免疫微环境　免疫治疗

227. Mitochondrial ribosomal protein S24 is associated with immunosuppressive microenvironment and cold tumor and serves a prognostic predictor in lung adenocarcinoma

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Objective: MRPS24 (Mitochondrial Ribosomal Protein S24) belongs to the mitochondrial ribosomal protein family, which participates in the protein synthesis of the mitochondrion. However, the relationship of MRPS24 with lung adenocarcinoma (LUAD) remained unknown. We aimed to identify its immunological and functional mechanisms in LUAD.

Methods: The analysis of MRPS24 expression, clinical features, diagnosis, prognosis, function analysis, genetic alteration, copy number variations, methylation, and tumor microenvironment was investigated by the TCGA, UCSC Xena, GEO, HPA, GEPIA, cBioPortal, MethSurv, TIMER, TIMER2.0, and TISIDB databases.

Results: MRPS24 was found to be more abundant in LUAD tumor tissue than in normal tissue. High levels of MRPS24 expression were found to be an independent prognostic factor by multivariate analysis. Functional analysis revealed that MRPS24 expression was associated with the immune, cell cycle and methylation. MRPS24 methylation level was inversely linked with its expression ($p < 0.001$). Patients with low MRPS24 methylation had a worse prognosis than those with high methylation ($p < 0.05$). In addition, the result revealed that the MRPS24 expression was inversely linked to the immune cell infiltration in LUAD. Finally, the validations of the expression

level, prognosis, and immune cell infiltration of MRPS24 were in accordance with our previous results.

Conclusions: This study systematically explored that MRPS24 expression was significantly correlated with prognosis, tumorigenesis, genetic alteration, copy number variations, methylation, and immune cell infiltration in LUAD. MRPS24 might be a potential immune-related biomarker in the development and treatment of LUAD, thereby acting as a promising predictor of immunotherapy response in LUAD.

Key Words ： MRPS24, Immunosuppressive microenvironment, Cold tumor, Lung adenocarcinoma, Copy number variations.

228. 基于集成机器学习构建肝细胞癌的 G2/M 检查点相关预后模型及机制研究

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背景:在细胞周期过程中，G2/M 检查点缺陷会增加双链断裂(DSBs)的可能性。在有丝分裂前发生的未修复的 DSB 会增加基因组不稳定和肿瘤细胞增殖的风险，从而影响 HCC 的肿瘤发生和进展。然而，它们在肝细胞癌(HCC)中的具体作用和潜在机制尚不清楚，需要进一步探索。本研究旨在构建 G2M 相关模型(G2MRS)来预测 HCC 的预后、肿瘤免疫微环境(TIME)和治疗反应。

方法:HCC 相关数据来源于三个平台:癌症基因组图谱(TCGA)、国际癌症基因组构建(ICGC)和基因表达 Omnibus (GEO)。从基因集富集分析中提取 G2M 相关基因(G2M)。在数据集中整合了 10 种机器学习算法和 167 种算法组合，建立 G2M 预后模型。利用 G2M 相关关键基因建立 G2MGS，并通过多变量 Cox 回归分析和 Kaplan-Meier 生存曲线进行评价。随后，通过福建省肿瘤医院(FCH) 64 例 HCC 患者样本的定量 PCR 验证了该特征。随后，进行功能富集分析、肿瘤体细胞突变分析、免疫检查点抑制剂(ICIs)应答和肿瘤免疫分析，以评估 G2MGS 相关基因标记(G2MGS)的潜在作用。

结果:116 个 G2Mg 被鉴定为差异基因, 151 个与 HCC 预后相关(均 $P < 0.05$)。使用 TCGA 队列，我们选择了三个基因来建立 G2MGS，发现 G2MGS 是 HCC 患者的独立危险因素。此外，我们在 ICGC 队列中验证了 G2MGS，并在来自 HCC 患者的 64 个样本和来自 FPH 的 26 个肿瘤癌旁组织中验证了其可靠性。此外，我们发现 G2MGS 与肿瘤免疫微环境特征和 ICIs 反应有关。此外，根据 IMvigor210、GSE140901 和 GSE109211 的数据，我们观察到与高 G2MGS 组相比，低 G2MGS 组的患者对索拉非尼有更多的应答($p < 0.05$)。高 G2Mgs 组与 ICIs 和分子靶向药物耐药显著相关，这可能是由于高 G2M 水平引起的铁死亡导致 Treg 上调。最后，我们建立了预后模型和 G2MGS 的列线图，与目前的分期系统和已发表的模型相比，该模型具有更好的区分和校准能力。

结论:G2MGS 可作为 HCC 的有效预测生物标志物，并可作为肿瘤免疫微环境和 ICIs 反应的潜在指标。

关键字：G2M, HCC，预后，治疗反应

229. 基于 E2F 相关基因的肝细胞癌预后模型构建 及治疗反应预测

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目的：E2F 转录因子靶向通路在肿瘤发生发展中起着重要作用。本研究旨在构建及验证预测性肝细胞癌（Hepatocellular Carcinoma，HCC）的 E2F 靶点预后模型，并挖掘其潜在机制，指导 HCC 患者的个体化治疗。

材料与方法：从癌症基因组图谱的（The Cancer Genome Atlas，TCGA）测序数据中筛选出在肿瘤和正常组织中差异表达并与预后相关的 E2F 相关基因（E2F-related Genes，E2FGs）。基于最小绝对收缩选择算子（Least Absolute Shrinkage and Selection Operator，LASSO）回归构建 E2F 相关基因模型（E2F Related Gene Signature，E2FRGS），根据 TCGA 队列中 E2FGS 评分的中位值将样本分为高评分组和低评分组，通过 Kaplan-Meier 生存曲线和受试者工作特征的曲线下面积（Area Under the Curve，AUC）评估 E2FGS 对总生存（Overall Survival，OS）的预测能力，并使用国际癌症基因组联盟（International Cancer Genome Consortium，ICGC）的 LIRI-JP 队列进行外部验证。在后续分析中，对 TCGA 队列中不同

E2FGS 评分组进行功能分析、突变分析、免疫治疗和分子靶向治疗疗效预测分析，并结合临床病理特征构建预测 HCC 患者的 OS 的列线图。

结果：从 TCGA 队列中筛选出 133 个预后相关差异表达 E2FGs，使用 LASSO 回归筛选出 3 个 E2FGs（CDCA8，KPNA2，NOP56）用于构建 E2FRGS。生存分析显示，高评分组的中位 OS 显著低于低评分组（P＜0.001），1、2、3 年的 AUC 值分别为 0.764、0.708 和 0.691，并且在 ICGC 外部验证队列中同样具有良好的预测价值。功能富集分析显示细胞周期、细胞衰老和 P53 信号通路在高评分组中显著富集，而免疫相关的 B 细胞受体、T 细胞受体和 TGF-β信号通路则在低评分组中显著富集。在高评分组中，PD-1、PD-L1 和 CTLA4 等免疫检查点基因高表达，TIDE 评分、免疫功能缺失评分和免疫排斥评分显著降低，在免疫检查点抑制剂治疗中的显著获益（均为 P<0.05）。药物敏感性分析说明低评分组对索拉非尼、舒尼替尼和替吡法尼的敏感性更高（均为 P＜0.05）。体细胞突变分析提示肿瘤突变负荷在高评分组中更高（P＜0.001）。与 AJCC 分期和多个已发表模型相比，结合 E2FRGS 评分和临床病理特征构建的列线图的预测效能更好。

结论：本研究建立了由 3 个 E2FGs 组成的 E2FRGS，可作为 HCC 预后的有效预测指标和分子靶向治疗及免疫治疗疗效的潜在预测指标。

关键字： 肝细胞癌，免疫，靶向药物，模型

230. CyclinB1 与泛素化相关蛋白在食管鳞状细胞癌的表达和意义

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目的：早期有丝分裂抑制剂 1（Emi1）介导蛋白的泛素化降解，Emi1 在许多恶性肿瘤中表达上调，其过表达导致有丝分裂缺陷，可能促使肿瘤的发生。泛素结合酶 10（UBCH10）又称泛素偶联酶 E2C（UBE2C），是细胞周期调控（细胞有丝分裂、纺锤体形成等）的重要调节器，UBCH10 在非小细胞肺癌、脑膜瘤、结肠癌、乳腺癌、骨肉瘤等肿瘤中高表达并且与肿瘤分期正相关。CyclinB1 是调控 G2 期的关键蛋白，对整个细胞周期的进程至关重要。有关 Emi1、UBCH10 和 CyclinB1 联合检测在 ESCC 中的表达及其与肿瘤增殖和凋亡的关系尚未见文献报道。本研究希望为提高 ESCC 治疗效果、改善预后提出新的依据。

方法：运用免疫组织化学方法、原位杂交技术检测 50 例正常食管黏膜组织和 50 例 ESCC 组织中 Emi1、UBCH10 及 CyclinB1 蛋白和 mRNA 表达，探讨蛋白表达与 ESCC 发生发展的关系。检测组织中 Ki-67 蛋白表达和凋亡水平，探讨 Emi1、UBCH10 及 CyclinB1 表达与 ESCC 增殖、凋亡的关系。

结果：Emi1、UBCH10 和 CyclinB1 mRNA 及蛋白在 ESCC 组织中高表达，在癌旁组织中低表达。其与肿瘤组织分级、淋巴结转移、病理分期有关，而与性别、年龄、肿瘤直径、浸润深度没有相关性。提示 Emi1、UBCH10 和 CyclinB1 是 ESCC 肿瘤进程中的重要参与者，能够影响肿瘤分化、淋巴结转移和病理分期。

Emi1、UBCH10、CyclinB1 蛋白及 mRNA 表达与增殖指数呈现明显的正相关性，伴随着 Emi1、UBCH10、CyclinB1 蛋白及 mRNA 高表达，肿瘤组织中细胞的增殖状态越活跃。Emi1、UBCH10、CyclinB1 蛋白及 mRNA 表达与凋亡指数呈现明显的负相关性，伴随着 Emi1、UBCH10、CyclinB1 蛋白及 mRNA 高表达，肿瘤组织中细胞的凋亡状态越弱。因此推测 Emi1、UBCH10、CyclinB1 蛋白及 mRNA 参与肿瘤的增殖和凋亡过程。

结论：Emi1、UBCH10 和 CyclinB1 在 ESCC 组织中高表达，与肿瘤组织分化、淋巴结转移和病理分期有相关性。Emi1、UBCH10 和 CyclinB1 协同促进 ESCC 的肿瘤增殖，抑制 ESCC 的肿瘤凋亡。

关键字： 食管鳞状细胞癌；Emi1；UBCH10；CyclinB1

231. 基于机器学习构建的肝细胞癌失巢凋亡相关预测模型及机制探索

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目的：失巢凋亡是一种程序性细胞死亡过程，其在肝细胞癌（Hepatocellular Carcinoma，HCC）的发生、侵袭、免疫逃逸和治疗抵抗中起重要作用。本文挖掘失巢凋亡在 HCC 中的潜在机制，并基于其相关生物学过程构建预后模型，用于指导 HCC 患者的个体化治疗。

材料与方法：从癌症基因组图谱的（The Cancer Genome Atlas，TCGA），国际癌症基因组联盟（International Cancer Genome Consortium，ICGC）以及基因表达综合数据库（Gene Expression Omnibus，GEO）获取 5 个 HCC 队列，通过单样本基因集富集分析量化失巢凋亡

活性水平，ErbB 受体信号活性以及 28 种免疫细胞的浸润程度，通过 GSEA 挖掘潜在通路并通过单细胞测序验证该生物学过程。通过整合了 10 种机器学习算法和 167 种算法组合开发出具有稳定而强大的性能的失巢凋亡联合 ErbB 受体信号相关基因模型 AERGS（Anoikis and ErbB Related Gene Signature），根据 TCGA 队列中 AERGS 评分的中位值将样本分为高低评分组，通过 Kaplan-Meier 生存曲线和受试者工作特征的曲线下面积评估 AERGS 对生存的预测能力，基于 4 个外部队列（ICGC，GSE144269,GSE14520,GSE116174）进行验证，并分析不同评分组的免疫和分子特征差异及对靶向免疫治疗疗效的价值。

结果：在 TCGA 队列中发现失巢凋亡高活性组的 ErbB 受体信号活性显著上调（P＜0.05），同时，当两者同时升高时，其 Treg 细胞浸润程度显著升高（P＜0.05），对此进行 GSEA 富集分析发现，Hedgehog(Hh)信号通路显著富集在失巢凋亡及 ErbB 信受体同时升高的样本组，以上结果在 4 个外部队列（ICGC，GSE144269，GSE14520，GSE116174）得到了验证（均为 P<0.05），基于此，我们推测失巢凋亡活性升高时，可能通过 ErbB 受体信号上调 Hh 信号通路活性，从而引起 Treg 细胞浸润，影响 HCC 的发生发展及预后，上述结果也在单细胞测序层面得到了验证。基于上述生物学过程，在 TCGA 队列中通过 LOOCV 框架拟合了 167 个预测模型，基于 5 个枢纽基因（CCT2，MARCKSL1，SLC2A1，ECT2，CDK4）构建的 AERGS 在所有队列中有最优的一致性指数（0.763）。多因素分析显示 AERGS 是总生存的独立风险因素，AERGS 也发现优于 73 个已发表的 HCC 相关预后模型。在高评分组中，TIDE 评分、免疫功能缺失和免疫排斥评分显著降低，在免疫检查点抑制剂治疗中的显著获益（均为 P＜0.05）。药物敏感性分析说明低评分组对索拉非尼、吉非替尼和达沙替尼的敏感性更高（均为 P＜0.05）。上述结果也在基于使用阿替利珠单抗治疗的 IMvigor210 队列和在接受索拉非尼治疗的 GSE109211 队列中得到验证。

结果：基于上述分析结果我们推测，失巢凋亡-ErbB 受体-Hh 信号通路-Tregs 可能是 HCC 发生发展的潜在机制，基于此构建的 AERGS 不仅是评估临床环境中 HCC 患者预后有希望的生物学标志，而且是为 HCC 患者量身定制临床决策的有力工具。

关键字： HCC,失巢凋亡，潜在机制，机器学习，单细胞

232. 基于孟德尔随机化挖掘肝细胞癌潜在治疗靶点

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目的：大多数肝细胞癌（Hepatocellular Carcinoma，HCC）由于起病隐匿，且进展迅速，确诊时已处于中晚期，在确诊时往往失去了根治性肝切除术的机会，需依赖靶向药物等系统治疗手段，目前肝癌针对已知 HCC 相关靶点的治疗响应率低，且相关靶向药物耐药机制不明。因此，亟需挖掘 HCC 新的潜在治疗靶点，用于指导临床治疗决策及个体化治疗。

材料和方法：从 IEU OpenGWAS project 官网下载 GWAS 数据集 ieu-b-4953，从 GWAS Catalog（Genome-Wide Association Study Catalog）下载 GWAS 数据集 GCST90092003、GCST90043858、GCST90041897。表达数量性状基因座（Expression quantitative trait loci，eQTLs）来源于 eQTLGen Consortium 数据库。将 eQTLs 当成工具变量，筛选具有显著（p<5.0×10-8）的人群中最小等位基因频率（Minor Allele Frequency，MAF）＞0.01 的 SNPs 作为工具变量，基于 SMR 软件（https://cnsgenomics.com/software/smr/#Overview）挖掘基因表达量与 HCC 结局之间的因果关系， P<0.05 认为有统计学意义。应用依赖工具的异质性检测方法（Heterogeneity in Dependent Instrument，HEIDI-outlier test）来检验观察到的基因表达与结果 HCC 之间的关联是否由于连锁平衡导致。

结果：在 4 个 GWAS 数据集中共鉴定出 11 个与 HCC 结局纯在因果关系的枢纽基因（均为 P＜0.05，HEIDI-outlier test＞0.05），分别为 PLCH2　RPS8，RPL31P11，LINC03063，TAPT1，UQCC2，ANP32B，DNAJB12，PIDD1，RPLP2，KLF13。孟德尔随机化研究使用遗传变异作为在暴露和结果之间进行因果推断的工具，其优势体现在混杂偏倚可以最小化，因为遗传变异在出生时被随机分配给个体。同样，反向因果关系是可以避免的，因为遗传变异是在疾病发展之前分配的。

结论： PLCH2 RPS8，RPL31P11，LINC03063，TAPT1，UQCC2，ANP32B，DNAJB12，PIDD1，RPLP2，KLF13 可能是 HCC 潜在治疗靶点，尚需进一步的研究来验证该结论。

关键字 ：HCC，孟德尔随机化，靶向药物

233. 基于机器学习探索的 EIF5A 通过 Hedgehog 通路上调肿瘤干细胞性介导的放疗抵抗的相关机制

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目的：放疗是直肠癌综合治疗中的重要一环，而现阶段直肠癌放疗整体疗效欠佳，易出现放疗抵抗。EIF5A 是促进 mRNA 在编码特定肽基序的序列处的翻译伸长的翻译起始因子，能通过刺激肽基-tRNA 的水解来协助翻译终止。EIF5A 的过表达与细胞迁移，侵袭和癌症转移有关，但其与直肠癌放射治疗耐受的相关性和机制仍有待探索。

方法：从 GEO 数据库中获取直肠癌放疗患者的基因表达数据(GSE145037、GSE150082、GSE35452，GSE68204 和 GSE87211)，使用 17 种机器学习方法（包括 glmBoost、Radon Forest、Ridge、LASSO、Enet、SVM、multiNom、plsRglm、RDA、LDA、amdai、GBM、KNN、XGBoost、Stepglm、NaiveBayes 和 LogisticR）对放疗敏感性队列进行模型构建，并通过 SHAP 算法筛选出放疗抵抗的核心基因 EIF5A。通过 GSVA 富集分析和 OCLR 算法探索肿瘤干细胞性及相关机制，并在单细胞队列（GSE132465、GSE166555 和 GSE178318）中进行验证。后续通过平板克隆、EdU 实验、细胞划痕愈合、Transwell 迁移和侵袭、流式检测细胞凋亡等实验评估直肠癌细胞增殖转移效应，使用并 Western Blot 检测肿瘤干细胞性及相关通路标志物的表达变化。

结果：使用 17 种不同的机器学习算法，以 ROC 的 AUC 值为效应评价指标，筛选出 ROC 最高的 4 个模型（glmBoost、Random Forest、Ridge 和 LASSO）,通过 SHAP 值筛选出 EIF5A 作为放疗抵抗的核心基因。转录组队列及单细胞列队分析显示，EIF5A 均在放疗抵抗组中显著增加（$P<0.05$），且高表达 EIF5A 的患者的预后较差。OCLR 算法提示放疗抵抗组的肿瘤干细胞性显著增加，并与 Hedgehog 通路活性的增加显著增加，且与 EIF5A 的表达量均为显著正相关（$P<0.05$）。后续通过 EdU 实验、细胞划痕愈合、Transwell 迁移和侵袭实验发现 EIF5A 显著增强直肠癌的迁移和侵袭作用，CCK-8、平板克隆、流式检测细胞凋亡等实验证实 EIF5A 显著增加直肠癌的放疗抵抗，并通过 Western Blot 发现 EIF5A 能够显著上调肿瘤干细胞标志物和 Hedgehog 通路标志蛋白。

结论：EIF5A 是预测放疗抵抗和预后的生物标志物，可能通过上调 Hedgehog 信号通路活性导致的肿瘤干细胞活性增加，从而导致直肠癌患者转移风险增加和对放射治疗耐受。

关键字： 放疗，直肠癌，机器学习，单细胞，体外实验

234. 外泌体 miR-181d-5p 介导 SPP1 蛋白调控 RhoA 信号通路促进结直肠侵袭转移 机制研究

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目的： 研究外泌体 miR-181d-5p 介导 SPP1 蛋白调控 RhoA 信号通路促进结直肠侵袭转移机制研究。

方法： 通过全基因测序及差异性基因表达结果，发现分泌型磷蛋白 1（SPP1）这一因子在细胞外基质通路和黏着斑通路中均存在显著性差异；生信分析和实验发现 miR-181d-5p 可调控 SPP1 表达影响 CRC 的转移，并通过双荧光素酶进行验证 。利用超速离心法和电子透镜进行外泌 体的制备及鉴定。 通过构建慢病毒敲低或过表达 miR-181d-5P 的 CRC 细胞系与裸鼠成瘤模型， 检测 miR-181d-5P 与 SPP1 在基因与蛋白水平的表达变化；利用 CCK-8 法、划痕实验、transwell 浸润及迁移实检测细胞增殖、侵袭、迁移能力的变化。

结果： 双荧光素酶 miR-181d-5P 与 SPP1 在 CRC 中的共表达分析差异具有统计学意义（P 均＜0.05）；qPCR 对正常组织及配对的癌组织分别检测 miR-181d-5P 的表达量，miR-181d-5P 在癌组织中表达高于正常，差异具有明显统计学意义 （P＜0.05）； qPCR 对 NCM460、SW620、SW480、HCT116、HT29 细胞分别检测 miR-181d-5P 的表达量，结果 miR-181d-5P 在高转移性 SW620 细胞表达高于其他细胞；SPP1 在 CRC 中高表达，在癌旁组织中低表达；SPP1 表达上调促进正常结肠上皮细胞迁移，下调 SPP1 表达抑制 CRC 细胞 迁移 ；裸鼠皮下成瘤实验结果显示，在 HT29 细胞中，与阴性对照组相比 LV-shRNA-SPP1 组肿瘤生长明显减慢，且差异具有统计学意义（P＜0.01）；。

结论 ： 外泌体 miR-181d-5P 靶向调控 SPP1 介导调控 Rho/ROCK 信号通路促进粘附反应增加肿瘤细胞的侵袭及转移能力。

关键词： 结、直肠肿瘤；细胞外基质；分泌型磷蛋白；外泌体

235. 基于机器学习探索直肠癌放疗抵抗靶点 AMD1 及相关作用机制

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背景：放疗是一种高选择性、非侵入式、高精准的治疗技术，已经应用于直肠癌全疾病周期的治疗，如何提高肿瘤对放疗的敏感性、提高放疗后患者产生有效的抗肿瘤免疫应答以及降低放射性损伤，是当前临床与基础医学研究的重点与难点。AMD1 是合成多胺精胺和亚精胺所需的关键酶。多胺是多种细胞过程所必需的，包括分化和细胞增殖，并且其水平受到严格调节。AMD1 的过表达与细胞迁移，侵袭和癌症转移有关，但其与直肠癌放射治疗耐受的相关性和机制仍有待探索。

方法：从 GEO 数据库中获取直肠癌放疗患者的基因表达数据(GSE145037、GSE150082、GSE35452、GSE68204、GSE56699、GSE93375 和 GSE87211)，使用 17 种机器学习方法（包括 glmBoost、Radon Forest、Ridge、LASSO、Enet、SVM、multiNom、plsRglm、RDA、LDA、amdai、GBM、KNN、XGBoost、Stepglm、NaiveBayes 和 LogisticR）对放疗敏感性队列进行模型构建，并通过 SHAP 算法筛选出放疗抵抗的核心基因 AMD1。通过 GSVA 富集分析和 OCLR 算法探索肿瘤干细胞性及相关机制，并在单细胞队列（GSE132465、GSE166555 和 GSE178318）中进行验证。后续通过平板克隆、EdU 实验、细胞划痕愈合、Transwell 迁移和侵袭、流式检测细胞凋亡等实验评估直肠癌细胞增殖转移效应，使用并 Western Blot 检测肿瘤干细胞性及相关通路标志物的表达变化。

结果：使用 17 种不同的机器学习算法，以 ROC 的 AUC 值为效应评价指标，筛选出 ROC 最高的 4 个模型（glmBoost、Random Forest、Ridge 和 LASSO）,通过 SHAP 值筛选出 AMD1 作为放疗抵抗的核心基因。转录组队列及单细胞列队分析显示，AMD1 均在放疗抵抗组中显著增加（$P<0.05$），且高表达 AMD1 的患者的预后较差。OCLR 算法提示放疗抵抗组的肿瘤干细胞性显著增加，并与 Hedgehog 通路活性的增加显著增加，且与 AMD1 的表达量均为显著正相关（$P<0.05$）。后续通过 EdU 实验、细胞划痕愈合、Transwell 迁移和侵袭实验发现 AMD1 显著增强直肠癌的迁移和侵袭作用，CCK-8、平板克隆、流式检测细胞凋亡等实验证实 AMD1 显著增加直肠癌的放疗抵抗，并通过 Western Blot 发现 AMD1 能够

显著上调肿瘤干细胞标志物和 Hedgehog 通路，并通过下调 cGAS-STING 通路显著改变肿瘤免疫微环境。

结论：AMD1 是放疗抵抗的核心基因，可能通过上调 Hedgehog 信号通路活性导致的肿瘤干细胞活性增加，并通过下调 cGAS-STING 通路改变肿瘤免疫微环境，进而导致直肠癌患者转移风险增加并形成放疗抵抗。

关键字： 放疗，直肠癌，机器学习，单细胞，体外实验

236. ATIP/ATIP1 通过线粒体动力学信号通路调控前列腺癌转移

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目的：血管紧张素 II AT2 受体相互作用蛋白（ATIP）有 4 个异构体，其中前列腺癌细胞 PC3 上主要表达的是定位在线粒体上的 ATIP1 异构体，以及定位于微管的 ATIP3 的异构体。ATCG 数据显示，ATIP 的表达与肿瘤的不良预后具有相关性，但是具体调控机制，特别是哪个异构体参与了肿瘤的恶性进程仍不清楚。本文拟研究 ATIP1 在前列腺癌患者中的表达情况，以及其与细胞迁移、侵袭和线粒体动力学之间的关系，明确 ATIP/ATIP1 在调节前列腺癌肿瘤转移和预测肿瘤预后中的作用。

材料与方法：从 GSE 数据库中提取数据，通过 R 语言分析了前列腺癌病人格里森分级评分与 ATIP 基因表达的相关性。在分子细胞水平，我们在敲低 ATIP 基因的 PC3 细胞中回复表达 ATIP1 或 ATIP3，通过 Transwell 和划痕实验分析了其对 PC3 细胞迁移侵袭能力和增殖能力的影响，通过共聚焦显微镜分析了线粒体形态变化；通过 Time-lapes 记录线粒体分裂频率；通过 2D 视频记录细胞的运动速度和轨迹。进一步，在 ATIP 缺失的 PC3 细胞继续沉默 Drp1，验证 Drp1 介导的细胞分裂对 ATIP 诱导的细胞迁移能力的影响。在动物整体水平，我们通过慢病毒载体转染构建了 ATIP1 shRNA 和 ATIP3 shRNA 稳定的 PC3 细胞系，将上述

细胞注射到 NOD-SCID 雄鼠的脾脏，借此评价 ATIP1 和 ATIP3 对 PC3 细胞体内转移能力的影响。

结果：ATIP 在前列腺癌组织中表达下调，与前列腺癌患者无病生存率呈负相关。ATIP 的沉默增强了肿瘤细胞的迁移、侵袭，激活粘着斑蛋白 FAK Y925 位点磷酸化；ATIP 的缺失激活了 Drp1 S616 位点磷酸化，增强了线粒体分裂，导致线粒体分裂/融合频率增加和线粒体片段化，最终促进了细胞侵袭迁移能力。回复表达 ATIP1 恢复了线粒体管状形态，抑制了线粒体分裂和运动能力，进而抑制了细胞的侵袭迁移能力。运用小鼠脾注射肝转移模型验证，ATIP1 的缺失能显著增加 PC3 细胞在小鼠肝脏中的转移灶数量和大小，而敲低 ATIP3 则无明显的促转移效果。

结论：综上，本研究证实了 ATIP 低表达与前列腺癌患者的转移和复发率高、前列腺癌的恶性及生存率显著增加息息相关。ATIP1 是线粒体动力学和肿瘤细胞远端转移的负调节因子，ATIP1 是通过抑制 Drp1 介导的线粒体裂变发挥作用来抑制细胞的运动能力，可以作为预测前列腺癌恶性的潜在生物标志物。

关键字： ATIP/ATIP1，Drp1，线粒体动态变化，远端转移

237. FAP is a potential prognostic biomarker that determines tumor progression and strongly correlated with tumor immune cells infiltration in HCC

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Objective: Cancer-associated fibroblasts are found in the stroma of epithelial tumors. They are characterized by overexpression of the fibroblast activation protein (FAP). This study is to explore the relationship between FAP expression, tumor immunity, and prognosis in hepatocellular Carcinoma (HCC).

Methods: FAP expression and its influence on tumor prognosis were analyzed by Tumor Immune Estimation Resource (TIMER) and Kaplan-Meier plotter. The relationship between FAP

expression and tumor immunity were analyzed by Gene Expression Profiling Interactive Analysis (GEPIA).

Results: FAP expression was significantly higher in HCC, than in corresponding normal tissues. FAP expression in HCC tissues correlated with prognosis. Low FAP expression associated with better overall survival and disease-specific survival in multiple cohorts of HCC patients, particularly in male, patients with micro- vascular invasion/virus hepatitis. FAP showed strong correlation with tumor-infiltrating B cells, CD4+ and CD8+ T cells, macrophages, neutrophils, and dendritic cells. Besides, FAP expression in HCC negatively correlated with expression of several immune cell markers, including PD-1, TIM-3, CTLA-4 and exhausted T cell markers, which means its importance in regulating tumor immunity.

Conclusions: These findings demonstrate that FAP is a potential prognostic biomarker that determines HCC tumor progression and strongly correlated with tumor immune cells infiltration.

Key Words： FAP, hepatocellular carcinoma, biomarker, tumor progression, immunity

238. Cinobufagin 通过 ATF3/GPX4 轴抑制胰腺癌恶性进程的机制探究

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研究目的：胰腺癌是一种高度致命的恶性疾病，由于早期诊断困难，大部分患者在诊断时已发生转移，失去了手术治疗的机会，化疗是进展期胰腺癌治疗的首要选择。目前的化疗药物虽可部分延长患者的生存期，但由于耐药机制复杂且不明确，化疗有效率仍较低。因此，亟待探索新的药物去拓宽化疗药物的选择。　近年来，由于中药抗癌在预防、增效减毒、减少复发、提高生命质量上均有西药不具备的长项，整体效果较佳而引发越来越多的关注。

本研究旨在探寻具有抗胰腺癌活性的天然化合物，并对其抗癌活性进行机制探索，为晚期胰腺癌患者治疗提供一个新的选择。

研究方法：对中药单体库中进行无偏倚高通量的筛选，开创性地提出将 Cinobufagin 用于胰腺癌的治疗。我们首先在胰腺癌细胞系中评估了 Cinobufagin 的抗癌活性。紧接着，我们对 Cinobufagin 处理后的胰腺癌细胞进行转录组学测序分析，差异基因显著富集到线粒体功能障碍、氧化应激和铁死亡相关通路。通过检测线粒体内的活性氧，透射电子显微镜观察线粒体超微结构，评估 Cinobufagin 处理后胰腺癌细胞的氧化应激情况。通过检测 Fe2+ 和细胞内脂质过氧化以及膜脂过氧化指标来检测铁死亡的发生。对转录组学测序数据进一步分析后，选取了富集程度最高的 ATF3 作为影响 GPX4 表达的潜在靶标。使用 siRNA 敲减 ATF3 后，验证 ATF3 的表达受损是否与铁死亡的抑制相关。使用超声内镜引导下细针穿刺获取的胰腺癌组织构建的类器官进行了药物有效性和上述分子机制的验证。最后，我们使用裸鼠皮下瘤和原位瘤模型，对药物的有效性和安全性进行了评估。

研究结果：Cinobufagin 以剂量和时间依赖性的方式抑制胰腺癌细胞的活性，IC50 在纳摩尔范围内。细胞实验表明，Cinobufagin 引发线粒体损伤，致使胰腺癌细胞内的活性氧水平增加，细胞发生氧化应激。转录组学测序数据表明铁死亡相关通路显著激活，细胞实验结果显示 Fe2+ 和细胞内脂质过氧化以及膜脂过氧化均增加。对转录组学数据进一步分析后发现，ATF3 是 Cinobufagin 处理后上调最显著的转录因子，敲除 ATF3 显著增加了 GPX4 的表达，同时降低了脂质 ROS 水平，导致了细胞活力的增加。类器官模型、皮下瘤和胰腺原位瘤模型均显示 Cinobufagin 具有强有力的抗癌活性和可控的毒性。

研究结论：Cinobufagin 是一种具有强大的抗胰腺癌活性的天然化合物，通过 ATF3/GPX4 诱导胰腺癌细胞发生铁死亡，拓宽了我们对 Cinobufagin 作为抗肿瘤药物的认识，为中药抗胰腺癌提供了新的思路。

关键字： 胰腺癌，铁死亡，类器官，Cinobufagin

239. 非编码 RNA 在卵巢癌中的研究进展

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目的：卵巢癌（Ovarian cancer, OC）是最致命的女性恶性肿瘤，其发生和发展过程中涉及到多种基因的异常表达和调控，发病机制尚不明确。本文通过纳入已发表的有关非编码

RNA（noncoding RNA, NcRNAs）与 OC 的研究，探讨 NcRNAs 在 OC 中的研究进展，了解 NcRNAs 对 OC 患者发病和预后的影响，以期为今后临床基础工作中提供新的思路。

方法：检索近 5 年发表的 NcRNAs 与 OC 的相关文献，并对纳入论文的参考文献进行补充检索。纳入关于 NcRNAs 与 OC 患者的相关研究，分别对文献摘要和全文进行阅读及筛选，对最终纳入的文献进行综述。

结果：（1）目前，卵巢癌（Ovarian cancer, OC）是世界上第二常见的妇科恶性肿瘤，也是最致命的女性恶性肿瘤。卵巢癌的早期诊断和筛查是预防和控制卵巢癌的关键。然而，目前尚无单一有效的早期筛查方法，尤其对于无症状的早期卵巢癌的筛查尤为困难，这导致了大部分患者在诊断时已达到晚期。(2)不编码蛋白质的 RNA 统称为非编码 RNA (NcRNAs)，NcRNAs 是包括微小 RNA（micro RNA, miRNA）、长链非编码 RNA（long noncoding RNA, lncRNAs）、环状 RNA（circular RNA, cirRNA）、核内小分子 RNA（small nuclear RNA, snRNA）、核仁小分子 RNA（small nucleolar RNA, snoRNA）和 PIWI 蛋白相互作用 RNA（Piwi-interacting, piRNA）等，NcRNAs 尽管不编码蛋白质，但 NcRNAs 在 RNA 水平上可通过参与染色体重塑、基因转录和转录后修饰来调节多种重要的生命活动。（3）NcRNAs 在卵巢癌发病中扮演着重要的作用。研究表明，非编码 RNA 参与了卵巢恶性肿瘤的调控机制，包括肿瘤细胞的增殖、侵袭、转移、耐药性和整个肿瘤微环境的形成等过程。(4)miRNA 是一类长度约为 22 个核苷酸的非编码 RNA 分子，能够通过基因沉默和转录后调控来影响基因的表达。在卵巢恶性肿瘤中，某些 miRNA 的表达水平异常改变，与肿瘤的发生和发展密切相关，也可作为 OC 诊断、治疗和预后的生物标志物。一些 lncRNA 在卵巢恶性肿瘤中的表达水平异常改变，与肿瘤的分化程度、浸润能力和预后相关。例如，OR3A4、MALAT1、CRNDE 等 lncRNA 的高表达与卵巢恶性肿瘤的发展和不良预后相关。这些 lncRNA 通过影响基因的表达和转录调控等方式，参与了肿瘤细胞的增殖、侵袭、耐药和转移。（5）虽然近年来关于 NcRNAs 与 OC 的相关研究取得了一定的进展，但是 NcRNAs 更多功能仍需被进一步探索，需要进一步来证实在 OC 发生发展中的作用机制，以求为 OC 诊治提供新的途径。

结论：NcRNAs 在 OC 的病理生理过程中发挥了重要作用，深入探索 NcRNAs 在 OC 中的分子机制有助于为 OC 防治提供新的见解，从而降低 OC 的发生率，延长 OC 患者生命和改善预后。

关键字 ：非编码 RNA；OC；发病机制

240. 肿瘤微环境单细胞组蛋白甲基化评分对肺腺癌转移的预测价值

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目的：转移是肺腺癌患者常见的致死原因之一。近年来，大量研究表明组蛋白甲基化修饰可通过多种机制促进肿瘤细胞恶性表型，加速肺癌转移进程。然而，目前关于肿瘤微环境中不同细胞亚群的组蛋白甲基化模式与肺腺癌转移间的关系研究却仍然较少。因此，本研究旨在通过整合单细胞转录组和 bulk RNA-seq 数据分析来评估微环境细胞中的组蛋白甲基化相关基因评分作为肺腺癌转移标志物的可能性。

方法：单细胞转录组数据集来自 GSE131907，采用 Seurat 软件对其进行质控、降维聚类等流程，之后进行细胞注释，并分析组蛋白甲基化相关基因在各种细胞亚群中的表达情况。采用 NMF 算法对细胞亚群进行聚类，并通过 monocle2 软件进行拟时序分析。利用 Ro/e 算法评估细胞在不同组织中的分布倾向， CellChat 软件分析细胞通讯。细胞亚群分化潜能通过 CytoTRACE 算法进行评估，使用 scMetabolism 算法评估细胞代谢情况。此外，使用 pySCENIC 软件推断细胞亚群特异性转录因子的活性。利用 ssGSEA 算法评估 TCGA-LUAD 队列的组蛋白甲基化评分。

结果：成纤维细胞、巨噬细胞及 B 细胞等被分别分为不同亚群，组蛋白甲基化相关基因和细胞通过与上皮细胞的信号交流广泛参与了肺腺癌的转移过程。其中，NELFE+成纤维细胞、NELFE+巨噬细胞的比例伴随转移进程逐渐增加，ASH1L+B 细胞主要在转移过程中出现，并且 CytoTRACE 分析结果显示这些细胞相较其它细胞亚群具有较高的干性（$P < 0.05$）。此外，KAT8+巨噬细胞的 M2 型评分较低，主要分布在正常肺组织中，其代谢活性广泛增强；而其它大多数组蛋白甲基化亚型巨噬细胞（如 SMARCA5+巨噬细胞、KANSL1+巨噬细胞等）具有较高的 M2 型评分，分布在肿瘤组织及转移组织中。每种细胞亚群具有不同的转录因子活性。此外，bulk RNA-seq 数据分析显示，相较于正常组织，组蛋白甲基化评分在肺腺癌组织中升高（$P = 1.3\times10\text{-}12$）。此外，相较于原发肿瘤组织，其在转移组织中同样有升高趋势。

结论：我们的研究表明，肿瘤微环境单细胞组蛋白甲基化是肺癌的一个显著特征，并且是预测肺腺癌转移的潜在标志物。

关键字： 肺腺癌，转移，肿瘤微环境，组蛋白甲基化，单细胞转录组

241. 基于血清糖基化外泌体 miRNA 生物标志物在胃癌早期诊断中的应用

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研究目的：胃癌的早期诊断对于改善患者的预后并选择适当的精准治疗方案至关重要。然而，目前用于诊断胃癌的肿瘤标志物具有有限的敏感性和特异性，对临床的需求尚未满足。本研究考虑到胃癌组织分泌的外泌体具有典型的异常糖链特征，因此基于血液中糖基化外泌体 miRNA 研究发现新型的胃癌生物标志物，开发一种无创且高准确度的胃癌早诊模型。

材料与方法：从 6 家医院共收集了 972 例样本队列，包含 258 例胃癌样本，胃炎、乳腺癌、肺癌、直肠癌、肝癌和健康对照共 714 例。采用热景生物自主研发的新型异常糖链外泌体捕获技术 GlyExo-Capture 从血清样本中分离提取糖基化外泌体。从外泌体中用试剂盒提取小 RNA。在发现队列中用二代测序测序（NGS）技术对外泌体的小 RNA 转录组进行测序，通过生物信息学分析，筛选出在胃癌和对照组之间差异最为显著的 miRNA 标志物组。显著差异的 miRNA 在验证队列中用 qRT-PCR 进行验证。然后利用机器学习，建立分类诊断 AI 模型，并在前瞻性队列中进行验证评估。

结果：通过 GlyExo-Capture 技术，11 分钟就能完成糖基化外泌体的快速分离提取。发现六个 miRNA 组成的 panel 在验证队列中得到成功验证，在胃癌和非胃癌对照组间显著差异，p-value <1e-5。基于这 6 个靶标，我们成功开发了胃癌诊断模型。该诊断模型在独立验证队列中表现出了很高的准确性、敏感性、特异性和稳定性，能够有效区分胃癌患者与非胃癌对照，受试者曲线下面积（AUC）为 0.850，准确率（ACC）为 82.72%，灵敏度和特异性分别为 80.23%，83.61%。本研究发现的 miRNA panel 的胃癌诊断性能远远优于当下临床上使用的癌胚抗原（CEA）(AUC=0.55)和胃蛋白酶原 I 和 II 比值（PGI/PGII）(AUC=0.58)。特

别值得注意的是，该模型在区分早期胃癌与良性患者方面也表现出了出色的性能，AUC 为 0.836。此外，所鉴定的标志物还显示出了良好的性能，可以指示周围神经侵犯状态、淋巴结转移和患者的 Lauren 分类。

结论：本研究筛选并验证了血清中糖基化外泌体内的 miRNA 能作为胃癌无创早诊的新型生物标志物。所开发的 AI 模型在胃癌患者诊断中表现出了较高的准确性、灵敏度、特异性和稳定性，尤其是在区分早期胃癌与良性患者方面。这六个 miRNA 对胃癌的诊断和制定治疗决策提供了重要依据。因此，来源于血清糖基化外泌体内的 miRNA 有望成为胃癌无创早诊的新型有效生物标志物。

关键字： 糖基化外泌体 microRNA 胃癌 无创诊断

242. SORBS2-Mediated Inhibition of Malignant Behaviors in Esophageal Squamous Cell Carcinoma through the TIMP3-MMP9 Axis

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Background: Esophageal squamous cell carcinoma (ESCC) is characterized by its high aggressiveness and poor prognosis. The role of Sorbin and SH3 domain-containing protein 2 (SORBS2) in ESCC remains largely unexplored.

Methods: The expression levels of SORBS2 mRNA in various malignant tumors were analyzed using the TCGA database, as well as in six ESCC RNAseq datasets from the GEO database. The biological role of SORBS2 in ESCC was investigated using cell proliferation, migration, invasion assays, and subcutaneous tumor formation in nude mice. Additionally, the molecular mechanism of SORBS2 in regulating ESCC was explored by examining its interaction with TIMP3 mRNA.

Results: SORBS2 expression was found to be significantly downregulated in ESCC tissues. The overexpression of SORBS2 in ESCC cell lines was observed to inhibit cell proliferation, migration, and invasion in vitro and tumor growth in vivo. It was found that SORBS2 binds to the 3'UTR of TIMP3 mRNA, enhancing its stability and thereby regulating the expression of TIMP3. The

downregulation of SORBS2 was associated with enhanced endothelial cell tube formation, which could be reversed by the upregulation of TIMP3 expression.

Conclusion: SORBS2 is suggested to act as a tumor suppressor in ESCC by inhibiting malignant biological behaviors and regulating TIMP3 expression through enhancing mRNA stability. The findings indicate that SORBS2 may serve as a potential therapeutic target for ESCC treatment.

Key Words： ESCC; SORBS2; TIMP3; Malignant Behaviors

243. PRDM10/COL5A1 Inhibits Migration and Invasion of Esophageal Squamous Cell Carcinoma by Regulating the EMT Pathway

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Background: Esophageal squamous cell carcinoma (ESCC) is a highly aggressive cancer with limited treatment options. The function of PRDM10 in the context of ESCC has not been extensively studied.

Methods: We conducted a comprehensive analysis of PRDM10 mRNA expression across various cancer types using data from the TCGA and GEO databases. The impact of PRDM10 on ESCC was assessed through in vitro assays evaluating cell migration and invasion. Additionally, the association between PRDM10 and the epithelial-mesenchymal transition (EMT) pathway in ESCC was explored using gene set enrichment analysis (GSEA) on RNA-seq data.

Results: Our analysis revealed a significant reduction in PRDM10 expression in ESCC samples compared to normal tissues. Functionally, the forced expression of PRDM10 in ESCC cell lines led to a marked decrease in cell proliferation, migration, and invasion. Furthermore, overexpression of PRDM10 resulted in reduced levels of COL5A1, a key component of the extracellular matrix. Notably, PRDM10 expression was found to be significantly correlated with the EMT pathway, suggesting its involvement in the regulation of this critical cancer progression mechanism.

Conclusion: These findings propose PRDM10 as a novel tumor suppressor in ESCC, with its downregulation contributing to enhanced malignant behavior and potential EMT pathway activation. The modulation of PRDM10 could offer new therapeutic avenues for the management of ESCC.

Key Words： ESCC; PRDM10; COL5A1;EMT; Migration and Invasion

244. 基于核酸适体富集的 CAR-T 细胞制备及肿瘤治疗研究

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嵌合抗原受体 T 细胞(CAR-T）细胞疗法已被用于 B 细胞血液肿瘤的临床治疗中。然而，在治疗过程中，存在靶抗原丢失或下调导致传统 CAR-T 细胞失效，以及细胞因子释放综合征等问题，限制了 CAR-T 细胞在临床上的广泛应用。

为提高CAR-T细胞疗法的安全性并扩大应用范围，本研究构建了通用型CAR-T细胞（抗FITC 的 CAR-T 细胞）开关模块的新方法。将靶向肿瘤相关抗原的抗体与 SpyCatcher 结构域构建抗体融合蛋白，并与 FITC-SpyTag（FITC-ST）多肽定点偶联，制备定点偶联的新型分子开关。只有当分子开关模块抗体端与肿瘤抗原结合时，介导通用型 CAR-T 细胞发挥杀伤作用，从而提高治疗安全性。在杀伤表达多种抗原的肿瘤细胞时，无需单独设计构建 CAR-T 细胞，只需更换分子开关模块蛋白，即可介导通用型 CAR-T 细胞精准杀伤靶细胞，为靶抗原丢失或下调时的治疗提供了新的选择。本研究中构建了靶向 CD19、PDL1 和 Her2 的分子开关模块，并介导抗 FITC-CAR-T 细胞针对肿瘤细胞的靶向治疗。

CD4 抗原为 T-ALL 及 AML 等一类难治复发性白血病中较为理想的靶点。为减少构建过程中对正常 CD4+ T 细胞的杀伤，在构建 CAR-T 细胞之前，通过 CD8 的核酸适体富集 CD8+ T 细胞，去除体系内正常 CD4+T 细胞的干扰。通过构建抗 FITC CD8-CAR-T 细胞，同时使用抗 CD4 抗原的分子开关模块（CD4-FITC-ST），在体外和小鼠模型中特异性杀伤表达 CD4 抗原的肿瘤细胞，达到治疗作用。

研究目的:（1）优化通用型 CAR-T 细胞分子开关模块的制备方法，验证其在 CD19、her2、PDL1 及 CD4 等肿瘤标志上介导 CAR-T 细胞杀伤能力，并联合增强 CAR-T 细胞的安全性和有效性，扩大 CAR-T 细胞疗法的应用范围；

（2）基于核酸适体的磁珠富集系统，富集 CD8+ T 细胞并制备通用型 CAR-T 细胞，联合靶向 CD4 抗原的 CD4-FITC-ST 开关模块，用于 CD4 抗原阳性肿瘤的治疗，为难治/复发性表达 CD4 抗原的肿瘤的治疗提供新方法。

材料与方法:（1）表达纯化靶向肿瘤并带有 SpyCatcher 序列的抗 CD19、her2、PDL1 及 CD4 的蛋白，与合成的 FITC-SpyTag 多肽定点偶联，构建开关模块蛋白。

（2）CD8 核酸适体联合磁珠富集 CD8+ T 细胞并制备通用型 CAR-T 细胞，联合抗 CD4 抗原的 CD4-FITC-ST 开关模块，用于 CD4 抗原阳性肿瘤的治疗。

研究结果: 定点偶联构建的新型安全分子开关模块，在 CD19、her2、PDL1 等肿瘤标志均表现出了显著的介导通用型 CAR-T 细胞抗肿瘤作用，增强了通用型 CAR-T 细胞的安全性和有效性。基于核酸适体的 CD8+ T 细胞高效富集系统，构建靶向 CD4 抗原的 anti-FITC CD8+CAR-T 细胞，能够有效杀伤表达 CD4 抗原的肿瘤。

结论: 新型定点偶联的开关模块，靶向 CD19、her2、PDL1 及 CD4 等肿瘤标志，能介导通用性 CAR-T 细胞有效杀伤肿瘤。为临床上 CAR-T 细胞疗法的应用，提供了新的治疗思路。

关键字 ：CAR-T 细胞疗法；开关模块；定点偶联；核酸适体

245. Genetic variants in m5C modification genes are associated with survival of patients with HBV-related hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common malignant tumors with a high mortality rate. The 5-methylcytosine (m5C), a type of RNA modification, plays crucial regulatory roles in HCC carcinogenesis, metastasis and prognosis. However, few studies have investigated the effect of genetic variants in m5C modification genes on survival of patients with hepatitis B

virus (HBV)-related HCC. In the present study, we evaluated associations between 144 SNPs in 15 m5C modification genes and overall survival (OS) in 866 patients with the HBV-related HCC. Expression quantitative trait loci (eQTL) analysis and differential expression analysis were conducted to investigate biological mechanisms. As a result, we identified that two SNPs (NSUN7 rs2437325 A>G and TRDMT1 rs34434809 G>C) were significantly associated with HBV-related HCC OS with adjusted allelic hazards ratios of 1.25 (95% confidence interval =1.05-1.48 and P=0.011) and 1.19 (1.02-1.38 and P=0.027), respectively, with a trend of combined risk genotypes (Ptrend<0.001). Moreover, the results of eQTL analyses showed that both NSUN7 rs2437325 G and TRDMT1 rs34434809 C alleles were associated with a reduced mRNA expression level in 208 normal liver tissues (P=0.007 and P<0.001, respectively). Taken together, genetic variants in the m5C modification genes may be potential prognostic biomarkers of HBV-related HCC after hepatectomy, likely through mediating the mRNA expression of corresponding genes.

Key Words ： hepatocellular carcinoma; Hepatitis B virus; m5C modification; genetic variants; survival

246. CCDC12 variant splicing isoforms promotes invasion and metastasis of breast cancer

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Objective: Breast cancer is one of the most common malignant tumors in Chinese women, and its incidence ranks first among female malignant tumors.The incidence of breast cancer in China is increasing at a rate of 2-3% per year, with about 210,000 new cases of breast cancer and 110,000 deaths across the country every year.The high recurrence rate of breast cancer is still a major problem puzzling the prognosis of clinical breast cancer.Studies have shown that CCDC12 protein

is abnormally expressed in a variety of malignant tumors, promoting the invasion and metastasis of malignant tumor cells by regulating cell transcription factors and changing cell proliferation cycle.However, how CCDC12 as a shear gene affects the biological activity of breast cancer remains to be further studied.

Methods: CCDC12 knockdown stable transmutation was constructed in breast cancer MDA-MB-231 cells, and the expression of CCDC12 was detected by western blot.The differences in cell proliferation between MDA-MB-231 and MDA-MB-231shCCDC12 cells were detected by CCK8, the ability of cell invasion and metastasis was detected by cell scratch and Transwell, and the effects of different expression levels of CCDC12 on the cell cycle of MDA-MB-231 were detected by flow cytometry. CCDC12 was used as a shear factor to explore the changes of different CCDC12 expression levels on MDA-MB-231 shear events by transcriptome sequencing, and to find downstream target candidate genes for further mechanism research.

Result: The analysis of tumor TCGA database showed that CCDC12 mRNA expression in tumor tissue samples was higher than that in paracancer tissues, and CPTAC database could reach the same conclusion, CCDC12 protein expression in tumor tissue samples was higher than that in paracancer tissues.The expression level of CCDC12 protein in MDA-MB-231shCCDC12 cells was significantly down-regulated. After the knockdown of CCDC12 in MDA-MB-231 cells, the proliferation rate of the cells in the knockdown group was significantly decreased compared with that in the WT and NC groups ($p<0.05$).In colony formation, the number of colony formation in knockdown group was significantly lower than that in WT group and NC group.The cell scratch test showed that the healing rate of CODC12 knockdown group was significantly lower than that of WT and NC groups.At the same time, in the cell transwell experiment, the number of cell metastasis in the knockdown group was significantly lower than that in the WT and NC groups.Analysis of cell cycle by flow cytometry showed that CCDC12 knockdown would lead to cell cycle arrest in G2/M phase.The NC group and KD group of MDA-MB-231 cells were transformed into tumors, and the tumor growth rate of KD group was significantly slowed down.When rescue experiments were performed in MDA-MB-231shCCDC12 cells to up-regulate the expression of CCDC12, the proliferation rate of MDA-MB-231shCCDC12 cells was accelerated, and the ability of migration and metastasis was enhanced.Transcriptomic sequencing of RNA extracted from MDA-MB-231 and MDA-MB-231shCCDC12 cells was performed to

analyze the changes of shear events, and differences of candidate genes were analyzed to find that genes such as ICAM4ITGA10, KIAA1217 and LAMA5 would be further studied.

Conclusion: This study explored the influence of differences in the expression of CCDC12 in breast cancer cells on the cell level and animal level, and comprehensively expounded the role of CCDC12 as a variable shear factor on breast cancer cells and its molecular mechanism. CCDC12 is involved in the proliferation and metastasis process of breast cancer and plays an important role in the occurrence and development of breast cancer.The specific mechanism of CCDC12 will be further analyzed from the changes of cellular gene shear events, and the downstream genes will be further studied. It is expected that the results of this study will deepen our understanding of CCDC12 in the treatment of breast cancer, and provide a basis for the discovery of new therapeutic targets and the development of new targeted drugs.

Key Words： CCDC12;Breast cancer;Invasion;metastasis; Splicing

247. DLX6 上调促进鼻咽癌转移和血管生成

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背景：早期鼻咽癌（NPC）常无症状，导致患者诊断延迟，不仅限制了治疗选择，而且增加了疾病复发和远处转移的风险。 因此，研究鼻咽癌的发病机制对于最大限度地减少复发和转移、最终提高晚期患者的生存率和生活质量至关重要。 先前的研究表明 DLX6 是口腔癌的潜在肿瘤标志物。 然而，DLX6 在鼻咽癌发生和进展中的作用尚未见报道。

目的：探讨 DLX6 在鼻咽癌发生、发展中的作用，为早期筛查和治疗提供潜在标志物。

方法：采用免疫组织化学方法检测非转移性和转移性鼻咽癌标本中 DLX6 的表达水平。采用伤口愈合实验、Transwell 实验、集落形成实验和 EdU 实验等体外迁移和侵袭模型来评估 DLX6 敲低对 NPC 细胞的影响。我们通过 WB 实验检测了 VEGFA 的表达，以研究 DLX6 敲除对鼻咽癌血管生成的影响。

结果：免疫组化显示 DLX6 在转移组中高表达。 上调的 DLX6 促进体外鼻咽癌细胞迁移和侵袭，并促进 VEGFA 的表达。

结论: 这些发现揭示了 DLX6 在促进鼻咽癌转移和血管生成中的特定关键作用，这表明 DLX6 可能具有作为潜在治疗药物的意义。 鼻咽癌个体化治疗的目标。

关键字： DLX6,转移，血管生成，VEGFA，鼻咽癌

248. BTG1 mutation correlates with inferior prognosis in diffuse large B-cell lymphoma

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Background: B celltranslocation gene 1 (BTG1) is a highly conserved gene, and were often considered as passengers in lymphomagenesis. BTG1 is recurrently mutated in the MCD subtype of diffuse large B-cell lymphoma (DLBCL). The specific enrichment of BTG1 mutation in the MCD subtype of DLBCL raises a potential hypothesis that they may actively contribute to lymphomagenesis. However, the biological characteristics and prognostic significance of BTG1 in DLBCL have not been studied in depth. Therefore, the objective of our study was to explore the roles of BTG1 mutation (BTG1-mut) in DLBCL.

Methods: The available clinical information and corresponding mutation data of DLBCL were retrieved and obtained from published articles. Ultimately, 2759 DLBCL patients in six cohorts were enrolled in the final analysis. Among the 194 DLBCL patients in the Jiangsu Province Hospital study cohort, all tumor tissue samples were collected to perform NGS while 162 samples were analyzed the gene expression levels using RNA-seq, among them, 40 samples were analyzed by non-targeted metabolomics.

Results: Among the 2759 DLBCL patients from the integrated cohort, 9.71% of DLBCL patients (268/2759) had BTG1-mut. Compared with BTG1 wild type (BTG1-wt) group, advanced age and stage, poor Eastern Cooperative Oncology Group (ECOG) performance status, MCD subtype and higher International Prognostic Index (IPI) scores were significantly associated with BTG1-mut. BTG1 mutations were related to shorter overall survival (OS) (P=0.0024). Multivariate analysis suggested that age >60y, advanced stage, elevated lactate dehydrogenase (LDH), poor ECOG, and BTG1 mutations had independent prognostic signifcance for OS. We performed differential

expression analysis by using RNA-seq in our cohort between BTG1-mut and BTG1-wt patients. GO functional enrichment analysis enriched metabolic pathways. Pathway enrichment analysis of the metabolome in positive and negative modes reveals changes to metabolisms of amino acids.

Conclusions: BTG1 mutations were promising prognostic predictor for DLBCL. The mechanism driving different survivals outcomes may be explained by the tumor metabolic reprogramming.

Key Words： diffuse large B cell lymphoma, BTG1, prognosis, biological mechanism, metabolome

249. The mechanism of USP25 deubiquitination regulating KIFC1 in the development of cervical cancer

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Objective: Cervical cancer is one of the most common malignancies in women, and although HPV vaccine and cervical screening have become effective strategies to prevent cervical cancer, cervical cancer still has a high incidence and mortality in low - and middle-income countries. In cervical cancer, 15%-20% of patients are HPV-negative, so it is necessary to deeply explore the specific mechanism of cervical cancer. KIFC1 has been identified as a driver protein in a variety of tumors to promote tumor progression, and overexpression of KIFC1 is necessary to maintain normal division of multiple centrosomal tumor cells. However, there are few studies on the role of KIFC1 in the pathogenesis of cervical cancer, and the specific mechanism needs to be further studied.

Materials and Methods: In this study, TCGA data were used to analyze KIFC1 mRNA expression in cervical cancer and adjacent tissues, and tissue microarray was used to detect KIFC1 protein expression in cervical cancer samples. The spatial and temporal localization of KIFC1 was

observed in Hela cell lines of cervical cancer. KIFC1 knockout and rescue experiments were performed on Hela cells to observe cell proliferation, metastasis and colony formation. The cervical cancer model was established in nude mice to explore the effect of different expression levels of KIFC1 on tumor formation. The USPX gene, which regulates the stability of KIFC1 protein, was screened in the deubiquitination USP family, and the function of USPX in Hela was verified. The co-immunoprecipitation study and the interaction between USPX and KIFC1 were conducted to reveal the biological activity of USPX-KIFC1 signal axis in cervical cancer.

Results: TCGA data analysis showed that the expression level of KIFC1 mRNA in cervical cancer cells was lower than that in adjacent tissues, and the prognosis effect of cervical cancer patients with high KIFC1 expression was worse than that of patients with low expression.Prognostic analysis of KIFC1 protein in tissue microarray of cervical cancer patients showed that the expression of KIFC1 protein in cervical cancer tissues was higher than that in adjacent tissues.After KIFC1 gene was knocked out and KIFC1 gene was overexpressed in Hela cells, the proliferation, metastasis and colony-forming ability of HelaKIFC1-/- was lower than that in Hela cells ($p<0.05$), the proliferation capacity of Hela OE KIFC1 was higher than that of Hela cells ($p<0.05$).It was found that deubiquitination USP25 protein has a regulatory relationship with the stability of KIFC1, and the function of USP25 was verified in Hela cells. The proliferation capacity of HelashUSP25 was lower than that of Hela cells, the cell cycle S phase was shortened, the cell cycle was stalled in the G/G1 phase, and the apoptosis rate was up-regulated ($p<0.01$).Co-immunoprecipitation results showed direct interaction between USP25 and KIFC1 protein. In vivo ubiquitination experiments showed that the expression level of KIFC1 protein in Hela cells after knockdown of USP25 was lower than that in the control group, while the expression level of KIFC1 protein in Hela cells after overexpression of USP25 was higher than that in the control group. Overexpression of KIFC1 in HelashUSP25 cells can restore cell proliferation and metastasis and reduce cell apoptosis.

Conclusion: Both TCGA database and cervical cancer tissue microarray analysis showed that the expression level of KIFC1 in tumor was higher than that in normal tissue, and the deletion of KIFC1 in Hela cells and nude mouse tumor formation experiments inhibited the biological activity of tumor. The deubiquitinating protein USP25 regulates the stability of KIFC1 protein by interacting with KIFC1. The decrease of USP25 in Hela cells leads to the degradation of KIFC1

protein, thus inhibiting the proliferation and metastasis of cervical cancer cells. This outcome can be saved by overexpression of KICF1 in HelashUSP25 cells.This study elucidated the mechanism of action of USP25-KIFC1 signal axis in cervical cancer cells, and provided a basis for a deeper understanding of the pathogenesis of cervical cancer, as well as the discovery of new therapeutic targets and the development of new targeted drugs.

Key Words ： Cervical cancer; KIFC1; Deubiquitination; USP25

250. Diagnostic performance and efficacy evaluation of NSE and CA125 in sarcomas.

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Background: Soft tissue sarcomas (STSs) and bone sarcomas(BSs) are described as diseases with many classifications, complex conditions, and usually delayed diagnosis. There lacks a simple and sensitive methods for disease monitoring of sarcomas clinically. This study examined whether NSE and CA125 are available markers for the diagnosis and efficacy evaluation of sarcomas.

Methods: 110 patients with sarcomas were enrolled, and 60 healthy people were selected as controls. We collected serum NSE and CA125 levels at diagnosis, recurrence, during treatment, and post-treatment to analyze their values of diagnosis and therapeutic assessment.

Results: Elevated serum NSE at diagnosis suggested the possibility of STSs (AUC=0.513), while elevated serum CA125 was correlated with STSs(AUC=0.589) and BSs(AUC=0.602). NSE's sensitivity and specificity for STSs were 46.25% and 63.33%, respectively. CA125 had a sensitivity of 95.0% for STSs and BSs, but a low specificity of 20.00% and 11.11%, respectively. During treatment of advanced sarcomas, the change of NSE was significantly

correlated with the effectiveness of treatment(P=0.007 for SD, P=0.006 for PD). However, CA125 was not specific for the treatment evaluation of sarcomas(P=0.070 for SD, P=0.071 for PD).

Conclusion: NSE and CA125 can be used as potential markers to assist in diagnosing sarcomas. Furthermore, NSE is a promising marker for disease monitoring of sarcomas.

Key Words： Tumor markers; NSE; CA125; Sarcomas.

251. circMETTL9 通过靶向 KRT16/NF-κB 通路调控胃癌增殖、凋亡、侵袭能力并逆转胃癌抗血管生成治疗耐药的作用及机制研究

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背景：2024 年国家癌症中心全国癌症报告显示，胃癌在我国发病率排第 5 位；5 年生存率为 31.5%。亚洲地区胃食管癌的发病率、死亡率、患病率均居于全球首位。靶向治疗是胃癌最常见的治疗方法之一，但是许多患者容易发生耐药，关于靶向治疗耐药的问题目前仍不清楚。VEGF 高表达是胃癌的特征之一，肿瘤的一大特征是具有合成新生血管的能力，因此，抗血管生成治疗被认为是治疗胃癌的一种有前途的策略，代表药物有贝伐珠单抗、雷莫芦单抗和阿帕替尼。研究发现胃癌耐药细胞差异表达多种 circRNA，可能调控了抗血管生成治疗的耐药。目前发现的 circRNA 的作用主要有作为 miRNA 分子的海绵进而间接调控 miRNA 下游靶基因的表达，作为蛋白分子的海绵，引起免疫响应和编码多肽等。研究表明，在多种肿瘤中，circRNA 表达失调，调控肿瘤增殖、凋亡、侵袭、迁移、血管生成、自噬和细胞周期，有研究表明，一些 circRNAs 在多种肿瘤中对靶向治疗的敏感性和耐药性起重要作用，但是，circRNA 在胃癌抗血管生成治疗耐药中的作用和机制尚不清楚。

方法：我们用裸鼠成瘤方法建立体外耐药模型，对裸鼠耐药模型和对照组的瘤体进行测序，分析发现了裸鼠耐药模型中高表达的 circMETTL9。体外功能实验和体内异种移植小鼠模型用于研究 circMETTL9 在胃癌进展过程中的作用。克隆形成实验和流式实验研究 circMETTL9 对胃癌抗血管生成治疗耐药的影响。质谱、pulldown、RIP 和 WB 等试验探索 circMETTL9 的潜在分子机制。

结果：我们鉴定了 circMETTL9 为环状结构，有较强的稳定性，主要分布在细胞质内。qRT-PCR 实验显示，与对照组相比，circMETTL9 在胃癌耐药细胞中高表达。然后，我们进行了体内和体外实验。Cck-8 和裸鼠成瘤实验结果显示，circMETTL9 增强了胃癌细胞的增殖能力。克隆形成实验显示，上调 circMETTL9 后细胞克隆形成能力增强。同时，流式细胞仪检测了细胞凋亡能力，结果显示，circMETTL9 增强细胞凋亡。Transwell 实验证明，circMETTL9 增强了胃癌细胞的侵袭和迁移能力。然后我们检测 circMETTL9 对耐药细胞的影响，发现 circMETTL9 调控了胃癌耐药细胞对抗血管生成治疗的敏感性。敲低 circMETTL9 抑制了胃癌耐药细胞在抗血管生药物作用下的克隆形成能力，增强了凋亡率。接下来，我们构建了含 MS2 标签的 circMETTL9 的过表达质粒进行 RNA pull-down 实验，然后质谱检测产物找到了 circMETTL9 的结合蛋白 KRT16。RIP 实验验证 KRT16 和 circMETTL9 的结合。Gene Set Enrichment Analysis （GSEA 富集分析）发现 circMETTL9 的下游蛋白 KRT16 可能调控了 NF-κB 通路。于是我们用 WB 等实验验证 circMETTL9 通过靶向 KRT16/NF-κB 通路调控胃癌细胞增殖、凋亡、侵袭能力，抑制 circMETTL9/KRT16/NF-κB 通路可以逆转胃癌抗血管生成治疗耐药。

结论：circMETTL9 调控胃癌耐药性，抑制 circMETTL9/KRT16/NF-κB 通路可以逆转胃癌抗血管生成治疗耐药。

关键字 ：胃癌；抗血管生成治疗耐药；circMETTL9；KRT16；NF-κB 通路

252. 睡眠行为、肾功能指标与重症非酒精性脂肪肝、肝硬化和肝癌发病风险的关联研究

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目的：尽管不良睡眠行为对肝肾功能的不良影响已得到了证实，但睡眠、肾功能与重症非酒精性脂肪肝（Non-alcoholic fatty liver disease, NAFLD）及其不良结局（肝硬化和肝癌）发病风险之间的潜在关联尚不明确。因此，本研究旨在探讨睡眠行为、肾功能指标与重症 NAFLD、肝硬化和肝癌发病风险之间的内在联系。

方法：本研究共纳入 305,257 名英国生物银行队列中基线时未患基础肝病的研究对象。采用多变量 Cox 比例风险回归模型计算睡眠行为、肾功能指标与重症 NAFLD、肝硬化和肝

癌关联的风险比（Hazard Ratio, HR）和 95%置信区间（Confidence interval, CI）。利用卡方检验评估基线时不同睡眠模式下肾功能水平之间是否存在差异。同时探究肾功能指标在睡眠评分与重症 NAFLD、肝硬化和肝癌的关联中是否起到了中介作用。此外，我们还采用两步孟德尔随机化（Mendelian randomization, MR）研究分别对遗传预测的睡眠行为（失眠、睡眠时间、长睡眠时间和短睡眠时间）与重症 NAFLD、肝硬化、肝癌和慢性肾病（Chronic kidney disease, CKD）进行了因果关联推断，并探讨了 CKD 是否介导了部分睡眠与重症 NAFLD、肝硬化和肝癌之间的关联。

结果：在平均 12.4 年的随访中，共发生 2,302 例重症 NAFLD、981 例肝硬化和肝癌。多因素模型校正后，不良睡眠评分与重症 NAFLD、肝硬化和肝癌的发病风险增加显著相关（Ptrend<0.001）。肾功能指标与重症 NAFLD、肝硬化和肝癌的发病风险也呈现明显的剂量-反应关系（Ptrend <0.010）。与睡眠模式健康且肾功能标志物评分最低组相比，睡眠模式较差且肾功能标志物评分最高组患重症 NAFLD、肝硬化和肝癌的的风险分别增加了 5.45（HR=5.45; 95%CI=3.88-7.66）和 3.47（HR=3.47; 95%CI=2.13-5.65）倍。我们还发现基线时不同睡眠模式下肾功能水平之间存在统计学差异（P<0.001）。同时，遗传预测的失眠可分别增加重症 NAFLD 和 CKD 发病风险的 23%（IVW：OR=1.23，95%CI=1.11-1.35，P=0.001）和 5%（IVW：OR=1.05，95%CI=1.01-1.08，P=0.007)。多变量 MR 的结果表明，在调整失眠后，CKD 与重症 NAFLD 之间也存在正相关的因果关系（IVW: OR=1.13, 95%CI=1.12-1.15, P=0.039）。进一步中介分析揭示，CKD 在失眠与重症 NAFLD 发病风险的关联中起到了中介作用（P<0.001）。

结论：不健康的睡眠行为、较差的肾功能可增加慢性肝病及其不良结局发生风险，且不良肾功能在睡眠与重症 NAFLD 发病风险的关联中起到了中介作用。本研究结果强调了肝-肾轴的双向沟通作用，并揭示了睡眠和肾功能对预防重症 NAFLD 的发生和进展的重要公共卫生学意义。

关键字： 睡眠；肾功能；肝病；队列研究；孟德尔随机化

253. CCNB1 的泛癌分析

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目的：细胞周期蛋白 Cyclin B1（CCNB1）是细胞周期蛋白家族的重要成员，可促进细胞从 G2 期进入 M 期，启动有丝分裂进程。先前的研究表明，CCNB1 在肝癌、乳腺癌、食管癌、宫颈癌中异常表达，且与患者较低生存率密切相关。然而，针对 CCNB1 在泛癌中的价值的研究仍未见报道。本研究旨在探索 CCNB1 在泛癌中的表达、预后、肿瘤微环境和体细胞突变等特征，探讨 CCNB1 在肿瘤发生和发展中的潜在作用。

方法：本研究使用在线工具 cBioPortal 分析了 CCNB1 在肿瘤中的基因表达模式。使用 TCGA 和 GTEx 数据库，比较 CCNB1 在人类正常和肿瘤组织中的表达水平，使用 R 包“survival”探究预后价值，随后我们探究 CCNB1 和肿瘤患者临床特征间的关系。TIMER 算法研究了免疫细胞浸润与 CCNB1 表达的关系，通过 R 包“maftools”分析肿瘤突变负荷相关性。最后使用 GeneMANIA 网络工具获取 CCNB1 相关基因并生成 PPI 网络，利用 GO 和 KEGG 富集分析探索 CCNB1 及其相关基因的生物学功能。

结果：CCNB1 在大多数肿瘤类型中以“深度缺失”和“突变”作为主要突变类型， 在 32 种肿瘤类型中具有显著高表达。预后分析发现高表达水平的 CCNB1 是 18 种肿瘤的不良预后因子。CCNB1 和多种肿瘤患者的临床特征密切相关，如 TNM 分期，组织分级等。“TIMER”免疫浸润分析观察到 CCNB1 表达与多种肿瘤的免疫微环境密切相关。肿瘤突变负荷相关性分析表面 CCNB1 与多种类型的肿瘤之间存在很强的相关性。最后使用 GeneMANIA 在线工具获取了 20 个 CCNB1 相关基因，GO 和 KEGG 富集分析显示 CCNB1 及其相关基因在细胞周期通路和 p53 信号通路等癌症相关通路富集。

结论：本研究系统分析了 CCNB1 在泛癌中的作用，发现 CCNB1 在多种癌症组织中的表达与正常组织存在显著差异，此外，CCNB1 在细胞周期中具有重要作用，且与免疫细胞浸润和肿瘤突变负荷呈显著正相关。因此，CCNB1 可能作为肿瘤诊断和治疗的一个潜在靶点。

关键字 ：CCNB1;泛癌分析;肿瘤免疫微环境;预后因子;临床特征

254. A Case Report on the Novel c.398T>G (p.Met133Arg) Mutation of the SDHB Gene in a SDHB-Deficient GIST Patient

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Purposes: It is reported that a germline mutation was present in the majority of SDHB-deficient GIST patients. To illustrate this, a case including a novel mutation in the SDHB gene was provided.

Materials and methods: To diagnose the primary and non-metastatic gastric specimen from surgery of a female patient, HE was used to stain the tissues and immunohistochemistry was carried out to test the expression of CD34, CD117, CK, Vimentin, S-100, SMA, SDHB and Ki-67 proteins using the tumor sections. Next generation sequencing was performed to define the genotype of a panel of genes comprising of KIT, PDGFRA, NF1, BRAF, KRAS, PIK3CA, SDHA and SDHB, in the cancerous and the marginal tissues.

Results: The patient was diagnosed as gastric gastrointestinal stromal tumor (GIST) based on the HE staining and immunohistochemistry data, which showed that CD34 and CD117 proteins were positive whereas CK, Vimentin, S-100 and SMA proteins were negatively expressed with the loss of the SDHB protein and 30-40% of the Ki-67 expression. It is indicated that the GIST case was an SDHB-deficient subtype. Furthermore, the data from next generation sequencing showed that a novel mutation c.398T>G p.Met133Arg was present in the SDHB gene with the variant abundance of 73.75% in the tumor section instead of the normal counterpart. The other genes except SDHB exhibited wild-typed genotypes. This suggests that the novel missense mutation is somatic despite the high mutation percentage. As the clinical data shown from the patient, no family member was affected by the malignancy. In addition, no adjuvant treatment was performed on the patient. It remains to be elusive for the clinical role of the novel variant in the pathogenicity of the GIST.

Conclusion: The novel c.398T>G (p.Met133Arg) mutation of the SDHB gene was not germline in the SDHB-deficient GIST patient, and more evidence was required to clarify the pathologic role in GIST.

Key Words： GIST; SDHB-deficiency; novel mutation

255. Ablation of TNIP1 induces the growth arrest and apoptosis of breast cancer cells

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Objective: The study is to illustrate the molecular mechanism of TNIP1 regulation in proliferation and apoptosis of breast cancer cells.

Materials and methods: Colony formation assay was conducted for MCF-7 or T47D cells stably transfected with TNIP1/CCNG1 shRNAs. Quantitative PCR assay was performed to assess the relative abundances of TNIP1, CCNG1 and CCND1 mRNAs. Immunoprecipitation and immunoblotting were used to detect the expression of proteins of TNIP1, CCNG1, and CCND1 etc. Dual-Luciferase reporter assay was used to explore the molecular mechanism of TNIP1 in signal transduction. Caspase activity was measured for MCF-7 or T47D cells stably transfected with TNIP1 shRNAs by Caspase-Glo 3/7 Assay.

Results: Ablation of TNIP1 induced breast cancer cells growth arrest. TNIP1 directly interacted with CCNG1, and TNIP1 knockdown increased the ubiquitination of CCNG1. CCNG1 knockdown induced MCF-7 or T47D cells growth arrest. TNIP1 knockdown activated the NF-κB pathway and induced the apoptosis of MCF-7 or T47D cells.

Conclusion: TNIP1 could control the proliferation and apoptosis of breast cancer cells, suggesting that TNIP1 might act as a potential marker for breast cancer.

Key Words： Breast cancer cells; TNIP1; CCNG1; Proliferation; Apoptosis

256. 肿瘤相关巨噬细胞协助 FAP +成纤维细胞塑造肿瘤微环境并与肝癌患者更差的临床结局相关

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背景：肝癌由于其广泛的细胞异质性而缺乏有效的治疗药物，导致较差的临床结局。肿瘤微环境的深入研究有助于发现新的治疗靶点促进治疗药物的开发。单细胞测序技术的逐渐成熟使得对肿瘤微环境异质性的解析达到前所未有的程度。成纤维细胞是肿瘤微环境的重要组成成分。最近的研究表明，肿瘤相关成纤维细胞与免疫细胞进行交互可介导抗肿瘤免疫障碍。尽管免疫检查点阻断策略的提出标志着癌症治疗方面已取得实质性进展，但肝癌患者的临床疗效并不乐观。目前，成纤维细胞与其它非肿瘤细胞的交互在肝癌中的研究相对较少，其在肿瘤发展中的作用尚不明确。

方法：联合单细胞、组织、空间转录组测序及多色荧光病理染色等多维整合分析揭示成纤维细胞与巨噬细胞的交流。通过单样本基因集富集打分量化交流强度，评估与患者生存和免疫治疗的关联。使用 sc2MeNetDrug 预测阻断交流的小分子药物。

结果：通过整合 235 例肝癌单细胞测序样本，纳入超过 120 万细胞，我们发现，除肿瘤细胞外，成纤维细胞和巨噬细胞在肿瘤样本普遍增加。其中，成纤维细胞在肝细胞癌（HCC）和肝内胆管癌（ICC）中增加尤为显著。特别地，FAP+成纤维细胞被鉴定为肝癌中主导的癌症相关成纤维细胞（CAF），并主要参与肿瘤纤维屏障形成及血管生成，与患者更差的总体生存相关。进一步地联合 1030 例肝癌组织、5 例空间转录组测序数据及 6 例多色荧光病理染色，我们揭示了成纤维细胞与巨噬细胞间的显著关联及空间共定位。功能及细胞通讯分析显示，DAB2 +和 SPP1 +巨噬细胞分别作为 HCC 和 ICC 中主导的肿瘤相关巨噬细胞（TAM），通过 PDGFB/ADM 等分子参与 FAP +成纤维细胞的细胞交流和功能强化。基于此，我们构建了 LRscore 评分以量化 TAM 和 FAP + CAF 间的交流强度。在 5 个独立的肝癌队列及 1 个抗 PD-L1 治疗队列中，LRscore 的增加预示了患者更差的总体生存和免疫治疗响应。最后，我们预测了一些小分子药物，如姜黄素和阿米洛利，对于阻断这种交流具有潜在的作用。

结论：我们的研究显示，阻断 FAP +成纤维细胞与肿瘤相关巨噬细胞间的交流可作为一种潜在的治疗策略用于改善患者的临床结局和免疫治疗响应。

关键字： 肿瘤相关成纤维细胞；肿瘤相关巨噬细胞；细胞交流

257. 整合肿瘤学教育：肿瘤标志物课程教学改革对学生发展的研究

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目的：医学教育肩负培养高素质医学专业人才的使命。《健康中国 2030”规划纲要》对医学人才培养提出了明确目标。《肿瘤标志物》一书正是基于整合医学（HIM）概念，围绕肿瘤防-筛-诊-治-康，整合传统标志物及新型标志物的专著。将该书作为医学生教材标志着医学教育课程改革走向深水区，对解决诸如过时的医学教材和停滞不前的教育理念等问题解决具有重要意义。

方法：采用增值评估方法，评估从入学到毕业学生在能力、社交能力和经济增长三个维度上的发展。能力增强是认知和专业技能的增长，包括基本学习能力、创新能力和专业技能水平。社交能力的提升涵盖了积极情绪和态度的增长，如决心、团队合作、组织领导和健康举止。经济增长衡量了就业机会的获得和收入增长，包括工作质量和职业发展的改善。目标设定：基本知识掌握水平提高 20%；思维能力和问题解决技巧提高 30%；培养专业认同感，使 90%的学生对医学专业产生兴趣和依赖。数据来源：学生课堂表现的观察记录；学生的考试成绩；学生的自我评价和同学评价；就业反馈。指标：基本知识掌握水平的改善幅度；思维能力改善程度；专业能力的提升。通过问卷调查和访谈进行评估。

结果：肿瘤标志物课程教学对学生能力产生了积极影响。接受本课程教育的学生在基本学习能力方面增加了 7.2%，在创新能力方面增加了 6.4%。值得注意的是，逻辑思维和自我意识方面的增长显著，而创造力和开放性的增长相对较小。参与本课程的学生在各项学习能力方面都获得了显著的增长。在能力评估中，逻辑思维和自我意识出现了显著增长的领域。这表明本课程不仅增强了基本学习技能，还培养了学生的批判性思维和自我反思能力。与逻辑思维和自我意识相比，创造力和开放性的增长相对较小。这表明，尽管本课程教育对各项能力产生了积极影响，但它可能对某些认知技能的影响更为显著。

肿瘤标志物课程教学改革显著提高了医学生团队合作和领导能力。在接受肿瘤标志物课程教学改革和未接受的学生之间进行比较，技能发展上的显著差异显现出来。具体来说，接受课程改革的学生在团队合作和组织领导能力方面都取得了显著的增长，分别增长了 12.1%和 25%。这些改善表明，运用《肿瘤标志物》教材，有效地整合了临床协作的工作环境中

所必需的技能。这种教育方法为学生提供了在团队环境中出色表现和承担领导角色所必需的思维方式。这些技能增长与经济增长的一致性表明，接受课程教学改革的学生有着良好的就业前景和职业发展。随着就业市场的不断发展，对其雇员在协作、解决问题和领导方面提出更高要求，看到这些学生正在逐渐走上临床医师岗位令人鼓舞。总之，该类医学生群体在团队合作和领导技能方面取得了显著增长，再加上这一群体的良好经济前景，突显了这种教学改革在为年轻人应对现代职场的需求方面的价值和相关性。

结论：将《肿瘤标志物》引入医学课程改革，特别是将课程内容融入教室、教材、临床实践、图书馆和题库，我们尝试建立一种医学教育的新模式。该门课程在的广泛采用和应用可能提升医学教育的标准，并促进医学生的成长，增强他们的实践能力和综合能力。此外，这种新的范式促进了教育资源的整合和共享，有助于中国“2030 年健康”目标实现。

关键字： 整合医学 肿瘤标志物 医学教育

258. GREM1 在非小细胞肺癌 EMT、侵袭和转移中的作用机制

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目的 探究 GREM1 在非小细胞肺癌（NSCLC）中的表达情况，进一步探究 GREM1 表达与 NSCLC 临床进展及患者预后的关系；在细胞水平研究过表达或敲降 GREM1 在 NSCLC 细胞侵袭和 EMT 中的作用并探索其分子机制，进而探讨 GREM1 作为 NSCLC 干预靶点的可行性及其潜在临床转化价值。

方法 利用生物信息学方法筛选出与 NSCLC 关联的差异表达基因 GREM1，分析其在不同分期的 NSCLC 组织中的表达水平，并分析其表达与患者生存期间的关系；进一步收集临床 NSCLC 组织及其对应癌旁组织，应用 qRT-PCR 和 Western blot 方法检测 GREM1 在组织样本中的表达，验证生物信息学数据；采用慢病毒感染技术建立稳定过表达 GREM1 的 NSCLC 稳转细胞株；利用 siRNAs 干扰技术实现 GREM1 基因的瞬时靶向敲降。运用 Western blot 方法检测 EMT 分子标志物（E-cadherin、Vimentin 和 Snail）及 GREM1 的表达水平，评

估 GREM1 在 NSCLC 细胞 EMT 中的作用；运用划痕-愈合、Transwell 迁移和侵袭等和裸鼠转移模型等手段检测 NSCLC 细胞的迁移、侵袭和转移能力。

结果 通过生物信息学分析和临床组织样本检测，我们筛选出与 NSCLC 关联的高表达基因 GREM1，其在 NSCLC 组织中高表达，且在转移性 NSCLC 组织中进一步高表达，且其高表达与 NSCLC（LUAD）患者的不良预后相关。过表达 GREM1 能够显著促进 NSCLC 细胞的 EMT、迁移和侵袭和转移能力；而敲降 GREM1 则显著抑制 NSCLC 细胞的 EMT、迁移和侵袭和转移能力。

结论 GREM1 在 NSCLC 中表达显著上升且与患者的预后不良有关。GREM1 异常高表达可能通过激活 NSCLC 细胞 EMT 进程，进而促进癌细胞的迁移和侵袭和转移能力。将 GREM1 列为靶向治疗 NSCLC 的潜在靶点具有一定的科学与应用价值。

关键字： GREM1；非小细胞肺癌；上皮间质转化（EMT）；侵袭与转移

259. Inhibition Probe Amplification Technology for High-Throughput, Rapid, and Highly Sensitive Detection of Colorectal Cancer

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Colorectal cancer remains a prevalent gastrointestinal malignancy in China, with persistently high incidence and mortality rates. Approximately 50% of colorectal cancer patients harbor mutations in the RAS gene.In our study, we employed blocker displacement amplification (BDA) technology in combination with multiplex fluorescence PCR to detect mutations in tissues and blood samples from colorectal cancer patients. The BDA method demonstrates robust and efficient detection and enrichment of multiple rare variants, achieving a limit of detection (LoD) of approximately 0.1% variant allele fraction (VAF). Specifically, we identified common mutations in the KRAS, NRAS, and HRAS genes in both patient tissues and corresponding plasma Circulating tumor DNA (ctDNA). Additionally, we conducted a comprehensive evaluation of a model based on age at diagnosis, preoperative CEA status, and the frequency of specific mutations in colon and rectal

sublocations. We validated the accuracy of BDA mutation detection using these clinical parameters. In conclusion, our study presents a rapid, straightforward, and cost-effective method for detecting RAS gene mutations. This approach offers valuable insights into prognostic stratification, drug response, and the development of personalized genome-guided targeted therapies and immunotherapies for colorectal cancer.

Key Words： Colorectal cancer, BDA technology, RAS gene mutation, liquid biopsy technology

260. 单细胞测序揭示 WNT 信号通路对结直肠癌 mXELIRI 疗法的结局存在负面影响

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目的：结直肠癌（CRC）源于胃肠道结肠或直肠内壁的上皮细胞，是全球第三常见的癌症，也是第二致命的癌症。尽管 mXELIRI 疗法在二线治疗中显示出良好的耐受性，但其在临床应用中仍然较少，且治疗效果在不同患者间存在显著差异。通过结合单细胞转录组学和全外显子组测序技术，本研究致力于揭示这些差异背后的分子机制，并寻找潜在的分子靶标，以优化 mXELIRI 疗法在临床上的应用，提高治疗效果。

材料和方法：本研究对一组接受 mXELIRI 疗法的结直肠癌患者进行了随访，这些患者在化疗后表现出不同的治疗结果。对患者治疗前的切除肿瘤样本进行了全外显子组测序和单细胞转录组测序。通过整合这两种组学数据，确认了肿瘤上皮细胞，并根据肿瘤残余情况对患者进行了分组。利用 limma 软件包进行差异表达分析，并结合 Cellchat 软件包的细胞通讯分析结果，揭示了 mXELIRI 疗法在临床应用中的新潜在靶点。

结果：本研究通过整合全外显子组和单细胞转录组数据，确认了带有 KRAS 突变的肿瘤上皮细胞簇。这些细胞簇的 KRAS 表达量、拷贝数变异、免疫逃逸评分和增殖评分与预期结果一致。差异分析揭示了一组与结直肠癌患者生存密切相关的基因集，特别是 LCN2 基因，在肿瘤残余样本中呈现出显著的负相关表达趋势，并且与 WNT 通路活性呈负相关。此外，研究发现一簇高表达 FAP 的肿瘤相关成纤维细胞与肿瘤上皮细胞之间存在强烈的

WNT 信号通讯，这种通讯在化疗效果最差的两组患者中尤为显著。这些发现为 mXELIRI 疗法的临床应用提供了新的潜在靶点。

结论：本研究识别到一组差异基因，这些基因可能导致 mXELIRI 疗法在结直肠癌患者中产生不同的治疗结果。特别是，LCN2 基因和 WNT 信号通路及肿瘤相关成纤维细胞三者之间的相互关系的发现，为 mXELIRI 疗法在临床上的应用提供了新的靶点，有助于改善结直肠癌患者的治疗效果和生存质量。

关键字： 单细胞测序、结直肠癌、mXELIRI、肿瘤相关成纤维细胞

261. 靶向 CD73 的免疫调节性肿瘤疫苗

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研究目的: 免疫调节性疫苗常以肿瘤细胞和肿瘤微环境（TME）中抑制性免疫细胞（如 M2 巨噬细胞、MDSC、Treg 等）表面高表达的抗原作为靶点，接种后可引发内源特异性 T 细胞反应，同时杀伤肿瘤和 TME 中的抑制性免疫细胞，从而发挥双重抗肿瘤作用。CD73（又称胞外-5'-核苷酸酶）是腺苷代谢通路的一种关键酶，与 CD39 共同催化 ATP 生成免疫抑制性腺苷。CD73 在多种肿瘤细胞及抑制性免疫细胞表面高表达，可作为免疫调节性疫苗的理想靶点。在本研究中，我们预测筛选获得一条高免疫原性靶向 CD73 的免疫调节性肽疫苗，在多动物模型中验证其抗肿瘤作用，以期解除实体肿瘤微环境关键限制性因素，为实体瘤免疫治疗领域提供新的治疗模式。

材料与方法:利用在线网站（timer.cistrome.org）分析 TCGA 数据库 CD73 表达与 STAD、BRCA 等实体肿瘤患者生存的相关性，利用 SYFPEITHI、RANKPEP、NetMHCpan4.1 等在线工具预测结合小鼠 MHC-I 分子的 CD73 短肽。利用流式细胞术检测各肿瘤细胞系表面 CD73 表达水平。取健康小鼠和肽免疫后小鼠的淋巴结获得单细胞悬液，体外肽刺激后检测淋巴结 T 细胞活化程度、IFN-γ释放情况及 T 细胞对肿瘤细胞杀伤能力。在多种实体瘤模型中验证 CD73 肽疫苗的抑瘤效果和对肿瘤免疫微环境的改善作用。

结果：通过分析 TCGA 数据库发现，CD73 高表达水平与 STAD、BRCA 等多种实体肿瘤较差预后显著相关。在多种小鼠肿瘤细胞系中，小鼠乳腺癌细胞系 4T1 表面 CD73 显著高表达，故而选择 4T1 模型进行后续实验。选择预测评分最佳的两条 9-10 氨基酸的短肽（EP1，

EP2）进行合成并体外刺激小鼠淋巴结细胞，结果显示两条短肽均可诱导 T 细胞表面 CD25、CD69、CD107a、CD137 等活化指标显著上升，并诱导 IFN-γ分泌增加，激活后的淋巴结细胞在体外对 4T1 肿瘤细胞的杀伤能力显著增强。在佐剂 CpG 存在的情况下，皮下注射 EP2 在高表达 CD73 的 4T1 肿瘤模型和低表达 CD73 的 CT26 肿瘤模型中均发挥显著的抗肿瘤效果，并可通过促进 T 细胞功能、减少 M2 巨噬细胞、诱导中性粒细胞成熟等方式改善肿瘤微环境。

结论：在本研究中，我们成功预测筛选获得一条高免疫原性靶向 CD73 的免疫调节性肽疫苗，其诱导产生的特异性 T 细胞可同时杀伤肿瘤细胞及肿瘤微环境中抑制性免疫细胞，从而发挥双重抗肿瘤作用，为乳腺癌及其他类型实体肿瘤提供潜在治疗策略。

关键字： 肿瘤免疫治疗，免疫调节性疫苗，CD73，肿瘤微环境

262. Selective Enrichment of Low-Abundance DNA Variants Based on Programmable Peptide Nucleic Acid Probes and Blocker probes

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Single-nucleotide variants (SNVs) are crucial in disease development, but their accurate detection is challenging due to their low abundance and interference from wild-type targets. Simulation of the thermodynamics of DNA hybrids is an effective approach for programmable detection of SNVs. Here, we present a computational method for calculating the stacking energy of peptide nucleic acid (PNA) and DNA hybrids, leveraging nearest neighbor parameters. This computational framework enables the design of PNA toehold probes for single point mutation detection via strand displacement reaction, which were screened via simulations and experiments. Furthermore, we have applied the Blocker Displacement Amplification technique, utilizing DNA nearest-neighbor thermodynamics, to detect mutation hotspots in hepatocellular carcinoma (HCC). Our strategy involves a meticulously designed 8-plex assay capable of covering 430 mutations, which was tested in both synthetic templates and formalin-fixed, paraffin-embedded HCC tissues.

Our results demonstrate the successful application of PNA toehold probes and Blocker probes with high sensitivity and specificity, achieving a selective detection of variants with a variant allele frequency of 0.5% and 0.04%, respectively.

Key Words： SNVs detection; peptide nucleic acid; thermodynamics; BDA detection; hepatocellular carcinoma

263. 基于多重免疫荧光技术的肝癌 EMT 多分子标志物研究

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研究背景：肝癌是世界第 5 大常见癌症，也是导致癌症相关死亡的第 2 大原因。每年全世界新发肝癌病例中>50%来自我国，是我国第 4 位常见恶性肿瘤及第 2 位肿瘤致死病因。肝癌是一种具有高度侵袭性的恶性肿瘤，其快速生长和扩散能力给临床治疗带来了巨大挑战。上皮间质转化(EMT)是肝癌侵袭性的经典机制，肝癌细胞通过 EMT 过程获得间质细胞特性，增强其迁移和侵袭能力。研究目的：本研究旨在通过多重免疫荧光技术（mIHC），进行多因子、高通量和高阶形态学分析，以进一步阐明 EMT 在肝癌扩散，侵袭所发挥的分子机制。探索新技术应用于形态学研究的可行性和可信性的同时，通过 mIHC 染色和多光谱技术获得组织定量的标志分子，定量分析 EMT 标志分子（E-cadherin，N-cadherin，Vimentin）与其他肿瘤抗原（BAP31）之间的相互作用和联系，深入探究肝癌发生发展过程中 EMT 过程的分子机制。

材料与方法：我们选择了人肝癌组织微阵列芯片（TMA）为实验对象。实验采用多重荧光免疫的方法来对肝癌和癌旁的 TMA 进行染色，获得了多分子染色的多光谱图像。应用 inForm 软件对多光谱图像进行拆色和机器学习分析，得到定量的分子表达数据和共定位比例数据。应用 Graphpad Prism10 进行统计学分析。

研究结果：统计学分析表明，E-cadherin 和 N-cadherin 的在肝癌中的表达呈现高度相关，这点并不符合经典 EMT 进程的分子变化。BAP31 在肝癌中随着病理学分期增加表达降低。共定位分析发现，BAP31 与 E-cadherin 和 N-cadherin 的共定位水平高，并且 BAP31 与 E-cadherin 的共定位水平与肝癌的病理分期变化相关。

结论：本研究表明，在肝癌的进展过程中 EMT 及相关通路发挥了作用但并不是完全以经典 EMT 过程来发生发展，同时 E-cadherin 和 N-cadherin 的在肝癌中的表达呈现高度相关表明经典的 E-cadherin，N-cadherin，Vimentin 三分子标志不适合表征肝癌的 EMT 进程。BAP31 的表达下调与肝癌的进展和不良预后相关。BAP31 与 E-cadherin 共定位与肝癌进展的高度相关提示 BAP31 通过抑制 EMT 过程影响着肝癌的进展。实验结果与早些研究的结论相互佐证，证明了 mIHC 和多光谱技术在形态学研究中的可行性，为肿瘤标识的研究提供了新方法，开拓了思路。

关键字： 肝癌；EMT；多重免疫荧光技术

264. 4’-去甲基鬼臼毒素对结直肠癌的作用和机制研究

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结直肠癌(CRC)是全球范围内发病率和病死率均较高的一种流行性恶性肿瘤尽管过去几十年取得了显著进展，包括早期筛查、手术切除、放疗和化疗方面的改善，但 CRC 的治疗仍面临挑战。目前，CRC 的标准化疗方案包括奥沙利铂和 5-氟尿嘧啶/亚叶酸钙(FOLFOX)2。然而，与 CRC 相关的不良预后主要归因于肿瘤复发和化疗耐药性。因此，寻找新的有效药物对于改善患者预后至关重要。药物的利用和开发严重依赖天然产物，超过 60%的新开发药物来自天然物质。鬼臼毒素是一种选择性木脂素，其结构在 20 世纪 30 年代被阐明，因此特别有趣。通过广泛的结构修饰，鬼臼毒素为开发临床上可行的抗癌药物如依托泊苷、替尼泊苷和依托泊苷铺平了道路。DOP 是一种存在于鬼臼根和盾叶薯蓣中的木脂素类化合物。其具有针对各种癌细胞系的潜在细胞毒性一。然而，尚未报道其在结肠癌中的潜在作用和机制。因此，这是一个值得探索的主观问题。

PI3K-AKT 通路是参与调节细胞生长、增殖和存活等生理过程的重要细胞信号通路。然而，PI3K-AKT 通路的失调与结直肠癌的化疗耐药性和不良预后有关。研究表明，PI3K-AKT 通路激活的增强会使肿瘤细胞对化疗和靶向治疗产生耐药性。抑制 PI3K-AKT 通路的激活可以阻碍肿瘤细胞的生长和增殖，从而发挥抗肿瘤作用。因此，靶向 PI3K-AKT 通路的药物可作为辅助治疗药物，提高化疗和靶向治疗的疗效。

在本研究中，我们从瑶族文库中进行了一项中药文库筛选，最终确定 DOP 是一种治疗 CRC 的药物。本实验结果显示，DOP 能显著抑制 CRC 细胞的增殖，诱导大量凋亡和干细胞化。此外，我们显示 DOP 在体外使 CRC 细胞对奥沙利铂致敏。机制研究表明，DOP 通过阻断 PI3K-AKT 通路发挥其阻碍 CRC 进展，从而促进肿瘤细胞死亡，诱导细胞周期停滞在 G2/M 期，并引起 DNA 损伤。这说明 DOP 是开发 CRC 有效治疗方法的一个有前景的候选药物。

方法：细胞实验：使用不同浓度的药物处理癌细胞，观察细胞增殖、迁移、周期和凋亡的变化

动物实验：将药物处理后的癌细胞接种至裸鼠皮下，观察肿瘤的生长情况

取皮下肿瘤组织进行免疫组织化学分析

机制研究：通过 WB 等技术，研究药物对细胞内信号通路的影响

结果：1、药物显著抑制癌细胞的增殖和迁移能力

2、药物通过诱导细胞凋亡和周期阻滞抑制细胞增殖

3、在动物模型中，药物显著抑制肿瘤生长

4、药物可能通过影响某些关键信号通路发挥抗肿瘤作用

关键字： 4’-去甲基鬼臼毒素；RPA 抑制剂 HAMNO ；结肠癌 ；药物筛选

265. An ultrasensitive method for detecting mutations from short and rare cell_x0002_free DNA

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Circulating tumor DNA (ctDNA), was short and rare, making the detection performance of the current targeted sequencing methods unsatisfying. We developed the One-PrimER Amplification (OPERA) system and examined its performance in detecting mutations of low variant allelic frequency (VAF) in various samples with short-sized DNA fragments. In cell line-derived samples containing sonication-sheared DNA fragments with 50-150 bp, OPERA was capable of detecting mutations as low as 0.0025% VAF, while CAPP-Seq only detected mutations of >0.03% VAF.

Both single nucleotide variant and insertion/deletion can be detected by OPERA. In synthetic frag_x0002_ments as short as 80 bp with low VAF (0.03%-0.1%), the detection sensitivity of OPERA was significantly higher compared to that of droplet digital polymerase chain reaction. The error rate was 5.9×10-5 errors per base after de-duplication in plasma samples collected from healthy volunteers. By suppressing “single-strand errors”, the error rate can be further lowered by >5 folds in EGFR T790M hotspot. In plasma samples collected from lung cancer patients, OPERA detected mutations in 57.1% stage I patients with 100% specificity and achieved a sensi_x0002_tivity of 30.0% in patients with tumor volume of less than 1 cm3. OPERA can effectively detect mutations in rare and highly-fragmented DNA.

Key Words： Cell-free DNA, Library preparation, Liquid biopsy ,Mutation, Next-generation sequencing

266. Oleandrin inhibits cell proliferation arresting at G0/G1 phase and induces cell apoptosis by promoting pro-death autophagy in gastric cancer

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Background: Oleandrin (Ole) is one of the most pharmacological phytochemicals of Nerium oleander. Although it possesses outstanding anti-tumour effects, the underlying mechanisms of Ole on gastric cancer has yet to be elucidated.

Methods: CCK-8 and clone formation assay were used to analyse cell proliferation. Calcein/PI assays and flow cytometry were used to determine cell apoptosis. Electron microscope and confocal microscope were used to observe the morphology of autophagy. Western blot was used to determine protein levels. The in vivo anti-tumour activity of Ole was evaluated by subcutaneously injecting Luciferase-positive HGC-27 cells in Balb/c nude mice. Immunohistochemistry was used to analyse H&E staining and Ki67 level of tumor tissue. Tunel staining was used to analyse apoptosis level in tumor tissue.

Results: Our research reported that Ole remarkably inhibits proliferation of HGC-27 and SNU-1 cells by arresting cell cycle at G0/G1 phase at low nanomolar concentrations and induces apoptosis of gastric cancer cells in an intracellular apoptotic pathway. Furthermore, Ole induces gastric cancer cells apoptosis by promoting pro-death autophagy and 3-MA reverses the apoptosis induced by Ole. In vivo study also reported that Ole inhibits gastric tumor growth in a pro-death autophagy dependent intracellular apoptotic pathway with no evident damage.

Conclusions: We revealed that Ole could inhibit tumor growth by arresting cell at G0/G1 phase and induce intracellular apoptosis by activating pro-death autophagy in gastric cancer in vitro and in vivo at low nanomolar concentrations within safe dosage. Our results provide a safe and effective candidate compound as a supplement to chemotherapy for the treatment of gastric cancer.

Key Words ： Oleandrin; gastric cancer; apoptosis; autophagy; G0/G1 phase

267. ANGPTL bibliometric analysis and the function of the ANGPTL1 gene in hepatocellular carcinoma

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Objective： This study aims to address the function of the ANGPTL1 gene in hepatocellular carcinoma and to describe the state of the research on the relationship between liver cancer and angiopoietin-like (ANGPTL).

Methods： Web of Science was used to collect literature and conduct quantitative analysis. From the CCLE database, we studied the expression of ANGPTL1 in a range of cancer cell lines.The HCCDB and Human Protein Atlas databases were used to analyze the differences in mRNA and protein expression of ANGPTL1 in HCC tissues.Additionally, the correlation between ANGPTL1 gene and clinicopathological features were assessed in the TCGA database by BEST website. The correlation between ANGPTL1 mRNA and overall survival was determined by the Kaplan-Meier plotter.

Results：The bibliometric analysis results show that a total of 45 documents were compiled. There was a significant correlation between the ANGPTL1 members and the prognosis of HCC patients according to the Kaplan-Meier plotter analysis (p <0:05).ANGPTL1 are involved in certain pathways that may influence the development of HCC.

Conclusion： The investigation into how the two are related is still in its early phases. To summarize, there was a strong correlation found between the expression of ANGPTL1 and the prognosis of HCC, indicating that ANGPTL1 might be a viable molecular marker for both HCC therapy and prognosis.

Key Words：human angiopoietin-like protein 1； liver cancer； para-cancerous tissue； recurrence

268. 从 Smad1 中解救被劫持的 p300 恢复 p53 乙酰化促进胶质母细胞瘤化疗敏感性

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目的：胶质母细胞瘤（GBM）的化疗耐药是导致预后不良和总生存率低的主要原因。乙酰化已被认为是 p53 功能激活和肿瘤抑制的关键条件，然而人们对 p53 乙酰化在 GBM 中如何调节仍知之甚少。

材料与方法：通过生物信息学分析、3D 培养及 GBM 组织微阵列确定 Smad1 表达水平与 GBM 进展、患者生存的相关性。构建 Smad1 敲除及过表达 GBM 细胞系，通过流式细胞、EdU 染色等体外功能学实验及裸鼠颅内移植验证 Smad1 对 GBM 增殖、DNA 合成及化疗的影响。构建野生/突变 p53 及组成型乙酰化模拟体稳转细胞株，通过免疫印记、组织芯片、ChIP 实验、qPCR 实验、免疫荧光及免疫共沉淀实验等探究野生型和突变型 p53 在 GBM 中低乙酰化机制。通过分子对接技术和 AI 辅助筛选针对抑制 Smad1-p300 的小分子化合物，经过体内外功能学实验验证化合物抑癌效果。

结果：研究发现在 GBM 中 p53 的乙酰化，无论 p53 状态如何，都是 GBM 的积极预后标志物，机制研究显示骨形态发生蛋白（BMPs）信号的细胞内效应因子 Smad1 分别通过 MH1 和 MH2 结构域与 p53 和乙酰转移酶 p300 形成三元复合物，使 p53 远离 p300，导致 GBM 中 p53 持续低乙酰化和 Smad1 高乙酰化，协同推动肿瘤促进和化疗耐药增强。在分子

对接的引导下，我们发现 Smad1 和 p53 通常结合在 p300 的乙酰转移酶（HAT）结构域，但特异性地结合在不同的氨基酸位点。通过组合氨基酸突变破坏 Smad1 与 p300 的相互作用界面，促进 p53 乙酰化。因此，通过虚拟筛选获得的一种小分子可以直接且唯一地解离 Smad1-p300 复合物，抑制 Smad1 乙酰化导致的恶性表型，并消除突变 p53 介导的 GBM 功能获得和化疗耐药。

结论：本研究揭示了 GBM 恶性表型和化疗耐药背后的一种新的调控机制，其中 Smad1 劫持 p300 实现野生型和突变型 p53 的低乙酰化，有利于 Smad1 高乙酰化并促进致癌特性。最初，我们证明 Smad1 作为 p53/p300 结合和乙酰化的抑制机制，降低野生型 p53 肿瘤抑制因子在 GBM 中的活性。我们进一步阐明了这种抑制机制是由 p53/Smad1 在 p300 的 HAT 结构域上的竞争性结合驱动的，从而影响乙酰化。其次，我们发现在 p53 突变的 GBM 中，Smad1 更难与 p300 分离，这种高度的相互作用可能是导致 p53 突变的 GBM 化疗敏感性降低的原因之一。此外，我们首次报道了 Smad1 可以被 p300 乙酰化，确定了 K373 是决定 Smad1 致癌功能的决定性乙酰化位点。此项研究强调将 p300 从 Smad1 劫持中解放出来可能是一种有希望的 GBM 干预策略。值得注意的是，本研究发现了一种新的小分子 cpd.618，机械抑制 p300-Smad1 相互作用而不影响蛋白质稳定性，促进野生型或突变型 p53 的乙酰化。该分子抑制肿瘤细胞增殖，但需要进一步评估，包括关键的血脑屏障穿透及其对非癌细胞的毒性。

关键字： 胶质母细胞瘤；p53；乙酰化；Smad1；p300；小分子抑制剂

269. 衔接蛋白 SHF 负向调控胶质母细胞瘤中 EGFR/EGFRvIII 再循环和稳定性的 功能及机制研究

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目的：表皮生长因子受体（EGFR）异常表达、稳定性和再循环失调及突变与胶质母细胞瘤（GBM）发生发展及预后密切相关，表皮生长因子受体 III 型突变体（EGFRvIII）是最主要的突变形式，其组成型活化导致 EGFR 及相关通路持续活化。因此，促进 EGFR 及其突变体降解是靶向 EGFR 相关癌症的一种非常有潜力的替代策略。前期研究我们发现 SH2 衔接蛋白 F（SHF）可通过其 SH2 结构域结合并抑制 STAT3 同二聚化和配体依赖的 EGFR/STAT3 异二聚化。本课题将深入研究 SHF 在 GBM 中通过促进 EGFR/EGFRvIII 降解

影响其再循环和稳定性的分子机制及基于 SHF 热点结构域的靶向潜力，为 GBM 靶向治疗提供新的理论和转化基础。

方法：通过免疫共沉淀、半衰期检测和抑制剂处理等蛋白组学实验及体内外功能实验对 SHF 促进 EGFR/EGFRvIII 泛素化修饰影响其稳定性、抑制再循环的分子机制进行深入研究；通过计算机模拟蛋白对接技术分析 SHF 结合 EGFR/EGFRvIII 关键结构域，并通过分子实验、体内外实验及 PDX 等临床前模型评估热点结合域是否具有靶向潜力，进一步分析该结构域在 EGFR 多个热点突变肺癌细胞中的靶向和降解潜能。

结果：机制研究发现 SHF 可结合 EGFR 及 GBM 种最常见的突变体 EGFRvIII 并促进其 Tyr1045 磷酸化水平，招募 E3 泛素连接酶 c-Cbl 促进活化的 EGFR 和组成型活化的 EGFRvIII 泛素化修饰和降解；进一步探索了基于 EGFR/EGFRvIII 的 SHF 热点结合区域的结合和促进 EGFR/EGFRvIII 降解的功能，通过体内外功能实验发现该结构域抑制肿瘤生长的功能及对 EGFR 多个热点突变体促进降解及肿瘤抑制作用，为后续继续优化、改进及转化研究奠定了基础。

讨论：SHF 属于非典型的 SH2 衔接蛋白，我们发现其 N 端缺少富含脯氨酸的区域和磷酸酪氨酸结合（PTB）结构域，使其成为唯一对酪氨酸激酶受体信号通路具有负向调节作用的成员。前期研究中，我们发现 SHF 抑制 STAT3 同/异二聚化的研究，进一步研究发现 SHF 通过促进 EGFR/EGFRvIII 的 Tyr1045 磷酸化水平，招募 E3 泛素连接酶 c-Cbl 促进 EGFR/EGFRvIII 泛素化降解从而抑制其促癌功能，并结合生信分析和体内外实验验证了基于 SHF 结合 EGFR 及其突变体的热点结构域的靶向功能，计划基于该结构域开发和优化具有靶向功能的抑制肽。结合我们前期基于内源抑癌因子 SHF 开发的靶向 STAT3 肿瘤抑制肽 C16，有望创新目前 STAT3 和 EGFR 靶向技术，并计划进一步对这 2 种抑制肽进行系列改造、优化及联合使用，希望得到稳定性、生物利用度和肿瘤细胞靶向性更强的衍生多肽，从而实现技术补充甚至替代，提升基于多肽类药物靶向递送和治疗的研究水平。

关键字：SHF，EGFR，EGFRvIII，胶质母细胞瘤，肿瘤抑制肽

270. AR 诱导的 SOX2-OT 通过靶向 miR-320a-5p/CCR5 轴促进三阴性乳腺癌细胞增殖

张文文

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目的：我们之前的研究表明，雄激素受体（AR）能够促进三阴性乳腺癌（TNBC）细胞的肿瘤生长，但其潜在机制仍不清楚。

材料与方法：在分别使用或不使用 AR 激动剂双氢睾酮（DHT）处理的两种 TNBC 细胞系 MDA-MB-231 和 Hs578t 中，使用 lncRNA 表达谱微阵列分析来鉴定与 AR 相关的 lncRNA。利用 FISH 实验检测 lncRNA SOX2-OT 在 TNBC 细胞中的表达和定位。通过 IHC 和 ISH 检测 165 名 TNBC 患者组织芯片中 AR 和 SOX2-OT 的表达和定位。双荧光素酶报告实验来证实 AR 和 SOX2-OT 之间的转录调控关系。双荧光素酶报告实验、RNA 免疫沉淀和 RNA 下拉实验探索 miR-320a-5p 与 SOX2-OT 或 CCR5 之间的靶向关联。利用异种移植小鼠模型证明 SOX2-OT 和 CCR5 在 AR 诱导的 TNBC 体内肿瘤生长中的作用。

结果：我们发现，AR 可作为转录因子激活 SOX2-OT 的表达，从而促进 TNBC 肿瘤的发生。机制研究表明，SOX2-OT 是 miR-320a-5p 调控 CCR5 表达的分子海绵。此外，SOX2-OT 还以一种依赖于 miR-320a-5p 的方式促进 TNBC 细胞增殖和抑制细胞凋亡。通过异种移植小鼠模型，我们发现 SOX2-OT/CCR5 轴可促进 TNBC 肿瘤在体内的发生。重要的是，AR/SOX2-OT/miR-320a-5p/CCR5 信号轴在 165 例 TNBC 患者的组织样本中得到证实。

结论：我们的研究结果表明，SOX2-OT 可通过 miR-320a-5p/CCR5 信号轴调控 AR 诱导的 TNBC 肿瘤发生，这为靶向 SOX2-OT 治疗临床 TNBC 患者提供了理论基础。

关键字 ：腺癌；TNBC；AR；lncRNA；CCR5

271. Effect of recombinant cisplatin with human endostatin combined on different phase Lewis lung cancer and its relationship with VEGF and p73

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Objective： The objective of this study was to explore the antitumor effect of recombinant cisplatin(DDP) with human endostatin (rh-ES) combined on Lewis lung cancer(LLC) in the vascular normalization time window and its molecular mechanism.

Methods： Thirty LLC transplanted tumor mice were randomly divided into six groups: NS group, rh-ES group, DDP group, rh-ES +DDP(d1~d3) group, rh-ES +DDP(d4~d6) group, rh-ES +DDP(d7~d9) group, each group have 5 mices. Mices in NS group was injected saline (0.2mL/d) in d1~d9 by intraperitoneal; mices in rh-ES group was injected rh-ES (5mg/kg.d-1) in d1~d9 by intraperitoneal; mices in DDP group was injected DDP (2mg/kg.d-1) in d1~d9 by intraperitoneal; mices in rh-ES +DDP (d1~d3) group, rh-ES +DDP (d4~d6) group and rh-ES +DDP (d7~d9) group was injected rh-ES (5mg/kg.d-1) in d1~d9, and each group in d1~d3, d4~d6, d7~d9 respectively was injected DDP(2mg/kg.d-1) by intraperitoneal. To observe the situation of tumor lung metastasis, changes of tumor VEGF, p73 and microvessel density（MVD）were detected by immunohistochemistry.

Results： Compared with each single drug group, the tumor volume of rh-ES combined with DDP group increased slowly and lowest expression rate of VEGF、MVD、p73，especially in rh-ES +DDP (d4-d6) group, the volume of LLC were the least ($P < 0.05$). The expression rates of VEGF and p73 were the lowest ($P < 0.05$), and the MVD value was the lowest ($P < 0.05$).

Conclusion： The inhibitory effect of recombinant human endostatin combined with cisplatin on tumor cell growth was significantly better than that of monotherapy.

Key Words ： recombinant human endostatin；cisplatin；lung cancer；MVD；VEGF；p73；

272. Clinical value of JAM3 and PAX1 gene methylation detection in cervical intraepithelial lesions and cervical cancer

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Objective: The methylation levels of JAM3 and PAX1 genes in cervical biopsy tissues were detected by multiplex PCR with specific fluorescent probe. To investigate the DNA methylation level of JAM3 and PAX1 genes in different degree of cervical lesions, combined with HPV, cytology and colposcopy results. To compare the methylation level of each gene in each group, to analyze its role in the occurrence and development of cervical cancer, to explore the relationship between gene methylation level and different types of HPV infection The advantages and disadvantages of JAM3, PAX1 gene methylation detection and HPV detection were compared.

Data and methods: from June 2020 to June 2023, patients were treated in the fifth people's Hospital of Chengdu, 15 patients with low-grade cervical intraepithelial lesion, 15 patients with high-grade cervical intraepithelial lesion, and 15 patients with cervical cancer were divided into three groups: LSIL Group, HSIL Group and LCC Group. Fifteen healthy women were collected as Healthy Control Group (NLM group) . The results of HPV typing, cytology and colposcopy or histopathology were collected, the methylation levels of JAM3 and PAX1 genes in cervical exfoliated cells were detected by specific multiplex PCR with fluorescence probe.

Results: 1. The methylation levels of JAM3 gene in exclaved cells of the control group, the LSIL group, the HSIL group and the cervical cancer group were 39.55±1.11、37.44±2.14、35.27±1.32、31.48±1.78,respectively, and the differences among groups were statistically significant (F=63.21,P<0.05)； The methylation level of PAX1 gene was 38.56±2.21、36.31±1.10、34.22±2.12、33.33±1.18, respectively, and the difference between groups was statistically significant(F=87.21，P<0.05). 2.In patients infected with HPV16/18 (high-risk carcinogenic type), the positive rates of JAM3 and PAX1 gene methylation were 87.5%and79.2% ; The positive rates of JAM3 and PAX1

methylation were 45.2% and 48.4% in patients infected with non-16/18 HPV. The positive rates of JAM3 and PAX1 methylation in patients with negative HPV test were 20.0% and 20.0%, with statistical differences among all groups (P<0.05). 3.The methylation levels of JAM3 and SOX1 genes were detected, and the ROC curves were drawn to distinguish cervical cancer from non-cancer cancer, and the areas under the ROC curves were measured, which were 0.7818(P<0.05)和 0.7810(P<0.05) ,respectively. By calculation, when the cut-off value of PAX1 methylation level was 32.05, the diagnostic efficiency was the best, and the sensitivity and specificity of PAX1 methylation level were 85.9% and 88.0% in the diagnosis of cervical cancer. By calculation, when the cut-off value of JAM3 methylation level was 31.08 the diagnostic efficiency was the best, and the sensitivity and specificity of the diagnosis of cervical cancer were 85% and 92%. 4.The positive rate of methylation of PAX1 gene was 100% , and more than 51.22% of HPV positive cases were confirmed by human papillomavirus test, the specificity was 93.22% , the sensitivity was 88.76% , the negative predictive value was 96.77% , and the positive predictive value was 82.98% .

Conclusion: 1. The methylation of JAM3 and PAX1 genes was found in cervical lesions and cervical carcinoma, and the methylation level of cervical tissue increased with the development of cervical lesions. 2.The methylation levels of JAM3 and PAX1 genes were associated with HPV infection types, and the methylation levels of JAM3 and PAX1 genes were higher in patients infected with HPV 16/18 high-risk oncogenic types. 3.JAM3 and PAX1 gene methylation tests have high sensitivity and specificity in the diagnosis of cervical invasive cancer, and the best truncation values (32.05 and 31.08) of JAM3 and PAX1 gene methylation tests according to ROC curve can be used in the differential diagnosis of cervical cancer. 4.The methylation of PAX1 and JAM3 genes was detected with high specificity. The combined detection of JAM3 and PAX1 gene methylation was superior to the single detection.

Key Words ： cervical squamous intraepithelial lesions 、cervical cancer、 JAM3 PAX1 DNA methylation

273. Prediction of the causal relationship between immune cells and lung cancer based on two-sample Mendelian randomization

Shuai Li,Lang He

Chengdu Fifth People's Hospital

Objectives: Lung cancer is one of the most prevalent malignant tumors worldwide. Despite extensive research, its etiology and pathogenesis remain incompletely understood. Recent studies have indicated a potential association between immune cells and lung cancer, although the exact causal mechanisms are still unclear. Our objective is to investigate the role of immune cells in the development of lung cancer.

Methods: We conducted a comprehensive analysis using data from two genome-wide association studies (GWAS). The first GWAS included summary statistics of immune cell traits obtained from a large cohort of 492,803 participants, consisting of 3791 lung cancer cases and 489,012 controls. The second GWAS utilized immune cells subsets from a distinct group of 3,757 individuals from Sardinia. Our investigation focused on genetically predicted immune cells. To assess the causal relationship between immune cells and lung cancer, we employed various statistical models, namely inverse variance weighting (IVW), MR-Egger, weighted median, and weighted models. These models provided robust estimates of the causal effects. Additionally, sensitivity analyses were conducted to evaluate thepresence of heterogeneity and horizontal pleiotropy.

Results： Our IVW analysis revealed several immune cell traits that were significantly associated with lung cancer risk.Immune cell traits that showed an inverse association with lung cancer risk included CD39+ secreting Treg %secretingTreg, CD8br AC, BAFF-R on IgD-CD38dim, BAFF-R on memory B cell, CD20 on B cell, CD28 on activated Treg,CD45 on CD33br HLA DR+ CD14dim, CD4 on CD39+ resting Treg, and CD39+ secreting Treg %CD4 Treg. On the other hand, some immune cell traits exhibited a positive correlation with lung cancer risk. These included Unswmem AC, IgD-CD38dim % B cell, IgD+ CD38br % B cell, CD25hi AC, EM CD4+ AC, T cell % lymphocyte, HLA DR+ CD4+ % lymphocyte, CD28- DN (CD4-CD8-) % T cell, CD3 on CD28+ CD4+, CD25 on CD39+ CD4+, CD45 on basophil, and SSC-A on myeloid DC.

Conclusions: Our two-sample Mendelian randomization study confirms a causal association between genetic predisposition to immune cell phenotypes and lung cancer, and these findings will provide new clues for the improvement of future personalized immunotherapy for lung cancer patients

Key Words ： immune；lung cancer；mendelian randomiztion(MR)；genome wide association study (GWAS)

274. Efficacy and safety of EGFR-TKI combined with WBRT versus WBRT alone in treatment of brain metastases from NSCLC: A systematic review and meta-analysis

Shuai Li,Lang He

Chengdu Fifth People's Hospital

Objective: The efficacy and safety of combining epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) with whole-brain radiotherapy (WBRT) in the management of brain metastases originating from non-small cell lung cancer remain unclear.

Methods: A systematic search was conducted utilizing databases including Pubmed, Embase, Web of Science, Cochrane, Wanfang, and China Knowledge Network, with the aim of identifying relevant clinical studies pertaining to the treatment of brain metastasis originating from non-small cell lung cancer through the combination of EGFR-TKI and WBRT. Statistical analysis was subsequently performed utilizing Stata 17.0 software. The search encompassed clinical studies published up to March 1, 2023.

Results: In total, 23 randomized controlled trials (RCTs) encompassing 2,025 patients were incorporated into this analysis. Of these, 1,011 were allocated to the EGFR-TKI+WBRT group, while 1,014 were assigned to the WBRT alone group. The study results demonstrate that combining EGFR-TKI with WBRT leads to improved intracranial objective remission rate (RR=1.57, 95%CI:1.42-1.74, P<0.001), an elevated intracranial disease control rate (RR=1.30, 95%CI:1.23-1.37, P<0.001), and a significantly enhanced one-year survival rate (RR=1.48,

95%CI:1.26-1.73, P<0.001). Additionally, a notable survival advantage and a reduced incidence of adverse effects were observed (RR=0.55, 95%CI:0.44-0.68, P=0.001). This advantage is particularly significant in the context of nausea and vomiting (RR=0.54, 95%CI:0.37-0.81, P=0.002) and myelosuppression (RR=0.36, 95%CI:0.20-0.68, P=0.001). However, the observed differences were not statistically significant in the instances of diarrhea (RR=1.15, 95%CI:0.82-1.62, P=0.42) and skin rash (RR=1.35, 95%CI:0.88-2.07, P=0.16).

Conclusions: In contrast to WBRT alone, EGFR-TKI combined with WBRT demonstrates notable efficacy in eliciting a favorable intracranial response. This combined therapeutic approach significantly enhances the objective intracranial response rate, disease control rate, and one-year survival rate among NSCLC patients with brain metastases. In addition, with the exception of mild rash and diarrhea, there is no statistically significant increase in the incidence of other adverse effects. Based on the cumulative evidence from these studies, the third-generation EGFR-TKI combined with WBRT is recommended as the first choice for NSCLC patients presenting with brain metastases, providing optimal control over metastatic lesions within the brain.

Key Words： EGFR-TKI; WBRT; non-small cell lung cancer; brain metastases; RCT

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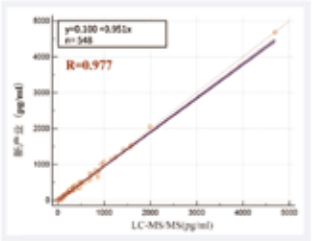

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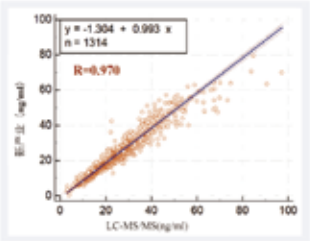
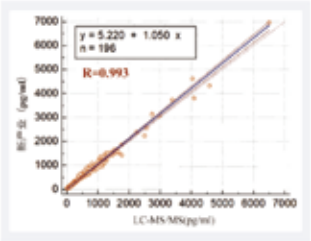


25-羟基维生素D



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癌胚抗原检测试剂盒（磁微粒化学发光法）	18 个月
糖类抗原 CA19-9 检测试剂盒(磁微粒化学发光法)	18 个月
糖类抗原 CA15-3 检测试剂盒（磁微粒化学发光法）	18 个月
糖类抗原 CA72-4 检测试剂盒（磁微粒化学发光法）	18 个月
糖类抗原 CA125 检测试剂盒（磁微粒化学发光法）	18 个月
糖类抗原 CA50 检测试剂盒(磁微粒化学发光法)	18 个月
糖类抗原 CA242 检测试剂盒（磁微粒化学发光法）	18 个月
前列腺特异性抗原检测试剂盒（磁微粒化学发光法）	18 个月
游离前列腺特异性抗原检测试剂盒（磁微粒化学发光法）	18 个月
鳞状细胞癌抗原检测试剂盒（磁微粒化学发光法）	18 个月
细胞角蛋白 19 片段检测试剂盒（化学发光法）	18 个月
神经元特异性烯醇化酶检测试剂盒（磁微粒化学发光法）	18 个月
胃泌素释放肽前体检测试剂盒（磁微粒化学发光法）	18 个月
人附睾蛋白 4 检测试剂盒（磁微粒化学发光法）	18 个月
胃蛋白酶原 I 检测试剂盒（磁微粒化学发光法）	18 个月
胃蛋白酶原 II 检测试剂盒（磁微粒化学发光法）	18 个月
胃泌素 17 检测试剂盒（磁微粒化学发光法）	18 个月
铁蛋白检测试剂盒(磁微粒化学发光法)	18 个月
异常凝血酶原检测试剂盒（磁微粒化学发光法）	18 个月
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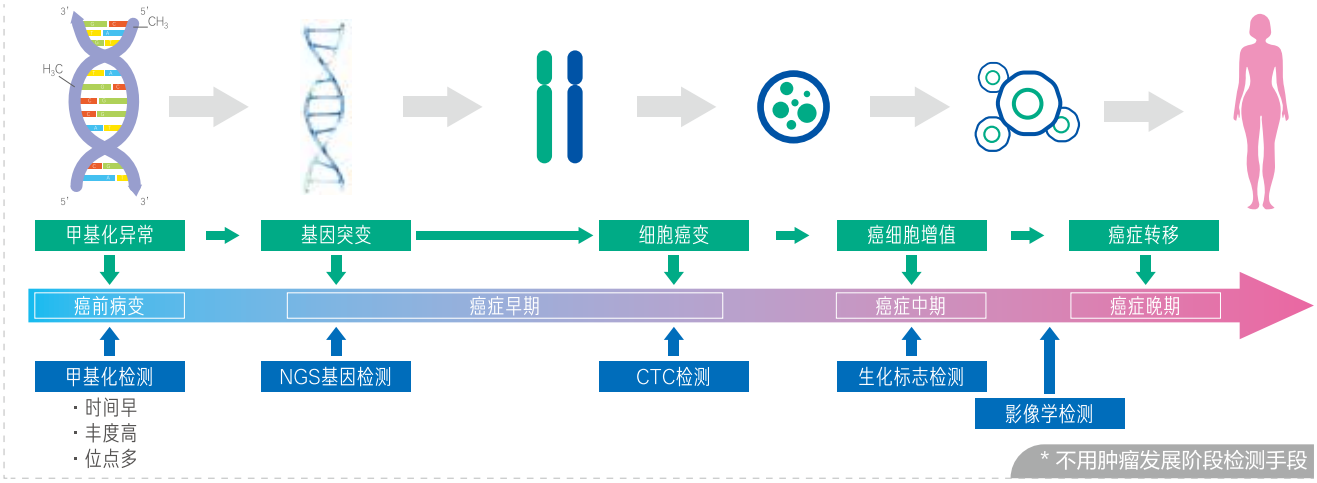
大量的DNA甲基化变异贯穿于正常细胞变为肿瘤细胞的全过程，且发生于肿瘤超早期，超前于基因突变。



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癌种可匹配报销政策

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筛查
癌症早期甲基化筛查

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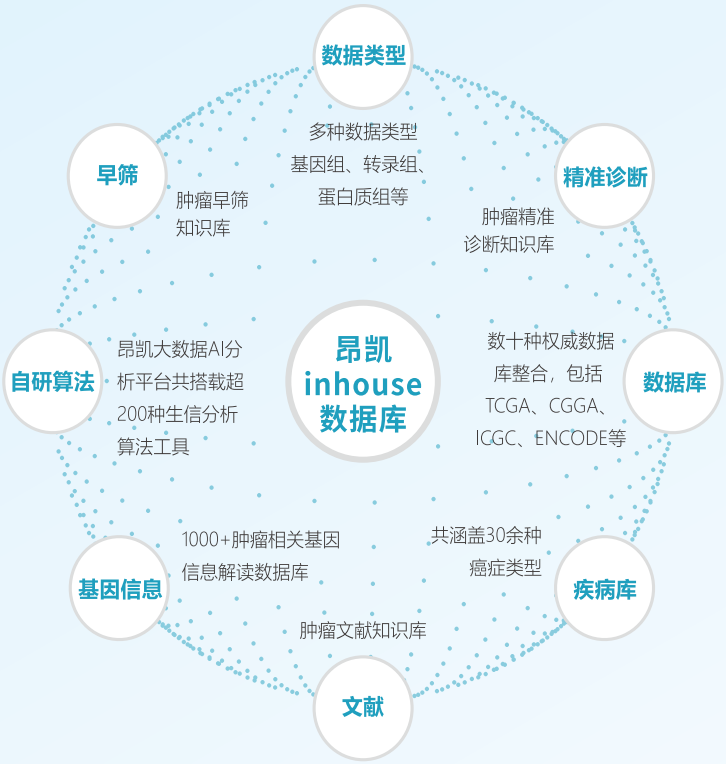

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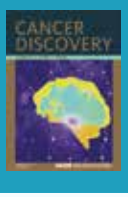

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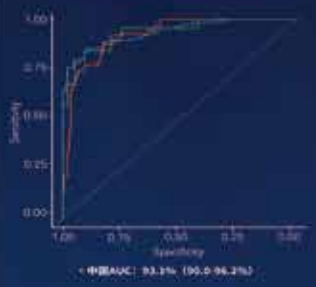
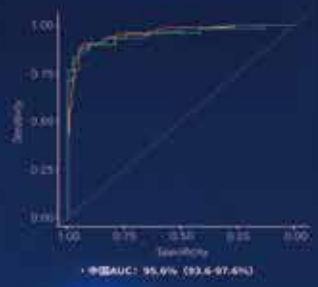


- 中国AUC：93.1%（90.0-96.2%）

所有HCC VS 慢性肝病



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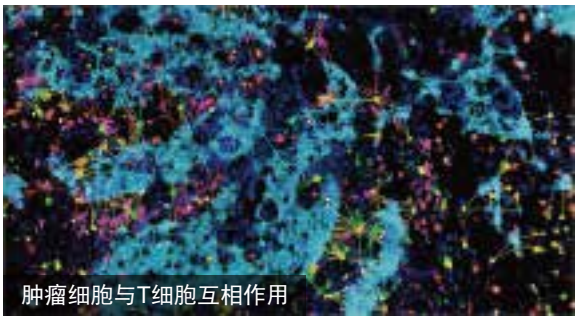
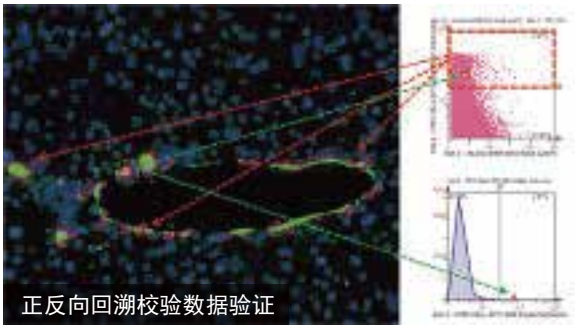


肿瘤细胞与T细胞互相作用



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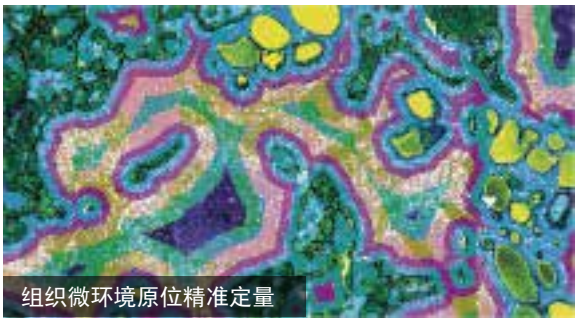
肿瘤微环境/标志物检测/肿瘤转移/肿瘤干细胞/肿瘤免疫/肿瘤侵袭能力/肿瘤转移能力等对肿瘤标记物的表达情况进行分析定量，对蛋白（核蛋白、膜蛋白、胞质蛋白等）阳性表达的空间立体信息进行定量分析，蛋白表达变化进行评估，以评价纳米抗肿瘤药物的药效。免疫因子、免疫识别活化、免疫效能、自身免疫性疾病等免疫微环境影响特异性蛋白表达及其调控相关机制，对阳性细胞数，空间分布进行定量分析。



组织微环境原位精准定量

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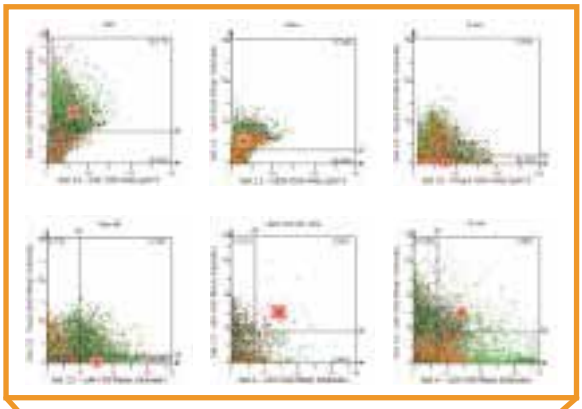
神经干细胞、星形胶质细胞、脑功能、神经退行性疾病，如帕金森、阿尔兹海默等细胞体和神经突起的大小、长度、分支数量进行识别定量，并根据不同功能与不同区域，区分单极、多级神经元。利用形态学识别的方法，在多种不同样本类型中，识别出神经元胞体和突起。按照神经元外型的差异，在免疫组化样本中，对细胞体和神经突的大小、长度、分支数量进行识别定量，并根据不同功能与不同区域，区分单极、多级神经元。



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- 动植物基因组De Novo
- 微生物基因组De Novo
- 人基因组重测序(遗传病)
- 人基因组重测序(感症)
- 小基因组测序

转录组测序
- 常规RNA测序
- 链特异性RNA测序
- 无参转录组测序
- LncRNA测序
- Small RNA测序
- 全转录组测序

10x单细胞测序
- 单细胞转录组测序
- 单细胞V(D)J免疫组库测序
- 单细胞CRISPR Screen测序

基因编辑检测
- CRISPR Screening
- CRISPR on/off-target突变检测(Amplicon-seq)
- CRISPR on/off-target突变检测(WGS)

靶向测序
- 扩增子测序
- 外显子组测序(遗传病)
- 外显子组测序(感症)
- 人目标区域捕获测序
- 整合位点测序

表观遗传学
- WGBS
- ChIP测序
- ATAC测序
- Cut&Tag

药企合规服务
- 生产细胞株安评服务
- 细胞治疗安评服务
- 基因治疗安评服务
- RNA药物安评服务
- 工程菌安评服务

三代测序
- 真菌精细图
- 细菌完成图
- 全长有参转录组测序
- 全长无参转录组测序
- 全长16S测序
- 三代扩增子测序
- 三代宏基因组测序

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- 抗体文库测序
- 免疫组库测序
- 杂交瘤抗体测序
- 单细胞免疫组

特色服务
- Olink蛋白组学检测
- 代谢组学
- 蛋白组学

宏基因组学
- 16S/18S/ITS测序
- 宏基因组测序
- 宏转录组测序
- 宏病毒组测序

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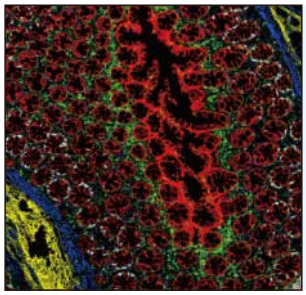
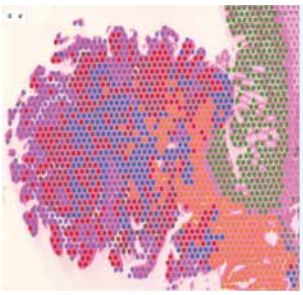
空间多组学技术平台

INFINITY SCOPE



成像质谱流式
(Imaging Mass Cytometry，IMC)

40+ 标志物同时检测，唯一一个无自发荧光干扰的平台。

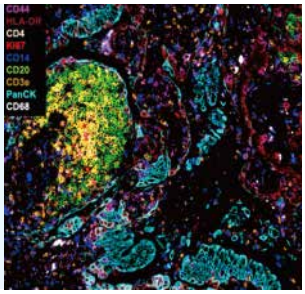


Visium CytAssist

在进行H&E形态学成像的同时，在50μm分辨率下绘制整张组织切片上的转录组图谱

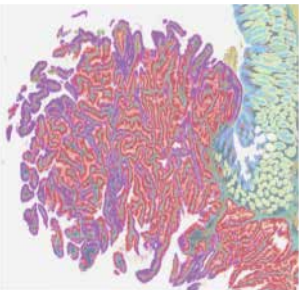
超多色原位荧光成像
(CODEX/PhenoCycler-Fusion)

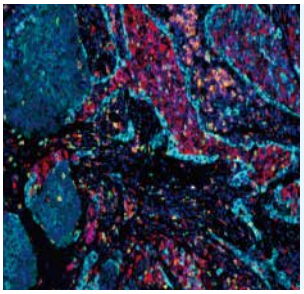
全片扫描绘制数百万个细胞表型、位置和相互作用的图谱。



10x Visium HD

基于2μm分辨率检测组织的转录本信息，以单细胞分辨率进行生物学分析



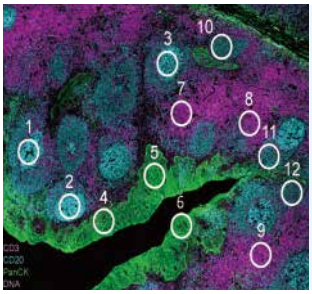


多重免疫荧光
(Multiplex Immunohistochemica，mIHC)

同步检测7-9种生物标志物，揭示组织空间异质性与复杂性疾病机制。

DynaSpatial & DynaSpatial HD

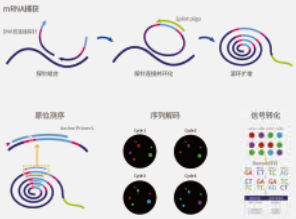
同样测序深度下比较基因总数和基因中位值，基因检出率比其他平台高约10%



GeoMx Digital Spatial Profiler (DSP)

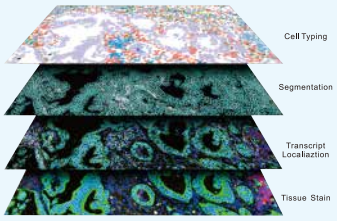
在200μm 分辨率下进行组织原位检测，实现多靶标蛋白和转录组的空间原位表达谱分析

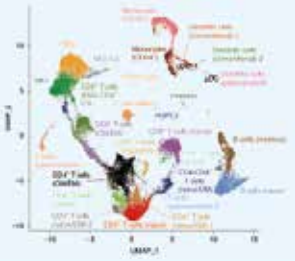
亚细胞水平定量细胞内多达上百种RNA的表达



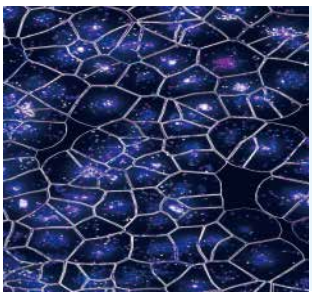
CosMx Spatial Molecular Imager (SMI)

在单细胞空间原位对6000+个基因的检测分析，实现单细胞研究的空间组学跃迁





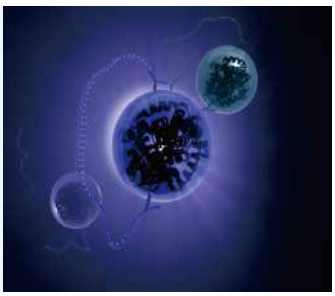
scRNA-seq
scTCR&BCR-seq
CITE-seq
FFPE单细胞测序
ONT单细胞全长测序



10x Xeium

以亚细胞分辨率观察同一张组织切片中的数百条RNA转录本和蛋白

精准检测微量样本的数千种蛋白表达



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电话:17305819912(微信同号)

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mRNA合成解决方案
小分子/生物试剂一站式供应

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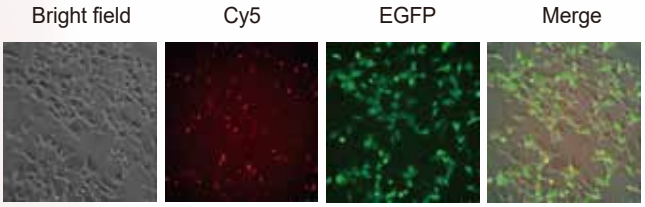
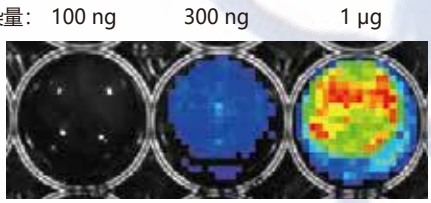


ARCA Cy5 EGFP mRNA (5-moUTP) in 293T cell;
48 hours post transfection



EZ CapTM Firefly mRNA (LNP) HeLa细胞转染效率测试

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关于APExBIO

APExBIO（APExBIO Technology LLC）拥有国内领先的mRNA体外转录合成平台，可生产克级高纯度的mRNA产品，并提供用于体外合成mRNA所需的修饰核苷酸、转录酶、加尾酶等各种原料，和完整的mRNA定制合成和LNP包装服务。

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联系电话：021-55669583

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	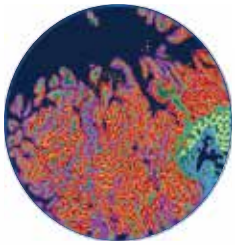	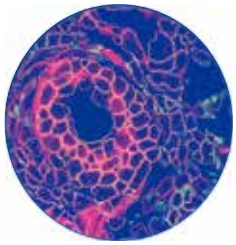
无偏的细胞发现	**无偏的空间发现**	**精确的单细胞空间分析**
全转录组	全转录组	几百至上千个转录本
转录组，VDJ，CRISPR gRNAs，蛋白质，染色质	转录组、蛋白质、组织形态学	靶向RNA、蛋白质、组织形态学
基于测序方法	基于测序方法	基于高分辨率的图像
单细胞分辨率	单细胞级别的清晰度	亚细胞分辨率
高度灵敏和全面的基因检出	全面的基因检出	高度灵敏的基因检出

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- 非标记蛋白质组定量（Label Free）
- 外周血单核细胞蛋白质组
- 宏蛋白质组
- 数据非依赖性蛋白质组定量（DIA）
- TMT标记蛋白质组定量
- 蛋白鉴定
- 蛋白质组靶向定量(PRM)
- 神经肽组
- 空间蛋白质组
- 外泌体蛋白质组

【蛋白修饰组】

- 糖基化修饰组
- 泛素化修饰组
- 磷酸化修饰组
- 乙酰化修饰组
- 甲基化修饰组

【基因组学】

- 全外显子测序
- 基因组重测序
- 微生物多样性
- 微生物基因组测序

【转录组学】

- 真核转录组测序
- 全转录组测序
- 空间转录组测序
- 单细胞转录组测序
- Small RNA测序
- miRNA测序

【转录因子组】

- 转录因子组（TFRE）
- 染色质开放域转录因子组

【代谢组学】

- 靶向代谢组学
- 非靶向脂质组学
- 非靶向代谢组学

【多组学整合分析】

上海爱谱蒂康生物科技有限公司是一家独立运营的、具有公信力的、专注于大健康领域的生物科技公司，致力于整合基础科研技术服务、生物医药质量分析服务、伴随诊断服务为一体的全流程解决方案，可不同程度的满足医疗机构、医药企业、各大相关高校、研究院的技术咨询、分析服务等需求。

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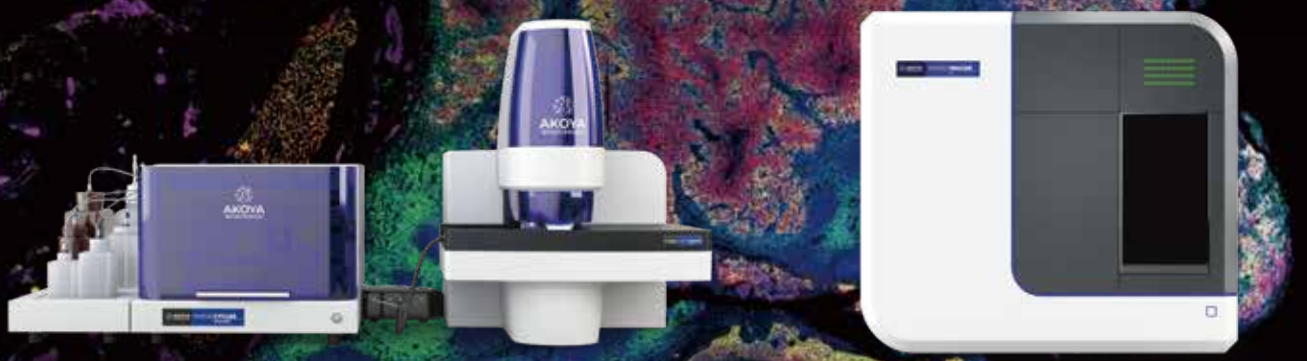

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实现 100+ 生物标志物检测

PhenoImager HT

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生物标志物定量分析	肿瘤微环境空间图谱	免疫细胞多样性
队列研究及患者分层	肿瘤微环境细胞通讯	疫苗及药效评估
体内外药效研究	肿瘤标志物原位分析	肿瘤免疫调控机制

Biomarker研究专家

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特点	组学或芯片进行生物标志物筛选 覆盖全，灵敏度高，重复性高 信息量大，专业数据分析很重要	对筛选结果进行验证，样本多， 指标多，可定量	诊断or药物研发 应用于临床实践或生物医学领域

指标数量	5000+	5000-1000	1000-100	100-10	10-1
核酸	基因芯片 单细胞转录组测序 DSP空间转录组	基因芯片 单细胞转录组测序 DSP空间转录组	基因芯片	多因子PCR阵列	荧光定量QPCR RNA原位检测
蛋白	抗体芯片 蛋白芯片	蛋白芯片 抗体芯片	蛋白芯片 抗体芯片 单细胞蛋白组测序 DSP空间蛋白组	液相芯片Luminex 流式细胞术 超敏电化学发光MSD 流式液相CBA 单细胞蛋白组测序 DSP空间蛋白组	酶联免疫ELIEA 酶联免疫斑点Elispot 超敏化学发光MSD 多色免疫组化 可视化蛋白互作PLA

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武汉友芝友医疗科技股份有限公司成立于2011年7月，以心血管、肿瘤等重大疾病的个体化诊疗为战略方向，是一家专门从事个体化医学诊断产品研发、生产和销售的高新技术企业。公司建立了ARMS荧光定量PCR、多重荧光定量PCR、核酸质谱、荧光原位杂交及循环肿瘤细胞检测等多种技术平台，自主研发生产了指导心脑血管疾病个体化用药的分子诊断产品，指导肿瘤诊疗的伴随诊断产品，荧光原位杂交产品以及循环肿瘤细胞检测产品，为精准医疗提供临床诊断依据。公司建设了2000㎡的研发中心和3200㎡GMP标准的产业化车间，成功开发了160余个基因诊断产品和多款体外诊断设备，其中110余个分子诊断试剂盒及体外诊断设备通过欧盟CE认证，16个分子诊断试剂盒获得NMPA三类医疗器械注册证。

公司被评为高新技术企业、国家基因检测技术应用示范中心、湖北省企业技术中心、湖北省专精特新“小巨人”企业、国家知识产权优势企业、湖北省知识产权示范建设企业、湖北省第三批支柱产业细分领域隐形冠军培育企业、武汉市“企业研究开发中心”、武汉市首批“千企万人”支持计划企业、省市区三级上市后备“金种子”企业，2016年至2022年各年度东湖高新区“瞪羚企业”。公司于2018年和2020年先后获得山东省和湖北省科技进步一等奖，并获得2020年中华医学科技奖二等奖。

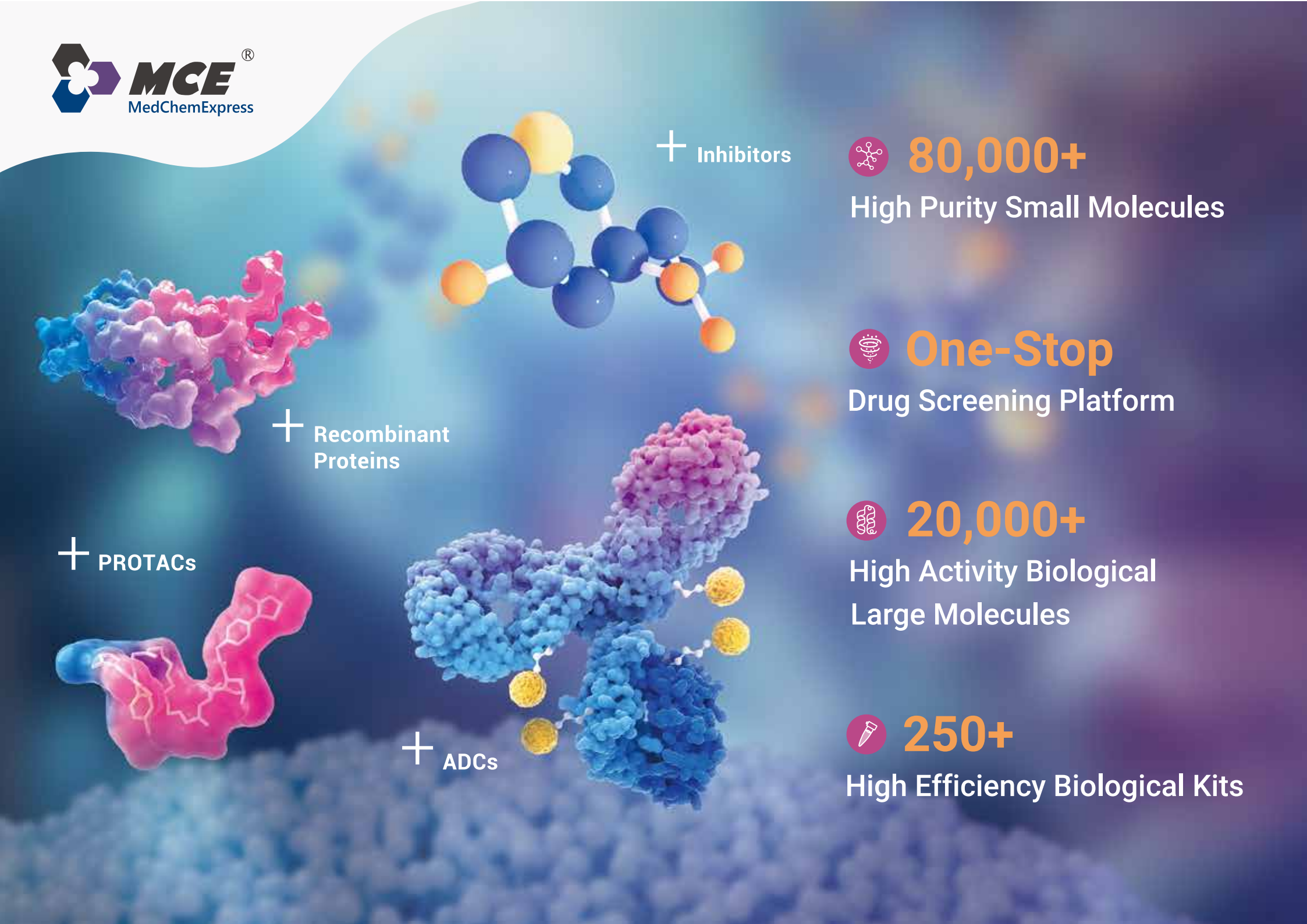
公司注重创新研发，已申请专利110余项，获得专利授权70余项。研发团队60余人，多人拥有海外或行业知名企业工作经历。公司产品已陆续进入全国各地600余家大中型医院使用并获得良好的市场反馈，在个体化医学领域树立了行业地位。

芝友医疗秉承“量体裁衣、因人施治”的企业使命，矢志成为个体化诊疗细分领域的龙头企业。

YZY MED
友芝友医疗科技

武汉友芝友医疗科技股份有限公司
Wuhan YZY Medical Science and Technology Co.,Ltd.
地址：武汉光谷国际生物医药企业加速器1.2期23号楼一单元4、5层
电话：4008-013-133 传真：027-65330986 邮编：430075

MCE®
MedChemExpress



80,000+
High Purity Small Molecules

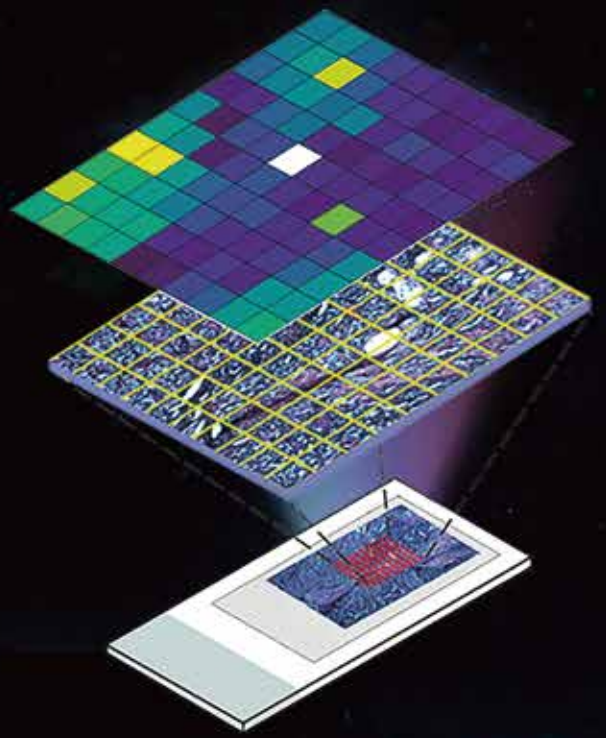
One-Stop
Drug Screening Platform

20,000+
High Activity Biological Large Molecules

250+
High Efficiency Biological Kits

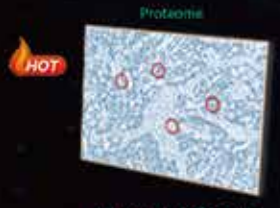
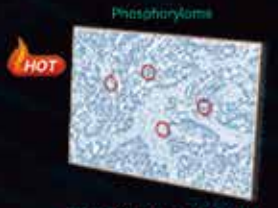
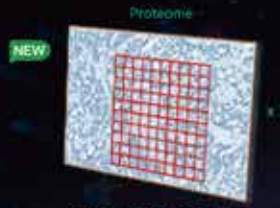
景杰生物
PTM BIO

划时代-
全息空间蛋白质组学



- 全面覆盖空间微环境的蛋白表达信息
- 从靶向到覆盖的空间蛋白组学革新发展
- 空间多组学联合的最佳方式

景杰生物空间蛋白组学整体性解决方案

分析方案	 经典空间蛋白组	 空间磷酸化修饰组	 全息空间蛋白组
数据量	单切片精准选取多个**点位** **分别检测蛋白组**	单切片精准选取多个**点位** **分别检测磷酸化修饰组**	单切片精准选取多个**区域** **分别检测区域中100个蛋白组**
组织兼容性	FFPE样本 新鲜冷冻样本 固定冷冻样本	新鲜冷冻样本 固定冷冻样本	FFPE样本 新鲜冷冻样本 固定冷冻样本

杭州景杰生物科技股份有限公司
TEL：400-100-1145
网址：www.ptm-biolab.com.cn
地址：浙江省杭州市钱塘新区福城路 291 号生物医药港小镇二期 8 号楼

精准医学与蛋白组学　景杰生物

Promega

Promega 微卫星不稳定

(MSI)检测技术

林奇综合征
Lynch Syndrome

免疫检查点抑制剂
PD-1 Inhibitors

结直肠癌
Colorectal Cancer

5-FU类化疗药物的选择
5-FU class chemotherapy drugs

久经验证的“金标准”检测方法

- NCCN指南和专家共识推荐
- 与默沙东，GSK, Incyte 及 Henlius 等知名药企合作开发Promega MSI检测技术作为其PD-1抑制剂的伴随诊断（CDx）试剂
- 已在市场中超过15年以上
- 超过260篇的同行评审文章发表

提供从样本制备到毛细管电泳的全面解决方案

扫描上方二维码联系
Promega 分子诊断

bio-techne®

NO.1

CiteAb 2024年ELISA试剂盒年度供应商大奖

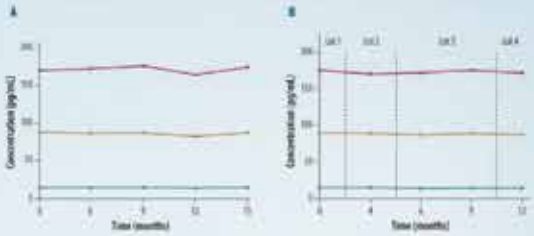
金标准ELISA试剂盒

- ELISA试剂盒金标准
- QC达到最严苛的诊断用试剂质控标准
- 助力CRO和药企安全可靠研发
- 种类繁多

文献引用占比

高性价比ELISA试剂盒

- 业内领先品质
- 高稳定性/批次间一致性
- 国内现货
- 控制成本优选



稳定性和可重复性

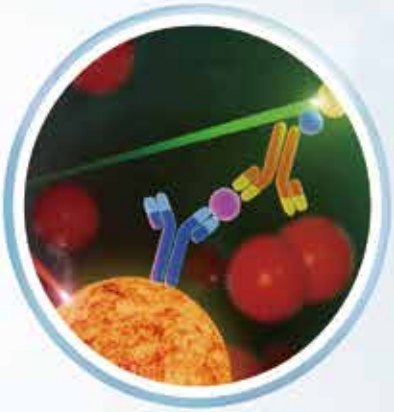
多因子检测助力肿瘤Biomarker筛选

NO.2

Luminex多因子检测试剂盒

Luminex多因子检测优势:

- **节约样本**:25μL/单孔,同时定量50个指标!
- **效率高**:是ELISA工作效率的50倍!
- **高通量**:480+指标库,可自由组合!
- **控制成本**:多因子检测,性价比高



明星产品推荐

产品名称	Human XL Cytokine Luminex® Performance Assay
货　　号	LKTM014B
指　　标	46

NO.3

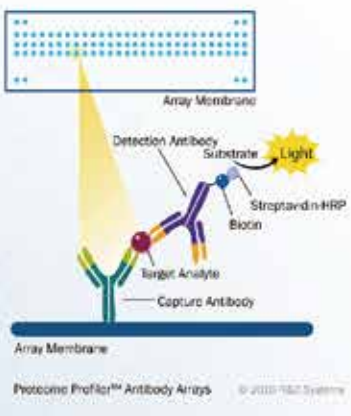
固相抗体芯片

- 高通量WB技术,更高效
- 每张膜最多可检测119个指标,一天内即可完成
- 无需特殊设备
- 样本兼容性强,节约样本用量

明星产品推荐

产品名称	Proteome Profiler Human XL Oncology Array
货　　号	ARY026
指　　标	84

扫码咨询



异常糖链糖蛋白(TAP)与肿瘤密切相关

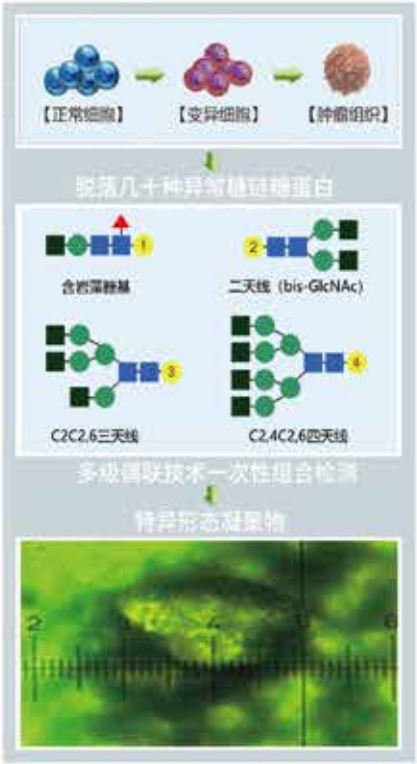
Tumor of Abnormal Protein (TAP) is closely related to tumor.

- 正常细胞恶变(肿瘤发生)时，通常没有明显的症状，所以我们不能及时察觉。但是，现代医学证明，肿瘤发生发展时会在血液中留下"痕迹"，国内外学术界公认糖基化异常与肿瘤密切相关。正常细胞恶变时，糖蛋白上的糖链结构发生异常改变，产生几十种糖链结构异常的糖蛋白(简称TAP)，当肿瘤发生发展时，血液中异常糖链糖蛋白TAP含量升高，它是早期发现肿瘤的重要线索。

异常糖链糖蛋白(TAP)检测

Tumor of Abnormal Protein (TAP) Examination.

- TAP检测通过独家专利的异常糖链组合检测(多级偶联技术)，在同一反应体系中，将二十多种与肿瘤密切相关的糖链结构异常的糖蛋白，进行一次性组合检测，敏感度和特异性高，可检测的肿瘤种类多。



异常糖链糖蛋白(TAP)检测项目用途

- 用于慢病和异常体征的肿瘤早期筛查和风险评估，可实现早诊早治，降低肿瘤发病率、死亡率。
- 用于临床病人和体检人群的肿瘤早期筛查，可减少肿瘤漏检、早期预警肿瘤风险。
- 用于肿瘤辅助诊断、疗效评估和复发转移监测，是病理诊断和肿瘤标志物检测的有益补充，可提高肿瘤诊断准确率。

项目荣誉

- TAP检测项目是国家973项目的产业化应用，是国家科技部主导引进的国际先进科技成果，是科技部验收合格的国家双引项目和国际科技合作重点项目，被列为国家火炬计划项目。

TAP早癌检测特点:早、全、准

TAP early cancer Examination: early, comprehensive and accurate.

早诊一例癌　挽救一条命　幸福一家人

RayBio
Empowering your proteomics

全能疾病标志物筛选专家

从单个指标匹克级检测，到一个样本8000个指标整体标志物检测解决方案

品种齐全（超16种种属） 海量抗体库（上万靶标） 高通量（多因子/大样本） 全方位

1 Target
ELISA

▶常规蛋白、低丰度蛋白、小分子、多肽检测/验证
▶药物疗效分析：药物反应检测，药物抗体/抗药物抗体含量分析
▶疫苗研发：受体-配体结合度分析

热门分类

细胞因子：IL系列、CSF系列、TNF系列、INF系列、趋化因子系列.....
磷酸化检测：AKT（S473）、AMPKa1 (S487)、JAK2 (Y1007/1008)、Jak1 (Y1022)、Stat(Y705) .....
药物/抗药物抗体：阿达木单抗、帕姆单抗、贝伐珠单抗、利妥昔单抗、帕妥珠单抗、阿替利珠单抗、西妥昔单抗.....

明星产品

细胞因子系列：ELH-IL6、ELH-IL8、ELH-TNFα、ELH-VEGF、ELH-INFγ、ELH-TGFβ、ELH-IP10.....
磷酸化检测系列：PEL-AKT-S473-T、PEL-Erk-T202-T、PEL-EGFR-Y1068-T、PEL-eNOS-S1177-T.....
药物抗体检测系列：EAD-Adli、EAD-Pemb、EAD-Nivo、EAD-Beva、EAD-Ritu、EAD-Uste、EAD-Tras.....
抗药物抗体检测系列：EAD-AnAdli、EAD-AnPemb、EAD-AnNivo、EAD-AnBeva、EAD-AnRitu.....

2-25 Targets
流式多因子

▶生物标志物筛选：蛋白多因子检测、验证
▶疾病诊断：肿瘤、炎症、感染、贫血等
▶疫苗效价评估：体液免疫评估、中和抗体检测
▶药效评估：免疫原性、药代动力学检测

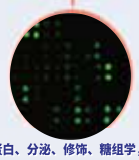
热门分类

人、小鼠、大鼠炎症检测试剂盒
人、小鼠T细胞辅助（Th）、遗血干细胞检测试剂盒
人细胞因子风暴25靶标检测试剂盒
人感染/抗病毒蛋白检测试剂盒
人毒性T细胞检测试剂盒
小鼠巨噬细胞检测试剂盒
人、小鼠、大鼠定制检测试剂盒

明星产品

炎症检测系列：FAH-INF-1、FAH-TH-1、FAH-BC-1、FAH-INF-1、FAM-MP-1、FAR-INF-1、FAM-TH-1
感染、抗病毒检测系列：FAH-STRM-1、FAH-VIR-1、FAH-CTC-1
干细胞研究相关：FAH-MSC-1、FAM-HSC-1
细胞迁移研究相关：FAH-HGF-1、FAH-CHEM-1、FAH-CD-1

10-8000 Targets
抗体芯片



▶组学研究：蛋白、分泌、修饰、糖组学，多组学联合分析
▶信号通路、疾病通路上下游通路研究验证
▶疾病生物标志物筛选、验证
▶人群分流：不同人群蛋白表达谱检测
▶药效评估：中/西医药分子作用机制研究、靶点筛选

热门分类

高通量检测：人1000靶标、640靶标、440靶标小鼠200靶标、大鼠282靶标检测试剂盒.....
磷酸化检测：磷酸化通路筛选、AKT、MAPK、JAK/STAT、TGFβ、NF-κB.....
疾病通路研究：肿瘤、败血症、干眼病、动脉粥样硬化、自身免疫疾病、牙周炎.....
PTM芯片：乙酰化、亚硝基化、过氧化、糖基化.....

明星产品

高通量蛋白组检测系列：AAH-BLG-8000、GSH-CAA-X00(1000靶标)、GSH-CAA-640、GSH-CAA-440.....
磷酸化多因子检测系列：AAH-PRTK、AAH-JAKSTAT、AAH-MAPK、AAH-AKT、AAH-PER、AAH-TGFB.....
疾病通路多因子检测系列：QAH-ADI、AAH-NEU、PAH-LCAG、QAH-GCB、QAH-BMA、QAH-DED.....
PTM系列芯片：AAH-ACK、AAH-ACYL、AAH-PTYR、AAH-PANP、GAH-GCM、AAH-SNO、AAH-PST.....

产品应用文章发表案例

RayBio产品和服务被全球的学术、政府和制药实验室广泛使用，用于**疾病标志物筛选、疾病诊断、药物筛选和基础研究**，已助力全球客户在Nature, Nature Medicine, Cell, Lancet, PNAS等世界顶级期刊上发表了数万篇文章。目前，累积SCI文章影响因子超过50000分，影响因子大于5的文章超过4500篇，影响因子大于10的文章超过500篇，影响因子大于20的文章超过100篇。

机制研究 | 疾病标志物研究 | 肿瘤研究 | 风湿免疫研究 | 干细胞研究 | 呼吸疾病研究

老年病研究 | 免疫研究 | 心血管疾病研究 | 肾病研究 | 眼部疾病研究 | 损伤修复研究

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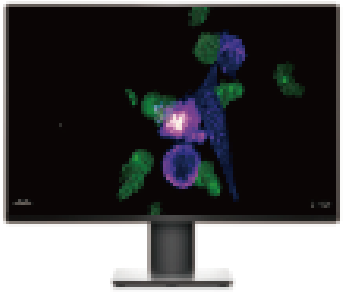
Empowering your proteomics

从机制研究到精准诊疗和预后

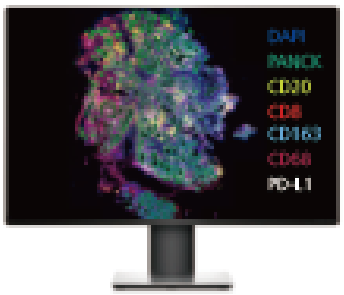
蔡司显微成像助力肿瘤标志物全流程

基于高清实时多维活细胞成像的肿瘤机制研究



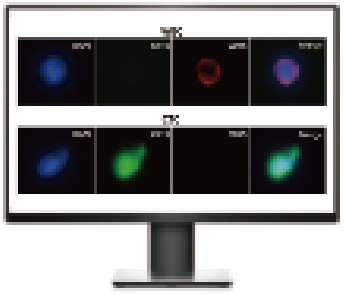
晶格混光显微镜 Lattice Lightsheet 7

基于空间多组学的肿瘤微环境研究和精准诊断

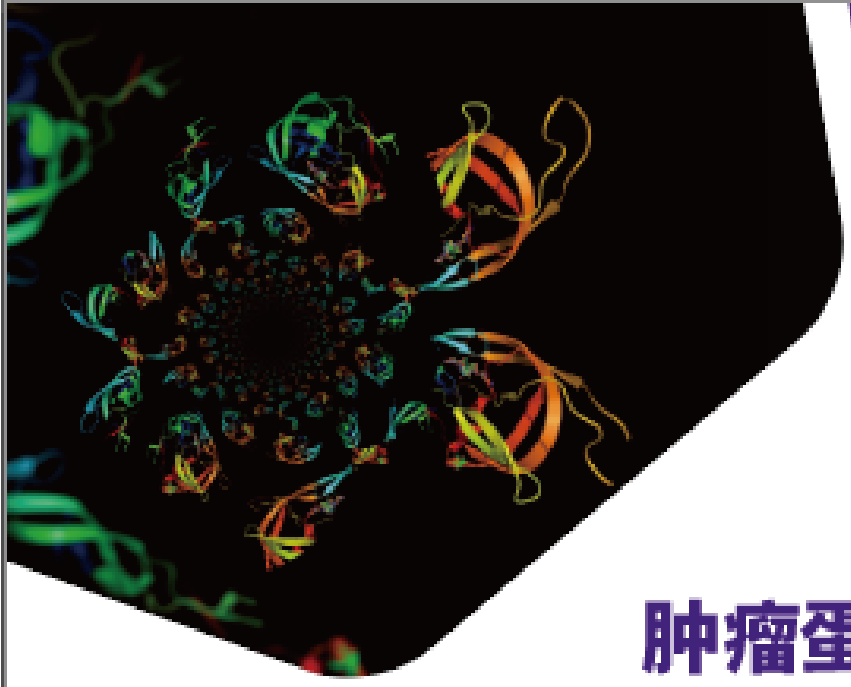


RIMA (Rapid Imaging & Multiplex Analysis) 一站式解决方案
基于蔡司宽场显微镜 Axio Observer 7，Axio Imager 2 和高性能玻片扫描系统 Axioscan 7

CTC 循环肿瘤细胞精准液体活检和预后



高通量全自动扫描和分析系统 Metafer
基于蔡司正置显微镜 Axio Imager.Z2



MERCK 默克

肿瘤蛋白标志物解决方案

蛋白质组学

- **高丰度蛋白去除kit**

  人、小鼠及豚鼠的血清/血浆：去除白蛋白、IgG (货号：PROTIA)

  人的血清/血浆：去除白蛋白、IgG/IgA/IgM/IgE/IgD (货号:LSKMAGHDKIT)

- **质谱标准品**

  SPLASH® LIPIDOMIX® 质谱标准品 (货号:330707)

  SILu™MAB稳定同位素标记的通用单克隆抗体标准品人 (货号:MSQC3)

- **同位素标记氨基酸 (部分)**

Cat.NO.	Description
608033	L-Arginine-$^{13}C_6$,$^{15}N_4$ hydrochloride
643440	L-Arginine-$^{13}C_6$ hydrochloride
600113	L-Arginine-$^{15}N_4$ hydrochloride
608041	L-Lysine-$^{13}C_6$,$^{15}N_2$ hydrochloride
643459	L-Lysine-$^{13}C_6$ hydrochloride
608092	L-Isoleucine-$^{13}C_6$,^{15}N
605239	L-Leucine-$^{13}C_6$
608068	L-Leucine-$^{13}C_6$,^{15}N
608106	L-Methionine-$^{13}C_5$,^{15}N
299154	L-Methionine-methyl-^{13}C,d_3
300616	L-Methionine-methyl-d_3
749915	L-Leucine-$^{13}C_6$,^{15}N,2,3,4,4,5,5,5-d_7,4-methyl-d_3
609021	L-Lysine-$^{15}N_2$ hydrochloride
643459	L-Lysine-$^{13}C_6$ hydrochloride
608041	L-Lysine-$^{13}C_6$,$^{15}N_2$ hydrochloride
749907	L-Lysine-$^{13}C_6$,$^{15}N_2$,2,3,3,4,4,5,5,6,6-d_9 monohydrochloride
609242	L-Methionine-^{15}N
749893	L-Methionine-$^{13}C_5$,^{15}N,2,3,3,4,4-d_5,methyl-d_3
608114	Proline-$^{13}C_5$,^{15}N
750018	L-Arginine-$^{13}C_6$,$^{15}N_4$,2,3,3,4,4,5,5-d_7 hydrochloride

默克公司生命科学业务在美国和加拿大以MilliporeSigma品牌运营。

MILLIPLEX® 蛋白多因子检测

1350多种蛋白因子供您选择，灵活自由组合，覆盖免疫，代谢，心血管，神经，代谢等多个研究领域和物种

飞摩尔级单分子蛋白发现平台

超高灵敏度，检测灵敏度达飞克级，轻松实现疾病标志物早期预测。

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3激光15色18通道流式细胞仪

棱镜泰克的CytoFLUX流式细胞仪结合了高精度的细胞分析能力与卓越的用户体验，具有稳定、可靠、易用、灵活、高分辨率等特点，能够满足现代科研与临床实验的严苛要求。

- 支持高达15色荧光检测。
- 最高采集速度可达65000 events/s。
- 激光器无需预热，开机30秒后即可进行检测。
- 操作界面简洁直观，实验设置灵活，降低实验门槛。
- 采用先进的激光和光电检测技术，性能稳定，确保实验数据的一致性和重复性，让长期的实验研究和大量的样本分析变得更可靠。
- 根据不同研究需求提供多样化的配置，包括但不限于激光器选择、检测通道和软件功能，确保您能够得到最适合您研究的定制化解决方案。

Sperm-Cyto流式精子分析仪

全国第一台以流式细胞术为原理专用于“男科”实验室精子检测仪器，实现对精子功能的全面检测，弥补传统精液常规无法检测的男性不育指标，解决传统精液检测方法偏形态、无法评估精子功能的痛点。

精 自动化分析程度高，易于操作；全自研人工智能算法平台，确保检测结果的准确性。

小 机身小巧，性能出众；简明的交互界面，开机立即响应。

灵 开机即检，高灵敏度，高分辨率，实现样本快速检测；超过10万小时的运行故障模拟测试，故障率低。

通 专利液流装置及核心控制算法，使得液流聚集稳定可靠。防止精子样本堵管，解决流式检测技术精子检测难点、痛点。

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特殊修饰的纳米磁珠富集材料与体液样本接触时，样本中具有更强亲和力的蛋白会与早期吸附的高丰度蛋白发生竞争性置换，从而实现低丰度蛋白的富集。

高效富集

有效检测蛋白跨越10个以上数量级，
结合最新4D质谱(Astral)半小时有效梯度，
体液样本检出蛋白数目**高达8000+**

适配性强

可兼容高通量自动化前处理平台
适用于各种型号蛋白分析质谱

微量提取

10 μL+血浆即可满足质谱检测需要

自主产权

专利技术，试剂盒已完成
一类医疗器械备案

用途广泛

适用于人，鼠等多物种的
多种体液样本

性能稳定

QC样本检出蛋白CV中位数低于10%

使用便利

一套试剂盒即可完成蛋白富集和蛋白、多肽
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- 18家子公司
- 覆盖约90个国家和地区
- 2000+全球员工
- ~7000全球客户
- ~20000SCI文章
- ~120000累计影响因子

科技服务解决方案

基因组学

- De novo 测序
- 图形泛基因组测序、T2T组装
- 全基因组重测序
- 全外显子测序
- 扩增子测序
- 宏基因组
- 液相芯片、数据库产品
- ASA芯片

转录组学

- 普通转录组测序
- 单细胞转录组
- 空间转录组
- lncRNA、small RNA
- 全长转录组测序
- 宏转录组测序
- 外泌体RNA测序
- 翻译组 (Ribo-seq)

表观组学

- DNA甲基化测序
- RNA甲基化测序
- ChIP-seq、CUT&tag
- Hi-C
- ATAC-seq
- EM-seq
- 935K甲基化芯片

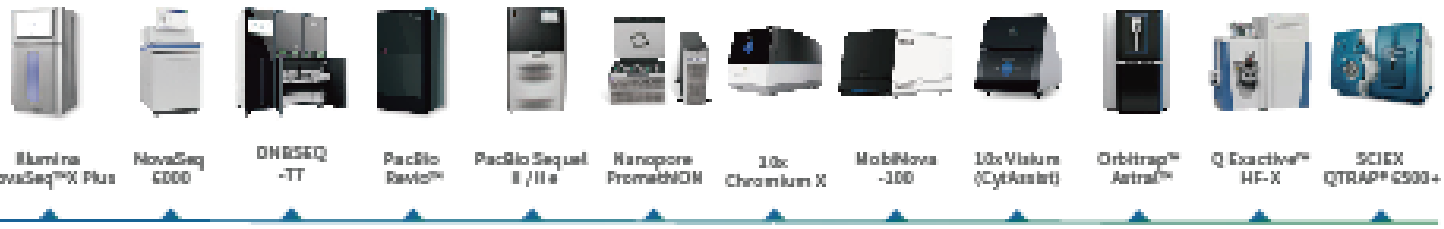
蛋白质组学

- 定性蛋白质组
- 定量蛋白质组
- 4D定量蛋白质组
- 修饰蛋白质组
- 质谱流式 (CyTOF)
- 多重因子检测
- 空间蛋白质组

代谢组学

- 非靶向代谢组
- 脂质组
- 炎靶向代谢组
- 靶向代谢组
- 代谢流
- 空间代谢组

技术平台



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- 国家工信部工业品牌培育示范企业
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- 国际市场优质供应商与合作伙伴
- 中国制造业企业500强
- 中国民营企业500强
- 山东工业突出贡献企业
- 山东民营企业100强
- 济南市市长质量奖（2个）

中国最具影响力医药企业之一

- 中国医药研发产品线最佳工业企业
- 中国药品研发综合实力前三强
- 中国化药研发实力前三强
- 中国生物药研发实力10强

中国最具社会责任感医药企业之一

- 全国劳动模范（2个）
- 全国五一劳动奖状（2个）
- 全国工人先锋号（2个）
- 中国企业信用500强
- 中国医药最具社会责任感企业
- 社会力量助力脱贫攻坚先进民营企业

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SINGLE MOLECULE
SYSTEM

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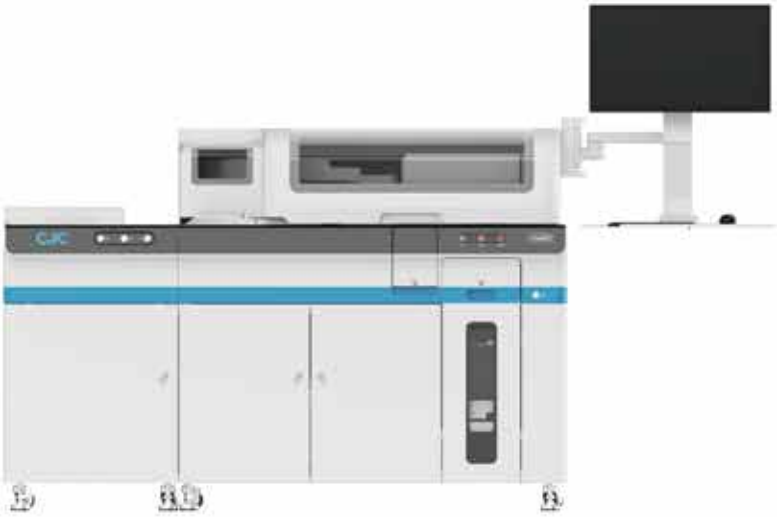
TARGETING DETECTION

全自动单分子免疫分析仪



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APPLIED PROTEIN TECHNOLOGY
中科新生命

展位号：C01

公司介绍

INTRODUCTION

上海中科新生命生物科技有限公司（APTBIO）成立于2004年，前身是原中国科学院上海生命科学研究院蛋白质组研究分析中心的对外服务平台。企业通过与国内外高等研究机构的技术合作和自有研发团队的创新能力组建了企业创新研究院，建立了大队列多组学研究技术平台、生物药物早研及临床前CMC研究分析平台、生物药及药械注册报批平台、AI大数据算法四大技术平台，布局科技服务、生物医药及大健康消费医疗CRO服务三大业务板块，构建了AI大数据结合质谱多组学技术应用的生命科学大健康商业版图。

体液标志物研究利器——P7k/11k（基于somascan平台）

产品优势

深 血液蛋白组覆盖**创纪录**
同时靶向**11000种蛋白**

准 媲美抗体法
FDA认可

稳 超高定量稳定性且无惧批次效应，
万人队列级别应用

应用方向：已被运用于

科学研究论文发表
nature | Cell | Science

生物银行构建
biobank | UK Biobank | EPIC

药物探索性临床试验
Vamorolone | Infliximab | Ozanimod | Cerebrolysin

临床诊断
SomaSignal™

整合解决方案

血液标志物 发现及临床转化	血液pQTL 及药物靶点发现	创新药物 探索性临床评价与研究

多组学技术服务

- 蛋白质组学
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- 时空组学
- 高通量测序

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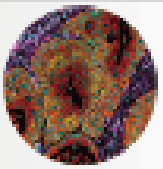

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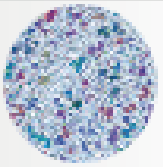
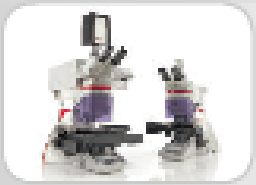
超多色免疫荧光
成像分析技术

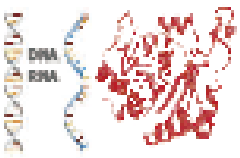
AIVIA
人工智能
深度学习技术

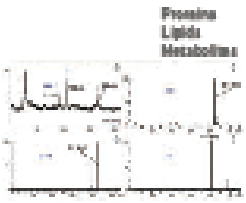


LMD
激光显微
切割技术



质谱、测序





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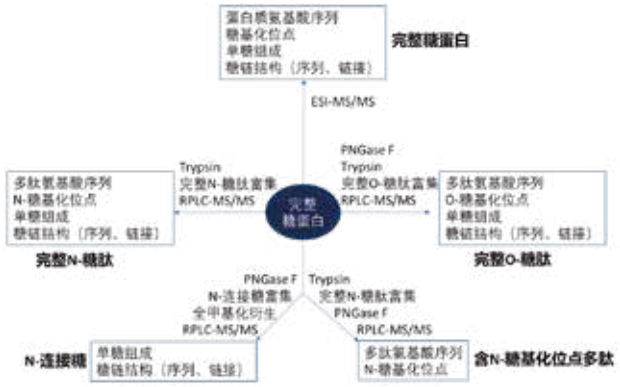
汉诺生物科技（苏州）有限公司
HANOL Biotechnology (Suzhou) Co., Ltd.

糖蛋白质谱完整解决方案

世界引领的糖基化解决方案：



- ★ 常见糖基化类型（N-连接糖、O-连接糖、O-GlcNAc）
- ★ 所有分子水平（聚糖、含糖基化位点多肽、完整糖肽、完整糖蛋白）
- ★ 常见物种（人、动物、植物、细菌、寄生虫）
- ★ 多种定量方法（非标、同位素标记、等重多重标记）

服务流程：

销售前端对接（明确实验目的、制定实验方案、确定项目报价、签订服务合同）

↓

正式进行实验（样本前处理、质谱上机检测、数据库匹配搜索、生物信息学分析、出具报告）

↓

售后服务阶段（实验报告解读、实验数据解析、更多生信分析及个性化可视化结果）

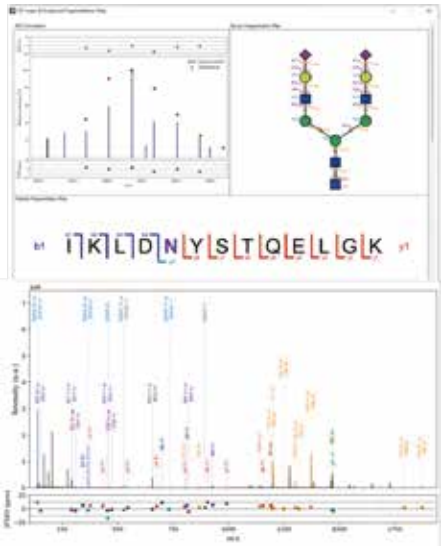
结果展示：

基于自主结构指纹靶向精准和高效识别专利技术，汉诺生物研发的“glyco（g）”系列完整N-糖肽数据库搜索引擎gPeptide覆盖各类常见物种N-糖基化修饰特征结构，包含70000余条糖链，为N-糖蛋白体系的结构特异定性定量分析提供更为准确高效的工具。

该软件可一键导出：

- 完整N-糖肽及相关多肽骨架、N-连接糖部分和完整N-糖蛋白的全面信息
- N-糖基化位点打分和确认
- N-连接糖结构打分和确认
- 非标或标记定量

同时可对所有数据实现可视化展示：



汉诺生物科技（苏州）有限公司
HANOL Biotechnology (Suzhou) Co., Ltd.
HANOL 汉诺生物

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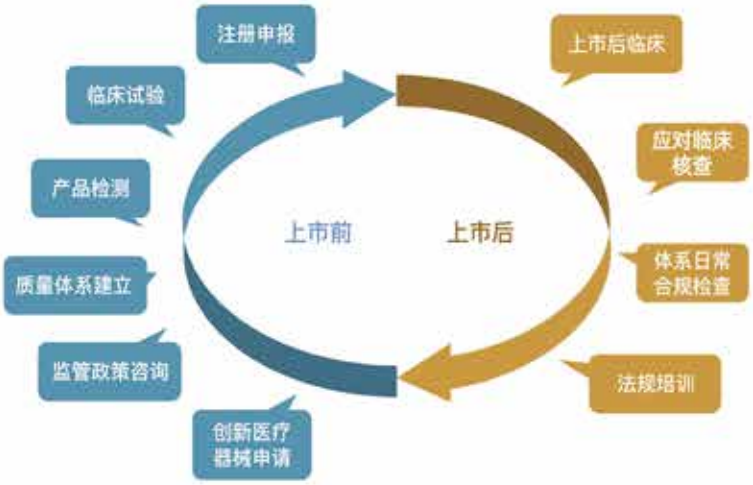

同泽合信（北京）医药科技有限公司作为科技部认定的“高新技术企业”、北京市“专精特新”中小企业，是一家专注于体外诊断（IVD）领域的法规咨询与临床技术服务合同研究组织（CRO）。我们致力于通过解决注册战略规划重大项目实施等最关键的问题，帮助客户实现上市前阶段的实质性突破，获得长远的市场发展。规范化的技术服务体系已通过德国莱茵ISO 9001认证、BSI ISO 13485认证。

同泽合信已为160余家国内外客户提供了逾500项服务，尤其在肿瘤检测产品方面积累了丰富的经验，包括肿瘤早筛、伴随诊断和辅助诊断项目，涵盖高通量测序、qPCR、数字PCR、FISH、免疫组化等技术平台。帮助国内首个肿瘤早筛产品和众多肿瘤伴随诊断产品、基于基因甲基化和mi-RNA检测的肿瘤辅助诊断产品成功上市。

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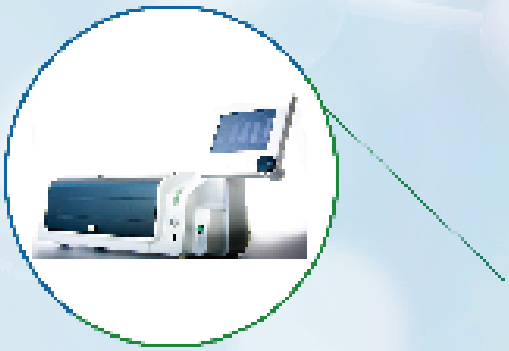

德国 OLS 类器官培养仪

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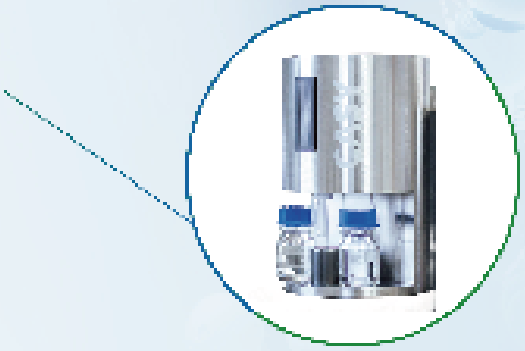

英国 ANGLE 循环肿瘤细胞分离系统

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美国 Thinkcyte 高内涵流式细胞分析、分选仪

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法国 NETRI 3D器官芯片

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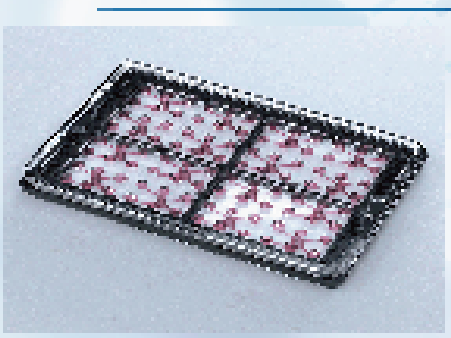

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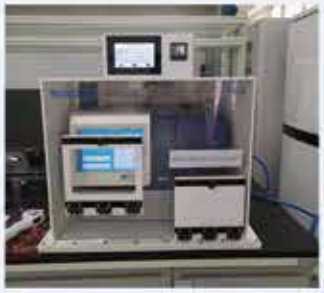
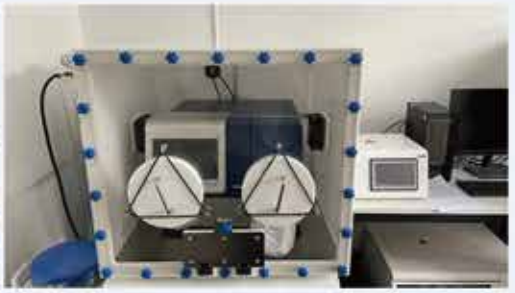
迈沃德定制系列产品案例

01 低氧培养箱 & 酶标仪-分子设备工作站

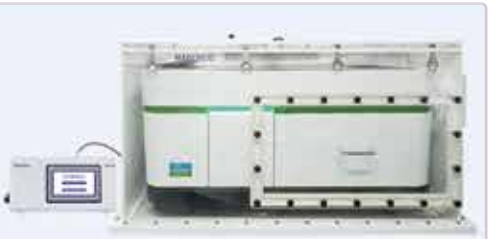



02 低氧培养系统 & SEAHORSE实时细胞代谢分析系统工作站

03 整合成像系统带有暗室的厌氧工作站

04 整合ACEA实时细胞分析的低氧环境培养箱


05 整合高内涵分析系统的低氧培养箱



06 整合ATMS细胞拉伸系统的低氧培养箱

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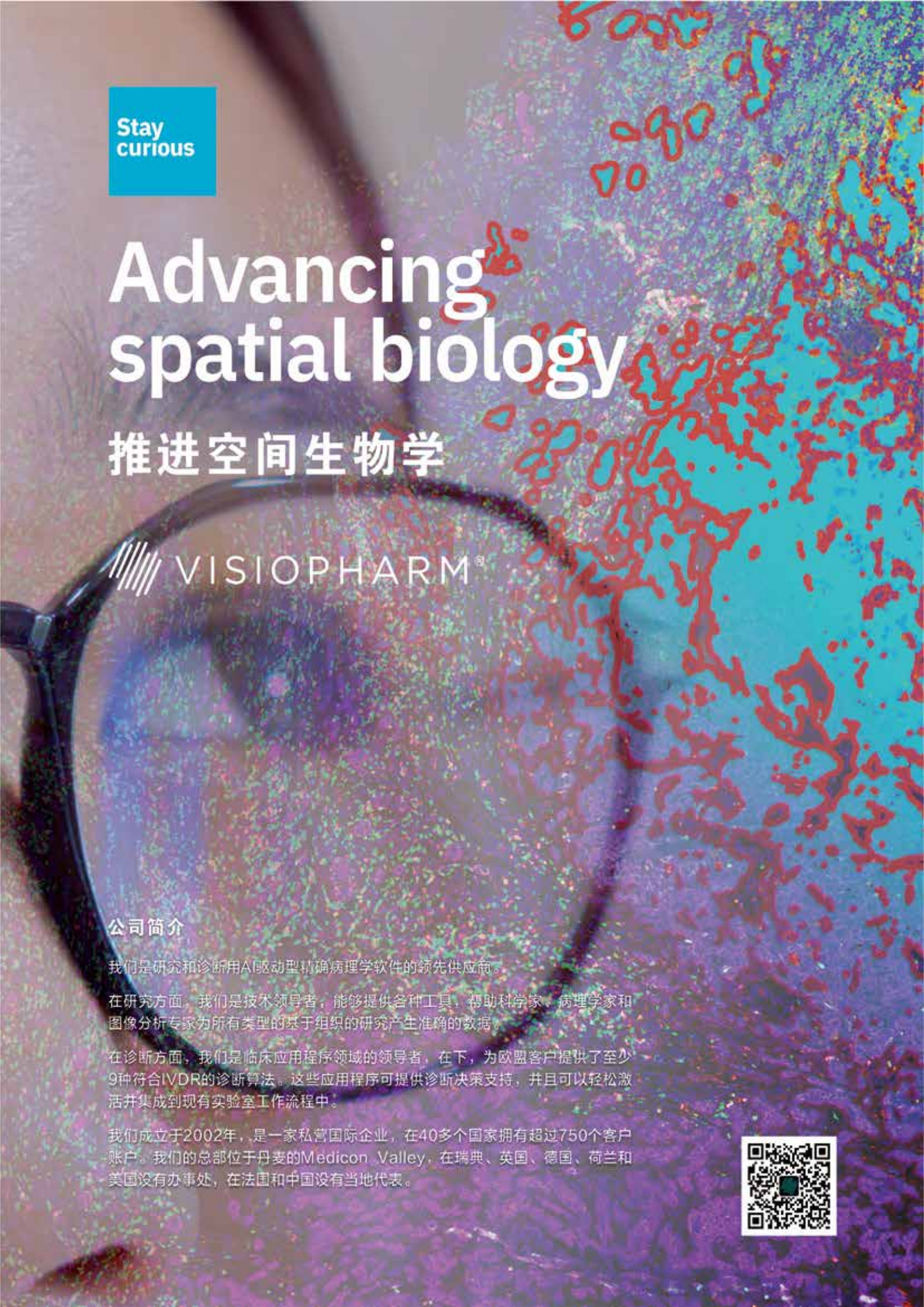

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在研究方面，我们是技术领导者，能够提供各种工具，帮助科学家、病理学家和图像分析专家为所有类型的基于组织的研究产生准确的数据。

在诊断方面，我们是临床应用程序领域的领导者，在下，为欧盟客户提供了至少9种符合IVDR的诊断算法。这些应用程序可提供诊断决策支持，并且可以轻松激活并集成到现有实验室工作流程中。

我们成立于2002年，是一家私营国际企业，在40多个国家拥有超过750个客户账户。我们的总部位于丹麦的Medicon Valley，在瑞典、英国、德国、荷兰和美国设有办事处，在法国和中国设有当地代表。

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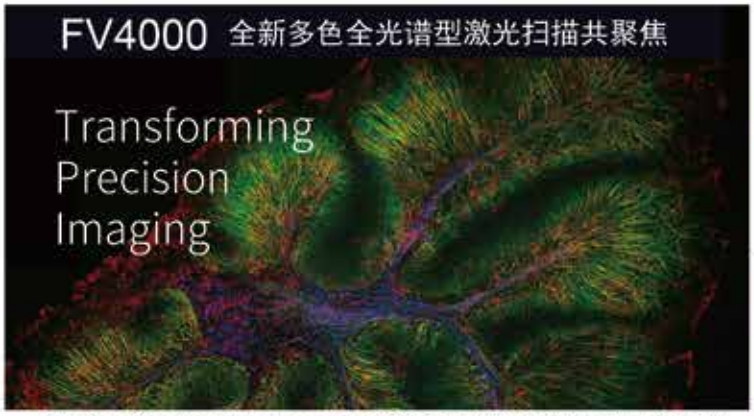

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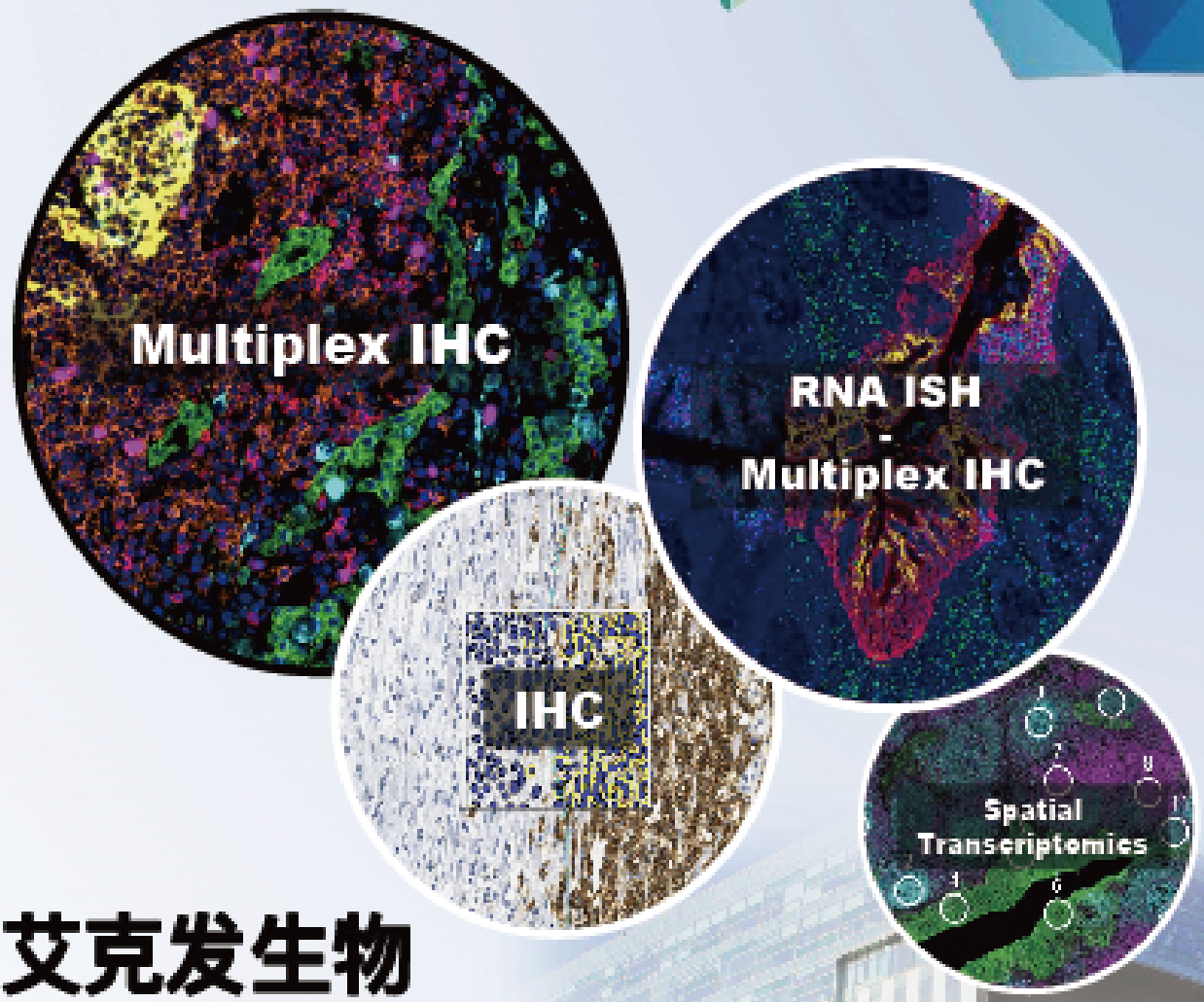

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Multiplex IHC等检测方式相互结合引领的空间多组学通过特异性标记特定目标、全景成像和专业病理软件实现单细胞级别的精准分析。通过蛋白+基因等染色信息的结合，实现单细胞层面的定量评估及细胞间的空间关系分析，为肿瘤免疫微环境研究、肿瘤治疗和预后评估提供可靠指导，在临床应用中具有巨大的可行性和价值。

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前列腺特异性抗原同源异构体测定试剂盒 p2PSA 和前列腺健康指数 *phi*

2008-2013 年中国前列腺癌联盟医院新诊断的前列腺癌患者中，局部进展性和转移性占 58%[1]，而美国 2005-2011 年前列腺癌患者中区域和远处转移的仅占 16%[2]，中国前列腺癌患者面临着发现晚、预后差的危局。

为了契合前列腺癌早发现、早治疗、改善预后的需求，贝克曼库尔特研发了 p2PSA 试剂盒，并推出了前列腺健康指数 *phi*（prostate health index，*phi*）多参数风险预测模型，由 PSA、fPSA 和 p2PSA 三个指标通过特定公式计算得出，研究表明 *phi* 值越高，前列腺癌风险越大。

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phi 支持前列腺癌精准诊断，避免不必要前列腺活检穿刺，减轻患者痛苦和负担

抗体专利

phi 的前列腺癌特异性和诊断准确度均高于传统指标，是前列腺癌的新型血清标志物

（专利号：US patents: US 7288636 and US7659073）

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phi 是对PSA Hybritech标准的传承延续，是对于中国目前前列腺癌现有诊断方法的有效补充和完善，将成为前列腺癌精准诊疗的新趋势

参考文献：

1. 中国前列腺癌联盟医院前列腺穿刺活检现状调查分析，中华泌尿外科杂志，2015,36(5):342-345

2. Cancer statistics, 2016. CA CANCER J Clin. 2016;66:7-30

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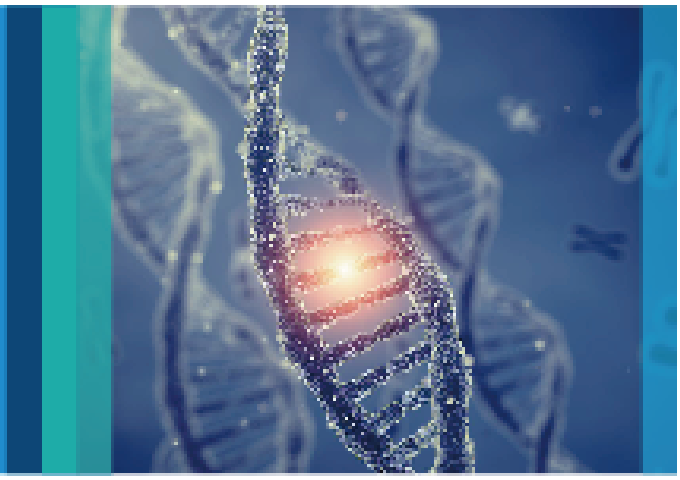

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- 捕获磁珠、纯化磁珠

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IGT-AS12自动化液体工作站，满足文库构建全流程，满足以浓度均一化、试剂、磁珠纯化、PCR反应到文库混样全流程建库的实验需求，全面满足全基因组建库、全外显子组建库、多重扩增子建库、转录组建库、杂交捕获等多种基因捕获实验的自动化升级需求。

预定义产品

TargetSeq®杂交捕获测序
- 全外遗传版、肿瘤版、定制版
- HRD/HRR
- HLA/MHC
- HPV/HBV/EBV

MultipSeq®多重扩增子测序技术
- BRCA1/2基因检测试剂盒
- 免疫组库TCR/BCR
- tNGS标准产品及定制

BisCap®甲基化捕获测序技术
- 甲基化CGI Panel
- 肿瘤早筛 Panel 定制

所有技术平台均提供定制、半定制服务

爱地希®
维迪西妥单抗
DISITAMAB VEDOTIN

RemeGen
荣昌生物

热烈祝贺

2023年CSCO胃癌诊疗指南

将 爱地希® 提升到 Ⅰ 级推荐

（注射用维迪西妥单抗）

针对晚期转移性胃癌抗HER2的后线治疗

是目前**唯一中国可及的新一代ADC药物**

改写胃癌HER2阳性新定义:HER2 IHC 2+/3+,无需Fish检测

三维一体
超强打击

更精准·更强效·更安全

1.《2023年CSCO胃癌诊疗指南》

公司地址：广东省中山市开发区神农路6号、广东省广州市黄埔区中新知识城康耀南路158号
电子邮件：pr@akesobio.com
企业网站：https://www.akesobio.com/
联系人：谢女士 13631209355

Akesobio 康方生物

康方生物（9926.HK）成立于2012年，是中国原创抗体新药研发的先行者，亦是新时代中国药物创新的代表企业之一。由富有国际新药开发经验的科学家团队创建，康方生物聚焦肿瘤、自身免疫、炎症、代谢疾病等重大疾病领域，专注于全球未被满足的临床需求，致力于研究、开发、生产及商业化全球首创或同类最佳的创新生物新药。

自成立以来，公司打造了独有以端对端的康方全方位新药研究开发平台（ACE Platform）和双特异性抗体开发技术（Tetrabody）、抗体偶联（ADC）技术平台、mRNA技术平台及细胞治疗技术为核心的一体化研发创新体系，国际化标准的GMP生产体系和运作模式先进的商业化体系。基于此，我们已开发了超过50个拥有完全自主知识产权的创新候选药物，包括6个双特异性抗体药物，19个产品在全球开展临床研究，公司也成为中国在研管线最丰富的创新抗体药物研发企业之一。

构筑领先技术平台，前瞻性布局创新领先产品

Tetrabody 双抗技术平台 | 抗体偶联 ADC 技术平台 | mRNA 技术平台 | 细胞治疗 技术平台

50+ 自主开发 创新候选药物

6 全球首创 双特异性抗体新药

100% 自主研究及开发创新药物实力（所有进入临床的新药品种都是自研）

同类首创 First-in-class

同类最佳 Best-in-class

以临床价值为导向，高潜力管线全球统筹科学推进

3个 上市产品 | **19个** 临床阶段创新药物 | **120+** 在研临床项目全球开展 | **13项** 关键注册性III期临床

全球首个获批的肿瘤免疫双抗

开坦尼® 2022年6月获批 首12个月销售额 **11.5亿**

差异化PD-1单抗商业化持续发力

安尼可® 2021年8月获批至2023年中已累计实现销售额约 **10亿**

持续建设国际标准规模化制药基地，有序扩充商业化产能

企业资质荣誉

- 国家知识产权示范企业
- 国家技术转移示范机构
- 重点华侨华人创业团队
- 广东省级企业技术中心、广东省智能制造试点示范项目
- 广东省企业重点实验室、广东省工程技术研究中心
- 珠江人才计划本土创新科研团队、引进创新创业团队
- 广东省博士工作站、博士后创新实践基地
- 广东省工程实验室

乐沙定®

注射用奥沙利铂 OXALIPLATIN FOR INJECTION

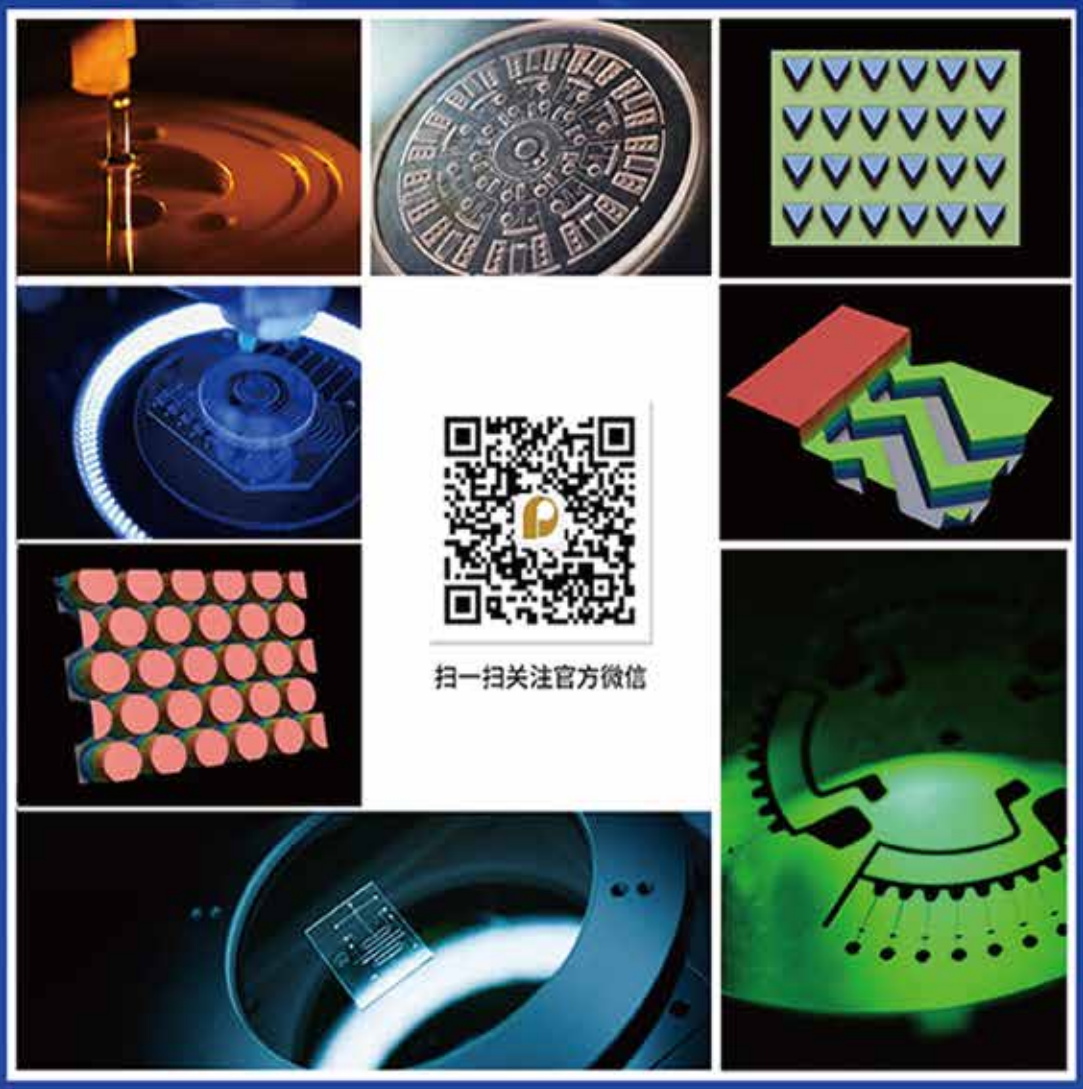
铂之经典 信赖之选

全周期使用含奥沙利铂方案获益更佳


Innovent
信达生物制药
达伯舒®
胃癌
唯一全人群医保
PD-1抑制剂
达伯舒®是中国首个且唯一
针对不可切除胃癌全人群医保的PD-1抑制剂
达伯舒®联合化疗一线治疗胃癌
较传统化疗OS延长 50% ，OS首次突破 19 个月
唯一全人群医保,不局限PD-L1表达
指南推荐为胃癌一线治疗金标准
*ORIENT-16研究，CPS≥5人群
Elizabeth C. Smyth, et al. Lancet 2020; 396: 635-48
2023 AACR. Abs#8733
Xu J, Jiang H, Pan Y, et al. JAMA. 2023;330(21):2064 - 2074. doi:10.1001/jama.2023.19918
审批编号：ZC20231220000 1
仅供医疗卫生专业人士学术交流使用

保利微芯科技有限公司
POLY MICROCHIP TECHNOLOGY CO., LTD.

专注于微流控芯片，承接芯片设计、制作及全流程产品解决方案



扫一扫关注官方微信

地址：北京市顺义天竺空港工业区B区裕华路26号
电话：(010)-80490886
邮箱：info@polymicrochip.com

远程智能蛋白抗体纯化系统

远程智能蛋白抗体纯化系统 能够开展各种常用的纯化技术，如亲和层析离子交换层析、脱盐和缓冲液交换，以及凝胶过滤。本系统可支持各种蛋白的纯化，包括标签蛋白、抗体、无标签的或天然蛋白，以及样品纯化

- 1；系统最大设计流速为20ml/min，兼顾分析与制备
- 2；使用高精度蠕动泵，脉动小，基线稳定，流量输出准确；
- 3；操作简单，所有流路、切换阀、检测器均通过软件界面呈现
- 4；样品环上样改进为直接上样，入口可实现系统和吸附柱的自动清洗，不同纯化任务切换简单
- 5；特定波长（280nm）的紫外检测器，耐用可靠，无需预热开机 即可使用
- 6；峰收集判断准确，避免遗漏与交叉污染，节约人力
- 7；整套系统小巧实用，节省空间
- 8；系统简洁，使用便利、满足不同习惯客户的需求

○ [CJY-03远程智能蛋白抗体纯化系统]

项 目	远程智能蛋白抗体纯化系统
型 号 (Model)	CJY-03
流速范围	0-20mL/min
压力范围	≤0.17MPa
检测波长	280nm
上样形式	自动
气泡检测	是

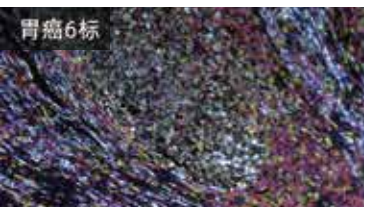
蛋白柱	外挂
显示	数显屏
屏幕尺寸mm	108mm×64.8mm
电源	DC24V
功率W	48W
重量Kg	≤6.5Kg
外形尺寸（长宽高）	长：220.1mm（含鲁尔穿板接头） 235.1mm（含外接鲁尔套头和外接管） 宽：229mm 高：157.78（含脚垫与置物台，不含管架）

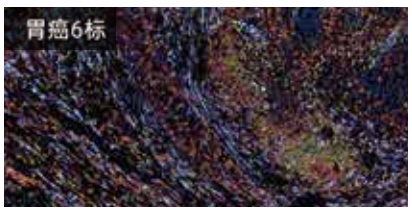
服务热线 service hotline 400 660 9091
南京巴傲得生物科技有限公司
www.bioworlde.com

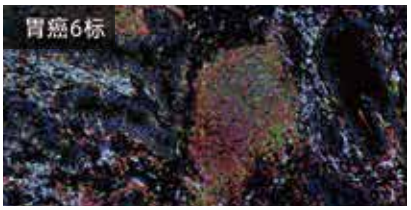
FreeThinking | 弗瑞思
做病理找弗瑞思

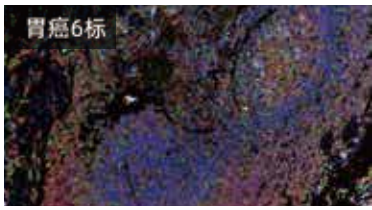
Freethinking
Multiplex immunohistochemical

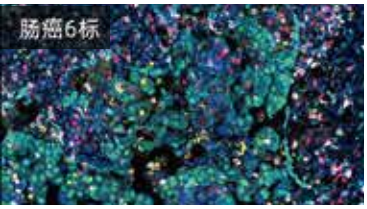
弗瑞思病理

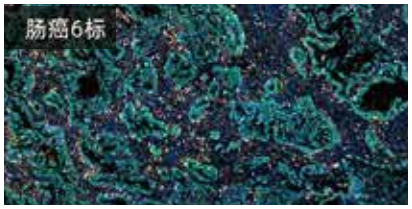


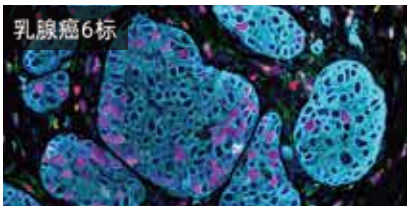


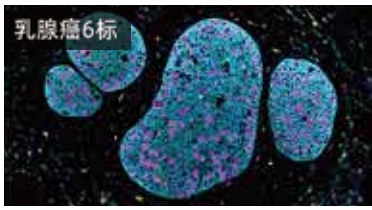




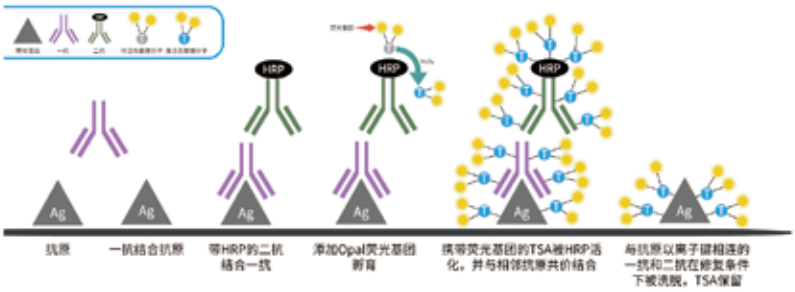








多靶标免疫荧光（TSA）的原理与步骤



弗瑞思病理是一家专注于组织病理学高端应用服务的企业，多色免疫荧光技术（mIHC）是新一代的荧光标记技术，可以实现一张切片多靶标染色；从全新视角洞察组织样本，为肿瘤微环境（TEM）、复杂样本组织原位研究提供强大的解决方案，弗瑞思病理提供病理制片–染色–全景扫描–定量及空间分析的全流程服务，利用这一技术对肿瘤微环境亚细胞群、空间分布、免疫状态以及诊断和预后评估的研究，提供丰富而详实的数据支撑，为您的课题进行和文章发表提供强劲助力。

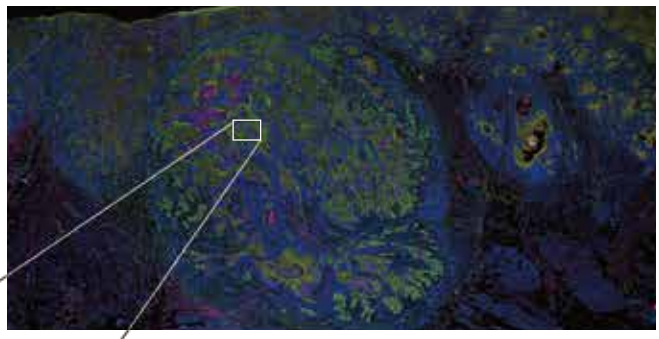
5 大优势

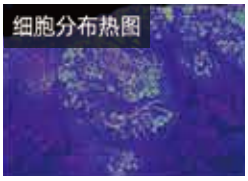
- 节省样本 提升实验效率
- 一抗无种属 冲突限制
- 更好的信号 放大效果
- 成片荧光 信号稳定
- 基于HALO平台 数据量丰富

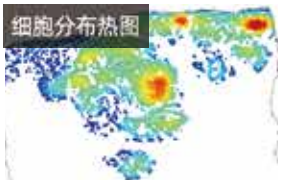
组织微环境全景分析

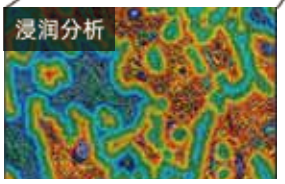
Tissue Microenvironment Landscape Analysis

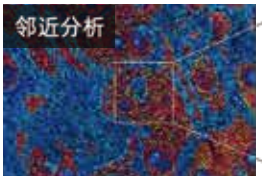
弗瑞思基于HALO 软件的病理分析平台，可以进行各类病理图像的定量分析，将样本中靶标的阳性水平，不同指标的共表达水平，以及空间分布特点等量化为数据，以便进行直观的比较和统计学分析，提高实验结果使用的准确度和区分度。

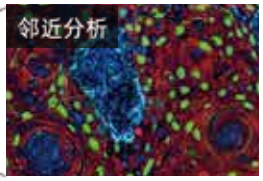












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弗瑞思生物科技有限公司
Freethinking Biotechnology CO.LTD.

玦芯生物

玦芯生物科技有限公司

玦芯生物成立于2022年9月30日，由科创板上市公司凌云光(股票代码：688400)科学图像BU孵化而来，拥有完整的智能光电设备开发能力、先进的微流控技术和领先的知识图谱构建、大数据挖掘能力。公司坚持以科技创新赋能生命科学研究与精准医疗，将始终秉持以客户为中心的理念，围绕肿瘤早筛与伴随诊断、核酸药物研发和个性化治疗主线，用一流的产品和服务为客户创造价值。

主要产品：Sminer液滴式数字PCR系统包含专用一体式液滴芯片，Sminer-PM液滴制备和PCR扩增仪，Sminer-PR阅读仪及Sminer-Analysis分析软件，系统集成、易用、快速、高灵敏，是科研人员的最佳选择。

- 操作简单
- 一体式芯片，全程封闭，消除交叉污染
- 可单独上样，无需积攒样本，最高支持16样本
- 每个样本液滴数不少于2w，4色荧光通道（ROX参考通道）

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缓慢进展EGFR突变晚期NSCLC(CTONG-1803/ALTER- L001)
入选ELCC

mPFS再延长 **9.2** 个月

DCR高达 ↗88%

治疗相关SAE仅 ↗7.8%

Leading PI

吴一龙 教授 / **陈华军** 教授

广东省人民医院

2023 ELCC POSTER

NP-LC-AN-2023.03-29 valid until 2025.03

仅供医学药学专业人士阅读

BIOTREE百趣

BIOTREE 上海百趣生物医学科技有限公司

上海百趣生物医学科技有限公司（前身为阿趣生物）于2012年在上海复旦科技创业示范园成立，专注于创新质谱技术在生命科学与医学健康领域的应用，致力于成为质谱检测领域权威的代谢组学与蛋白质组学等多组学产品和服务的提供者。

自成立以来，百趣生物相继被认定为国家高新技术企业、高新技术成果转化项目、上海市科技型中小企业技术创新资金资助项目，百趣实验室相继取得了病原微生物实验室BSL-2备案、ISO9001、CMA等认证。同时百趣及其下属公司共拥有96项专利及软件著作权。

经过十多年的发展，公司目前已建立了完善的代谢组学平台，包括非靶标代谢组学、高通量靶标代谢组学、脂质组学、广泛靶标代谢组学、代谢流检测，同时建立了蛋白质组学平台和抗体测序等检测分析平台。

百趣生物是国内代谢组学科研服务市场的专业品牌。业务服务遍及全国各省市，港澳台地区和海外。服务项目数量25000+，样本年检测通量50+万例，服务的单位包括高校，研究所，医院，企业等1500+，其中三甲医院360+。

非靶标代谢组学

- 新一代代谢组学NGM Pro
- 新一代代谢组学NGM
- 植物NGM
- 植物NGM Pro
- 中药入血组
- 中药质量评价
- 中药NGM Pro
- 4D-脂质组学
- 经典脂质组学
- GC-MS非靶标代谢组学
- GC-MS+LC-MS非靶全代谢
- 风味组学(VOCs)
- 肠道菌群非靶标代谢组学
- 血清代谢组学
- 土壤非靶标代谢组学
- 外泌体非靶标代谢组学
- 中药成分鉴定

高通量靶标代谢组学

- 600MRM
- 血清300MRM
- 精准植物激素
- 氨基酸
- 短链脂肪酸
- 游离脂肪酸
- 中心碳代谢
- 一碳代谢
- 神经递质
- 多胺及其合成通路物质
- 胆汁酸
- 氧化三甲胺及相关代谢物
- 定量脂质组学
- 氧化脂质
- 色氨酸
- ICP-MS离子组学
- 单双糖
- 有机酸
- 脂酰辅酶A
- 绿原酸
- 酚酸单体
- 类胡萝卜素
- 单宁单体
- 花青素
- 黄酮类
- MRM定制靶标

蛋白质组学

- 蛋白冠™蛋白质组学
- iTRAQ/TMT标记定量蛋白质组研究
- Label free非标记定量蛋白质组研究
- DIA定量蛋白质组学研究
- 定性鉴定蛋白质组学
- 修饰蛋白组定性研究
- 微量蛋白质组学
- 多肽组学
- PRM靶向蛋白质组学
- Olink蛋白质组学
- 自身抗体检测芯片
- MetPro-II代谢物与蛋白相互作用组学研究
- 磷酸化修饰蛋白组学
- 乙酰化修饰蛋白组学
- 泛素化修饰蛋白组学
- 糖基化修饰蛋白组学
- 琥珀酰化修饰蛋白组学

功能组学

- 空间代谢组学
- 靶标代谢流分析
- 非靶标代谢流分析
- mRNA转录组
- lncRNA测序
- circRNA测序
- small RNA测序
- 全转录组测序
- 全长转录组（三代）
- 单细胞转录组测序
- 空间转录组测序
- 16S/18S/ITS等扩增子测序（二代/三代）
- 宏基因组测序
- 宏病毒组测序
- 宏真菌组测序
- 宏古菌组测序

精准广泛靶标代谢组学

- 精准植物广泛靶标代谢组学

分子细胞检测

- Western Blot（蛋白质印迹）
- ELISA（酶联免疫吸附测定）
- qPCR（实时荧光定量PCR）

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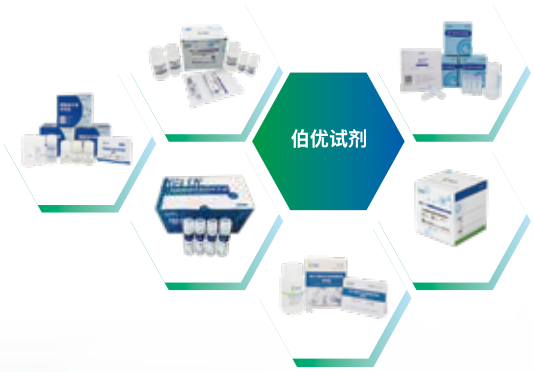
SHANGHAI BIOTECHNOLOGY CORPORATION

展位号：五楼B17

伯豪生物时空多组学
产品+服务一站式解决方案

单细胞多组学

超15000⁺例样本服务经验，涵盖30⁺物种500⁺组织类型，自主研发伯优®系列科研试剂保驾护航。



空间转录组

超1000⁺例样本服务经验，涵盖20⁺物种，动植物样本均可。

Xenium原位分析

时空多组学联合应用（套路）：

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【联合】Xenium+单细胞转录组

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- 小分子钓靶
- PET-CT成像

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- 细胞因子筛选
- 蛋白互作筛选

药物分析
- 外泌体多组学
- 外泌体示踪
- 单外泌体蛋白组

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西湖欧米
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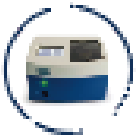
公司简介 Company Introduction

西湖欧米(杭州)生物科技有限公司创立于2020年7月，是一家专注于AI赋能的微观世界数据公司。西湖欧米致力于以蛋白质组大数据技术创新为驱动力，联合人工智能，助力精准医学和药物研发。西湖欧米凝聚了百余位具有生物、医疗、AI等不同学科背景的高素质人才队伍。

目前西湖欧米已与百余家国内外知名高校及科研院所、医院、药企等建立了合作，并且拥有多项国家专利和计算机软件著作权。

产品特色 Features



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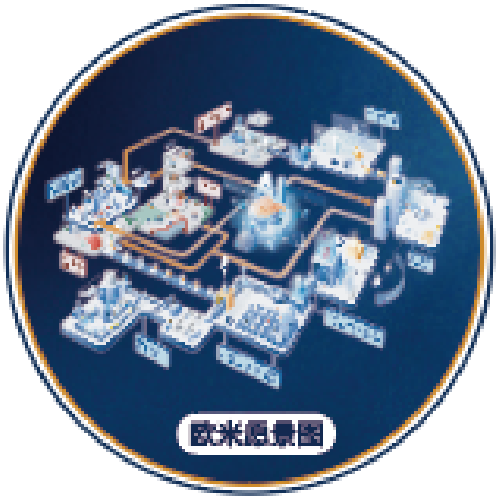


欧米服务图

临床大队列蛋白组学设计

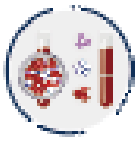
- 多项大队列样本研究经验
- 高深度蛋白组检测技术
- AI赋能的蛋白质组大数据分析

高通量宏蛋白组学解决方案

- 自主创新高通量流程，分析结果快速准确
- 4D-DIA前沿技术平台，更灵敏更多面群蛋白
- 千人以上队列研究经验，一站式组学分析方案

ProteomEx空间蛋白组学解决方案

- 特色膨胀水凝胶技术，实现细胞512倍放大
- 实现多种组织样本膨胀以实现精准取样
- 特色胶内酶解技术，高稳定性高重复性



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贝格尔医学检验实验室是CTC检测的引领者，并将公司旗下CTC项目命名为贝烁尔。贝烁尔检测技术用全球顶尖的CTC捕获技术，并结合基因检测、蛋白检测等分子检测技术为广大客户在生命科学研究和临床检验领域提供专业服务。贝烁尔检测技术由中美科学家历经多年并花费巨资研发而成，其CTC捕获效率、产物纯度、检测的准确率、稳定性以及覆盖的癌症种类等核心技术指标均位居世界前列。贝烁尔检测技术不仅能够用于已确诊癌症患者的精准治疗和病情监控，更适合用于癌症早期诊断、早期筛查，为早期发现癌症提供一种准确、安全、便捷的手段。

贝烁尔CTC技术优势

1.提供简单、高效的细胞转移方法，可用于进一步检测分析：细胞从芯片转移至下一 步检测的转移率高达95%；

2.最大限度保留样本完整性：洗脱体积极低（<5uL），背景污染极小；

3.富集的细胞可完美适应多种下游检测方式：计数、qPCR（基因表达，突变分析）、NGS、免疫表型分型（IHC,IF）、染色体畸变分析（FISH）。

样本要求：10ML 外周中段血 冷链运输

贝烁尔CTC技术特点

- 结合磁珠法的特异性和微流控技术的灵敏性等技术优点；
- 捕获的CTC纯度高、体积小、损伤小；
  纯度＞5%,最高达到25%
  体积＜5微升
  99.9%以上细胞具有活性
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- 可同时检测上皮性和间皮型CTCs；
- 可富集直径＜8微米的CTCs；
- 可灵活定制磁珠、抗体组合，同时满足临床和科研双重需求；
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累计检测肿瘤样本	肿瘤领域合作专家	SCI文章发表	制药企业合作伙伴

（以上数据统计截至2024年2月）

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英文名称：Toripalimab Injection
商品名称：拓益
汉语拼音：Terupuli Dankang Zhusheye
【成份】[illegible]
【规格】240mg(6ml)/瓶；80mg(2ml)/瓶。
【适应症】
[illegible]
【用法用量】[illegible]
【禁忌】[illegible]
【注意事项】[illegible]
【孕妇及哺乳期妇女用药】[illegible]
【药物滥用】[illegible]
【批准文号】
[illegible]
【药品上市许可持有人】
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生产企业名称：苏州众合生物医药科技有限公司
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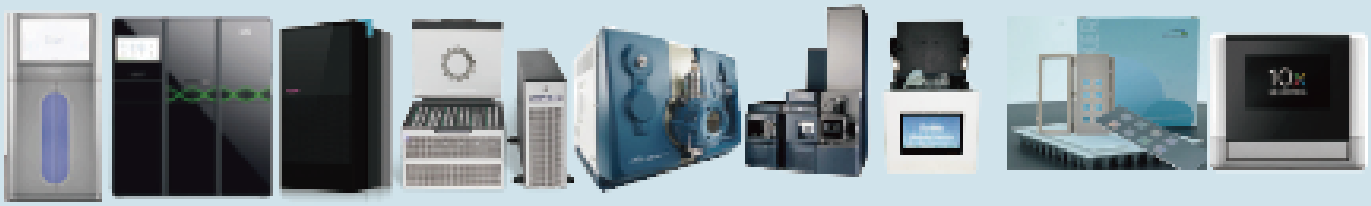

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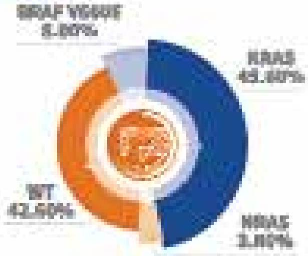
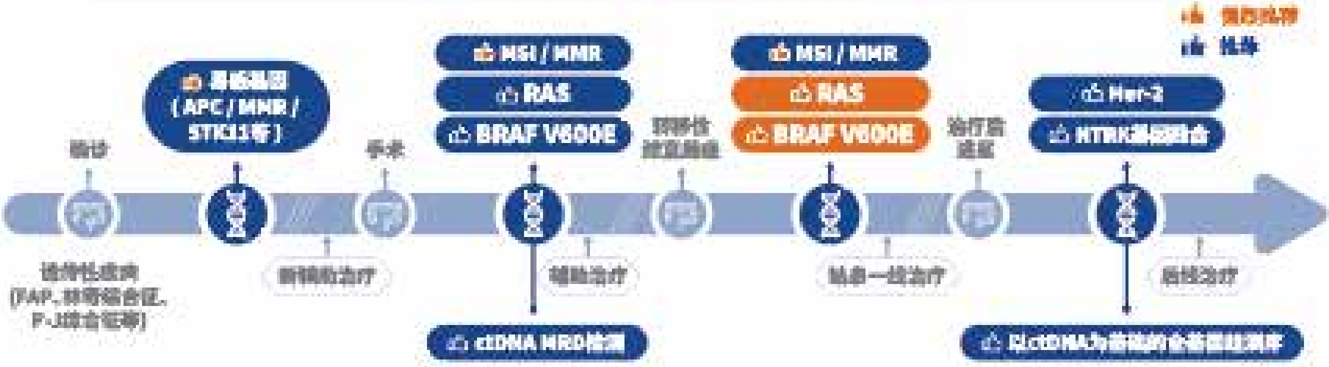
精准诊疗 检测为先



结直肠癌RAS/BRAF突变率

规范化结直肠癌精准诊疗[2,3]



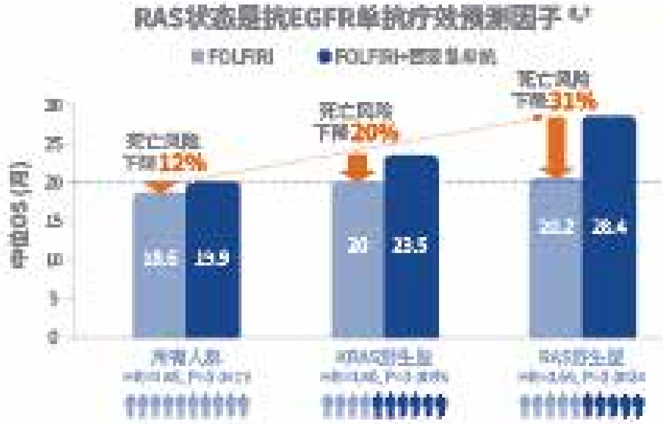
FAP：家族性腺瘤性息肉病；P-J综合征：黑斑息肉病；MMR：错配修复基因；MSI：微卫星不稳定；ctDNA：循环肿瘤DNA

- 强烈推荐复发或转移性结直肠癌患者进行RAS和BRAF基因突变检测[3]
- 推荐早期结直肠癌患者进行RAS和BRAF基因突变检测[3]

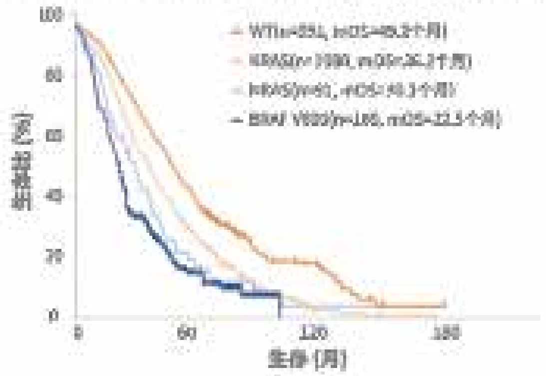
- RAS基因检测位点包括KRAS和NRAS的第2、3、4号外显子[4,5]
- 使用NGS等定量检测方法检测RAS和BRAF基因突变时，建议以5%作为突变丰度的截断值[2,4]

RAS & BRAF精准导航

RAS状态是抗EGFR单抗疗效预测因子[6,7]



RAS / BRAF突变是结直肠癌的独立预后不良因子[1]



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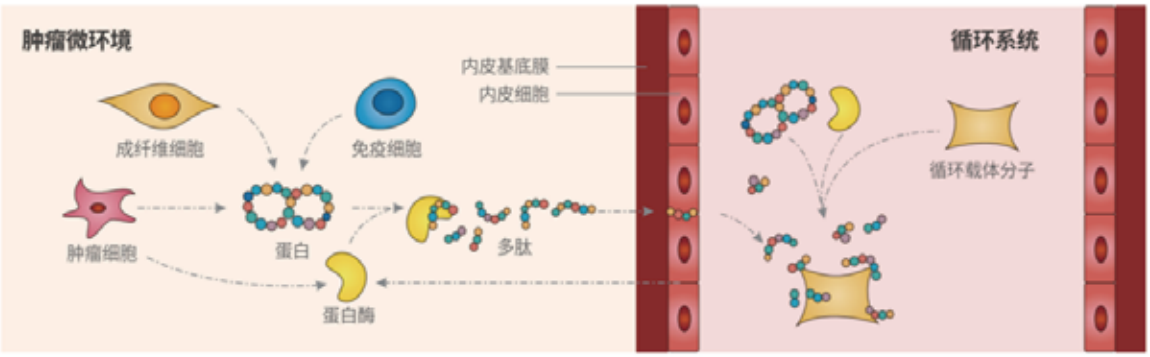
- 聚焦肿瘤和心脑血管两大疾病的早筛早诊领域
- 基于中国人群的独家专利技术，助力科技转化和临床应用
- 从靶点开发、DNA高效富集、快速稳定硫化到甲基化稳定扩增的Tmet-DX技术平台
- 产学研结合，建立临床数据中心，共赢发展
- 专注早诊技术，延长治疗窗口期，有效挽救患者生命

企业微信公众号

杭州汇健科技有限公司（以下简称“汇健科技”）成立于 2016 年，是一家集体外诊断、生命科学工具、工业检测分析为一体的国家高新技术企业。汇健科技运用纳米材料技术（MT）、生物检测技术（BT）、数据库及 AI 算法（IT），构建了高通量质谱平台和超灵敏人工嗅觉传感平台，为医疗机构、科研院所及高校、工业企业提供先进的检测产品、服务及解决方案。



在肿瘤发生发展过程中，肿瘤及肿瘤微环境基质细胞会产生特异性多肽，在肿瘤组织高压和血管高通透性的作用下快速进入血液循环系统[1-3]。血液循环多肽具有更敏感、肿瘤相关性强、可读信息全面、即时性等特征，被认为是目前最理想的液体活检标志物之一[4-8]。

[1] Lung Cancer. 2016,99:46.

[2] Oncologist. 2014,19:1028.

[3] Nat Rev Cancer. 2006,6(12):961

[4] Clin Chem. 2014,60(8):1052.

[5] Lancet. 2003,359:572

[6] J Natl Cancer Inst. 2002,94:1576.

[7] Proteomics. 2004,4:2357

[8] Nature. 2003,425:905.

汇健科技以 Bio-pSi®血清多肽检测试剂盒、ClinMS-Plat® I 飞行时间质谱仪和汇健智云®AI 分析软件为核心，建立了全自动肽谱分析系统，基于该平台系统分析血清肽谱变化，结合人群大队列构建的 AI 算法模型，可评估罹患恶性肿瘤的风险，例如肺结节良恶性鉴别、结直肠癌早期检测等。全自动肽谱分析系统是国内首款集多肽纯化富集、检测、分析功能于一体的肽谱分析系统，具有高通量、高稳定性、高灵敏性的特点，解决了肽谱技术临床应用瓶颈问题。是 2022 年质谱组学领域唯一一个入选工信部人工智能医疗器械创新任务榜单产品，亦是 2022 年度唯一入选浙江省首台（套）产品工程化攻关重点项目的高端医疗设备。

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- 臻和肿瘤专科门诊部无锡有限公司

臻和科技成立于2014年，是中国领先的创新肿瘤分子诊断及检测公司，是中国开发创新肿瘤分子诊断及检测技术、产品和服务的行业领导者，技术全面覆盖治疗选择、预后及监测、早期筛查三大业务领域。公司所提供的技术可以协助诊断癌症、评估及优化癌症治疗方案，在更早阶段检测出癌症复发风险，以提高患者的治疗效果和生活质量；并为高危人群检测早期癌症。

在中国，臻和科技是第一家推出基于MRD技术用于癌症术后复发预后及监测服务的公司。根据弗若斯特沙利文的资料，以基于NGS的癌症预后及监测的收入计，2020年及2021年公司在国内市场的份额最大。截至最后实际可行日期，公司已经商业化五款癌症预后及监测产品，在中国排名首位。

目前，臻和科技建立了一支覆盖中国30个省份医院的营销团队，已经有超过600家医院使用公司的产品及服务。

百奥智汇

单细胞测序数据分析领军者

百奥智汇成立于2018年，是一家拥有全球视野的生命科学技术公司，致力于将单细胞机理研究平台和生物信息学大数据/AI平台充分应用于癌症等重大人类疾病的诊断和治疗中，充分利用自身强大的科研能力、自有平台和数据，创建人类疾病的精准细胞图谱，寻找具突破性的疾病诊断和治疗靶标、开发颠覆性的治疗方法。

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- 满足研究者对特定生物学和临床问题的需求，进行深入的针对性分析

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- 由专门的生信分析工程师利用前沿的数据分析算法为研究者提供分析服务，并针对课题提出科学建议

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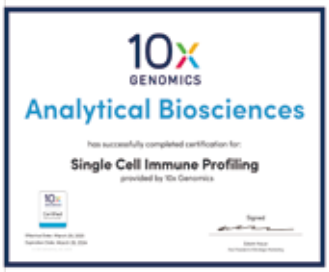

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【在DropXpert C4数字PCR芯片上生成、PCR扩增后的五色荧光结果图】

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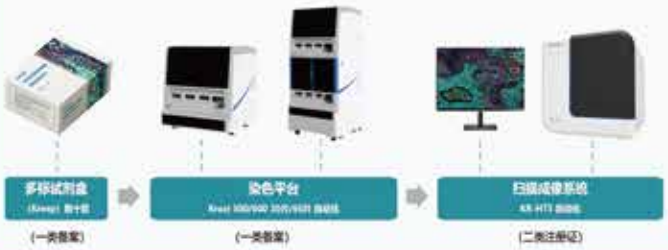

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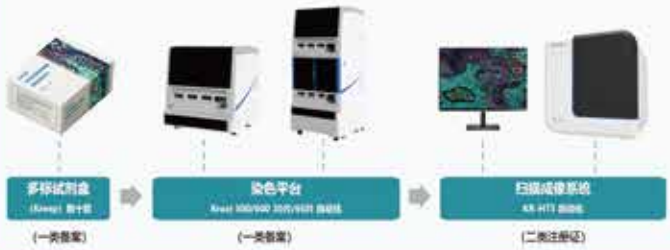

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公司简介

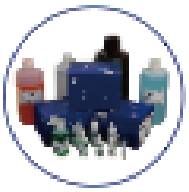
百道医疗致力于临床病理的标准化、智能化、自动化和精准化，自主研发出一系列适用于临床病理检测与诊断的产品并提供专业的技术服务，为病理医生、科研机构与新药研发伙伴提供智能病理整体解决方案。公司汇集多位海内外知名专家，他们在临床诊断产品以及人工智能开发领域有着丰富的经验和广泛的资源，公司在中国苏州和美国圣地亚哥分别设有研发生产以及医疗信息和人工智能中心。

病理为医学之本，临床病理的检测水平是衡量国家医疗质量的重要标准。百道医疗专注于辅助病理诊断试剂、仪器设备的研发及生产以及人工智能系统的开发，打造完善的辅助病理诊断生态链，为病理行业的精准诊断提供有力的科学保障。

产品介绍

PathAb™病理抗体

PATHAB™是百道医疗自主研发用于辅助病理诊断的免疫组化抗体系列，产品将覆盖药监局审批的用于临床病理诊断的450+个靶点，具有灵敏度高，特异性强，性价比高等优点，适用于手动自动2套系统。



PathKit™病理学试剂盒

PATHKIT™是百道医疗为辅助病理诊断而研发的通用试剂盒系列，致力于满足所有临床病理检测所需，例如HE染色，免疫组化（IHC），以及荧光原位杂交（FISH）等。

PathEq™病理学辅助设备

PATHEQ™是百道医疗辅助病理诊断的医疗器械系列，目前包含FAIP-48T全自动病理染色系统及百道鹰眼全自动数字病理扫描系统。FAIP-48T染色仪独有的STIR™固液相混匀和SWEP™清洗专利技术，配合百道高灵敏一抗，能出色完成病理染色需求；百道鹰眼全自动数字病理扫描系统是“互联网+医疗”病理远程诊断的实现基础。

科研合作

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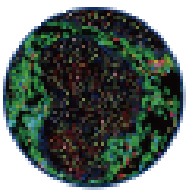

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疾病模型建立
诊疗一体化临床前研究
其余动物实验服务

精密设计与制造平台
精密模块设计与制造
流体控制
自动化方案设计与制造

诊断研究平台
涵盖免疫、生化、细胞、分子、测序等技术的多组学、全病种、高通量诊断应用平台

科研方向

- 新型IVD诊断技术开发
- 疾病诊断panel开发
- 重大慢性疾病诊断新靶标开发
- 诊疗一体化策略研究

MAGICL 6200
全自动化学发光测定仪

肿瘤标志物

胃泌素释放肽前体	ProGRP	癌胚抗原	CEA
胃蛋白酶原 I	PG I	总前列腺特异性抗原	tPSA
胃蛋白酶原 II	PG II	糖类抗原50	CA50
胃泌素17	G17	癌抗原125	CA125
人附睾蛋白4	HE4	癌抗原15-3	CA15-3
鳞状上皮细胞癌抗原	SCC	糖类抗原19-9	CA19-9
癌抗原72-4	CA72-4	细胞角蛋白19片段	CYFRA21-1
神经元特异性烯醇化酶	NSE	糖类抗原242	CA242
游离前列腺特异性抗原	fPSA	*甲胎蛋白异质体比率	AFP-L3%
甲胎蛋白	AFP	*异常凝血酶原	PIVKA-II

注：“*”为即将推出产品

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越智汇 悦检验

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“汇”聚精准
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7种微小核糖核酸（microRNA）检测试剂盒(PCR荧光探针法)

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- 我国首个获得国家食品药品监督管理总局批准的肝癌分子检测产品
- 基于7个microRNA的检测试剂盒对漏检率高达40%的AFP检测阴性肝癌的敏感度为77.7 %，有助于AFP阴性肝癌的早期诊断
- 极早期肝癌检出率比AFP等传统方法高30%
- 比影像学检查平均提前11.5个月提示肝细胞癌风险

DUNWILL
领慧医疗

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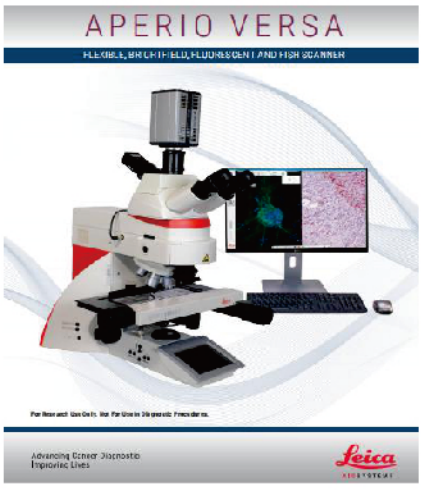
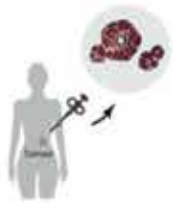


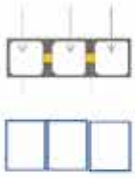
艾玮得
AVATARGET

类器官/器官芯片药物敏感性分析服务

肿瘤患者的试药替身

1.肿瘤组织获取	2.类器官体外培养	3.模型构建	4.药敏检测	5.出具药敏报告







24/48孔U型培养芯片


肿瘤类器官培养试剂盒


肿瘤类器官微环境试剂盒


药敏芯片


孔 板


动力系统:摇摆灌注仪


高内涵智能分析系统


报告自动化样本追溯系统

产品优势

- 通过仿真的体外模型模拟肿瘤微环境，更准确呈现药敏反应
- 利用摇摆灌注仪提供动力系统，实现类器官动态培养，促进样本生长分化速度，提高药物筛选的效率和成功率
- 类器官高内涵智能分析系统可进行大量成像数据的自动成像、AI智能分析、定量分析数据，高效、精准地输出药敏结果
- 所有实验操作均在智能类器官培养工作站中进行，减少污染风险，降低人员操作的批次间差异

取样要求

项 目	手术样本	胸腹水	穿刺样本
样本要求	3个黄豆粒大小（1CM3为佳），重量＞0.5G的团块组织，采集富集肿瘤细胞部位	＞200ML，离心后有细胞沉淀（可使用医院无菌输液袋，外面加一层防护塑料袋，防渗出）	＞3条 每条＞1CM
是否需要冲洗	消化系统需要	否	否
保存时间	2-8°C保存，建议不超过24小时		
所需耗材及培养基	保存液，无菌，15ML离心管取样，物料2-8°C保存		
报告周期	3-4周，样本质量较差时，可能需要4-5周		

江苏省苏州市高新区富春江路188号1号楼8楼
bd@avatarget.com.cn
www.avatarget.com.cn
0512-65367666

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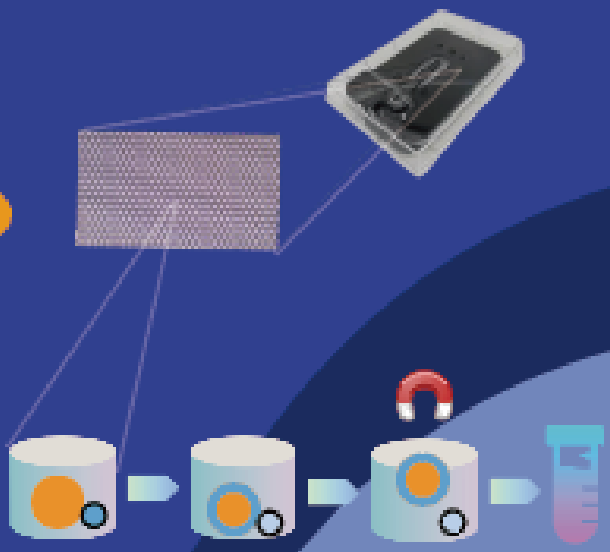
JIANGSU AVATARGET BIOTECHNOLOGY CO.,LTD

烈冰生物
NovelBio

单细胞测序

NovelCyto单细胞服务方案

- 烈冰智造单细胞捕获建库试剂盒
- 华大T7测序仪



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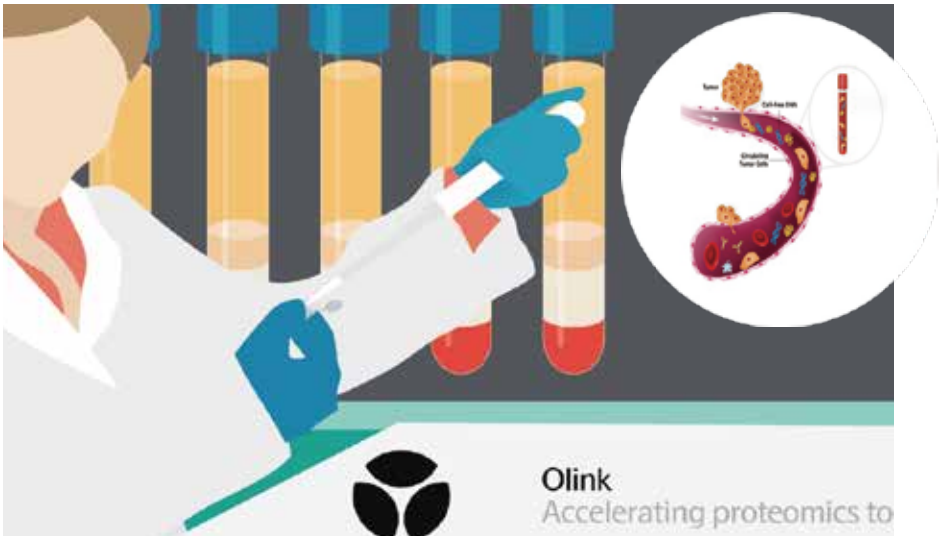

Interception/Prevention

Screening & Early Detection

Recurrence Monitoring

Treatment & Th Selection

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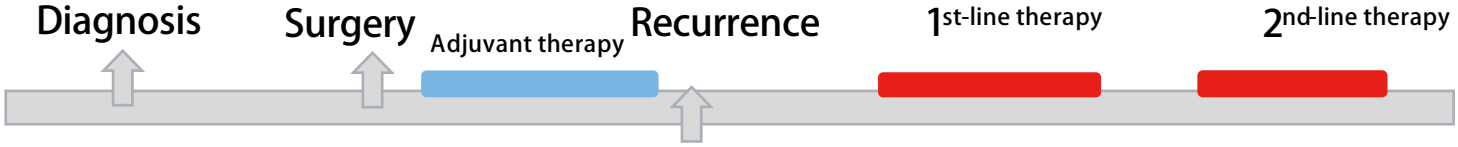

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MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

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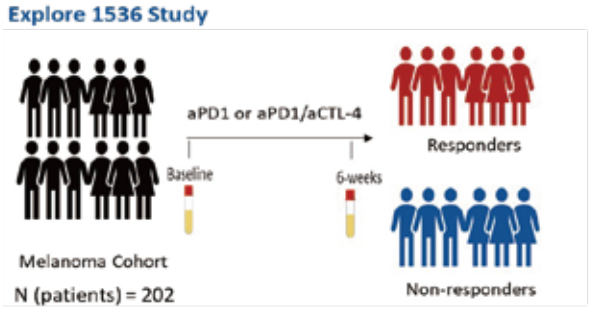

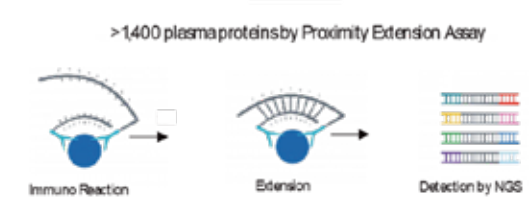

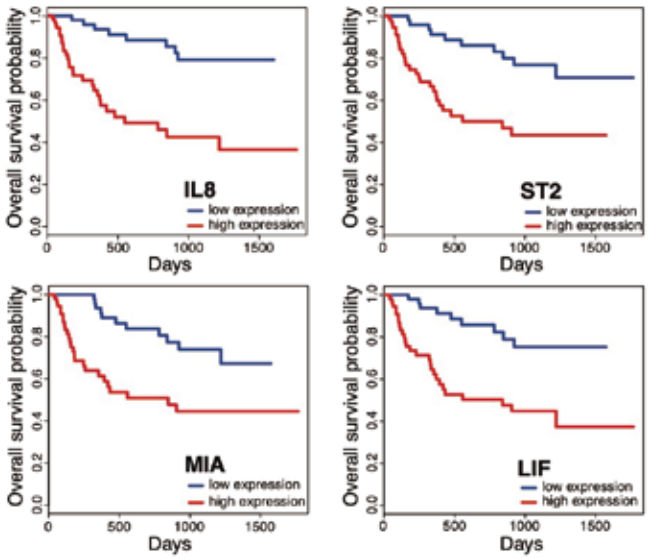

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! 循环蛋白生物标志物可有助于揭示重要的生物学通路和潜在反应机制1

慧算基因
SMARTQUERIERGENE

从MRD到早筛

BF Marker —— 高质量泛癌种biomarker

BF Marker(Butterfly Marker)：是慧算基因结合自有样本数据库，经由大数据挖掘全新发现的分子标志物，该marker甲基化具有泛癌种特征，在多种实体瘤中表现出高度特异性甲基化。

经多项临床样本研究验证，BF Marker甲基化为恶性肿瘤特异性生物标志物，可有效用于临床病程监控和疗效评估（从MRD检测到早筛），同时具有提示交界性肿瘤（如：乳头状黏液性肿瘤）恶化的功能。在胰腺导管腺癌中，其灵敏度达95.9%，特异性达100%，AUC达0.997。对于尿路上皮癌、乳腺癌、宫颈癌、胆管癌、结/直肠癌、食管癌、多形性胶质母细胞瘤、头颈部鳞状细胞癌、肺癌、卵巢癌、胰腺癌、前列腺癌、胃癌、子宫内膜癌的围手术期或其他根治性治疗后患者都可适用。

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项目优势

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2 精准
灵敏度高
可检出低至1拷贝甲基化

3 实时
可针对肿瘤全程动态监测
实时评估肿瘤进展情况

4 经济
同比NGS技术体系更经济、更快速

公司介绍

慧算基因，专注于生物医学大数据智能分析应用，为用户提供精准医疗产品及服务。目前主要业务是为医疗健康决策提供肿瘤、慢性病、遗传病等疾病的基因检测及个性化用药指导。公司致力于成为值得信赖、受人尊敬、不断创新、国际一流的生物数据智能医疗企业。为此打造了AI+疾病诊疗biomarker 开发与产品转化平台，为客户提供含肿瘤在内的AI+精准诊疗全面解决方案。目前，公司自主研发的MRD检测系列试剂盒、肿瘤甲基化早期诊断检测试剂盒及生物信息分析软件，已获 CE-IVD 认证。

Roche

Elecsys® PIVKA-II

早期诊断是提高患者生存率的关键因素

PIVKA-II和AFP的组合诊断提升早期检测HCC的灵敏度

早期HCC是没有症状的

单纯超声检查用于早期患者45%

超声检查+AFP用于早期患者63%

AFP + PIVKA-II 敏感性
用于早期患者87%

肝癌患者从筛查诊断到治疗管理的全程都应得到关注

聚焦全程管理

01 **筛查**

对肝癌**高危人群**的筛查与监测有助于肝癌的早期发现

02 **诊断**

早期诊断后尽早治疗是提高肝癌疗效的**关键**

03 **治疗**

针对不同分期的肝癌患者选择**合理的治疗方法**可以使疗效最大化

04 **管理**

管理治疗中**相关不良事件**，提高肝癌患者生活质量使患者**获益最大化**

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2.冯钰，等. 肝癌电子杂志.2021;8(02)16-22.

MC-CN-03040 有效期：2026年5月30日
专业资料，仅供医疗卫生专业人士参考

晴安欣®
马来酸阿伐曲泊帕片

晴安欣®——强效升板，安欣守护

快速 3～5天起效，10～13天达峰

强效 高达93%的高基线患者和69%的低基线患者的血小板计数≥$50\times10^9/L$，高达88%的高基线患者和69%的低基线患者在手术后7天内不需要输注血小板或任何出血急救

安全 不良事件发生率与安慰剂相当，未提示存在肝毒性风险

方便 口服方便，无食物类型限制

晴安欣®（马来酸阿伐曲泊帕片）简要处方资料

【适应症】

本品适用于择期行诊断性操作或者手术的慢性肝病相关血小板减少症的成年患者。

慢性肝病患者不得通过服用本品来恢复正常的血小板计数。

【用法用量】

本品为本品为口服给药，应与食物同服，每天一次、连续口服 5 天。

【不良反应】

发生率≥3% 的不良反应：发热、腹痛、恶心、头痛、疲劳、外周性水肿。

【注意事项】

血栓形成 / 血栓栓塞并发症

阿伐曲泊帕是一种血小板生成素 (TPO) 受体激动剂，TPO 受体激动剂与慢性肝病患者的血栓形成 以及血栓栓塞并发症有关。在接受 TPO 受体激动剂治疗的慢性肝病患者中已有门静脉血栓形成的报 道。在本品开展的 ADAPT-1 和 ADAPT-2 两项临床试验中，共有一名接受阿伐曲泊帕治疗的合并血 小板减少症的慢性肝病患者 (n=1/430) 在治疗期间发生门静脉血栓形成事件。合并已知血栓栓 塞危险因素的患者，包括遗传性血栓前期状态（凝血因子 V Leiden 突变，凝血酶原基因 20210A 突变，抗凝血酶缺乏，蛋白 C 缺乏或蛋白 S 缺乏），在接受阿伐曲泊帕治疗时会增加血栓形成的风险。慢性肝病患者不得通过服用阿伐曲泊帕恢复正常的血小板计数。应参照【用法用量】使用本品。治 疗期间应注意观察患者是否有血栓栓塞的症状和体征，一旦发生应及时治疗。

【禁忌】无

【规格】20mg(按 $C_{29}H_{34}Cl_2N_6O_3S_2$ 计)

【有效期】60 个月

【贮藏】30°C 以下保存

国谈双通道

参考文献
1、Norah Terrault,et al.Gastroenterology 2018;155:705–718.
2、阿伐曲泊帕说明书
3、Patrick G. Northup,et al.Clin Gastroenterol Hepatol.2019 Mar;17(4):595-606.
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Tellgen 透景

上海透景生命科技股份有限公司

上海透景生命科技股份有限公司（简称“透景生命 "，证券代码：300642）成立于 2003 年，总部坐落于上海张江高科技园区，专业从事高端体外诊断产品的研发、生产、推广和销售，致力于推动新型检测技术在临床检验领域的应用。目前已累计获得近 340 余项产品注册（备案）医疗器械注册证，形成以流式荧光技术、化学发光技术、多重荧光 PCR 技术和液相色谱串联质谱技术为主要技术平台，以肿瘤全程监测、自身免疫、心血管疾病、病原体感染及生殖健康等为主要应用方向的多系列产品；将流式荧光技术与化学发光技术完美整合形成拥有检测速度天花板的“免疫双子岛”；“八个步骤一机完成”的全自动质谱样本前处理系统；更推出了第三代检验流水线 - 快线精灵 T9，该流水线延续了透景流水线的一贯优点，真正做到“高度集成，高速智能”；与日立诊断联合推出了“日立 - 透景兼容性流水线”，开启了国内兼容性流水线的崭新模式。

透景生命坚持“对接全球技术资源，立足本土创新创造”的理念，力争成为生命科技领域具有国际影响力的公司，为人类的健康事业作出贡献。

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开启中国原创三代EGFR-TKI新篇章

- 首个自主原研三代EGFR-TKI，获得多国专利授权
- 两次被国家药品监督管理局纳入优先审评审批
- 首个进入国家医保目录的国产三代EGFR-TKI
- 一线III期AENEAS研究刊登JCO

行业荣耀
成就斐然获多方赞誉

- 知识产权领域最高奖项-第24届中国专利金奖
- 两次获国家重大新药创制重大专项支持
- 第十三届健康中国论坛“年度突破新药”
- 首届江苏专利金奖

翰森制药
HANSOH PHARMA

阿美乐
甲磺酸阿美替尼

强4出击 美乐无限

4th ANNIVERSARY
阿美乐上市4周年

重要里程碑
开启中国原创三代EGFR-TKI新篇章

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仅供研究使用。不得用于诊断。

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更多多组学应用

通过提供具有业界领先的数据质量、灵活性和可扩展性的解决方案，Illumina 为多组学分析提供支持最适合您研究需求的方法。

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万泰生物
WANTAI BioPharm

国际首创·全球独家

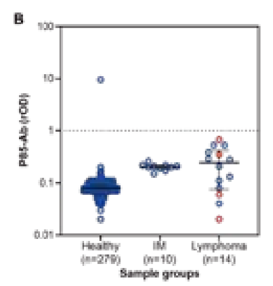
鼻咽癌筛查及辅助诊断生物标志物BNLF2b-Ab(P85-Ab)

22% 早期检出率 **提高22%**

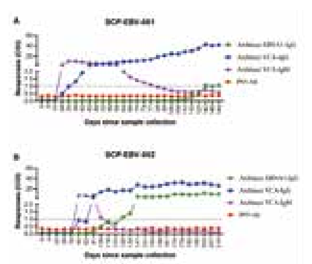
40% 阳性预测值 **提升40%**

25% 灵敏度 **提升25%**

98.3% 具有极高特异性

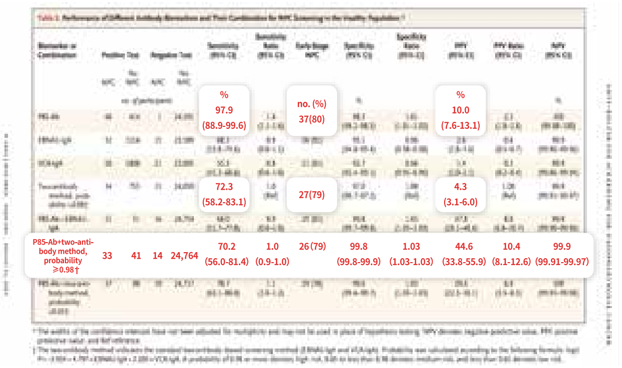


P85-Ab在健康对照组、传染性单核细胞增多症(IM)和淋巴瘤中的特异性



两组EBV IgM血清转换盘的不同标志物反应

不同抗体生物标志物及其组合在健康人群鼻咽癌筛查中的性能*



P85-Ab研究成果由万泰生物转化,适配高通量、自动化检测平台。

即将上市,敬请期待

万泰生物EB病毒BNLF2b抗体测定试剂盒(磁微粒化学发光法)

*参考文献:Li, Tingdong et al. "Anti-Epstein-Barr Virus BNLF2b for Mass Screening for Nasopharyngeal Cancer." The New England journal of medicine vol. 389,9 (2023): 808-819.

雅培ARCHITECT & Alinity i 肿瘤标志物检测

ProGRP SCC CYFRA21-1
PG I PG II PIVKA-II
HE4（仪器可自动生成ROMA值）
AFP CEA
CA125 CA15-3 CA19-9
tPSA fPSA

完善的肿瘤标志物检测全菜单 覆盖中国人群高发癌症

创新开发肿瘤风险评估模型

LCBP 肺癌风险评估模型[1] =
患者病史+ CT 信息+ 雅培肺癌4 项标志物
(ProGRP, SCC, CYFRA21-1, CEA)
(肺癌标志物：ProGRP, SCC, CYFRA21-1, CEA)

ASAP肝癌风险评估模型[2] =
年龄(Age) + 性别(Sex) + 甲胎蛋白(AFP) + 异常凝血酶原(PIVKA-II)

ROMA卵巢癌风险评估模型[3] =
女性绝经状态 + CA125 + HE4

中国抗癌协会肿瘤标志物专委会 **推荐使用**

1. Yang DW, et. al., Cancer, 2018, 124(2):262-270
2.Yang T, Xing H, et.al., Clinical Chemistry 65:12 (2019)
3.Sheng FX, Lu SM, et.al., Clinica Chimica Acta 471(2017) 119-125

ADD-00072984-ZH-CN

智能 **“癌症风险评估”** 微信小程序

北京鑫诺美迪基因检测技术有限公司

更全面 更精准 更通用 更快速 更经济

鑫诺基因聚焦肿瘤分子诊断产品开发，坚持分子检测技术创新，致力于让肿瘤诊断更精准，治疗更有效，助力精准医疗发展

一代测序(Sanger)技术 —金标准

荧光定量PCR技术 —更通用

肿瘤个体化诊疗产品

结直肠癌诊疗用药全面指导
微卫星不稳定性(MSI)、B-raf、N-Ras、K-Ras

子宫内膜癌分子分型用药指导
微卫星不稳定性(MSI)、POLE

胃肠间质瘤靶向用药指导
C-KIT、PDGFRα

肺癌靶向用药指导
微卫星不稳定性(MSI)、B-raf、N-Ras、K-Ras、EGFR、ALK、ROS1、MET

脑胶质瘤诊断用药预后指导
IDH1/2、TERT、B-raf 1P/19Q、H3F3A、MGMT

甲状腺癌靶向用药指导
B-raf、N-Ras、K-Ras、TERT

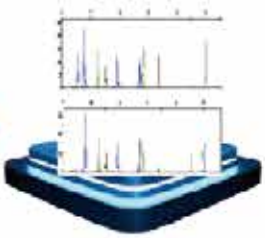
微卫星(MSI)检测

全自动核酸提取仪

NMPA获批试剂盒

集成式U盒设计基因分析仪

仪器适配专业分析软件



整体解决方案

自动化提取仪 | 有证试剂+测序仪 | 标准SOP | 3.5h检测时间 | 结果直观易读

应用场景

1 免疫治疗指导
FDA/NMPA批准多个免疫治疗药物用于治疗有卫星不稳定高度性(MSI-H)或错配修复缺陷(dMMR)的实体瘤患者，NCCN结肠癌诊疗指南2023.V1版和V2版中，MMR/MSI状态已成为结肠癌诊疗的全局分类标准

2 预后评估
MSI-H是II期CRC预后良好的指标；
MSI-H的结直肠癌患者5-FU药物化疗基本无效；
MSI-H的结直肠癌患者不受BRAF(V600E)突变影响

3 Lynch综合征筛查
Lynch综合征是一种常染色体显性遗传肿瘤综合征，由错配修复基因(MMR)胚系突变引起，可引起结直肠及其他部位(包括子宫内膜、卵巢、胃、小肠、肝胆、上尿道、脑和皮肤等)癌肿瘤，NCCN指南建议对所有结直肠癌和子宫内膜癌进行普遍筛查

4 辅助分子分型
NCCN指南提出子宫内膜癌的分子分型，分为4类：POLE突变型、MSI-H型、低拷贝型、高拷贝型；TCGA分型及ACRG分型，将MSI作为胃癌的分子亚型之一。

赛普汀®(伊尼妥单抗)HOPES研究设计与术后复发转移一线亚组分析

关键入选标准

- 组织病理学确诊的晚期乳腺癌
- HER2过表达：IHC检测+++或FISH检测阳性
- 接受过一次及以上化疗，未接受抗HER2治疗

n=315，R2:1

- n=212：伊尼妥单抗（首剂4mg/kg，维持剂量每周2mg/kg，ivgtt）+长春瑞滨（25mg/m²，第1、8、15天/28天，ivgtt）→ 化疗不耐受 → 伊尼妥单抗（首剂8mg/kg，维持6mg/kg，Q3W，ivgtt）→ PD
- n=103：长春瑞滨（25mg/m²，第1、8、15天/28天，ivgtt）→ 化疗不耐受或PD

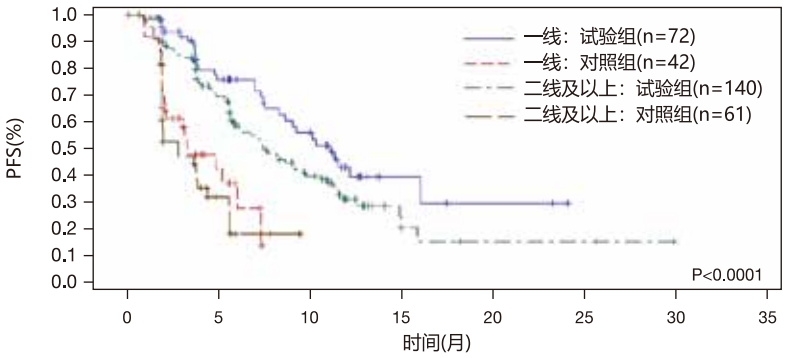
分层因素

- 激素受体状态(ER和/或PR阳性 vs ER及PR阴性)
- DFS (≤2年与＞2年)
- 内脏转移
- 年龄

	病例数(例)		
	试验组	对照组	合计
HOPES研究总病例数	212	103	315
术后一线复发转移病例数	72	42	114

备注：
1. HOPES研究是在既往接受过紫杉类治疗后但未经抗HER2治疗的HER2阳性转移性乳腺癌患者中的随机、对照、多中心、前瞻性III期临床试验。
2. 本研究入组受试者，包括了一线至四线治疗的患者。入组患者接受过一次及以上化疗，包括在新辅助、辅助或晚期阶段。
3. 在研究中试验组患者如果化疗不耐受，则赛普汀单药三周方案继续治疗直至疾病进展；对照组患者如果出现疾病进展或者化疗毒性不耐受，序贯伊尼妥单抗单药治疗(首剂8mg/kg，维持剂量每3周6mg/kg，静滴)直至疾病进展(此数据不纳入统计)。
4. Q3W=每3周一次； PFS=无进展生存期； ORR=客观缓解率； DCR=疾病控制率； RECIST=晚期实体瘤疗效评价标准。

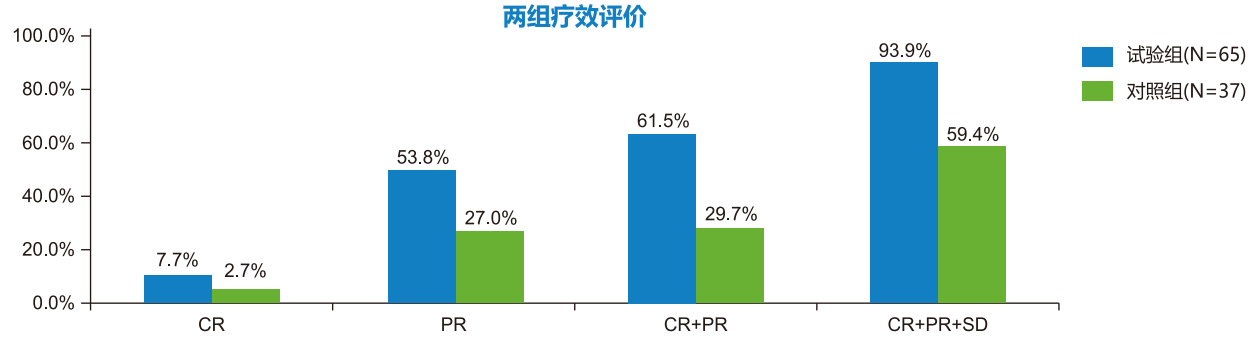
术后复发转移一线：伊尼妥单抗联合化疗治疗患者mPFS显著延长达11.1月



试验组赛普汀联合化疗与对照组单用化疗无进展生存期亚组分析

	mPFS (月)		P值
	试验组	对照组	
一线患者	11.1 (95% CI: 8.25-NE)	3.3 (95% CI: 2.00-5.98)	P<0.0001
二线及以上患者	7.4 (95% CI: 5.27-9.72)	2.8 (95% CI: 1.84-4.37)	P<0.0001

术后复发转移一线：伊尼妥单抗联合化疗治疗ORR为61.5%，DCR为93.9%



备注：ORR 两组间比较P=0.0224，DCR 两组间比较P=0.0003

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百济神州 BeiGene

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11项医保适应症

2024年1月1日正式执行

- **不可切局晚/晚期食管鳞癌一线**
- 经治局晚/晚期食管鳞癌
- 不可切局晚/晚期鳞状NSCLC一线（联合白紫/紫杉方案）
- 不可切局晚/晚期非鳞NSCLC一线
- 经治局晚/晚期NSCLC
- 复发/转移性鼻咽癌一线
- **PD-L1高表达不可切局晚/晚期胃或胃食管结合部腺癌一线**
- 至少经过一种全身治疗的肝细胞癌
- 经治MSI-H/dMMR实体瘤
- 含铂化疗失败的尿路上皮癌
- 复发/难治性经典型霍奇金淋巴瘤

中国

欧盟、英国、韩国、中国澳门

国际认证：截止2023年12月替雷利珠单抗已在欧盟、英国、韩国、中国澳门国家地区获批

全能王者：替雷利珠单抗获NMPA批准11项适应症；根据RATIONALE-306、KEYNOTE-590、CheckMate 648、ESCORT-1st、ORIENT-15和JUPITER-06的mOS和mPFS进行对比，且均为非头对头比较，在前述六项研究中，RATIONALE-306研究mOS和mPFS最长

材料制作日期：2024年1月2日

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- ☑ 改善生活质量
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*仅供医疗卫生专业人士参考

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Pfizer

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药品信息

【商品名称】法玛新®

【剂　　型】注射粉剂

【活性成分】盐酸表柔比星

适应症

用法用量

禁忌

警告：无

药物相互作用

药物过量

不良反应

注意事项

有效期为 48 个月，遮光，密封保存

制药公司名称及地址

详细资料参见药品说明书。

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PP-ELL-CHN-0098　2022-08-31

上海云纹生物科技有限公司

专注领域：病理图像研究 & AI辅助诊断系统

“病理”是肿瘤诊断金标准，也是科学研究的基石。利用**人工智能图像分析系统**协助病理诊断，不仅能够定性、定量诊断，还能够发掘更多的形态学特征。

“病理·归墟”计划——即提供**自助式病理切片扫描业务**，牵线上下游科研平台，为临床、科研、教学和医疗工作提供服务。

服务项目：

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4. 动物实验
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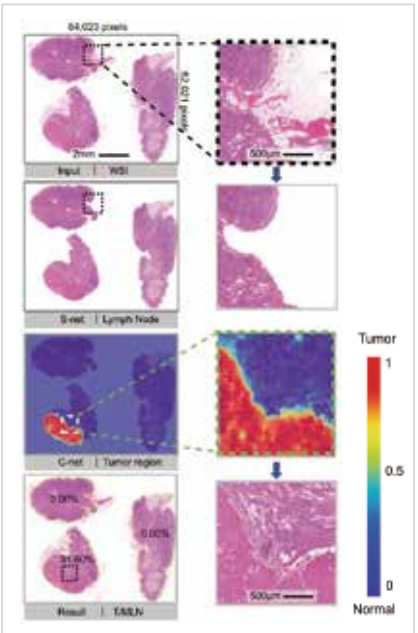
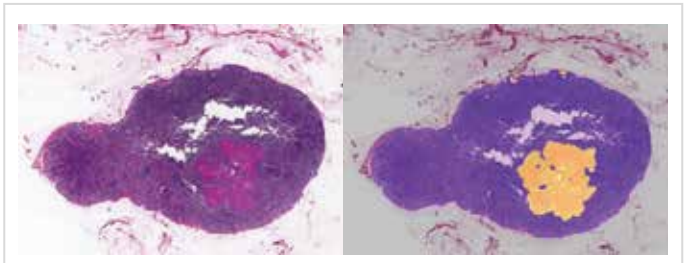
6. 分子诊断
7. 医学研究相关耗材
8. 慢病毒载体
9. 科研设计/咨询
10. 人工智能图像科研服务与产品研发



· 人工智能图像分析

· 组织芯片

· 切片扫描设备 & AI辅助诊断系统



· 病理切片扫描图

· 耗材（血清）

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金域医学
KingMed Diagnostics

金域实体肿瘤疾病中心

Solid Tumor Diagnostic Center

客服电话：4001-111-120

金域医学将实体瘤肿瘤的临床检测与精准医疗作为重点发展方向，构建了包括肿瘤标志物、分子检测、病理诊断在内的多样的精准检验体系。本中心可提供覆盖19种癌种的400余项临床检测项目，致力于提供包含风险评估、筛查、诊断、治疗、预后评估等完善的全方位肿瘤检测服务链。金域医学实体肿瘤NGS检测量超6万例/年，肿瘤筛查甲基化检测量超20万例/年。

深入清晰的报告

享受五星级的服务标准

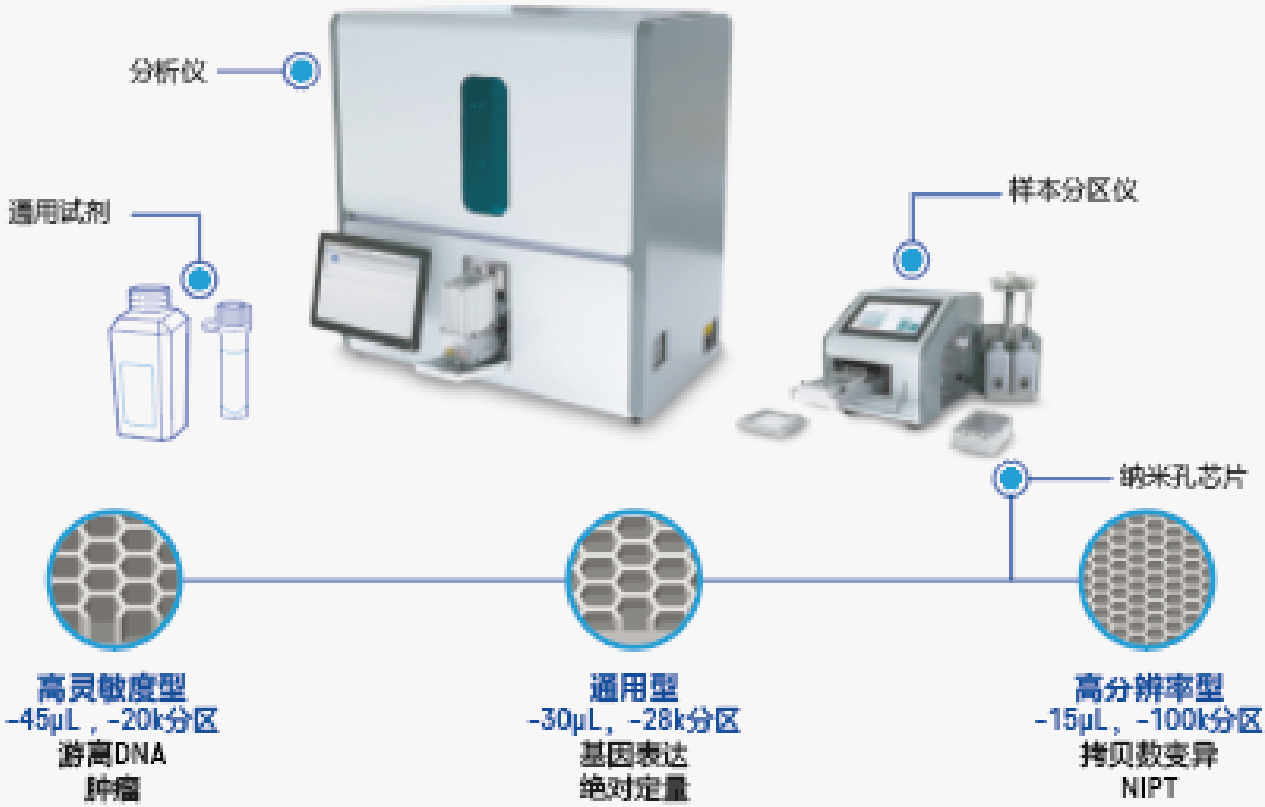
全面： 提供从肿瘤筛查——病理诊断——分子个性化检测完善的服务链；

优质： 首批国家基因检测技术应用示范中心、室间质评满分标准等；

严谨： 检测结果多平台相互验证，如NGS/Sanger、NGS/FISH等；

综合： MAPS综合报告整合组织病理与分子病理结果，提供综合诊疗建议；

专业： 根据AMP、ACMGG、ASCO等指南，综合数据库及研究性文章，多方位专业的解读报告。



隆重推出 Digital LightCycler® 系统：

专为数字PCR性能的新水平而生

罗氏新开发的Digital LightCycler®系统将数字聚合酶链反应（dPCR）提升到临床应用的新水平。Digital LightCycler®系统将提供颠覆性组合：三种独特的纳米芯片、六通道多重检测功能、5倍浓缩的试剂预混液和高技术含量的光学元件。

优异的评估结果显示，该系统可提供：优异的实验数据-出色的无用紧密簇(cluster tightness with no rain)、直观灵活的工作流可适用于不同种类的实验室 - 临床检测*、独立检测实验室*、疾病控制检测、临床研究及开发、生物制药质量控制及科学研究等。

系统亮点

可适配三种不同纳米孔芯片，实现一台仪器配置多种不同应用，在各种特殊应用皆可实现优异的检出效果：

- 高灵敏芯片 - 20,000微孔：45μL超大上样体积，可有效降低取样误差、节约检测成本、提高低拷贝样本检出率
- 通用芯片 - 28,000微孔：适用于大多数基因表达、绝对定量等常规应用
- 高分辨率芯片 - 100,000微孔：针对拷贝数变异等应用，可实现高分辨率的检出

配备高品质的硬件配置，在各种不同检测场景下，皆可输出高品质结果：

- 最快2小时完成1-96个样本的检测运行
- 最多支持6色荧光检测通道+1个专用的参考通道

双操作系统，既可实现按需求灵活分析，也可实现按标准输出的可靠实验结果：

- 可链接LIS系统，实现数据化管理
- 符合21 CFR Part 11要求

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公司简介

江苏英科新创医学科技有限公司始创于1996年，是一家致力于为临床医学检验及生命科学研究领域提供整体产品技术解决方案及综合服务的创新型企业。

多年来一直秉持“诚信做人、用心做事”的核心价值观，赢得了客户及合作伙伴的广泛认同和信任，已经发展成为江苏省内具有行业领先地位的专业化服务型科技企业

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共享商业逻辑：单一产品从厂家到客户端的运营成本如是100元，借助平台（产品组合+服务组合）的集约化服务仅需50元

共享商业的价值：平台服务节省的成本作为渠道伙伴、制造企业、平台服务商三方共享收益

集约化平台服务

（专业化、规模化、属地化、一站式）

政府事务、市场推广、客户关系、渠道选择、售后服务、临床应用、仓储物流、区域人员等相关成本

占企业销售额的15-30 %

制造企业

终端代理商

仓储物流、办公场地、商务人员、收货对账、资金成本等相关成本

占公司销售额的5-15 %

平台集约化一站式解决

集约化后的运营成本约11%，节约30%-70%的综合成本

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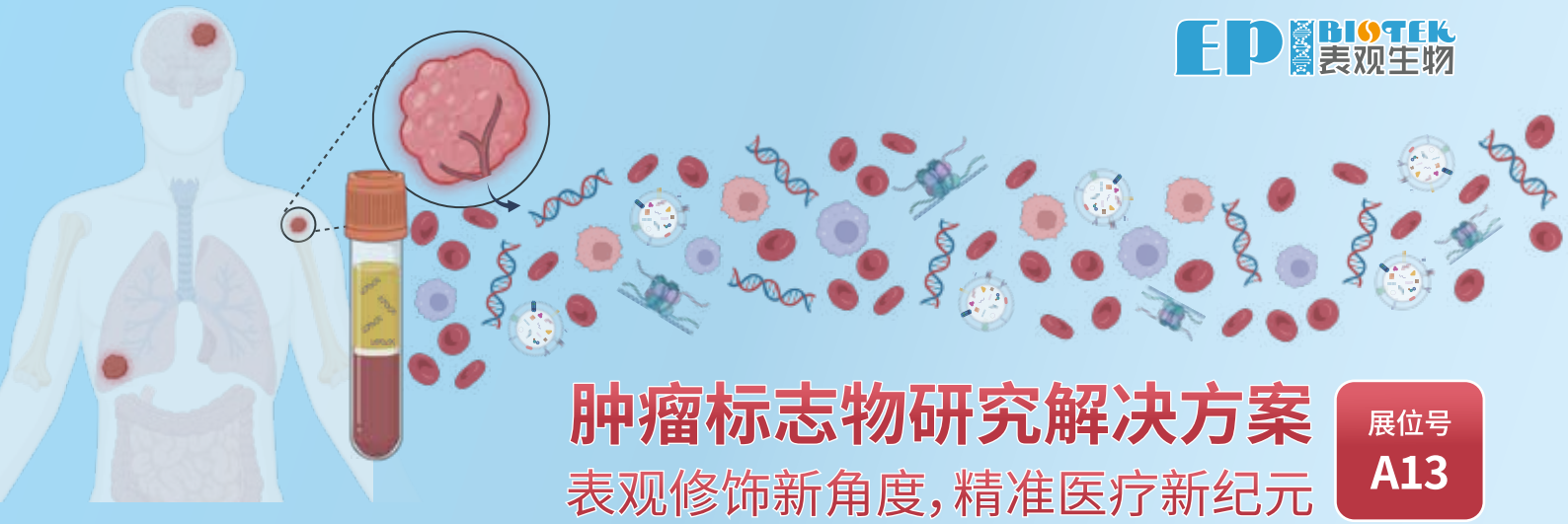

肿瘤标志物研究解决方案

表观修饰新角度，精准医疗新纪元

展位号 A13

液体活检，千亿蓝海。表观生物在国内率先推出cfRNA测序服务潘多拉测序和HEBER-seq，覆盖了tsRNA、rsRNA、长RNA等极具潜力的液体活检标志物；还有cfDNA甲基化靶向测序EM-seq、游离核小体组蛋白修饰测序，以表观修饰新角度，开启精准医疗的新纪元。

cfDNA 甲基化测序 Targeted EM-seq

极具潜力的新型生物标志物

技术优势

1. 二代测序，不仅检测已知甲基化位点，还能发现新的甲基化位点
2. 达到单碱基分辨率，可检测部分 SNP 位点
3. 双链探针设计，提高文库复杂度及检测效率
4. 相对于芯片杂交，测序数据重复性高
5. 样本起始量低，适用于 cfDNA

结果示例

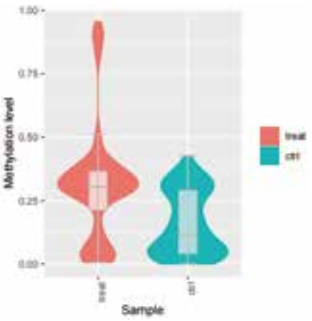

图 1. CpG 甲基化频率直方图

cfRNA 测序 PANDORA-seq、HEBER-seq

tsRNA rsRNA piRNA 长RNA全面覆盖

技术优势

1. 样本要求量低，适用样本类型丰富
2. 无需富集胞外囊泡，减少过程损失，灵敏度高
3. 去 rRNA 建库，同时获得 mRNA 和 lncRNA 数据
4. 自动化高通量建库，缩短一半以上时间，快捷高效
5. 充分发挥深度学习算法的优势，多靶点提高诊断性能

结果示例

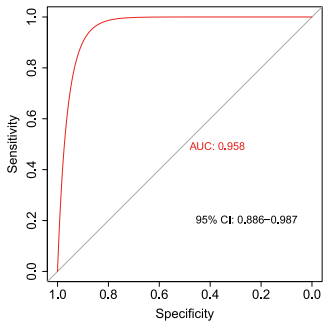

图 2. 疾病诊断和预后模型构建 ROC 分析 training 数据集

游离核小体 多组学测序 EPINUC

同步检测组蛋白修饰和DNA甲基化

技术优势

1. 只需 1mL 血浆即可分析
2. 同步获得多层面的信息
3. 达到单分子分辨率

结果示例

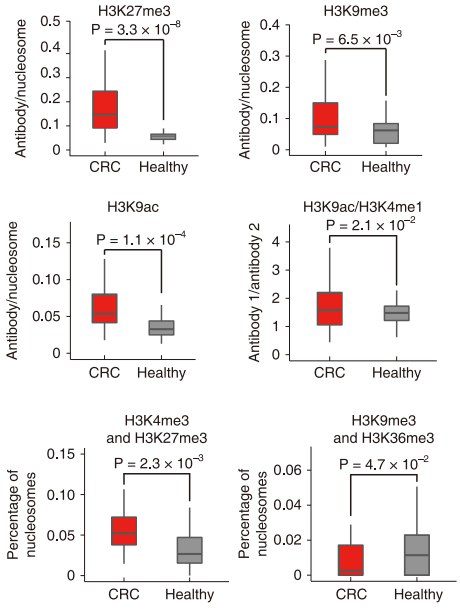

图 3. EPINUC 分析多种组蛋白修饰 (Fedyuk V, et al. Nat Biotech 2023)

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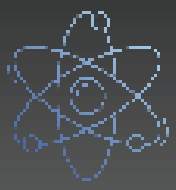
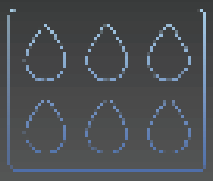
(updated March 18, 2024)

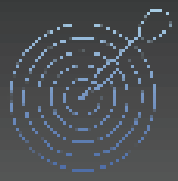
7,701
总蛋白数



20 µL
样本量

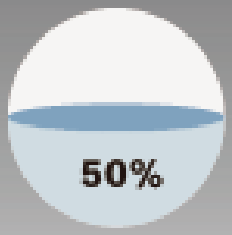


9 logs
动态范围

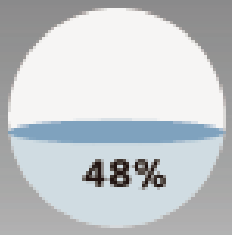


覆盖Olink、Somalogic等数据库 超50%

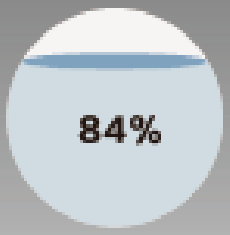
Olink 5K
2,699



SomaLogic 11K
4,672



HPPP
3,855



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CSCO: 中国临床肿瘤学会

mCRC: 转移性结直肠癌

OS: 总生存期

PFS: 无进展生存期

参考文献:

1.2023CSCO结直肠癌诊疗指南.

2.Li J,et al. JAMA.2018;319(24):2486-2496.

3.bai y,et al. 2018 ASCO Abstract 3544.

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参考文献：
1. https://www.nmpa.gov.cn/zwfw/sdxx/sdxxyp/yppjfb/20220602104656165.html. 登陆日期: 20230712.

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样本采集/前处理	分子检测			结果分析注释
样本保护 核酸提取	qPCR (ADx-ARMS®/ Super-ARMS®)	NGS (ddCapture® /Handle®)	Sanger seq.	NGS数据分析系统 数据管理与分析系统
		ddPCR	FISH	IHC

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- 每年数十万肿瘤患者从中受益

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2023版最新国家心衰指南大力推荐

可溶性生长刺激表达基因2蛋白(ST2)

临床应用	B型利钠肽和(或) N末端B型利钠肽原		心肌肌钙蛋白I或T		可溶性 生长刺激表达基因2蛋白	
诊断和鉴别诊断	I类	A级	I类*	A级	-	-
危险分层及预后评价	I类	A级	I类△或 I b类▲	A级△或 B级▲	II a类	B级
治疗效果评价	II a类	B级	-	-	-	-
指导治疗	II b类	B级	-	-	-	-
高危人群筛查	II a类	B级	II a类	B级	II b类	C级

注: *: 针对心力衰竭病因急性冠状动脉综合征或急性心肌炎的诊断和排除; △:针对急性心力衰竭患者; ▲:针对慢性心力衰竭患者; -: 无相关推荐。

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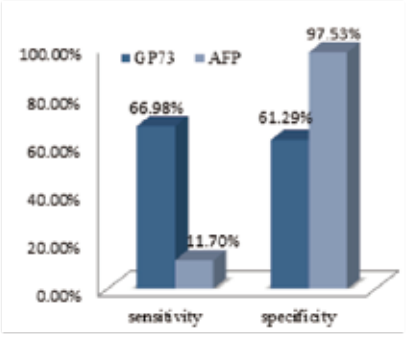
- 首个自主原研三代EGFR-TKI，获得多国专利授权
- 两次被国家药品监督管理局纳入优先审评审批
- 首个进入国家医保目录的国产三代EGFR-TKI
- 一线III期AENEAS研究刊登JCO

行业荣耀
成就斐然获多方赞誉

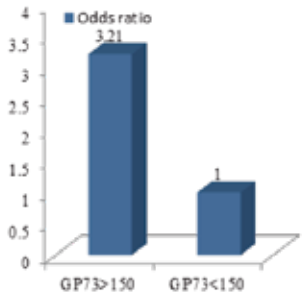
- 知识产权领域最高奖项-第24届中国专利金奖
- 两次获国家重大新药创制重大专项支持
- 第十三届健康中国论坛“年度突破新药”
- 首届江苏专利金奖

四、血清GP73是早期肝癌发生的强风险因子

包括944例肝硬化患者的研究显示: 1-11个月的随访发现, GP73> 150ng/ml的患者发生肝癌的比例是GP73<150ng/m患者的3.21倍。



GP73 和 AFP 在肝硬化患者中诊断肝癌的预测价值

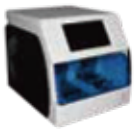


不同 GP73 的水平，发生肝癌的风险比

Clinical Biochemistry 2014 47(16-17):216-222

高尔基体蛋白73测定试剂盒(化学发光法)

注册号：国械注准20173401315



MQ60 proB

MQ60 AUTO

C900

C2000

C3000

产品特点

- 国家重大专项支持项目
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- 配套MQ60系列、C900、C2000及C3000全自动化学发光免疫分析系统
- 既有单人份化学发光试剂又有大包装试剂
- 样本类型:血清、血浆
- 线性范围: 50-500ng/ml
- 包装规格: 60人份/盒, 100(A)人份/盒, 100(B)人份/盒

高尔基体蛋白73测定试剂盒(上转发光法)

注册号：国械注准20163400156

产品特点

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- 试剂常温储存，无需冷藏
- 检测范围:20-500ng/mL
- 产品规格:20T/盒、40T/盒

UPT 2800

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注册号：国械注准20143401816

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CAPSTONE-1 HENGRU

Ying C, et al. ELCC 2024: 198P

*III期注册研究安全导入研究结果

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反映**凝血**系统状态	反映**纤溶**系统状态	反映**内皮**损伤状态	反映**内皮**损伤、**纤溶**系统状态

新血栓四项—填补血栓及血栓前状态的诊断空白

血栓检测 → 评估量表 → 影像检查 → 凝血检测

全血新血栓四项（TAT/PIC/TM/tPAI·C）

Caprini、Padua、Wells-Geneva量表

血管内超声、冠脉造影...

常规凝血项目（APTT/PT/TT/FIB）...

临床应用方向

- **动脉血栓性疾病的早期辅助诊断**
  全血检测有利于缩短院前急救时间、完善评估，是急危重症患者早期诊疗的关键。
- **院内静脉血栓栓塞症（VTE）的防治管理**
  助力下肢深静脉血栓（DVT）、肿瘤并发VTE等患者围术期出凝血风险、预后疗效评估管理。
- **弥散性血管内凝血（DIC）的早期诊断、进展分型**
  TAT/PIC的比值可协助DIC病型分类，在脓毒症DIC诊断、优化治疗方案等方面具有重要的临床意义。

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南京诺唯赞生物科技股份有限公司（股票代码688105）成立于2012年，坐落于南京国家级经济技术开发区，是一家围绕酶、抗原、抗体等功能性蛋白及高分子有机材料进行技术研发和产品开发的生物科技企业。依托于自主建立的关键共性技术平台，先后进入了生命科学、体外诊断、生物医药等业务领域，是国内少数同时具有自主可控上游技术开发能力和终端产品生产能力的研发创新型企业，致力于智造“生物芯片”，持续为 生物科技行业发展注入新活力。

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- 基于单 B 细胞的高性能抗体发现平台
- 规模化多系统重组蛋白制备平台
- 量子点修饰偶联与多指标联检技术平台

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生命科学

成长型业务

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