2024年度四川省科学技术奖提名公示

一、推荐奖种：四川省自然科学奖

二、项目名称：针对肿瘤免疫微生态的新型妇科肿瘤靶向治疗应用基础研究

三、提 名 者：四川大学

四、提名意见：

该项目针对妇科恶性肿瘤缺乏早期诊断标志物，尚无有效的综合性靶向治疗策略，且治疗过程中易发生耐药的临床关键科学问题，聚焦妇科恶性肿瘤发生发展和治疗过程中普遍存在的肿瘤免疫微生态失衡问题，系统开展了一系列应用基础研究，取得创新成果如下：

1、率先表征了妇科恶性肿瘤细胞恶性转化内在分子机制。该团队利用临床和基础优势资源，对妇科恶性肿瘤发生发展以及治疗耐药过程中肿瘤细胞的关键调控分子进行了系统筛选，发现了多个具有潜在临床转化潜力的肿瘤治疗分子靶点。

2、全面揭示了妇科恶性肿瘤免疫微生态失衡分子特征。通过多组学技术和整合分析，解析了妇科恶性肿瘤演进、治疗耐药等过程中肿瘤免疫微生态内部免疫细胞与肿瘤细胞互作的时空关系，筛选发现了多个靶向免疫微生态失衡相关靶点。

3、开展了基于靶向肿瘤免疫微生态失衡的新型联合治疗增敏策略临床研究并建立了临床预测体系。通过开展前瞻性临床试验，筛选发现卵巢癌早期诊断联合标志物，同时在复发妇科肿瘤中，探索了针对肿瘤免疫微生态失衡的新型联合治疗增敏策略的临床价值，将复发妇科肿瘤患者生存率大幅提升。

该团队以通讯作者/第一身份在 Science Advances、PNAS、Genome Biology、Oncogene 等 SCI 杂志发表 50 余篇论文，成果得到 Nature、Nature Reviews Drug Discovery、Nature Reviews Molecular Cell Biology 等权威期刊正面引用，总他引共计 2608 次。该团队还获得包括国家杰青、国家优青，科技部重点研发计划（首席），2030 科技创新四大慢病重大专项（首席）等在内共计 10 项国家级项目资助，团队成员包括国家杰青、国家优青、国家优青（海外）等国家级人才，获得国之名医青年新锐奖，中国肿瘤青年科学家奖，受邀参加 2024 年中国抗癌协会开幕式主旨报告及 Cell 出版社 2024 年 Cell Symposia Hallmarks of Cancer 大会报告，同时团队获授权发明专利 2 项，参与临床指南/共识撰写 14 项，多次组织或参加妇科肿瘤指南/共识培训活动。

提名该项目为 2024 年度四川省自然科学奖。

五、项目简介

妇科恶性肿瘤严重威胁女性生命健康，如何延长妇科恶性肿瘤患者生存期并提高生活质量，是我国妇幼健康领域面临的重大需求。妇科恶性肿瘤预后差，主要原因在于多数肿瘤缺乏早期诊断标志物，尚无有效的综合性靶向治疗策略，且治疗过程中易发生耐药。本团队针对上述关键科学问题，聚焦妇科恶性肿瘤发生发展和治疗过程中普遍存在的肿瘤免疫微生态失衡问题，系统开展了一系列应用基础研究，取得创新成果如下：

1、率先表征了妇科恶性肿瘤细胞恶性转化内在分子机制。本团队利用临床和基础优势资源，对妇科恶性肿瘤发生发展以及治疗耐药过程中肿瘤细胞的关键

调控分子进行了系统筛选，发现了 SORBS2，ERβ等具有潜在临床转化潜力的肿瘤治疗分子靶点，相关研究成果发表在 Genome Biology、PNAS 等国际权威期刊，受邀在 Endocrine Reviews、Genome Biology 等杂志发表肿瘤治疗新靶点综述。

2、全面揭示了妇科恶性肿瘤免疫微生态失衡分子特征。通过多组学技术和整合分析，解析了妇科恶性肿瘤演进、治疗耐药等过程中肿瘤免疫微生态内部免疫细胞与肿瘤细胞互作的时空关系，筛选发现了 CXCL14、miR-330-3p 等多个靶向免疫微生态失衡相关靶点，相关研究成果发表于 Science Advances、Cancer Research、Oncogene 等杂志，受邀在 Trends in Immunology，Cell Reports Medicine 等杂志发表免疫冷肿瘤免疫微生态失衡分子特征综述。

3、开展了基于靶向肿瘤免疫微生态失衡的新型联合治疗增敏策略临床研究并建立了临床预测体系。本团队通过开展前瞻性临床试验，筛选发现卵巢癌早期诊断联合标志物，同时在复发妇科肿瘤中，探索了针对肿瘤免疫微生态失衡的新型联合治疗增敏策略的临床价值，将复发妇科肿瘤患者生存率大幅提升。相关研究发表在 J ImmunoTher Cancer、BMC Medicine 等权威杂志，受邀在 Trends in Cancer 等杂志发表多篇阐释基于肿瘤免疫微生态构建肿瘤早期诊断体系和探索靶向治疗新策略综述。

本团队以通讯作者/第一身份在 Science Advances、PNAS、Genome Biology、Oncogene 等 SCI 杂志发表 50 余篇论文，成果得到 Nature、Nature Reviews Drug Discovery、Nature Reviews Molecular Cell Biology 等权威期刊正面引用，总他引共计 2608 次。本团队还获得包括国家杰青、国家优青，科技部重点研发计划（首席），2030 科技创新四大慢病重大专项（首席）等在内共计 10 项国家级项目资助，团队成员包括国家杰青、国家优青、国家优青（海外）等国家级人才，获得国之名医青年新锐奖，中国肿瘤青年科学家奖，受邀参加 2024 年中国抗癌协会开幕式主旨报告及 Cell 出版社 2024 年 Cell Symposia Hallmarks of Cancer 大会报告，同时团队获授权发明专利 2 项，参与临床指南/共识撰写 14 项，多次组织或参加妇科肿瘤指南/共识培训活动。

五、代表性论文专著目录

序号	论文（专著）名称/刊名/作者	年卷页码（xx 年 xx 卷 xx 页）	发表时间（年月日）	通讯作者（含共同）	第一作者（含共同）	国内作者	他引总次数	检索数据库	论文署名单位是否包含国外单位
1	Plasma cells shape the mesenchymal identity of ovarian cancers through transfer of exosome-derived microRNAs/Science Advances/ Yang Z, Wang W, Zhao L, Wang X, Gimple RC, Xu L, Wang Y, Rich JN, Zhou S.	2021;7(9):eabb0737.	2021-2-24	汪源，Jeremy N. Rich，周圣涛	杨正楠，王伟，赵林桔	杨正楠，王伟，赵林桔，王鑫，徐炼，汪源，周圣涛	26	SCI-E	是
2	Pharmacological activation of estrogen receptor beta augments innate immunity to suppress cancer metastasis/PNAS/Zhao L, Huang S, Mei S, Yang Z, Xu L, Zhou N, Yang Q, Shen Q, Wang W, Le X, Lau WB, Lau B, Wang X, Yi T, Zhao X, Wei Y, Warner M, Gustafsson JÅ, Zhou S.	2018；115(16):E3673-E3681.	2018-4-17	Jan-Åke Gustafsson，周圣涛	赵林桔，黄爽，梅胜林	赵林桔，黄爽，梅胜林，杨正楠，徐炼，周年鑫，杨琪莲，沈秋红，王伟，乐小兵，王鑫，易韬，赵霞，魏于全，周圣涛	50	SCI-E	是
3	The RNA binding protein SORBS2 suppresses metastatic colonization of ovarian cancer by stabilizing tumor-suppressive immunomodulatory transcripts/Genome Biology/Zhao L, Wang W, Huang S, Yang Z, Xu L, Yang Q, Zhou X, Wang J, Shen Q, Wang C, Le X, Feng M, Zhou N, Lau WB, Lau B, Yao S, Yi T,	2018;19(1):35.	2018-3-19	周圣涛	赵林桔，王伟，黄爽，杨正楠，徐炼	赵林桔，王伟，黄爽，杨正楠，徐炼，杨琪莲，周秀，王津津，沈秋红，王琛璐，乐小兵，冯敏，周年鑫，姚少华，易韬，王鑫，赵霞，魏于	60	SCI-E	是

	Wang X, Zhao X, Wei Y,Zhou S					全，周圣涛			
4	An integrated analysis identifies STAT4 as a key regulator of ovarian cancer metastasis/ Zhao L, Ji G, Le X, Luo Z, Wang C, Feng M, Xu L, Zhang Y, Lau WB, Lau B, Yang Y, Lei L, Yang H, Xuan Y, Chen Y, Deng X, Yi T, Yao S, Zhao X, Wei Y, Zhou S	2017;36(24):3384-3396.	2017-6-15	周圣涛	赵林桔	赵林桔，姬改利，乐小兵，罗忠悦，王琛璐，冯敏，徐炼，张亚光，杨艳菲，雷玲子，杨辉亮，宣煜，陈亿，邓祥兵，易韬，姚少华，赵霞，魏于全，周圣涛	69	SCI-E	是
5	肠道菌群在免疫检查点抑制剂治疗肿瘤中作用的研究进展/四川大学学报（医学版）/ 武梦芮，汤沐亚，郑博豪，周圣涛	2021;52(5):735-739	2021-09-20	周圣涛	武梦芮	武梦芮，汤沐亚，郑博豪，周圣涛	0	中国科学引文数据库(CSCD)	否

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蓝春燕	4	主任医师	中山大学肿瘤防治中心	中山大学肿瘤防治中心
徐沁	5	主任医师	福建省肿瘤医院	福建省肿瘤医院
瞿大成	6	副主任医师	川北医学院附属医院	川北医学院附属医院

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4	川北医学院附属医院

CANCER

Plasma cells shape the mesenchymal identity of ovarian cancers through transfer of exosome-derived microRNAs

Zhengnan Yang[1,2]*, Wei Wang[3]*, Linjie Zhao[4]*, Xin Wang[5], Ryan C. Gimple[4], Lian Xu[6], Yuan Wang[2†], Jeremy N. Rich[4†], Shengtao Zhou[1†]

Ovarian cancer represents a highly lethal disease that poses a substantial burden for females, with four main molecular subtypes carrying distinct clinical outcomes. Here, we demonstrated that plasma cells, a subset of antibody-producing B cells, were enriched in the mesenchymal subtype of high-grade serous ovarian cancers (HGSCs). Plasma cell abundance correlated with the density of mesenchymal cells in clinical specimens of HGSCs. Coculture of nonmesenchymal ovarian cancer cells and plasma cells induced a mesenchymal phenotype of tumor cells in vitro and in vivo. Phenotypic switch was mediated by the transfer of plasma cell–derived exosomes containing miR-330-3p into nonmesenchymal ovarian cancer cells. Exosome-derived miR-330-3p increased expression of junctional adhesion molecule B in a noncanonical fashion. Depletion of plasma cells by bortezomib reversed the mesenchymal characteristics of ovarian cancer and inhibited in vivo tumor growth. Collectively, our work suggests targeting plasma cells may be a novel approach for ovarian cancer therapy.

INTRODUCTION

Ovarian cancer ranks among the most lethal malignancies for women, displaying substantial heterogeneity in tumor biology and clinical outcome (*1*, *2*). Genomic changes in cancer cells stratify patients into different subgroups with distinct prognosis and response to therapies (*3*). As cancer tissues are composed of both cancer cells and nonneoplastic cells (*4*, *5*), the functions of these nonneoplastic cells are less well studied. The success of oncoimmunology has prompted the interrogation of infiltrating immune cells to predict clinical outcome and response to treatment (*6*).

Large-scale transcriptional profiling of patient specimens has led to the pioneering work of molecular subtyping for ovarian cancer (*7*). Later, it has become well recognized that ovarian cancer, primarily high-grade serous ovarian cancer (HGSC), could be categorized into four distinct transcriptional subtypes: immunoreactive, differentiated, proliferative, and mesenchymal subtypes, among which the mesenchymal subtype has a relatively poor overall survival, confirmed by RNA sequencing data for about 500 patients with serous ovarian cancer by The Cancer Genome Atlas (TCGA) network (*3*). However, rare reports could be found on whether different subtypes of ovarian cancer exhibit distinct patterns of immune infiltration (*8*, *9*), which is critical to the design of precision medicine for this deadly disease.

On the basis of this background, we hypothesized that deconvolution of the transcriptomic signatures from whole-tumor specimens can distinguish tumor and immune cell contributions and yield insights into subtype-specific immunologic responses in ovarian cancer. A recently described gene expression deconvolution algorithm (CIBERSORT) estimates the relative proportions of 22 distinct functional subsets of immune cells (*10*, *11*). Using this method, we quantified the immune infiltration of the four subtypes of HGSC, the most common pathological subtype of ovarian cancer, and found a significant correlation with subtypes. In particular, using this integrated computational analysis together with further functional experiments, we identified an immune-associated cellular, molecular, and clinical network that highlights the defining role of plasma cells in the mesenchymal identity of HGSCs.

RESULTS

Plasma cells are enriched in the mesenchymal subtype of HGSCs

To investigate the subtype-specific immune infiltration pattern in ovarian cancer, we applied CIBERSORT to bulk gene expression profiles (GEPs) of ovarian cancer in the publicly available Bonome dataset (*12*) to infer the proportions of 22 subsets of immune cells in the four subtypes. The most prevalent immune cells were $CD8^+$ T cells, plasma cells, M2 macrophages, and follicular helper T cells in the ovarian cancer microenvironment (Fig. 1A). For external validation, we further interrogated the abundance of plasma cells in the mesenchymal-subtype HGSCs in two other training cohorts (both excluding non-HGSC patients): Mateescu dataset (*13*) and Tothill dataset (table S1) (*7*). It was found that the plasma cell abundance was significantly higher in the mesenchymal subtype compared with that in other three subtypes in both Mateescu dataset and Tothill dataset (Fig. 1B). Moreover, in both Bonome dataset and Mateescu dataset, the mesenchymal-subtype patients were prone to have higher plasma cell abundance compared with nonmesenchymal-subtype patients (fig. S1A). Further analysis indicated that M1

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Pharmacological activation of estrogen receptor beta augments innate immunity to suppress cancer metastasis

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Contributed by Jan-Åke Gustafsson, March 6, 2018 (sent for review February 22, 2018; reviewed by Yunlong Lei and Haineng Xu)

Metastases constitute the greatest causes of deaths from cancer. However, no effective therapeutic options currently exist for cancer patients with metastasis. Estrogen receptor β (ERβ), as a member of the nuclear receptor superfamily, shows potent tumor-suppressive activities in many cancers. To investigate whether modulation of ERβ could serve as a therapeutic strategy for cancer metastasis, we examined whether the selective ERβ agonist LY500307 could suppress lung metastasis of triple-negative breast cancer (TNBC) and melanoma. Mechanistically, while we observed that LY500307 potently induced cell death of cancer cells metastasized to lung in vivo, it does not mediate apoptosis of cancer cells in vitro, indicating that the cell death-inducing effects of LY500307 might be mediated by the tumor microenvironment. Pathological examination combined with flow cytometry assays indicated that LY500307 treatment induced significant infiltration of neutrophils in the metastatic niche. Functional experiments demonstrated that LY500307-treated cancer cells show chemotactic effects for neutrophils and that in vivo neutrophil depletion by Ly6G antibody administration could reverse the effects of LY500307-mediated metastasis suppression. RNA sequencing analysis showed that LY500307 could induce up-regulation of IL-1β in TNBC and melanoma cells, which further triggered antitumor neutrophil chemotaxis. However, the therapeutic effects of LY500307 treatment for suppression of lung metastasis was attenuated in *IL1B*$^{-/-}$ murine models, due to failure to induce antitumor neutrophil infiltration in the metastatic niche. Collectively, our study demonstrated that pharmacological activation of ERβ could augment innate immunity to suppress cancer metastatic colonization to lung, thus providing alternative therapeutic options for cancer patients with metastasis.

ERβ | LY500307 | cancer metastasis | neutrophil | IL-1β

Cancer metastasis is one of the most important causes of cancer-related mortalities worldwide. Clinical metastasis is described as a multistep process, and the basic steps for metastasis formation occur in the context of different organs, emerge at different rates, and are clinically managed in different ways depending on the type of cancer. A number of the metastasis-directed therapies under development are cytostatic, not cytotoxic, and in preclinical models, making their clinical validation problematic (1). Therefore, skepticism exists in the pharmaceutical industry on the druggability of the metastasis disease.

Estrogen receptors (ERs) are intracellular transcription factors whose activity is fine-tuned by the naturally occurring estrogens in the body or by synthetic, nonsteroidal, nonhormonal agonist and antagonist ligands (2, 3). Currently, there are two known ER subtypes: ERα, encoded by the ESR1 gene on chromosome 6; and ERβ, encoded by the ESR2 gene on chromosome 14. Both ERα and ERβ are expressed in a wide range of normal tissues and cell types throughout the body. They are also widely expressed in different pathological tissues, including cancer. Previous reports showed that ∼75% of all breast cancers are positive for ERα, which is positively correlated with response to endocrine therapy (4). However, 10 to 20% of all breast cancers are triple-negative breast cancer (TNBC), which lacks expression of ERα, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) amplification. As patients with TNBC do not benefit from targeted therapies with tamoxifen or trastuzumab, they have a poorer prognosis and a higher rate of distant recurrence than women with other breast cancer subtypes (5). In contrast to ERα, ERβ has been shown to be expressed in all molecular subtypes of breast cancer, including

Significance

Cancer metastases have caused the major mortality rate for cancer patients, with limited options of treatment and unsatisfactory therapeutic efficacy. Unlike the tumor-promoting role of estrogen receptor (ER)α, ERβ has shown potent antitumor effects in many cancers. In this study, we showed that the selective ERβ agonist LY500307 could potently suppress lung metastasis of cancer by recruitment of antitumor neutrophils to the metastatic niche. These chemotactic effects of LY500307 for neutrophils were primarily mediated by ERβ activation-induced IL-1β release by the tumor cells. Our study provides the rationale that pharmacological activation of ERβ could augment innate immunity to suppress cancer metastatic colonization to lung, implicating the potential use of selective ERβ agonists for the treatment of cancer patients with metastasis.

Author contributions: J.-Å.G. and S.Z. designed research; L.Z., S.H., Z.Y., L.X., N.Z., Q.Y., Q.S., W.B.L., B.L., and T.Y. performed research; L.Z., S.H., S.M., W.W., X.L., X.W., X.Z., Y.W., M.W., J.-Å.G., and S.Z. analyzed data; and J.-Å.G. and S.Z. wrote the paper.

Reviewers: Y.L., Chongqing Medical University; and H.X., University of Pennsylvania Perelman School of Medicine.

The authors declare no conflict of interest.

Data deposition: High-throughput sequencing data have been deposited in the Gene Expression Omnibus (GEO) database (accession nos. GSE110769 and GSE110770).

[1]L.Z., S.H., and S.M. contributed equally to this work.

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Genome Biology

RESEARCH Open Access

The RNA binding protein SORBS2 suppresses metastatic colonization of ovarian cancer by stabilizing tumor-suppressive immunomodulatory transcripts

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Abstract

Background: Ovarian cancer constitutes one of the most lethal gynecologic malignancies for females. Currently, early detection strategies and therapeutic options for ovarian cancer are far from satisfactory, leading to high diagnosis rates at late stages and disease relapses. New avenues of therapy are needed that target key processes in ovarian cancer progression. While a variety of non-coding RNAs have been proven to regulate ovarian cancer metastatic progression, the functional roles of RNA-binding proteins (RBPs) in this process are less well defined.

Results: In this study, we identify that the RBP sorbin and SH3 domain containing 2 (SORBS2) is a potent suppressor of ovarian cancer metastatic colonization. Mechanistic studies show that SORBS2 binds the 3′ untranslated regions (UTRs) of *WFDC1* (WAP four-disulfide core domain 1) and *IL-17D* (Interleukin-17D), two secreted molecules that are shown to act as metastasis suppressors. Enhanced expression of either *WFDC1* or *IL-17D* potently represses SORBS2 depletion-mediated cancer metastasis promotion. By enhancing the stability of these gene transcripts, SORBS2 suppresses ovarian cancer invasiveness and affects monocyte to myeloid-derived suppressor cell and M2-like macrophage polarization, eliciting a tumor-suppressive immune microenvironment.

Conclusions: Our data illustrate a novel post-transcriptional network that links cancer progression and immunomodulation within the tumor microenvironment through SORBS2-mediated transcript stabilization.

Keywords: RNA binding protein, SORBS2, Ovarian cancer, Metastasis, mRNA stability, Immunomodulation, WFDC1, IL-17D

Background

Ovarian cancer has been reported to be the most lethal among gynecologic malignancies, with over 21,000 patients diagnosed and more than 14,000 deaths in the United States in 2014 [1]. The majority of ovarian cancer histological subtypes are high grade serous ovarian carcinoma (HGSOC), with relatively poor prognosis due to the advanced stage of disease at diagnosis, widespread metastasis, and high relapse rate [2]. However, the molecular mechanisms that mediate ovarian cancer progression are far from elucidated, rendering the diagnosis and treatment of ovarian cancer still unsatisfactory.

Ovarian cancer predominantly metastasizes via pelvic dissemination directly to adjacent organs instead of through lymphatic or hematologic channels [3]. Recently, the tumor microenvironment has gradually been recognized to be critical for ovarian cancer intraperitoneal metastasis. Interacting with tumor cells via secretory reciprocal communication, the surrounding

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ORIGINAL ARTICLE

An integrated analysis identifies STAT4 as a key regulator of ovarian cancer metastasis

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Epithelial ovarian cancer (EOC) is one of the most common gynecological cancers, with diagnosis often at a late stage. Metastasis is a major cause of death in patients with EOC, but the underlying molecular mechanisms remain obscure. Here, we utilized an integrated approach to find potential key transcription factors involved in ovarian cancer metastasis and identified STAT4 as a critical player in ovarian cancer metastasis. We found that activated STAT4 was overexpressed in epithelial cells of ovarian cancer and STAT4 overexpression was associated with poor outcome of ovarian cancer patients, which promoted metastasis of ovarian cancer in both *in vivo* and *in vitro*. Although STAT4 mediated EOC metastasis via inducing epithelial-to-mesenchymal transition (EMT) of ovarian cancer cells *in vivo*, STAT4 failed to induce EMT directly *in vitro*, suggesting that STAT4 might mediate EMT process via cancer–stroma interactions. Further functional analysis revealed that STAT4 overexpression induced normal omental fibroblasts and adipose- and bone marrow-derived mesenchymal stem cells to obtain cancer-associated fibroblasts (CAF)-like features via induction of tumor-derived Wnt7a. Reciprocally, increased production of CAF-induced CXCL12, IL6 and VEGFA within tumor microenvironment could enable peritoneal metastasis of ovarian cancer via induction of EMT program. In summary, our study established a model that STAT4 promotes ovarian cancer metastasis via tumor-derived Wnt7a-induced activation of CAFs.

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INTRODUCTION

Epithelial ovarian cancer constitutes one of the most common gynecological malignancies, with an incidence rate of 3–12/100 000 woman per year. Because the ovaries lie in the deep pelvic cavity, most ovarian cancer patients are asymptomatic, rendering the majority often diagnosed at an advanced stage.[1] Although traditional therapeutic strategies could temporarily trigger an initial tumor response, cancer cells will eventually develop resistance and relapse.[2] Thus, the development of more effective treatment agents or therapeutic targets is imperative. Considering that the major biological hallmarks that distinguish malignant from benign tumors is the ability to metastasize, it is of great significance to characterize the molecular events that occur during ovarian cancer metastasis.

High-throughput proteomic measurements reflect quantitative proteome-wide changes but fail to provide a direct perspective of the upstream regulatory mechanisms responsible for these changes. Identifying potential regulatory mechanisms responsible for proteome changes could facilitate unraveling of disease mechanisms and enable the discovery of diagnostic biomarkers and therapeutic targets.[3,4] Here, we presented an integrative experimental and computational approach for identifying and ranking clinically significant upstream transcription factors probably responsible for the observed proteome changes. We computationally predicted that STAT4 is involved in ovarian cancer metastasis. STAT4 is a member of signal transducers and activators of transcription (STATs) family, which is required for the biological functions of IL12, including the differentiation of Th1 cells and optimal IFN-γ production. Unlike other STAT proteins (for example, STAT1 and STAT3), which appear to be constitutively expressed in a variety of tissues, STAT4 expression is restricted to hematopoietic cells.[5] Apart from physiological conditions, recent researches reported dysregulation of STAT4 under pathological circumstances like malignancies.[6–8] However, the role of STAT4 in ovarian cancer and underlying regulatory mechanisms remain largely unexplored.

Cancer development is manipulated by the crosstalk between tumor cells and tumor microenvironment.[9] Cancer-associated fibroblasts (CAFs) constitute one of the most abundant cell types in different tumor entities, which stem from heterogeneous cell types. Recent researches have demonstrated that CAFs participate in cancer development and progression directly and indirectly as they secrete classical growth factors, enable inflammation, enhance angiogenesis, remodel the extracellular matrix and enhance stiffness, and promote stemness.[10] However, the functional role of CAFs in ovarian cancer pathogenesis still remains poorly understood. Here, using an integrated approach, we identified STAT4 as a key regulator of ovarian cancer metastasis via Wnt7a-induced activation of CAFs.

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肠道菌群在免疫检查点抑制剂治疗肿瘤中作用的研究进展*

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【摘要】 近年来，免疫疗法作为抗肿瘤新兴治疗方法，在实体瘤和血液系统肿瘤中均展现出极大的治疗潜力。越来越多的临床前和临床证据将肠道微生物组成与免疫检查点抑制剂抗肿瘤疗效及不良反应联系起来。本文对肠道微生物在不同免疫检查点抑制剂抗肿瘤治疗中的调控作用进行综述，并对目前研究的局限性及进一步临床策略的发展进行展望。

【关键词】 肠道微生物组 肿瘤免疫治疗 免疫检查点抑制剂

Tracking Research Progress in the Modulatory Role of Gut Microbiome in Immune Checkpoint Inhibitors Applied in Cancer Treatment

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【**Abstract**】 In recent years, immunotherapy, as an emerging anti-tumor therapy, has shown great potential in the treatment of both solid and hematologic tumors. There is increasing preclinical and clinical evidence linking the composition of gut microbiome with the efficacy as well as adverse effects of immune checkpoint inhibitor anti-tumor therapy. We summarized in this review the modulatory role of the gut microbiome in antitumor therapy with different immune checkpoint inhibitors. We also discussed the limitations of existing research and prospective development of the further clinical strategies.

【**Key words**】 Gut microbiome Cancer immunotherapy Immune checkpoint inhibitors

目前，传统的肿瘤治疗方法效果不佳和肿瘤复发率升高已成为抗肿瘤治疗亟待解决的问题[1]。近年来，作为一种新兴的治疗方法，免疫治疗已在癌症治疗中被广泛应用，免疫检查点抑制剂（immune checkpoint inhibitors, ICIs）在其中扮演着至关重要的角色。免疫治疗通过作用于免疫系统发挥抗肿瘤作用，最初被发现在部分转移性黑色素瘤和肺癌患者中效果显著，逐渐展现出治疗血液系统恶性肿瘤和实体瘤的潜力[2]。但是，其疗效仍然受到患者免疫应答异质性与不同肿瘤间异质性[3]的限制，接受治疗的患者中仅有10%～30%对目前可用的免疫疗法有反应[4]，且部分患者治疗期间会发生原发性或获得性耐药及相关的不良反应，这极大阻碍了抗肿瘤免疫治疗的广泛临床应用[5]。

随着二代测序技术的广泛应用，越来越多的研究已证实肠道菌群在癌症治疗过程中起关键调控作用。人体肠道微生物组约有3×10^{13}个细菌，其中的大多数为共生菌[6]，一直在机体免疫反应中发挥着不容忽视的作用。虽然成年人肠道和其他上皮屏障的微生物组成成分相对稳定，但仍然可以随着饮食和生活节奏的调整、疾病发生和疾病治疗等变化发生改变[7]。已有研究发现肠道菌群参与了肠道和肠外组织各种类型癌症的发生、发展和转移过程[8-10]。此外，肠道微生物还可以参与诱导炎症或免疫抑制间接参与癌症治疗，最终影响抗肿瘤治疗效果[11]。近年来的临床前研究及临床研究已将肠道菌群组成与ICIs的特异性反应和毒性反应联系起来[12-15]。本文旨在回顾近年来不同ICIs治疗中肠道微生物组的调控作用，并对目前研究的局限性进行阐述，对临床策略的进一步发展方向进行展望。

1 肠道微生物对ICIs治疗的调控

作为新型的免疫治疗策略，ICIs已在晚期血液系统恶性肿瘤治疗中表现出可喜的临床结果。单克隆抗体（monoclonal antibodies, mAbs）阻断细胞毒性T淋巴细胞抗原4（cytotoxic T-lymphocyte antigen 4, CTLA-4）和程序性细胞死亡蛋白1（programmed cell death protein 1, PD-1）等治疗策略的成功应用同样证明了这一点[16-17]。

1.1 PD-1/PD-L1 mAb

近五年来，已有多项动物模型实验和临床试验研究证实肠道微生物组成与PD-1/PD-L1阻断治疗反应有较强的相关性。2015年，SIVAN等[18]探索了具有不同肠道共生

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