· 论著 ·

雄激素剥夺治疗对前列腺癌免疫微环境影响的多层级研究

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[摘 要] **目的**:从免疫水平、动物模型转录组及单细胞组学层面系统评估雄激素剥夺治疗(androgen deprivation therapy,ADT)对前列腺癌免疫微环境的影响,阐明 ADT 介导的肿瘤免疫重塑特征。**方法**:纳入北京大学人民医院接受 ADT 治疗的前列腺癌患者 12 例,动态检测血清前列腺特异性抗原(prostate specific antigen,PSA)、睾酮水平、外周血免疫细胞比例与细胞因子表达变化;从基因表达汇编(gene expression omnibus,GEO)数据库下载前列腺癌人源肿瘤异种移植(patient-derived tumor xenograft,PDX)模型去势前后转录组数据(GSE41193,共 5 例),进行相关生物信息学分析;另对 4 例前列腺癌组织(2 例接受 ADT 新辅助治疗、2 例未接受)行单细胞 RNA 测序(single-cell RNA sequencing,scRNA-seq),解析肿瘤微环境细胞组成及 T 细胞功能状态。**结果**:ADT 显著降低患者血清 PSA 及睾酮水平,但外周血免疫细胞比例及大多数细胞因子无明显影响。PDX 模型分析显示,前列腺癌患者去势后差异表达基因富集于神经相关及免疫调控通路,多种免疫细胞浸润特征呈现趋势性改变。scRNA-seq 结果表明,ADT 治疗后肿瘤内效应性 $CD8^+$ T 细胞比例下降,*GZMA*、*GZMB*、*GNLY*、*NKG7* 等细胞毒相关基因表达下调,而调节性 T 细胞(Treg)相对富集。Hallmark 通路分析显示干扰素信号通路受到抑制。**结论**:ADT 可诱导前列腺癌肿瘤免疫微环境发生趋势性的改变,表现为 T 细胞杀伤功能减弱及免疫抑制性细胞富集,提示 ADT 可能促进抑制性肿瘤免疫微环境(tumor immune microenvironment,TIME)形成,为 ADT 联合免疫调节治疗策略提供了理论依据。

[关键词] 前列腺癌;雄激素剥夺治疗;肿瘤免疫微环境
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A multi-level study of androgen deprivation therapy on the immune microenvironment in prostate cancer

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ABSTRACT **Objective**: To systematically evaluate the impact of androgen deprivation therapy (ADT) on the immune microenvironment of prostate cancer at the levels of systemic immunity, animal model transcriptomics, and single-cell omics, and to elucidate the characteristics of ADT-mediated tumor immune remodeling. **Methods**: Twelve prostate cancer patients who received ADT at Peking University People's Hospital were enrolled. Dynamic monitoring of serum prostate specific antigen (PSA), testosterone levels, peripheral blood immune cell proportions, and cytokine expression changes was performed. Transcriptomic data from patient-derived tumor xenograft (PDX) models before and after castration (GSE41193, 5 cases in total) were downloaded from the gene expression omnibus (GEO) database for relevant bioinformatics analyses. Single-cell RNA sequencing (scRNA-seq) was performed on 4 prostate cancer tissue samples (2 received neoadjuvant ADT, 2 untreated) to analyze tumor microenvironment cell composition and T-cell functional states. **Results**: ADT significantly reduced serum PSA and testosterone levels in the patients, but had no significant effect on peripheral blood immune cell proportions or most cytokines. PDX model analysis showed that differentially expressed genes after castration were enriched in neural-related and immune regulation pathways, with trending changes observed in the infiltration characteristics of various immune cells. scRNA-seq results indicated a decreased proportion of intratumoral effector $CD8^+$ T cells after ADT treatment, with downregulated expression of cytotoxicity-related genes, such as *GZMA*, *GZMB*, *GNLY*, and *NKG7*, while regulatory T cells (Tregs) were relatively enriched. Hallmark pathway analysis revealed suppression of interferon signaling pathways. **Conclusion**: The preliminary results of this study suggest that ADT can induce a trend of change in the tumor immune micro-

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environment of prostate cancer, characterized by weakened T-cell killing function and enrichment of immunosuppressive cells. This suggests that ADT may promote the formation of an immunosuppressive tumor immune microenvironment (TIME), providing a theoretical basis for ADT combined with immune-modulating therapeutic strategies.
KEY WORDS Prostate cancer; Androgen deprivation therapy; Tumor immune microenvironment

前列腺癌是全球男性最常见的恶性肿瘤之一,也是男性肿瘤相关死亡的重要原因[1]。雄激素剥夺治疗(androgen deprivation therapy,ADT)是局部晚期及转移性前列腺癌的基础治疗手段[2]。尽管ADT可在初期显著抑制肿瘤进展,但绝大多数患者最终进展为去势抵抗性前列腺癌(castration-resistant prostate cancer,CRPC),提示ADT不仅影响肿瘤负荷,也深刻改变肿瘤生物学行为[3]。

近年来研究发现,ADT可通过调控多种转录因子及信号通路参与肿瘤进展,如激活磷脂酰肌醇3-激酶/蛋白激酶B信号通路(phosphatidylinositol 3-kinase/protein kinase b signaling pathway, PI3K-AKT)、促进上皮-间质转化(epithelial-mesenchymal transition,EMT)以及诱导神经内分泌表型转化[4-5]。然而,除肿瘤细胞内在改变外,ADT对肿瘤免疫微环境(tumor immune microenvironment,TIME)的影响仍未完全阐明。既往研究提示,ADT可增加炎症因子表达和免疫细胞浸润,但这些变化究竟是增强抗肿瘤免疫,还是导致免疫抑制性重塑,目前尚存争议[6]。

传统转录组学难以解析肿瘤微环境的细胞异质性,而单细胞RNA测序(single-cell RNA sequencing,scRNA-seq)技术可在单细胞分辨率下揭示不同细胞群体的组成、状态及相互作用,为研究ADT相关免疫重塑提供了重要工具[7]。

本研究从外周免疫状态、动物模型转录组及人肿瘤单细胞组学三个层面,系统评估ADT对前列腺癌免疫微环境的影响,重点分析T细胞亚群分布及功能改变,旨在为ADT联合免疫治疗的策略优化提供依据。

1　资料与方法

1.1　临床病例资料

纳入于2024年12月至2025年12月于北京大学人民医院经组织病理学确诊,接受一线ADT治疗的前列腺癌患者12例,所有患者均采用标准促黄体生成素释放激素(luteinizing hormone-releasing hormone,LHRH)激动剂±口服抗雄激素药物方案,治疗时间≥12个月,无联合化疗、免疫治疗或其他系统性合并治疗。收集患者年龄、基线血清前列腺特异性抗原(prostate specific antigen, PSA)、f/t(free/total)PSA、Gleason评分及临床分期等信息(表1)。患者含局限期及转移性病例。本研究开始前已经北京大学人民医院伦理委员会审查批准(2024PHB566-001),所有参与研究的患者均签署知情同意书。

1.2　血清学及激素监测

于ADT治疗前及治疗后1、3、6、12个月采集患者外周血,检测血清PSA、游离睾酮及总睾酮水平,用以评估治疗反应。

1.3　外周血免疫细胞及细胞因子检测

流式细胞术分析外周血B细胞、Breg、$CD4^+$ T细胞、$CD8^+$ T细胞及调节性T细胞(Treg)比例动态变化。选取8例患者血浆样本进行抗体芯片检测,分析免疫相关细胞因子水平。

1.4　PDX模型转录组学分析

从基因表达汇编(gene expression omnibus,GEO)数据库下载5例前列腺癌人源肿瘤异种移植(patient-derived tumor xenograft,PDX)模型去势前后RNA-seq数据(GSE41193),行差异表达分析、基因本体(gene ontology,GO)富集分析、单样本基因集富集分析(single-sample gene set enrichment analysis,ssGSEA)免疫细胞浸润评估及基因集变异分析(gene set variation analysis,GSVA)通路富集分析,此部分为探索性分析,未行严格多重检验校正,结果以趋势提示为主。

1.5　单细胞RNA测序

同期另取4例前列腺癌组织进行scRNA-seq(2例接受ADT新辅助治疗,2例未接受),质控后获得19 227个细胞。基于标志基因进行细胞分群和亚群注释,并对T细胞亚群进行功能基因表达及GSVA通路富集分析。此研究采用常规组织解离,未进行免疫细胞富集;数据分析中已进行批次效应校正。

2　结果

2.1　ADT显著降低PSA及雄激素水平,但对外周免疫状态影响有限

本研究共纳入12例ADT治疗的前列腺癌患者且均完成了1年随访(表1)。血清学结果显示,ADT治疗后患者血清PSA水平迅速下降,于治疗3个月时达到谷值,12个月时仍维持在低水平状态

（图 1A）。血清游离睾酮及总睾酮水平亦在治疗后明显降低，并长期维持去势水平（图 1B、C），提示 ADT 治疗效果确切。

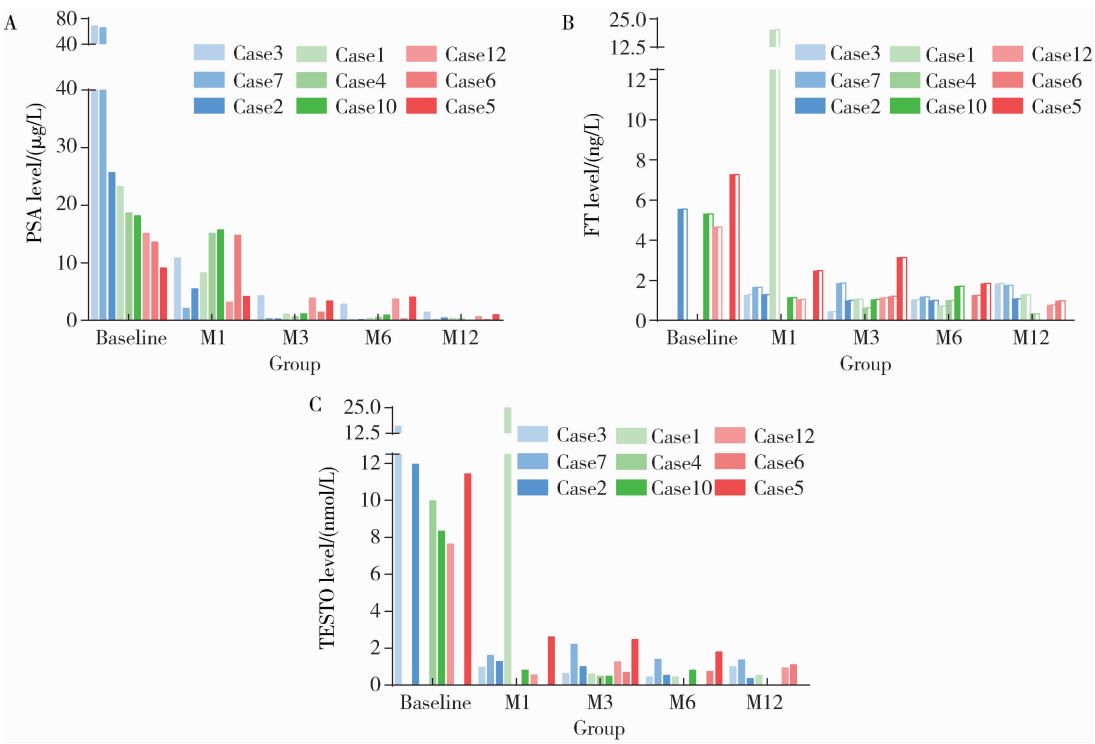
采用流式细胞术分析外周血免疫细胞比例变化，发现在 ADT 治疗后半年内，B 细胞、Breg 细胞、$CD3^+$T 细胞、$CD4^+$T 细胞、$CD8^+$T 细胞及 Treg 细胞比例均未见明显变化趋势（图 2A）。抗体芯片检测免疫相关细胞因子发现，大多数细胞因子在治疗前后差异无统计学意义，仅 IL-8、IL-1ra、IL-16 及 MCSF 差异有统计学意义，但热图分析提示差异主要由个别样本驱动，整体变化趋势不明显（图 2B）。上述结果表明，ADT 可能对全身免疫状态影响有限。

表 1 接受 ADT 治疗患者临床信息

Table 1 Clinical information of the patients undergoing ADT treatment

Case	Age/years	Baseline PSA/(μg/L)	f/t PSA	Gleason score	Clinical stage
1	79	23.21	0.09	3 + 4	T4N0M0
2	84	25.64	0.09	4 + 3	T2N0M0
3	77	68.44	0.05	4 + 5	T3bN0M0
4	81	18.63	0.07	3 + 4	T1cN0M0
5	81	9.06	0.14	3 + 4	T2N0M0
6	77	13.61	0.23	3 + 3	T1cN0M0
7	64	65.84	0.07	4 + 3	T2N0M1b
8	80	76.27	0.2	3 + 4	T2N0M1b
9	64	172.70	0.08	4 + 3	T4N1M1b
10	83	18.17	0.24	3 + 3	T2N0M0
11	83	17.86	0.11	4 + 4	T4N0M0
12	85	15.08	0.08	4 + 3	T4N0M0

PSA, prostate specific antigen; ADT, androgen deprivation therapy.



The dynamic changes of serum PSA (A), serum free testosterone (B), and serum testosterone (C) in 12 patients undergoing ADT treatment over a one-year period. PSA, prostate specific antigen; ADT, androgen deprivation therapy.

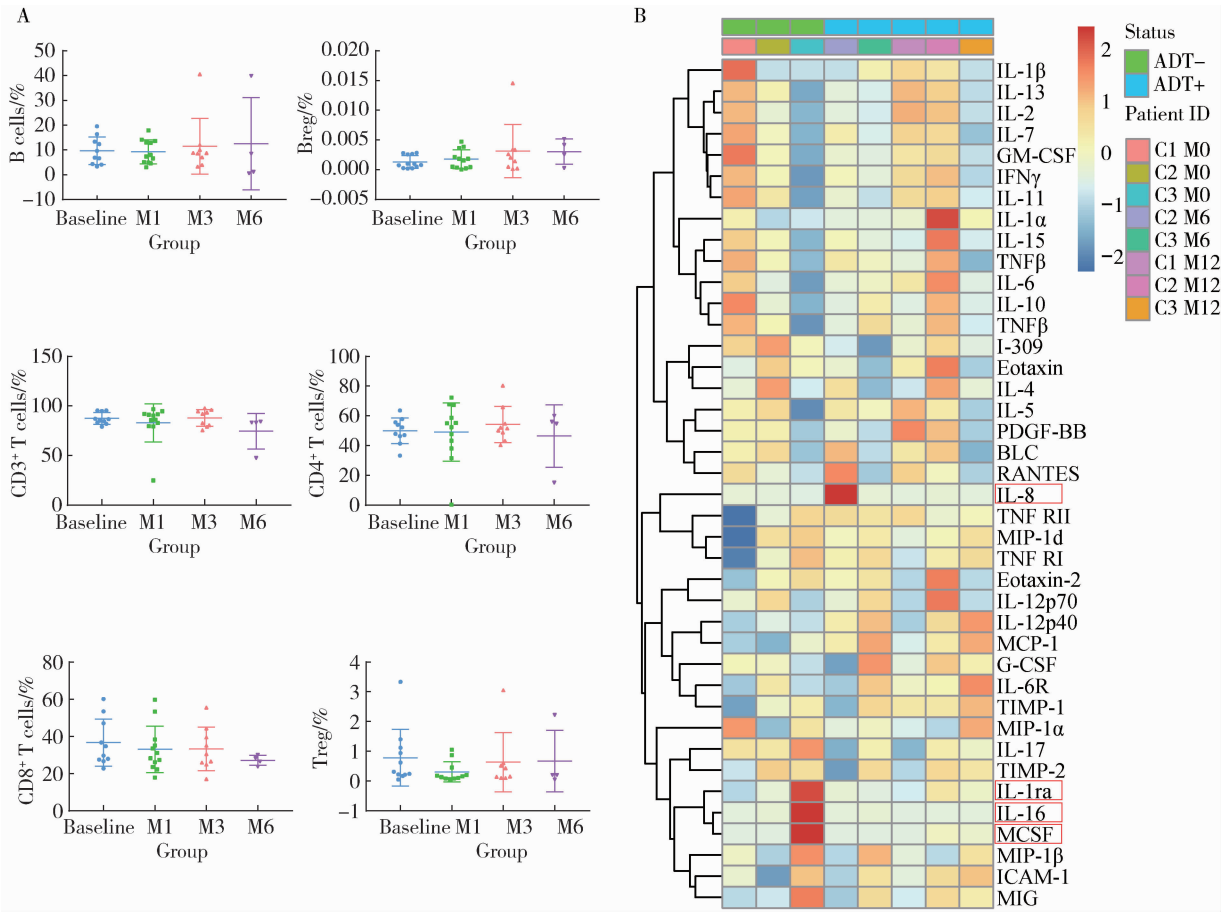
图 1 接受 ADT 治疗的前列腺癌患者血清 PSA 和雄激素变化趋势

Figure 1 Trends of serum PSA and androgen changes in prostate cancer patients undergoing ADT treatment

2.2 去势诱导前列腺癌 PDX 模型基因表达及免疫微环境重编程

为进一步分析 ADT 对肿瘤局部微环境的影响，对 GEO 数据库中 5 例 PDX 模型（GSE41193）去势前后 RNA-seq 数据进行系统性分析。差异表达分析结果显示，去势后上调基因 284 个，下调基因 136 个（$|\log_2 FC| > 1.0$，$P < 0.05$，图 3A、B），基于 Top200 差异基因的无监督聚类分析清晰地区分了

去势前后样本(图 3C)。GO 富集分析提示,去势后上调基因显著富集于嗅觉/味觉感知、神经肽信号传导及垂体发育等神经系统相关通路,同时在细胞组分层面富集于离子通道复合物、转运蛋白复合物等膜结构,在分子功能层面富集于嗅觉/味觉受体活性(图 3D)。ssGSEA 分析显示,去势前后多类免疫细胞浸润呈趋势性改变,包括 $CD4^+$ T 细胞、$CD8^+$ T 细胞、Treg、肿瘤相关巨噬细胞(tumor-associated macrophage,TAM)及骨髓来源的抑制性细胞(myeloid-derived suppressor cell,MDSC)(图 3E)。GSVA 对 MsigDB C7(molecular signatures database C7)免疫相关通路分析显示,多条免疫调控通路在去势后呈趋势性改变(图 3F)。上述结果提示去势治疗可诱导肿瘤转录组及免疫相关信号网络的系统性重塑。



Flow cytometry was used to detect the changes in the proportion of peripheral blood immune cells in patients before and after ADT treatment (A), and antibody arrays were used to detect the changes in immune-related factors (B). IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; TNF, tumor necrosis factor; PDGF, platelet derived growth factor; BLC, B lymphocyte chemoattractant; RANTES, regulated on activation normal T cell expressed and secreted; MIP, major intrinsic protein of lens fiber; MCP, membrane cofactor protein; G-CSF, granulocyte colony-stimulating factor; TIMP, tissue inhibitor of metalloproteinases; MCSF, macrophage colony-stimulating factor, ICAM, intercellular adhesion molecule; MIG, monokine induced by interferon-γ.

图 2　接受 ADT 治疗的前列腺癌患者外周血免疫细胞及免疫相关因子动态变化

Figure 2　Dynamic changes of peripheral blood immune cells and immune-related factors in prostate cancer patients undergoing ADT treatment

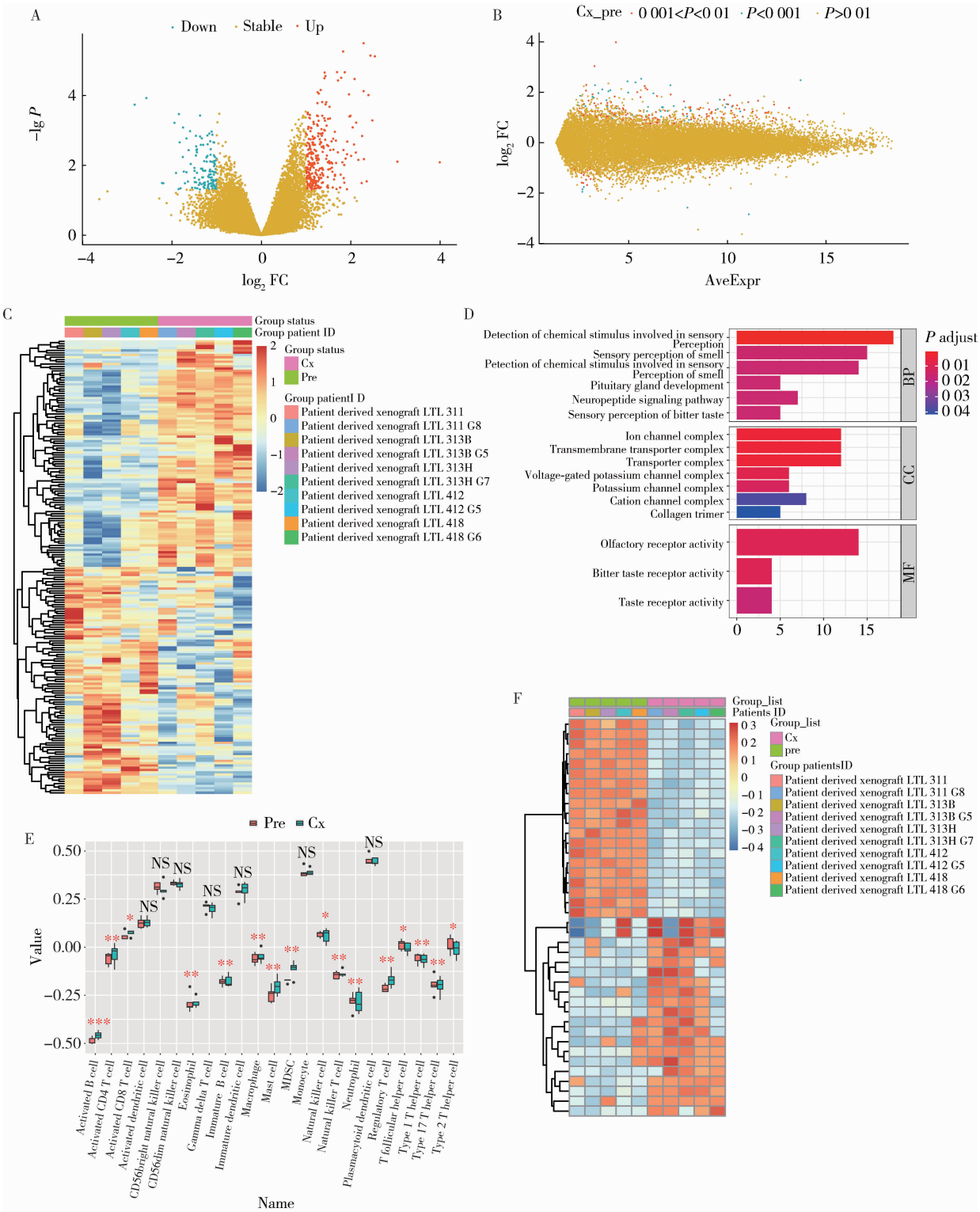
2.3　ADT 治疗后肿瘤微环境细胞的组成

对 4 例前列腺癌组织进行 scRNA-seq 分析,其中 2 例接受 ADT 新辅助治疗。质控后共获得 19 227 个细胞,其中 ADT 组 11 657 个,未治疗组 7 570 个。基于标志基因将细胞初步分为免疫细胞、基质细胞及上皮细胞三大类,先以 t-SNE(t-distributed stochastic neighbor embedding)降维,展示局部细胞亚群的聚类关系(图 4A),再用 UMAP(uniform manifold approximation and projection)降维,清晰地呈现不同细胞类型的分布特征(图 4B),共同验证了细胞分群的稳定性与生物学可靠性。进一步注释为 8 个细胞亚群,包括 T 细胞、B 细胞、髓系细胞、肥大细胞、内皮细胞、成纤维细胞、肌成纤维细胞及上皮细胞(图 4C),上皮细胞比例偏低可能与前列腺组织解离特性、单细胞捕获偏好相关。不同病例间各类细胞比例存在明显差异(图 4D),提示 ADT 可能影响肿瘤微环境细胞组成。

2.4　ADT 治疗后 T 细胞亚群分布的变化

共获得 T 细胞 11 367 个,其中 ADT 组 7 440 个,未治疗组 4 055 个。聚类分析将 T 细胞分为 13 个亚群(图 5A),根据标志基因注释为 $CD4^+$ T 细胞、$CD8^+$ T 细胞及 Treg 等亚群(图 5B、C)。比较不

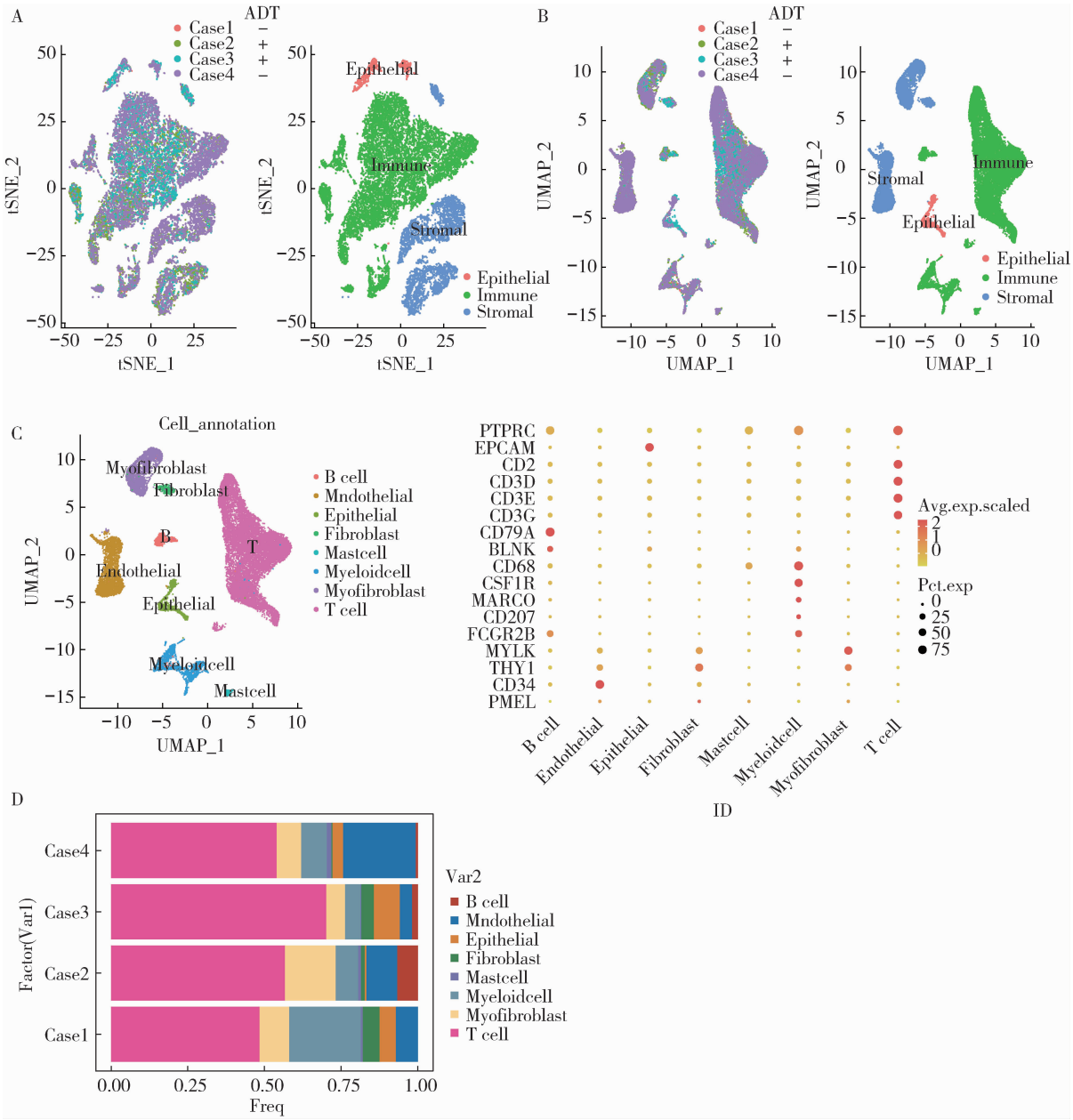
同治疗状态下 T 细胞分布，发现细胞毒效应 T 细胞标志基因 *KLRF1*、*GZMA* 阳性细胞主要来源于未接受 ADT 的病例，而 Treg 细胞在 ADT 组中明显富集（图 5D），提示 ADT 治疗与免疫抑制性 T 细胞重塑相关。



RNAseq data from five prostate cancer PDX models of GEO（GSE41193）were analyzed before and after surgical castration. Differential genes were displayed, with A being a volcano plot, B being a MA plot, C being a Top200 differential gene heatmap, and D being a GO analysis. ssGSEA was applied to analyze the expression ratios of various immune cells before and after surgical castration, and Wilcoxon rank-sum test was used for inter-group difference comparison, with $*P<0.05$, $**P<0.01$, $***P<0.001$ (E). GSVA was also applied to perform enrichment analysis on immune-related pathways, with $|NES|>1$ and $FDR<0.05$ as the significant criteria for pathway enrichment (F). FC, fold change; PDX, patient-derived tumor xenograft; GEO, gene expression omnibus; MA, mean-difference; GO, gene expression omnibus; ssGSEA, single-sample gene set enrichment analysis; GSVA, gene set variation analysis; NES, normalized enrichment score; FDR, false discovery rate.

图 3 转录组学分析去势对前列腺癌 PDX 组织基因表达及肿瘤微环境的影响

Figure 3 Transcriptomic analysis of the effects of castration on gene expression and tumor microenvironment in prostate cancer PDX tissues



Using marker genes, single cells were initially grouped into three major populations: immune cells, stromal cells, and epithelial cells, which were then visualized using tSNE (A) and UMAP (B). Subsequently, subpopulation analysis was performed on these three major populations, resulting in the identification of eight subpopulations (C). The distribution of each subpopulation in each case was statistically presented (D). tSNE, t-distributed stochastic neighbor embedding; UMAP, uniform manifold approximation and projection.

图 4　四例前列腺癌组织 scRNAseq 数据细胞初次分群(两例接受 ADT 治疗)

Figure 4　Initial cell clustering of scRNAseq data from four prostate cancer tissues (two cases received ADT treatment)

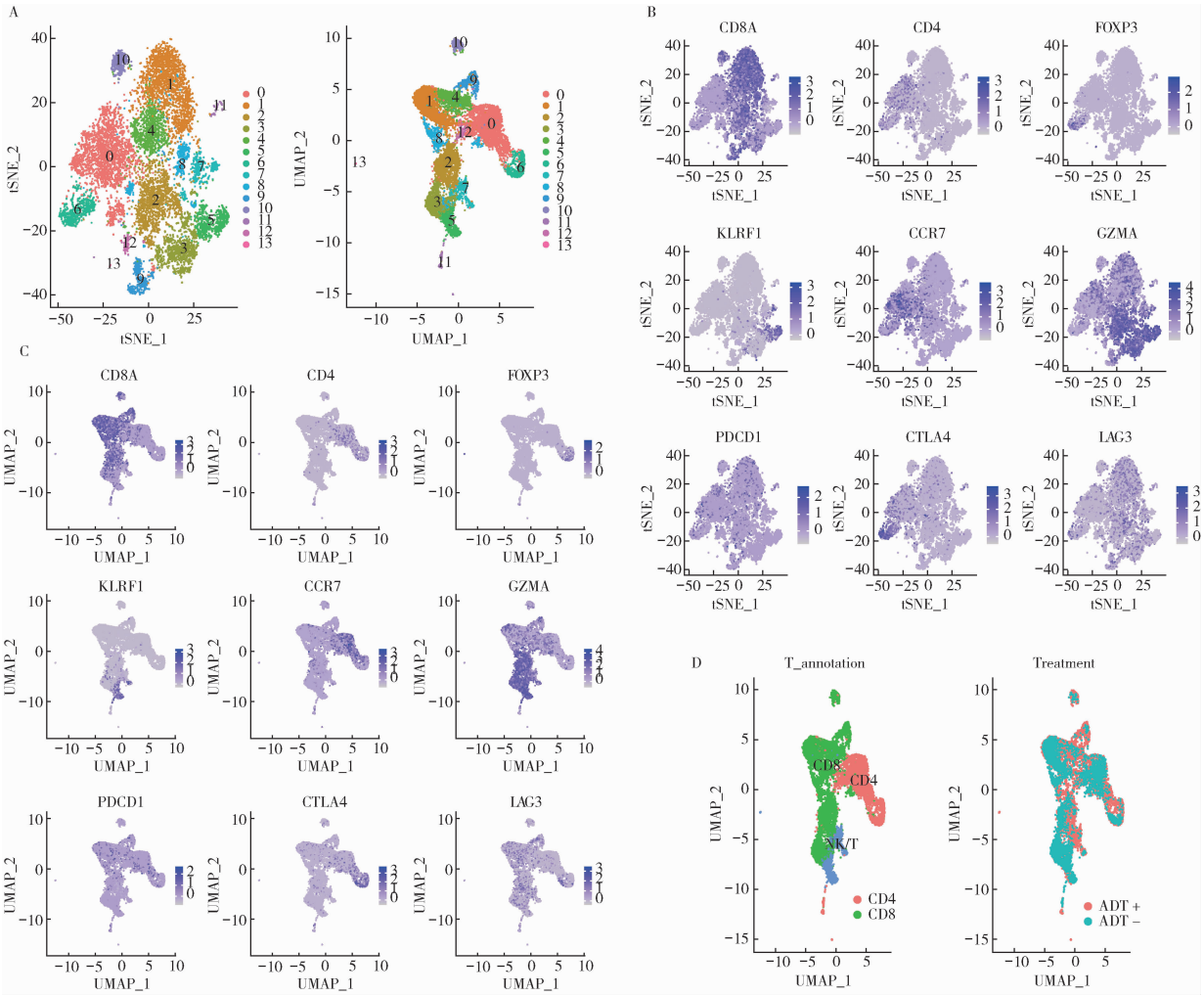
2.5　ADT 抑制 T 细胞细胞毒功能并下调干扰素通路

进一步分析 T 细胞功能状态发现,ADT 组 T 细胞中细胞毒相关基因 *GNLY*、*NKG7*、*GZMB*、*GZMA* 表达明显下调(图 6A)。在 $CD8^+$ T 细胞亚群中,上述细胞毒分子表达同样显著降低;同时,部分 Treg 功能相关基因表达改变(图 6B)。Hallmark 通路 GSVA 分析显示,ADT 治疗后 $CD4^+$ 及 $CD8^+$ T 细胞中干扰素信号通路整体活性降低,呈抑制趋势(图 6C)。上述结果提示 ADT 可能导致 T 细胞效应功能受损。

3　讨论

ADT 是晚期前列腺癌的基础治疗手段,但其对肿瘤免疫微环境的影响具有复杂性和双重性。本研究为单中心探索性研究,未设立独立验证队列,通过临床样本、PDX 模型转录组及单细胞测序多层级分析,系统揭示了 ADT 相关免疫重塑特征,结果显示

ADT 在有效抑制肿瘤负荷的同时，可能诱导免疫抑制性肿瘤微环境形成。



Through clustering analysis of T cells, a total of 14 T cell subpopulations were obtained (A). T cell subpopulation markers were used to annotate the subpopulations (B, C), with a focus on the expression of CD4 $^+$ T cells and CD8 $^+$ T cells in different groups (D).

图 5 前列腺癌 T 细胞亚群分群注释

Figure 5 Annotation of T-cell subpopulations in prostate cancer

3.1 ADT 对全身免疫和局部微环境的影响

本研究发现，ADT 治疗后患者 PSA 及雄激素水平显著下降，但外周血免疫细胞比例及大部分细胞因子未见明显变化，提示 ADT 对系统免疫稳态影响相对有限。本结果与部分研究报道的“ADT 增强全身免疫活性”观点存在差异，可能与观察时间、检测指标及患者分期有关[6]。外周血无法完全反映肿瘤局部免疫生态，ADT 诱导的免疫调控更可能发生于肿瘤组织微环境，这也凸显了直接研究 TIME 的重要性[8]。

3.2 去势诱导肿瘤转录组重编程与免疫信号改变

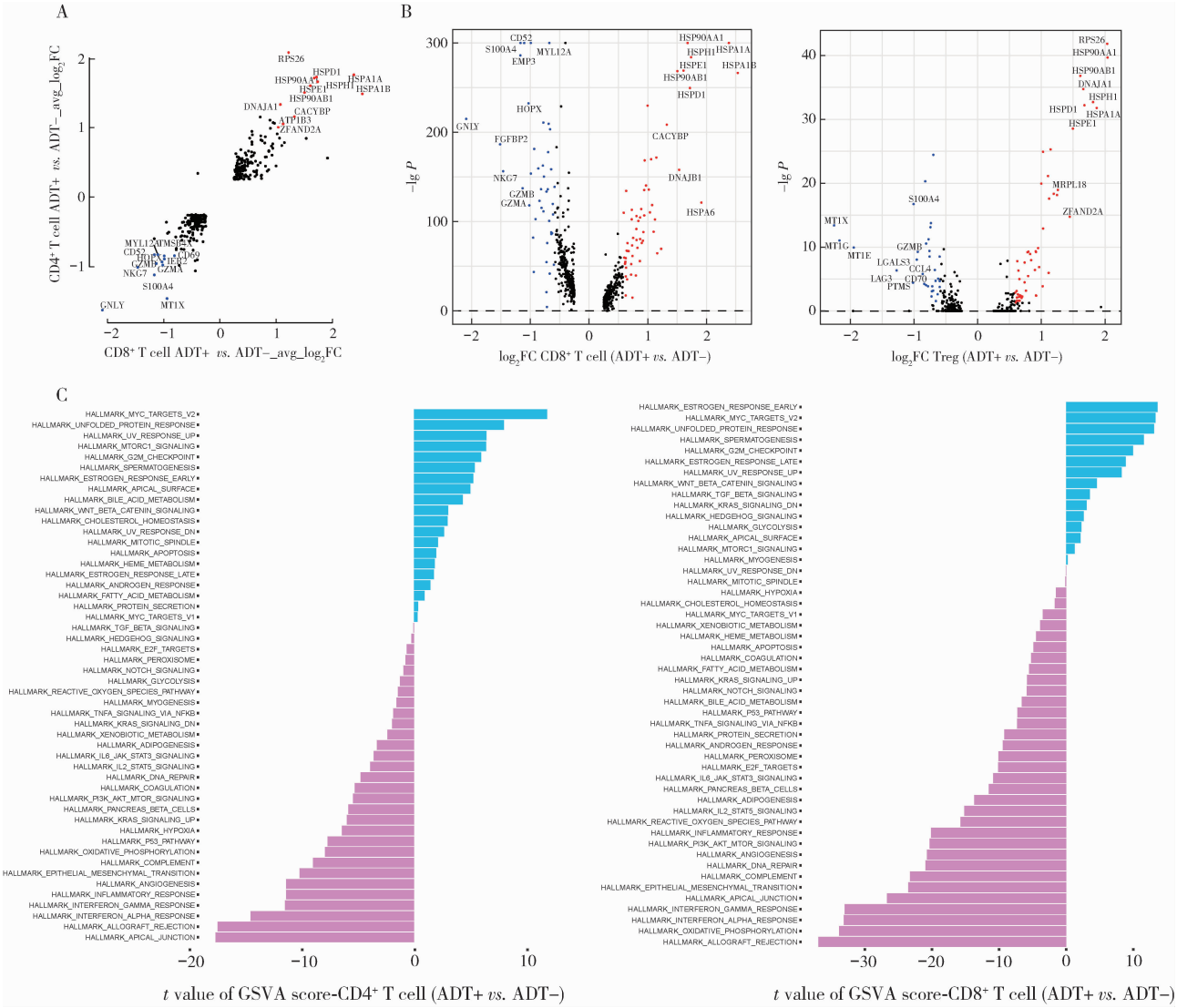
PDX 模型转录组分析显示，去势后差异基因显著富集于神经相关及发育调控通路，提示雄激素信号缺失可能促进肿瘤细胞表型可塑性，向神经内分泌样表型转化[9]。这一现象与 CRPC 及神经内分泌前列腺癌的发生机制相吻合。

同时，免疫相关通路及免疫细胞浸润呈趋势性改变，提示雄激素轴不仅可能调控肿瘤细胞生长，也可参与调节肿瘤免疫生态[10]。AR 信号可能通过调控趋化因子、细胞因子及免疫检查点分子表达，间接影响免疫细胞募集及功能状态[11]。

3.3 ADT 诱导 T 细胞功能抑制及 Treg 富集

单细胞分析揭示 ADT 后肿瘤内 T 细胞亚群构成发生显著改变，表现为效应性 CD8 $^+$ T 细胞比例下降，*GZMA*、*GZMB*、*GNLY*、*NKG7* 等细胞毒分子表达下调，Treg 细胞相对富集，这些变化提示 ADT 可能削弱抗肿瘤免疫效应，同时增强免疫抑制。Treg 的富集可通过分泌 IL-10、TGF-β 及表达 CTLA-4 等途径抑制效应 T 细胞功能，从而促进肿瘤免疫逃逸[12]。值得注意的是，Hallmark 分析显示干扰素

信号通路被抑制。干扰素通路是抗肿瘤免疫激活的重要轴线,其下调可能进一步削弱抗原呈递和细胞毒 T 细胞活化,形成“低免疫反应性”肿瘤微环境[13]。



After ADT treatment, the expression of genes related to T cells and cytotoxicity was downregulated (A). Specifically, the expression of *NKG7*, *GZMB*, and *GZMA* in CD8 + T cells was significantly downregulated, and the expression of genes related to T regulatory cell function, such as *CCL4*, *LGALS3*, and *LAG3*, also showed a downward trend. GSVA enrichment analysis was performed on the differential genes of CD4 + T cells and CD8 + T cells in the Hallmark 50 gene pathways. ADT treatment led to the downregulation of the interferon pathway (C). ADT, androgen deprivation therapy; FC, fold change; GSVA, gene set variation analysis.

图 6　ADT 治疗对 T 细胞功能的影响

Figure 6　Effect of ADT treatment on T cell function

3.4　ADT 可能促进 CRPC 形成的免疫学基础

ADT 诱导的免疫抑制性 TIME 可能为肿瘤细胞在低雄激素环境下存活及克隆选择提供“免疫庇护”。T 细胞功能衰竭及 Treg 增加可能降低机体对耐药克隆的清除能力,从而参与 CRPC 的进展过程[14],这一机制为传统“内分泌耐药”模型补充了免疫学维度解释。

3.5　对免疫治疗策略的启示

前列腺癌对免疫检查点抑制剂总体反应率较低,本研究结果提示,ADT 本身可能诱导免疫抑制微环境,单纯免疫检查点抑制剂(immune checkpoint inhibitor,ICI)治疗难以逆转 ADT 后 T 细胞功能低下状态[10],ADT 联合免疫治疗的时序与组合方式可能至关重要,未来可考虑在 ADT 早期或间歇期联合 Treg 抑制、干扰素通路激活或 T 细胞功能恢复策略,以抵消 ADT 诱导的免疫抑制效应。本课题组后续也将通过 Treg 细胞敲除/过表达实验、干扰素通路激活实验、ADT 联合免疫调控的动物模型实验等功能学研究,来验证本研究探索出的潜在机制,以便为 ADT 联合免疫治疗策略提供更坚实的实验依据。

3.6 研究局限性

本研究为单中心探索性研究,未设立独立验证队列;仅纳入 12 例样本,且患者肿瘤分期从 T1cN0M0 跨度至 T4N1M1b,异质性较大,统计学稳定性不足,混杂干扰因素较多;外周血免疫指标仅采用自身前后配对比较,未设置独立对照组,缺乏外部参照,结果解读存在局限;PDX 通路分析未严格多重检验校正,存在假阳性可能,结论为探索性的;scRNA-seq 为横断面分析,尚不能完全反映免疫动态变化过程。此外,本研究通过基因组学及生物信息学分析揭示了 ADT 介导的免疫微环境重塑特征,但相关机制尚未通过实验证实,有待进一步功能实验进行验证。

综上所述,ADT 在抑制前列腺癌生长的同时,可诱导肿瘤免疫微环境重塑,表现为 T 细胞杀伤功能减弱、Treg 富集及干扰素通路抑制趋势,形成免疫抑制性 TIME。这一变化可能参与 CRPC 发生,并对 ADT 联合免疫治疗提供初步依据。

利益冲突 所有作者均声明不存在利益冲突。

作者贡献声明 谭仲宇:分析数据,撰写论文;杜依青:收集、整理和分析数据;秦彩朋:收集临床样本,设计研究方案,指导统计分析;徐涛:提出研究思路,指导完成研究。所有作者均参与论文修改,并对最终文稿进行审读和确认。

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