Deciphering single-cell heterogeneity and cellular ecosystem dynamics during prostate cancer progression

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Background:

Prostate cancer (PC) is a highly heterogeneous disease with diverse clinical, pathological, and molecular features. Androgen receptor (AR) signaling is an effective therapeutic target in hormone-sensitive PC (HSPC), yet progression to castration-resistant PC (CRPC) is common. Approximately 17% of CRPC cases acquire neuroendocrine features (CRPC-NE), with some advancing to poorly differentiated neuroendocrine PC (NEPC), a highly lethal and incurable subtype. Most previous studies relied on bulk tissue analyses, which offer only limited insight into the tumor microenvironment (TME) and its role in PC progression. Advances in single-cell RNA sequencing (scRNA-seq) now allow deeper dissection of the cellular and molecular heterogeneity within the TME at different disease stages. Although recent studies have highlighted previously underestimated TME complexity, their scope remains constrained by small sample sizes, limited numbers of analyzed cells, and the absence of genomic integration or long-term follow-up, limiting comprehensive understanding of therapy resistance and survival outcomes.

Methods:

We compiled publicly available scRNAseq datasets to create a comprehensive Prostate Cancer Cell Atlas (PCCAT) from 197 samples representing a range of benign and malignant prostate pathologies. This atlas offers a cohesive, high-resolution perspective of various PC stages, including normal healthy (N), benign prostate hyperplasia (BPH), normal adjacent to tumor (Adj), primary PC (Pri), invasive cribriform carcinoma and intraductal carcinoma (ICC/IDC), CRPC, metastatic HSPC (mHSPC) as well as metastatic CRPC (mCRPC) and NEPC. We performed an in-depth dissection of cell populations to uncover the key cell types and molecular features associated with PC progression, treatment resistance, and prognosis. We also substantiated specific transcriptomic distinctions using spatial transcriptomics and bulk expression profiles.

Results:

Using the largest scRNA-seq atlas of PC, we delineated malignant and nonmalignant epithelial subtypes, showing that basal, hillock, and club cells adopt luminal-like states during progression, with club cells contributing to tumorigenesis. Lum_PCA3, Lum_ERG, and NE-like states were linked to aggressive

features, poor prognosis, and enzalutamide resistance. Endothelial and stromal subtypes displayed stage-specific signaling alterations, with mCAFs, pericytes, and distinct fibroblasts associated with recurrence. Immune profiling revealed enrichment of Tregs, exhausted CD8+ T cells, and SPP1+ macrophages, alongside an exhaustion-based immunotherapy signature. Spatial analysis uncovered mCAF–macrophage–tumor interactions forming an immune barrier tied to poor survival. We developed an interactive web portal called PCCAT (https://pccat.net) to maximize broad access to this PC atlas and provide an automated mapping tool enabling the rapid cell type annotation of cells from PC.

Conclusions:

Overall, this study provides a deep view into the cellular and molecular characteristics of PC, from early indolent disease through tumorigenesis and metastasis. These findings held the potential to advance PC diagnosis, refine patient stratification, and inform future research aimed at developing therapeutic strategies that address the complexity of these tumors and their microenvironments.

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