Single-cell atlas of epithelial and stromal cell heterogeneity by lobe and strain in the mouse prostate

Background:
The mouse prostate is comprised of four lobes: anterior, dorsal, lateral, and ventral. While the lobes are known to differ in tissue morphology and secretions, rigorous single-cell assessments of the transcriptional profile of both epithelial and stromal cell types for each lobe and in multiple mouse strains are lacking.

Methods:
We dissected individual prostate lobes from two commonly used mouse strains, FVB/NJ (N = 2) and C57BL/6J (N = 3), and prepared single-cell RNA-sequencing (scRNA-seq) libraries for each lobe. Mouse prostate scRNA-seq data (27,896 cells) were pre-processed using CellRanger and Seurat, and visualized using Uniform Manifold Approximation and Projection (UMAP) dimensionality reduction and Louvain clustering, as implemented in Seurat (v 3.1.5).

Results:
Data dimensionality reduction and clustering analysis revealed that epithelial cells possessed strain-specific differences, with luminal cells also displaying striking lobe-specific differences. However, two populations of luminal epithelial cells clustered independently of lobe and strain, including a rare population of luminal cells (0.25%) expressing Foxi1 and components of the vacuolar ATPase proton pump (Atp6v1a, Atp6v0d2), and a progenitor-like population (1.8%) expressing stem cell-associated genes (Ly6a/Sca-1, Tacstd2/Trop-2, Psca). In contrast to the epithelial cells, stromal cell clusters (smooth muscle, pericytes, immune cells, and fibroblasts) were largely conserved across strain and lobe. Notably, two fibroblast populations clustered separately when data dimensionality was restricted to stromal cell types, with one cluster having an upregulation in the immune-associated chemokine receptor, Ccr2, as assessed by Ingenuity Pathway Analysis.

Conclusions:
In these foundational single-cell studies of strain and lobe-specific differences in the mouse prostate, we have uncovered previously uncharacterized cell types and nominated unique molecular markers for a more granular in situ examination of prostate tissues. The combination of lobe-specific differences in luminal cells and the stromal composition in the mouse prostate likely contribute to the histological differences observed between lobes. Overall, the findings of this study help establish the fundamental cell types residing in the normal mouse prostate of common mouse strains and serve as a reference to better understand how genetic alterations in transgenic mouse models are impacted by the normal biology of cells in the prostate.