Single-cell transcriptomics identifies a prostate luminal progenitor cell

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BACKGROUND:
Identification of prostate stem/progenitor cells is critical for characterization on the prostate epithelial lineage hierarchy and for understanding prostate cancer initiation. The current taxonomy of prostate epithelial cells that classify them into luminal, basal, and neuroendocrine is based on histological location and expression of a few markers. Whether there are specific prostate epithelial subclasses that maintain prostate homeostasis and can serve target of malignant transformation is poorly understood.

METHODS:
Using the droplet-based scRNA-seq, we profiled 8,545 individual cells from freshly dissociated prostates of 4 healthy adult male *Tmprss2*$^{CreERT2/+}$*; Rosa26*$^{EYFP/+}$ (T2Y) mice 2 weeks after tamoxifen administration at the age of 10 weeks. Unbiased clustering analysis identified 11 distinct cell clusters which consisted of 4 to 2773 cells per cluster. To trace the fate of Luminal-C cells, we generated two Luminal-C-specific lineage tracing models by knock-in of the CreERT2 cassette which expression was controlled by Ck4 or Psca promoter.

RESULTS:
Here we characterized 8,545 cells from mouse prostates by using unbiased single-cell RNA sequencing. We identified a distinct type of luminal cells, Luminal-C cells (termed Dist-Luminal-C cells), which are located at the invagination tips (INTs) of distal prostate lumen. Compared to other luminal cells, Dist-Luminal-C cells exhibited greater capacity for organoids formation *in vitro* and prostate epithelial ducts regeneration *in vivo*. Genetic lineage tracing and computational cell trajectory analysis indicated that DILCs reconstituted prostate luminal lineages through self-renewal and differentiation. In addition, targeted deletion of Pten in Dist-Luminal-C cells resulted in prostate cancer formation.

CONCLUSIONS:
Our study provides fundamental insights into the prostate lineage hierarchy, uncovers previously unidentified stem/progenitor cell population and suggests the cell origin of prostate cancer.

CONFLICT OF INTEREST:
No related conflict of interest to this study.

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