Urethral epithelia extend into the proximal prostate stem cell niche and are increased in prostate cancer

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Background: The proximal prostate niche is the putative site of androgen-independent stem cells. Many studies have identified individual markers to enrich these cells in facultative assays, but their full identity is poorly understood due to a lack of anatomical context. We previously used single cell RNA sequencing (scRNA-seq) to create a cellular anatomy of the human prostate and discovered two novel epithelial cell types, club and hillock, which are enriched in the prostatic urethra and proximal ducts. Here, we identify a cognate hillock epithelial cell type in the mouse urethra and demonstrate the precise transition from urethra to prostate occurs well into the proximal prostatic niche. Analysis of previously generated prostate stem cell signatures reveals that commonly cited prostate stem cell markers are highly enriched in urethral epithelia, suggesting that androgen-independent cells enriched in castration include urethral hillock cells. Our newly developed tools will help determine whether urethral epithelia of the proximal niche are prostate progenitors.

Methods: We used an unbiased approach by scRNA-seq to identify cognate cell types of the mouse and human prostate and prostatic urethra and developed new flow cytometry and IHC antibody panels to purify and localize each cell type. The frequency of urethral epithelia in hormone-naïve and ADT-treated human prostate cancer and mouse prostate cancer models was assessed using scRNA-seq, flow cytometry, and immunofluorescence.

Results: Hillock and club epithelial identity is established before prostate development and these cells extend into the proximal niche in the normal adult human and mouse. Urethral epithelia are increased in primary, high grade hormone-naïve cancer and are further enriched in ADT-treated prostate tumors.

Conclusions: Our results suggest that assays used to isolate putative prostate stem cells from the proximal prostate are enriched with urethral epithelia. However, it is still unclear whether urethral epithelia are an androgen-independent progenitor in prostate development and tumorigenesis or whether they are bystanders responding to microenvironmental cues such as inflammation. Future work includes lineage tracing of urethral epithelia to determine their contribution to prostate development, regeneration, and disease.

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