Spatial transcriptomics reveals a transition from a prostate luminal to club-like cell state in 5-alpha reductase inhibitor treated BPH patients

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Introduction

Understanding how prostate luminal cells adapt and survive in a low androgen environment is critical to the clinical treatment of benign and malignant diseases. 5-alpha reductase inhibitors (5ARIs) block the conversion of testosterone to dihydrotestosterone (DHT) and are used to treat Benign Prostatic Hyperplasia (BPH). 5ARI treatment reduces tissue DHT levels and causes involution of prostate glands. However, the histologic response to 5ARIs is heterogeneous and lower urinary tract symptoms in treated BPH patients often persist or worsen, leading to surgical intervention. We examined transcriptional changes accompanying 5ARI treatment to determine the cellular mechanisms of treatment resistance.

Approach

Frozen sections from untreated and 5ARI treated prostate were placed on Viskum slides. The grid of barcoded capture dots on the slides binds to mRNA from the tissue. mRNA template is used to synthesize cDNA on the slide. Following the ligation of sequencing primers and indices, libraries are prepared and sequenced. Data is processed using Space Ranger from 10x genomics followed by secondary analysis using Seurat. Capture dots were assigned an ID based on their transcriptional similarity to our previous defined prostate cell types.

Morphological changes in club-like adaptation

To study the transition between the prostate luminal and club state, we binned prostate luminal and club dots into 4 categories (A). The categories were overlaid on tissue sections on which the Viskum experiment had been performed (B-C). The glands underlying the different categories were manually outlined in ImageJ (D-H). Using in built functions in ImageJ, gland area (I) and gland circularity (J) were calculated. Gland area decreased after 5ARI treatment compared to untreated. Gland circularity was highest in club-like categories indicating a loss of epithelial infolding. Prostate luminal cell heights (K) decreased after 5ARI treatment compared to the untreated condition.

Prostate luminal to club-like adaptation

Prostate luminal epithelium undergoes a transition to a club-like state in 5ARI-treated prostate. Plotting dots that identify as prostate luminal and club against probability scores of being prostate luminal or club, we found that 5ARI treated samples displayed a prostate luminal to club spectrum (A). Notably, untreated samples were largely prostate luminal cells with a low club probability score (B).

Conclusions

1. 5ARI response is heterogeneous and results in localized atrophy.
2. Atrophied regions display a club-like signature and have loss of androgen receptor signaling.
3. Atrophied regions have increased NF-κB activation.
4. Epithelial cells in prostate glands undergo a survival adaptation from a prostate luminal to a club-like state in response to low androgen levels.

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