Decoding Stromal Heterogeneity across BPH Phenotypes

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Introduction

Benign Prostatic Hyperplasia (BPH) is a non-malignant enlargement of the prostate that occurs with aging and is associated with Lower Urinary Tract Symptoms (LUTS). Therapeutic options often fail, necessitating surgical resection of the prostate. The phenotypic and cellular heterogeneity of BPH is thought to contribute to treatment resistance. BPH patients present with multiple nodules grouped around the prostatic urethra in the transition zone. The composition of these nodules vary with some being solely comprised of stromal cells and others containing a mixture of stromal and epithelial cells. In addition, some patients present with a band of fibrotic tissue around the prostatic urethra that we term as peri-urethral fibrosis. Here, we describe stromal cell heterogeneity in the normal human prostate and across the different BPH phenotypes.

Approach

Normal prostates were obtained from organ donors aged 18-40 after consent at the Southwest Transplant Alliance according to approved IRB protocols. BPH tissues were obtained from UT Southwestern patients undergoing simple prostatectomy. Prostates and urethras were harvested from C57BL6/J male mice between 8-12 weeks of age.

BPH presents a major clinical challenge that occurs with aging and is associated with Lower Urinary Tract Symptoms (LUTS). Benign Prostatic Hyperplasia (BPH) is a non-malignant enlargement of the prostate. Therapeutic options often fail, necessitating surgical resection of the prostate.

Regional and phenotypic differences in fibroblast density

The stromal regions surrounding the prostate, peri-urethral and peri-urethral ducts in the transition zone are rich in fibroblasts. The stromal composition of the peripheral zone is high in prostatic smooth muscle. Fibroblasts are present in thin bands around individual ducts and scattered in the interstitium. Stromal nodules are often found in the transition zone of BPH patients. These nodules are mostly comprised of fibroblasts with a few wisps of smooth muscle. Stromal nodules resemble the peri-urethral stroma in the normal prostate and could represent a localized expansion of fibroblasts due to inflammatory or other stimuli.

Spatial distribution of fibroblast sub-types in the mouse

Single cell RNA sequencing was performed on cells from normal and BPH prostates. Stromal nodules were isolated from the data and sub-clustered separately. The human prostate consists of two fibroblast and two smooth muscle sub-types. Fibroblast 2 was found to highly express Apolipoprotein D (APOD). APOD+ fibroblasts appear to be a sub-set of the majority of prostate fibroblasts expressing microfibril-associated glycoprotein 4 (MFAP4).

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