Establishing and characterizing a patient-derived xenograft model of benign prostatic hyperplasia

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INTRODUCTION AND OBJECTIVE:

Benign Prostate Hyperplasia (BPH), a condition faced by millions of men globally, causes non-cancerous prostate enlargement that results in lower urinary tract symptoms, reduced quality of life, and increased burden on healthcare systems. Treatment options for BPH are limited due to poor understanding of its precise underlying mechanism, which at least in part can be attributed to the absence of a clinically relevant animal model of BPH. Our goal was to establish and characterize an authentic BPH xenograft model using patient-derived tissues, i.e. patient-derived xenografts (PDXs), as a realistic preclinical model to elucidate the molecular and cellular mechanisms of BPH growth and survival.

METHODS:

Fresh BPH and normal prostate tissues were implanted under the renal capsule of $RAG2^{-/-}\gamma C^{-/-}$ male mice supplemented with testosterone. Tissue grafts were explanted after 1 week, 1 mo., 2 mo., or 3 mo. and subsequently weighed, formalin fixed and paraffin embedded. Tissue morphology and histology was visualized by hematoxylin and eosin staining (H&E). Immunohistochemistry (IHC) was performed using antibodies against Ki-67 and cleaved caspase-3 to quantify cellular proliferation and apoptosis, respectively.

RESULTS:

The weight of BPH PDX tissue was consistently greater than the weight of normal prostate PDX tissue derived from the same patient at 1 week, 1 mo., 2 mo., or 3 mo. after implantation. The most notable difference was observed after 1 mo., where the BPH PDX tissue was 2.5 times heavier than the paired normal PDX tissue. Correspondingly, the proliferative index in BPH PDX tissue was significantly higher than that in normal PDX tissue. In particular, an average proliferation index of 4.9±0.5% was observed in BPH PDXs at 1 month after implantation while an average proliferation index of 1.9±0.6% was detected in normal PDXs. The apoptosis index was significantly higher in BPH tissue than normal with the most notable change occurring at 1 week after implantation. Together, these results demonstrated that BPH tissue exhibited significant growth under the renal capsule of $RAG2^{-/-}\gamma C^{-/-}$ mice, while the growth of normal prostate tissue is minimal.

CONCLUSIONS:

Our study represents the first attempt to establish and characterize the most clinically relevant preclinical model of BPH. The differential growth rates of BPH and normal prostate PDXs over time recapitulate the proliferation property of parental tissues. These PDXs can be used to study BPH pathogenesis and potential targets for intervention as well the underlying molecular and cellular mechanisms of BPH, such as which cell types are responsible for proliferation and apoptosis (e.g., stroma, epithelial).