Title: Androgen play critical roles in epithelium proliferation in BPH not normal adjacent

Authors: Wei Chen, Laura E. Pascal, Rajiv Dhir, Uma Chandran, Alex Chang and Zhou Wang

Background: The androgen receptor (AR) is expressed by both stromal and epithelial cells in the prostate, and plays a critical role in normal development and homeostasis as well as prostate pathogenesis. Our preliminary data showed that stromal AR signaling was essential for the proliferation of epithelial cells in BPH, but not in normal adjacent prostate (NAP). However, the underlying mechanisms of this phenomenon are still unknown.

Method: Human prostate specimens obtained from BPH patients undergoing simple prostatectomy for symptomatic BPH. Patient derived explants (PDE) and stromal cell cultures from BPH and NAP tissues were established and utilized to evaluate the impact of androgens. Proliferation, cytokines and androgen-responsive genes were quantified in clinical BPH specimens and paired normal prostatic specimens via immunohistochemistry, RNA-Seq and qPCR.

Results: PDEs derived from BPH and paired NAP tissues were able to maintain their original architecture and AR signaling in culture for at least 4 days. Androgen could induce epithelial proliferation in BPH, but not NAP explants. Stromal cells derived from BPH tissues secreted higher levels of CCL family proteins (CCL8, CCL7, CCL11, CCL13 and CCL28), CXCL proteins (CXCL6, CXCL12), interleukins (IL6, IL7 and IL32), and growth factors than those derived from the paired NAP tissues. RNA sequencing identified several cytokines and growth factors which were up-regulated after androgen stimulation in BPH, but not NAP. These results were confirmed by qPCR.

Conclusions: Androgens could increase epithelial proliferation in BPH but not NAP in the PDE model. Androgens were shown to influence the expression of several genes including CXC and interleukins in BPH stromal cells, but not NAP stromal cells. Our results suggest that androgen signaling in BPH stromal cells is dysregulated and could contribute to prostatic epithelial growth and provide a strong foundation to elucidate the mechanisms of androgen-dependent stromal regulation of epithelial cell growth in BPH.