Identification of Signature Genes/Pathways and Novel Therapeutic Strategies to Target Benign Prostatic Hyperplasia

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Benign Prostatic hyperplasia (BPH) – a hyperproliferation of epithelial and stromal compartments, is a common pathological condition affecting older men and severely impacting the quality of life. Currently, treatments are limited to 5-ARI and/or Alpha-blockers, which commonly fail. Therefore, there is an urgent need for identifying new alternative, molecular-based therapies for more effective management of BPH. We integrated three human BPH RNA-Seq datasets to eliminate these caveats and identified common differentially expressed genes (DEGs) among the three data sets.

Datasets and expression profiles were downloaded from Gene Expression Omnibus (GEO) and Genotypes and Phenotypes (dbGap) database. DEGs were identified by DNASTAR and Array star and analyzed/represented using RStudio, GSEA, DAVID, STRING, Cytoscape, Immunohistochemistry (IHC), cell proliferation assays and organoid culture.

We identified common DEGs enriched for biological processes identified with BPH. By comparing the common genes with the 5ARI treatment group, we found SLIT3 as one of the candidate genes that play a role in BPH development. We subsequently validated the results with IHC staining in a fourth BPH cohort and investigated the molecular function of SLIT3 by performing studies based on genetic modulation. Our studies showed that reduced SLIT3 expression resulted in decreased proliferation of both epithelial and stromal human BPH cells when compared with the respective control cells. SLIT3 knockdown resulted in smaller and fewer organoids. In summary, we identified SLIT3 as a key player contributing to BPH pathogenesis.