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Challenges in Translational Benign Prostatic Hyperplasia Research: Identifying limitations in translational research

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Background

Benign Prostate Hyperplasia (BPH) has a lifetime histologic prevalence of 80% or more.[1] Moderate to severe Lower Urinary Tract Symptoms (LUTS) occur in 26% to 41% of men, typically from bladder obstruction from BPH.[2, 3] This chronic disease progresses to kidney dysfunction, infection, and urinary retention without adequate treatment.[4] BPH is associated with $4-5 billion in annual costs in the United States.[5, 6] Despite medical treatment, 10.2% of men progress to surgery every 5 years.[7] This indicates a gap in the medical management of non-responders. Current medication focuses on smooth muscle and the androgen pathway.[8] Additional targets are needed to develop new medical treatments for BPH.

Current clinical treatment of BPH includes treatment with 5-alpha reductase inhibitors, which prevent the conversion of Testosterone to the more potent Dihydrotestosterone in the prostate. The other mainstay of medical management are alpha-adrenergic receptor blockers such as tamsulosin, which cause smooth muscle relaxation of the prostate. Taken together, these can result in a significant relative risk reduction in the progression of symptoms.[4] For patients who progress to more bothersome urinary symptoms, including inability to urinate, surgical interventions such as Transurethral Resection of the Prostate (TURP) are required.

However, there are challenges and limitations in the available research approaches for BPH. These include challenges in obtaining adequate patient control tissue, as well as limitations in available models of BPH. In this article, we discuss the main theories of BPH from a basic science perspective, and provide an overview of challenges and approaches in human tissue for BPH and in model systems available for BPH.

Theories of BPH development

Multiple theories of the underlying pathophysiology of BPH have been advanced to date, including fibrosis,[9, 10] inflammation,[9, 11] growth factors,[12] hormonal pathways such androgens,[13] estrogens[14, 15] and glucocorticoids,[16] prostaglandins,[17] the microbiome,[18] age,[19] stem-cell reawakening,[20] and autoimmunity.[21] Despite research, a unifying underlying pathophysiology has not been uncovered, and the only agreed-upon feature of BPH is that androgen plays a required role in its development, meaning that testosterone is necessary (although alone not sufficient) for BPH to occur. The exact mechanism of downstream signalling in androgen in BPH is not well understood. The levels of androgens in the prostate appear to be similar in patients with BPH and younger non-BPH patients.[22] Testosterone is converted to Dihydrotestosterone in the prostate by 5-alpha reductase, which is the more potent androgen receptor signalling molecule. 5-alpha reductase inhibitors prevent this conversion and are an effective treatment in some patients.[22] However, AR signalling pathways alone in BPH do not appear to convert to proliferative drivers.[22] This suggests that additional pathways must be involved in the development of BPH. The relative importance of specific downstream AR pathways in BPH is not well understood.

The definition of BPH can be challenging. The pathophysiology of male lower urinary tract symptoms (LUTS) is complex and involves the bladder, bladder outlet, and pelvic floor, a larger prostate worsens symptoms.[23] Benign changes in the prostate are the focus of this project, as more severe LUTS is associated with impingement upon the urethra from larger central and transitional zones.[24-26]

However, lower urinary tract symptoms can also be from other causes and determining whether a given patient's symptoms are from BPH or another cause can be difficult.

Castration prevents and reverses Benign Prostate Hyperplasia, indicating that androgens are necessary for BPH.[12] Estrogens and androgens are known to have a synergistic effect in the induction of BPH.[27] Progesterone receptor agonism reduces prostate volume in rats by 40-70%,[28] and has shown symptom improvement in humans.[29, 30] Previous research established that glucocorticoids are elevated in tissue from patients who need surgery for BPH.[16] One theory for the observed elevation of glucocorticoids in medication refractory BPH is the accumulation of steroid precursors. These may accumulate through an excess of Testosterone, whose conversion to Dihydrotestosterone is inhibited by 5ARIs. Testosterone precursors then accumulate, resulting in an excess availability of substrates for conversion to glucocorticoids.[16] Together, these suggest that major hormonal pathways which are closely related to androgen signalling play a role in BPH development. Glucocorticoids are known to operate as an "escape" pathway in prostate cancer when androgen is suppressed.[31] Despite interest in inflammation in BPH and the known mechanism of glucocorticoids in prostate cancer, the direct role of glucocorticoids in BPH proliferation has not been well studied. We previously found elevated glucocorticoids in BPH, especially in patients refractory to 5ARIs.[16] While glucocorticoid antagonism in BPH is not well clinically studied, direct targeting of the glucocorticoid receptor could have wide-ranging side effects due to the high distribution of the glucocorticoid receptor. However, synergistic targeting of either the downstream pathway of the glucocorticoid receptor, or inhibition of their synthesis through Testosterone precursor shunting holds promise.

Limitations and Challenges in Human Tissue Research in BPH

BPH is known to have up to 60% heritability.[32] However, efforts to identify drivers via Genome Wide Association studies have been inconsistent.[32] Multi-omic approaches have not shown clear genetic or transcriptomic proliferative drivers of BPH.[33] One obstacle is that each type of available control in BPH research has different limitations. The limitations in control tissue include adjacency to cancer, differences in age, zonal differences, or that the control tissue is not truly BPH-free, but is simply BPH at an earlier timepoint prior to clinical manifestations of obstruction.

Previous publications from our group have compared specimens from transurethral surgery for obstruction secondary to BPH to benign transitional zone tissue from radical prostatectomy specimens.[16, 17] This approach has the advantage of knowing that the "case" tissue from patients undergoing outlet surgery is diseased and likely the cause of severe LUTS. The control group is less likely to be diseased. The International Prostate Symptom Scores (IPSS) scores from the control group were assessed to ensure that lower urinary tract symptoms were minimal or absent. However, it cannot be known if the control group had early tissue changes consistent with BPH that have not yet progressed to clinical male lower urinary tract symptoms. Any tissue analysis could be confounded by this variable.

Other approaches have been taken, including assessing benign histologic BPH tissue from radical prostatectomy specimens from patients with elevated IPSS scores.[34] Using this approach, a thorough transcriptomic analysis was performed including on areas containing histologically stromal BPH and mixed stromal/epithelial BPH. However, the control tissue used was taken from benign peripheral zone in the same specimen.[34] With this approach, one cannot be certain if observed differences are due to BPH or due to variation between prostate zones. Cellular differences are known to exist when comparing the peripheral zone to the central/transitional zones of the prostate.[35] Even within a single patient with BPH, there is significant heterogeneity of phenotype which can confound attempts at molecular analysis.[36] Single-cell RNA sequencing is one possible solution to this issue, whereby the transcriptome of individual cells can be assessed. This allows for a more detailed understanding of the molecular machinery of discrete cell types in this heterogenous disease.[36] Spatial transcriptomics offers even further detail, and has been used to characterize local sub-populations of medication responsive and refractory areas of the prostate.[37]

In addition, stroma-epithelial differences are under-explored in studies that use only bulk tissue. The relative ratio of stroma is greater in smaller prostates causing obstruction, and conversely more epithelial-type nodules are visible in larger prostates.[38] This means that studies comparing normal to abnormal tissue without separating compartments may

simply be detecting stromal versus epithelial signals which overshadow true disease-modifying signals. In addition, the abundance of proteins, which enact the functions of the cell through the central dogma, can differ significantly from messenger RNA abundance. [39, 40]

Proteomic Analysis of BPH provides insights into the disease process

Due to limitations in genomic and transcriptomic profiling, proteomics in BPH provides a promising avenue for investigation. Firstly, using messenger RNA abundance as a surrogate for altered function of a cell has limitations, as protein abundance can differ significantly.[39, 40] Furthermore, unlike in prostate cancer, genomic and transcriptomic profiling has not found evidence of traditional proliferative driver mutations in BPH in prostate tissue.[33] Signatures are most consistent with aging, and epigenetically, hypermethylation of DNA is dominant, unlike the global hypomethylation of neoplastic processes.[33] While the transcriptome of BPH using numerous case and control tissues has been assessed,[33, 34, 36] these limitations point toward proteomic analysis as new frontier for our understanding of the changes in cell machinery in BPH. The proteome in prostate cancer shows a majority of differentially expressed genes that are distinct from the transcriptome,[41] and we expect similar findings in BPH to uncover new pathways. Existing proteomic studies of BPH are relatively limited. In one study, the proteome of the stromal compartment of BPH for men with LUTS in comparison to adjacent normal tissue.[42] Findings included altered levels of proteins involved in cellular junctions, extracellular matrix, and focal adhesion within BPH nodules, suggesting a role in the disease. The analysis was limited to three men,[42] possibly due to the difficulties in obtaining tissue and the cost of proteomic studies. Other previous proteomic analysis of BPH tissue has been performed mainly as a control compared to prostate cancer.[43, 44] This does not provide insight into the pathophysiology of BPH, because we cannot detect changes in protein expression compared to non-hyperplastic benign prostate tissue.

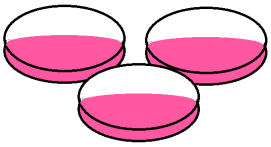
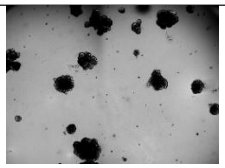
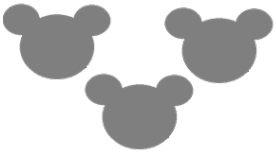
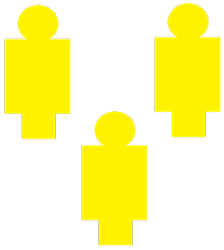
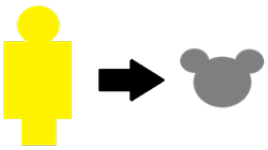
The role of steroid hormones in BPH provide a promising avenue of inquiry, and proteomics in other fields has contributed to understanding how these metabolically agile molecules impact cellular functioning.[45] Steroids such as estrogens[14, 15] and glucocorticoids,[16] and lipid hormones including prostaglandins[17] have been implicated in BPH. As signalling molecules, steroid hormone metabolism is fast and a "snapshot" of steroid hormone presence and location in tissue samples may not provide a complete understanding of their dynamic effects. However, proteomic remodeling in hyperplastic states may provide insight into the downstream effects of these molecules.

Model systems in BPH

In vitro analysis of BPH requires model systems. The main categories of available model systems in BPH include cell lines, animal models, and patient derived models including xenografts (Table 1). Numerous cell lines are utilized in BPH *in vitro* research. Epithelial cell lines include BPH-1, RWPE-1, and PZ-HPV-7.[46] Additional epithelial cell lines used include NHPrE-1, BHPrE-1,[16] pRNS-1-1, PNT1A, and PrEC.[46] The stromal/myofibroblast cell line WPMY-1 can be utilized for stromal or stromal/epithelial interaction assessment.[47] Cell line analysis in BPH, as in other areas of basic science, has the advantage of relative homogeneity within and between studies. The cell lines act as a more or less fixed variable, allowing for assessment of transcriptomic and proteomic differences under different conditions. The drawback of cell lines is that given the rapid proliferation of cells, these may or may not represent the true molecular profile of BPH.

BPH cells can be grown in traditional 2D culture, or in increasing popularity in 3D "organoid" culture.[16] Two-dimensional cell culture of benign prostate cells has utility, but does have significant limitations as a model system. These include a lack of AR expression, possibly due to lack of differentiation from basal-cell state which have low to no AR. There is also a lack of budding/branching morphology.[48] By comparison, three-dimensional organoid culture of BPH cells shows AR and PSA expression and has shown luminal and basal differentiation, making for a more realistic model.[48, 49] Organoid models in BPH show promise for testing efficacy of new compounds. For example, an organoid model was used to show the efficacy of anethole trithione, a mitochondrial reactive oxide species production inhibitor, in reducing growth.[50] A difficulty in both 2D and 3D model systems is that stroma and epithelium thrive in different culture media.[51] One approach to this issue is to study each cell type *in vitro*

Table 1. Select model systems in Benign Prostate Hyperplasia research.

Model	Schematic	Advantages	Disadvantages
2D Cell Culture		**✓ Accessible ✓ Affordable ✓ Reproducible ✓ Consistent ✓ May have one factor altered easily for analysis (eg gene silencing or upregulation)**	**⊘May not mimic the complexity of cell-cell interactions ⊘Does not represent phenotypic heterogeneity ⊘Lacks Androgen Receptor expression and PSA expression**
3D Organoid Culture		**✓ Relatively accessible and affordable ✓ May be reproducible and consistent, although less so than 2D culture**	**⊘May lack cell-cell interaction ⊘Phenotypic heterogeneity is lacking ⊘Expense and expertise are increased**
Animal Model		**✓ Includes cell-cell interactions ✓May study prostate throughout aging, including embryo and effects of aging ✓Response to pharmacology mimics humans**	**⊘Requires specialized equipment, facilities, and personnel ⊘High cost ⊘Small sample size ⊘Experiments may take longer**
Human Tissue		**✓ Human biology is directly studied ✓ Most relevant for pharmacology ✓ Manipulating pathways with gene silencing or upregulation is not possible or very difficult ✓ Heterogeneity of disease is captured**	**⊘Laboratory access to patient tissue may be difficult due to appropriate ethical considerations ⊘Expense is high for recruitment and tissue processing ⊘Heterogeneity between patients may obscure findings related to the disease**
Patient Derived Xenografts		**✓Human tissue is included ✓Heterogeneity of disease ✓Hormonal or pharmacologic milieu can be stimulated**	**⊘Very high expertise, facility, and personnel ⊘Slow and expensive experiments ⊘Reproduction of findings may be difficult**

separately, sometimes with exposure to an extract from the other cell type as a stimulus. Alternatively, co-culture models are available but require specialized equipment.[51]

Patient-derived cell culture is possible as well. Cell lines that are available were originally immortalized from patients with BPH, and this process could be repeated although this is somewhat time and labor-intensive.[49] Patient cells can instead be extracted, processed, and grown directly *in vitro* using media that selects for a given cell type.[52]

Several animal models are used in BPH research. Mouse models are popular, in part because of relative cost and ease of animal handling compared to larger animals. The mice can be stimulated with hormones (testosterone and estrogen) in order to induce benign prostate hyperplasia.[53] This has been shown to induce bladder outlet obstruction, including enlargement of the bladder and prostate. Alternatively, mice are found to have increased frequency of urination consistent with lower urinary tract symptoms (LUTS) and related prostate changes with normal aging.[54] Either of these mouse models can be utilized, with the advantage of the former being a faster and more predictably onset of disease. The advantage of the pure aging mouse model, conversely, is that it may represent a more physiologic disease.

Finally, patient derived xenografts represent an opportunity for implantation of patient cells in a more natural microenvironment. Patient BPH cells, isolat-

ed and purified, can be implanted beneath the renal capsule of immunodeficient mice.[55] This model responds appropriately to therapeutic intervention and has an appropriate molecular profile, indicating utility as a model system. For example, a translational success with this type of model showed an appropriate response of xenografted prostate cells to the 5-alpha reductase inhibitor Finasteride, including reduced proliferation and increased apoptosis.[55] This mimics the response *in vivo,* and suggests that further stimuli may be examined using this model.

Conclusions

BPH is a prevalent disease, with limited available medical options currently. In order to target novel pathways, laboratory investigation will be required using a combination of patient tissue and model systems. Each system has advantages and limitations. A challenge in BPH research is obtaining adequate and appropriate patient and control tissue.= Patients with this disease require dedicated researchers to advance the field. Future research should include validation and improvement of existing model systems, and creation of new models for BPH. Multi-omic approaches across multiple model systems will allow for identification of new key pathways in BPH and/or improved treatment of existing pathways.

Declaration

The authors declare that they have no conflicts of interest to declare.

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