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Review article

Targeting phenotypic heterogeneity in benign prostatic hyperplasia

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ABSTRACT

Benign prostatic hyperplasia and associated lower urinary tract symptoms remain difficult to treat medically, resulting in hundreds of thousands of surgeries performed annually in elderly males. New therapies have not improved clinical outcomes since alpha blockers and 5 alpha reductase inhibitors were introduced in the 1990s. An underappreciated confounder to identifying novel targets is pathological heterogeneity. Individual patients display unique phenotypes, composed of distinct cell types. We have yet to develop a cellular or molecular understanding of these unique phenotypes, which has led to failure in developing targeted therapies for personalized medicine. This review covers the strategic experimental approach to unraveling the cellular pathogenesis of discrete BPH phenotypes and discusses how to incorporate these findings into the clinic to improve outcomes.

1. Introduction

Benign prostatic hyperplasia (BPH) is a slow expansion of the transition zone that results in the progressive manifestation of obstructive lower urinary tract symptoms (LUTS). The incidence rates of BPH and LUTS increase approximately 10% per decade of life starting at 40 years of age (Platz et al., 2012). Chronic progressive diseases in general are increasing along with life expectancy, where it is estimated that the number of people in the US over 80 years old will increase from 9.3 million in 2000 to 19.5 million in 2030 (CDC, 2013). Moreover, the number of men in the US suffering from LUTS is projected to reach 11 million by 2030 (Jacobsen et al., 1995). The economic costs of treating LUTS is estimated at more than $4 billion each year mainly due to increased therapeutic intervention (Saigal and Joyce, 2005). Together with an increase in comorbidities of BPH/LUTS (Parsons et al., 2006; Mozumdar and Liguori, 2011), the incidence and progression rates of BPH/LUTS as well as the economic burden will surely rise.

The non-diseased human prostate is about the size of a walnut and divided into four basic anatomical zones: transitional, central, peripheral, and anterior fibromuscular stroma (McNeal, 1981). At approximately 40 years of age, the prostate transition zone begins to grow slowly at 1.6% per year, and this rate accelerates with age (Roehrborn et al., 2000). The first clinic visit for a patient complaining of LUTS requires a detailed physical examination and history. LUTS can derive from dynamic dysfunction of bladder and prostate smooth muscle or from static bladder outlet obstruction due to prostatic enlargement (Roehrborn, 2008). A digital rectal examination is typically the first indication of potential prostatic enlargement as a cause of obstructive LUTS. Once prostate cancer is ruled out, more estimations of LUTS severity are collected including uroflowmetry, symptom scores, and a measurement of prostate volume by ultrasound.

In the absence of tissue, blood or urinary biomarkers, clinical variables must be used as markers of BPH/LUTS severity and progression. Baseline variables such as age, prostate volume > 40 cc, high PSA levels, low peak flow rate, and high post-void residual (PVR) are good clinical predictors of acute urinary retention (AUR) and BPH-related surgery (Roehrborn, 2006). Dynamic variables such as an increase in the AUA symptom score (AUASS) and PVR worsening are also good indicators of patients at risk of BPH progression (Emberton, 2006a). In early stage disease, modifiable risk factors are discussed for management of symptoms (Parsons and Kashefi, 2008). However, when symptoms become moderate to severe (AUASS > 8), medical therapies are discussed.

Unfortunately, the few medical therapies approved for BPH/LUTS only mitigate the risk of symptomatic progression by 30–40% across a

Abbreviations: AR, Androgen Receptor; BPH, Benign Prostatic Hyperplasia; LUTS, Lower Urinary Tract Symptoms; PVR, Post-Void Residual; AUR, Acute Urinary Retention; AUASS, American Urological Association Symptom Score; PSA, Prostate Specific Antigen; 5ARI, 5 Alpha Reductase Inhibitor; DHT, Dihydrotestosterone; MTOPS, Medical Therapy of Prostate Symptoms; TURP, Transurethral Resection of the Prostate; BCH, Basal Cell Hyperplasia; MRI, Magnetic Resonance Imaging; PZ, Peripheral Zone; TZ, Transition Zone

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large and diverse cohort (McConnell et al., 2003a). The two predominant therapies prescribed for LUTS are alpha adrenergic receptor blockers (α-blockers) and 5 alpha reductase inhibitors (5ARI). Alpha blockers are recommended as a first-line therapy for patients with moderate symptoms, PSA ≤ 1.5 ng/mL, and a prostate volume ≤ 40 cc (Roehrborn et al., 2011). The mechanism of action of α-blockers is to reduce smooth muscle tone, which increases peak urinary flow rate. It is notable that the clinical response to α-blockers is proportional to the percent of prostate tissue occupied by smooth muscle (Shapiro et al., 1992a; Isen et al., 2001), meaning that those patients with glandular hyperplasia are less likely to demonstrate a clinical response. Men with prostate volume > 40 cc are most likely to show a clinical response to 5ARI treatment. This is likely due to the fact that larger prostates are more likely to take on the form of glandular hyperplasia (Schuster and Schuster, 1999; Price et al., 1990; Franks, 1953), tissues that are rich in androgen receptors to which 5ARIs are targeted. The mechanism of action of 5ARIs is to reduce local dihydrotestosterone (DHT) levels by inhibiting the conversion of testosterone to DHT, causing apoptosis of luminal epithelia. 5ARI treatment reduces prostate volume by an average of 19% across a patient population, which slows the progression of lower urinary tract symptom worsening (Gormley et al., 1992). Despite the availability and widespread use of these therapies, more than 250,000 men per year in the US undergo some form of surgical intervention for their obstructive LUTS (Wei et al., 2008).

Even though α-blockers and 5ARIs target specific cell types, the clinician is virtually blinded to the underlying tissue composition of prostatic growth when administering these medications. Making decisions on medical treatment is predominantly based on prostate volume. The evolution of prostate tissue composition with increasing volume was first surveyed in an autopsy series by Franks over 60 years ago (Franks, 1953). Since then there have been various attempts to classify the anatomical and cellular subtypes of prostatic growth (Guneyli et al., 2016; McNeal, 1978), but very little is understood about the underlying molecular pathways driving disparate cellular phenotypes. The 2008 NIDDK Prostate Strategic Plan identified a Research Priority Recommendation: *develop research efforts for phenotype-specific therapies for LUTS, BPH, and prostatitis based on respective pathological criteria for enhancing efficacy, avoiding treatment failures, and improving cost effectiveness*. The expectations of such research were intended to molecularly define specific "phenotypes" of patients and therefore provide a better definition of disease than the current use of clinical parameters such as PSA and prostate volume (NIDDK, 2008). Nearly 10 years later, we have yet to develop a deeper molecular and cellular understanding of BPH phenotypes.

The observed variation in clinical response to BPH medications suggests that we have yet to target the assortment of BPH pathogeneses. The purpose of this review is to clarify the experimental approach to solving the molecular underpinnings of morphological heterogeneity in BPH/LUTS in order to develop personalized treatments for this multifaceted disease.

2. Clinical diagnosis and management of BPH/LUTS

Up until the 1990s, the most common treatment for LUTS arising from BPH was surgical resection or enucleation of the prostate. Novel medical treatments have since surpassed surgical intervention. In the early 1990s the role of the adrenergic innervation of the bladder neck, prostate and prostatic capsule was elucidated. Based on the observation that there is a strong presence of alpha 1a receptors, the class of alpha adrenergic receptor blocker drugs was progressively introduced, which is now made up by five drugs in clinical use (terazosin, doxazosin, tamsulosin, alfuzosin and silodosin) (Lepor et al., 2012). The alpha adrenergic receptor blockers (α-blockers) were developed to relieve dynamic bladder outlet obstruction by acting to relieve smooth muscle tone and were also shown to significantly reduce symptomatic progression (Lepor et al., 1992).

Research at UT Southwestern demonstrated that the prostate expresses 5 alpha reductase, an enzyme that converts testosterone to its more potent derivative dihydrotestosterone (DHT) (Pelletier et al., 1998). The 5 alpha reductase inhibitor (5ARI) finasteride was developed and approved in 1993 to treat male LUTS secondary to BPH. It works to decrease static bladder outlet obstruction due to BPH by lowering intra-prostatic dihydrotestesterone (DHT) levels by nearly 97%, which causes apoptosis of androgen-dependent luminal epithelium (Span et al., 1999; Andriole et al., 2004; Bauman et al., 2014), a reduction in total prostate size by about 20–25%, a reduction in serum PSA by about 50%. The treatment is most effective in men with prostate volume > 40 cc, but typically takes several months for symptomatic improvement (Group, 1993). Later, David Russell at UT Southwestern cloned and identified two 5 AR isoenzymes, type 1 and type 2, of which type 2 is more important in the prostate (Thigpen et al., 1993; Russell and JD, 1994), and inhibited by finasteride. There is a second commercially available 5ARI, dutasteride, which inhibits both types of the 5AR isoenzymes. It is unclear what molecular mechanisms drive resistance to 5ARI treatment with either drug. This may be due to the fact that some regions are responsive while other regions are resistant, even within the same patient (Fig. 1).

Although α-blockers are considered a first-line therapy due to their fast-acting effects, longitudinal clinical trials such as MTOPS (McConnell et al., 2003a), CombAT (Roehrborn et al., 2010), and PREDICT (Kirby et al., 2003) demonstrated that combination therapy with an α-blocker and a 5ARI provided superior LUTS relief compared to monotherapy, particularly in men with a prostate volume greater than 40 cc. Moreover, a baseline prostate volume greater than 40 cc and unresponsiveness to α-blocker treatment serve as key predictors of LUTS progression (Emberton et al., 2006b; Boyle et al., 1996).

One obvious observation from these clinical trials is the patient-specific response to treatments. No individual drug treatment mitigates the risk of symptomatic progression by more than 35–40% across a cohort; however, individual patients can display a range from very good to undetectable responses. This is likely due to the individual's specific tissue composition. While combination treatment with α-blockers and 5ARIs decreases the risk of symptomatic progression by 66%, their combined use must be targeted to men with larger prostates to be clinically and economically superior to monotherapy with α-blockers (Lepor, 2011). Nearly 5–7% of men that present with symptoms will eventually require surgery without medical therapy. Regardless of the treatment regimen, longitudinal trials suggest that, even on sustained treatment, symptoms will continue to worsen (albeit at a slower pace). It is also worth noting that nearly 20% of patients have such strong adverse effects from these therapies that medication must be discontinued (McConnell et al., 2003a). In fact, data suggest that most men do not stay on 5ARI therapy for longer than a year (Cindolo et al., 2015). While α-blocker monotherapy is certainly the fastest-acting and most inexpensive option, combination therapy with a 5ARI is the most cost-effective long-term medical treatment for those who can afford it, providing maximum symptomatic relief for moderate symptoms (Bjerklund Johansen et al., 2012). For those with severe symptoms, TURP is still the most effective treatment in terms of cost and clinical outcome (DiSantostefano et al., 2006).

The efficacy of α-blockers is at least partially dependent on the percent of smooth muscle that composes the prostate (Shapiro et al., 1992a). Although stromal hyperplasia is thought to dominate the initial phases of BPH (Marks et al., 1994; Deering et al., 1994; Rohr and Bartsch, 1980), as prostate volume surpasses 50 cc, most patients display an enlargement of glandular nodules that occupy a large percentage of the total prostate volume (Price et al., 1990; Franks, 1953; McNeal, 1978).

More recently some patients with LUTS secondary to BPH are also being treated with anticholinergic drugs usually in combination with alpha blockers (Fullhase et al., 2013; Kaplan et al., 2012, 2011), as well as one drug in the PDE5 inhibitor class, tadalafil, which presumably is