Benign Prostatic Hyperplasia- what do we know?

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Abstract

OBJECTIVES

Benign prostatic hyperplasia (BPH) is a prevalent disease with significant health and economic impacts on individuals and health organisations across the world, whilst the cause/initiation of the disease process has still not been fully determined

METHODS

This review presents historical and contemporary hypotheses on the pathogenesis of benign prostatic hyperplasia, with the potential implications in regards to current medical therapies.

RESULTS

In BPH, pathways involving androgens, oestrogens, insulin, inflammation, proliferative reawakening, stem cells and telomerase have been hypothesised in the pathogenesis of the disease. A number of pathways first described over 40 years ago have been first rebuked and then have come back into favour. A system of an inflammatory process within the prostate, which leads to growth factor production, stem cell activation and cellular proliferation encompasses a number of pathways and is currently in vogue. This review also highlights the physiology of the prostate cell subpopulations and how this may account for the delay/failure in treatment response for certain medical therapies.

CONCLUSION

BPH is an important disease, of which the pathogenesis is not fully understood that impacts the effectiveness of medical therapies. This impacts patients, with further research potentially highlighting novel therapeutic avenues.

Benign prostatic hyperplasia, commonly known as BPH, results in a benign enlargement of the prostate gland, due to unregulated hyperplastic growth of either the epithelial and fibromuscular tissues of the transition zone and periurethral area (1). Despite many years of scientific study there is still no basis for the hyperplasia, which restricts attempts to devise new treatments.

Prevalence

The normal prostate size is considered to be 20g, which is achieved between 18-20 years of age (2). Studies of prostate histopathology in autopsy samples, have demonstrated that the number of men with a histological diagnosis of BPH increases each year from 41 to 90, and 50% of men between the ages of 51 and 60 show the pathological features in keeping with BPH (3). The most common problem caused by BPH is lower urinary tract symptoms (LUTS), although not every man is affected.

Symptoms

Men with BPH may experience symptoms such as poor urinary flow, frequency, hesitancy initiating flow, post terminal dribbling and nocturia (voiding LUTS). This can sometimes be difficult to distinguished from "storage LUTS", which includes urgency, frequency, nocturia and occasional incontinence (most commonly due to bladder overactivity, sometimes independently of prostatic enlargement). Whilst overall LUTS can also be caused by other conditions, such as diabetes, neurological diseases or urinary tract infections (UTIs), voiding LUTS is most frequently the result of the prostatic enlargement in BPH (4).

Studies conducted in the 1990's in the UK demonstrated a prevalence of 10-41% for moderate-to-severe LUTS associated with BPH in men aged 40 or older, which increased with age, from 3.5% in 45-49 year olds to >30% in those aged >85 years(5). A recent study has put the lifetime prevalence worldwide at 26.2%, with no statistically significant change in this rate over the last 20 years (6). The main risks associated with LUTS to the patients include UTIs and episodes of acute urinary retention (AUR). In addition to increasing incidence of BPH with age, the incidence of cardiovascular disease also increases (7). Treatment for this may include the use of diuretics. The

increase in renal urine production may therefore worsen LUTS for men with significant health consequences as described below.

Health consequences

For the patients, there is a significant impact on their quality of life due to the symptoms and complications associated with BPH-induced LUTS. The rate of moderate–to-severe LUTS within patients suffering from depression is higher than men without depression, 79% vs 57% (8). Nocturia, as a consequence of BPH, has a huge impact on patients' sleep. Men with nocturia due to BPH scored much lower Nocturia Quality of life Questionnaire scores compared to men with no nocturia 46.1 vs 60.9 ($P<0.001$)(9). Nocturia impacts energy levels, concentration and productivity and has the potential to also affect their partner's sleep, along with other areas within a patient's relationship with their partner (10). In older adults, nocturia is a significant risk factor for falls. Falls are associated with significant morbidity in the form of fractures, head injuries and extended hospitalisation (11).

Economic consequences

The economic burden for society of this condition is significant. In 2003, the management of LUTS due to BPH was a substantial cost to the NHS. £44 million was spent in primary care, £69 million on drug treatment and £101 million for treating the complications associated with BPH, such as AUR(12). 14 years later, with an increasingly elderly population, the financial impact to the NHS and society will only have increased and will continue to do so. The number of UK men aged between 60-84 is set to rise from 5.7 million (2008) to 7.9 million by 2028 (13).

The significant impact upon the quality of life of men with BPH and the financial impact in treating the complications of it to society, means greater awareness and investment in research is needed than it currently receives. Development of new effective therapies is required to improve lives and reduce complication costs.

Since BPH is a disease of aging, the incidence and prevalence increases as men get older, the exact cause(s) remains disputed despite much research. Theories on the role of

genetics, androgens, hormones, cytokines, chemokines and stem cells have all been put forward. Some theories have been considered essential for the maintenance of the disease, however, as yet, the initiating factor/factors have not reached a consensus.

Pathophysiology of BPH

Genetics/hereditary factors

Genetics and hereditary induced factors impact a wide variety of disease processes and their role in BPH has been examined. Hereditary influence for the development of BPH has been shown in the increased relative risk (RR= 3.3) of disease concordance in monozygotic twins compared to dizygotic (14) and increased incidence risk in siblings with an early onset of BPH disease (15).

The specific genetic risk factors have ranged from loss of the Y chromosome (16), to the action of single nucleotide polymorphisms (SNPs). As the influence of androgens is suspected in prostate cancer and BPH, translational science studies have found a link between androgen metabolism (eg: 5 alpha reductase type II gene variants) and BPH incidence (17). Other SNPs located near genes associated with increased prostate cancer risk (*IRX4, ITGA5 &RFX6)* have been linked with more aggressive BPH disease (high IPPS scores) (18), whilst SNPs linked to metabolic syndromes have correlated with increased prostate volumes (19). Despite these discoveries, a recent large genome-wide association study was unable to identify significant susceptibility loci for BPH development (20).

Androgens

Whilst aging is considered essential for BPH development, another factor is the presence of androgens. The role of male sex hormones has been extensively examined, however the exact mechanism of action or mechanistic importance is still disputed.

Androgens, especially testosterone-derived, play a central role in the normal functional development of the prostate. The main mode of action is via the transcription factor, Androgen receptor (AR), which is predominately located within the luminal epithelial cells, is almost non-existent in basal cells and present at a lower density in a proportion of human prostate stromal cells(21) Androgen receptor expression may be up-regulated in BPH compared to normal tissue(22), however no consistent evidence has been demonstrated for this (23).

A key step in the AR signalling pathway is the conversion of testosterone to dihydrotesterone (DHT), via the 5α reductase enzyme, in particular the isozyme type 2. DHT then binds to AR with a 10-fold higher affinity than testosterone.
The importance of androgens in the prostate is demonstrated by the effect of pre-existing deficiency in 5α reductase. Affected males are found to have significantly smaller prostates than aged matched controls, and histology from these subjects demonstrated the presence of fibrous connective tissue and smooth muscle, but no epithelial tissue(24).

So whilst androgens are required for normal prostate development, their role in BPH pathogenesis is still debated.

Perhaps counter-intuitively, as the incidence of BPH increases with age, the levels of circulating testosterone in serum generally decreases (25). Paradoxically, Hypogonadal patients who are treated with androgens have no increased risk of BPH development (26). One answer to this may be that true DHT concentrations are higher in BPH compared to normal tissues (27), but remain stable during ageing (26). It is therefore hypothesised that the prostate is insensitive to circulating testosterone level variations, because the AR in prostate cells is normally saturated by relatively low androgen intra-tissue concentrations (28). Thus androgens can maintain the growth of prostate cells within BPH. Additionally, there is a reported 8-10% prevalence of Basal cell Hyperplasia in BPH (29), which will account for a proportion of the incidence of BPH cases, despite lower circulating androgens.

Due to this perceived importance of androgens (particularly DHT) in BPH, the clinical use of 5-alpha reductase inhibitors (5α RI's) (e.g. Finasteride) for treatment has long been established (23). Indeed clinically, improvements in International Prostate Symptom Score (IPSS), max urinary flow rate and decrease prostate volumes are seen after treatment with 5αRI treatment (30). This improvement does take a significant length of time to occur, around 6 months, implying that perhaps the true driver(s) of the disease is not targeted by this treatment.

Oestrogens

Often observed to work in opposition to androgens, it has been suggested that oestrogens could be the primary hormone driver behind BPH. This has stemmed from the observational animal studies in which oestrogen dosage induced murine prostatic hyperplasia (31).

Osetrogens, in particular Oestradiol, act similarly to androgens, but via their own nuclear hormone receptors, namely Estrogen receptor alpha (ERα) and Estrogen receptor beta (ERβ). In addition, the cellular Aromatase converts androgens to oestrogens (32).

In men with metabolic dysfunction, larger adipose tissue volumes can lead to increased aromatase conversion of androgens to oestrogens. This is combined with decreased secretion of testosterone (33), altering the balance between the two sex hormones, which may account for the increased prostate volumes in this cohort (34). Additionally, in the aging male, serum androgen levels decrease, whilst oestrogen levels remain constant or decrease slightly, resulting in an increased oestrogen:androgen ratio (35). This may be significant in the development of BPH. It could therefore be the combination of higher oestrogen and androgen levels that works together in the pathogenesis of BPH (35).

One reason for this might be the cellular locations of different oestrogen receptors and their perceived actions. The ERα receptor has been shown to be predominately located within prostatic stromal tissue (22), whilst the ERβ receptor is mainly located within the prostatic basal epithelial cells (22). Thus, ERα can not only cause stromal cell

proliferation (36), but also has a paracrine influence on the adjacent epithelial cells (37). However, decreased levels of ERα have been detected in BPH (22).

The evidence therefore remains contradictory. Whilst ERβ has a pro-apoptotic effect, ERβ knockout mice develop BPH during aging (37), and in human cells, activation of ERβ, via an agonist, causes apoptosis within BPH tissues (31). Why then does the action of the two different receptors not cancel each other out? This may be explained by the higher level of the enzyme Aromatase located within stromal cells (38), implying that ERα may nevertheless be the dominant receptor leading to the hyperplasia.

However all attempts to block the influence of ERα or aromatase have failed to yield conclusive clinical results in BPH (39).

Insulin

A role for insulin has been proposed in BPH, since epidemiological studies have shown an increased incidence of BPH in patients suffering from diabetes (34). Hyperinsulinemia and insulin resistance are both considered independent risk factors for the disease (40).

Insulin's effect within the prostate is mediated via insulin-like growth factor 1 (IGF 1), whose receptor has been found to be expressed at higher levels within the stroma of BPH cases. IGF-1 acts to increase proliferation of stromal cells in BPH (41), whilst also having a paracrine effect on the neighbouring epithelial cells (42). Indeed, increased levels of insulin and IGF1 increased the risk of presenting with BPH compared to controls, and even could be used to predict prostate size, where larger prostates expressed the highest levels of insulin and IGF1(43).

The targeting of insulin/IGF-1 may therefore have a potential therapeutic benefit for BPH and the use of Metformin has been demonstrated to inhibit the proliferation of BPH cells by disrupting the IGF-1 axis, namely inhibiting IGF-1 receptor expression and the phosphorylation of IRS-1, a substrate of IGF-1 receptor (44). Further studies on the effectiveness of this drug on BPH tissue and patients would be needed to clinically evaluate this as a treatment strategy.

Growth factors/ inflammation

Changes in the sex hormone balance are important in BPH, but it may provide the mechanism of maintaining the hyperplastic process rather than being the initiating/ causative factor. This is why current opinion deems the process of inflammation (indeed chronic inflammation) and the role of growth factors as key to the understanding of BPH.

Androgen receptor and growth factors.

Growth factors are chemicals that cause cells to act in a number of ways, mainly either to proliferate or to undergo apoptosis. They include Keratinocyte growth factor (KGF), Epidermal growth factor (EGF), Fibroblast growth factor (FGF) and Insulin-like growth factor (IGF), all of which promote proliferation whereas transforming growth factor-1 (TGF-1) treatment results in apoptosis (45).

Within the prostate, growth factors are normally released by the stromal cells and maintain prostate cellular homeostasis through autocrine and paracrine pathways (46), as seen in the very earliest stages of human prostate development, where stromal factors determine cell fate (see below). An alteration in the balance of cellular homeostasis is at the core of BPH development. Activation of the androgen receptor leads to the increase in growth factors responsible for proliferation. For example, in BPH fibroblasts expressing androgen receptor, FGF-2 and FGF-7 are overexpressed (47). TGFβ1 induces the differentiation of fibroblasts into myofibroblasts in the stroma and regulates the epithelial cells' response to IGF-1 (above) mediated stromal-epithelial cell axis (48), resulting in the hyperplasia linked to BPH.

This complexity underpins the difficulty in determining the causes of BPH. However the increased levels of growth factors do contribute to BPH, but what causes the increase in the levels of these molecules? Current thought is that inflammation plays a key role, particularly as a recent study has demonstrated that pro-inflammatory macrophages induced an increase in stromal proliferation in BPH tissue via AR signalling pathways. Xu et al, also found that AR located within stromal cells of the transition zone of the prostate had an increased ability to recruit inflammatory macrophages compared to elsewhere within the prostate, potentially explaining why BPH is mostly seen with this zone(49).

Role of chronic inflammation

An inflammatory process is believed to be the link between the initial cause and the growth factor-led hyperplasia and gland re-modelling seen within BPH.
The suggestion for this link came from the study of over 8000 men who had BPH/LUTS and were entered into the REDUCE trial (reduction by dutasteride of prostate cancer events). Within this population, 77.6% had chronic inflammation in their prostate biopsy at initial trial entry (50).

The normal prostate contains multiple cells important for maintaining immunity, as the prostate can be exposed to many pathogens from the urinary tract. In non-BPH tissue, T lymphocytes represent the majority of these cells (>90%), with mostly CD8 T cells (the predominant type) located within the peri-glandular region, whilst CD4 T cells are present in the stroma (51). In samples of BPH tissue, a reversal of this ratio is seen, with a higher proportion of CD4 cells seen, along with CD-3 T cells, demonstrating a picture of chronic inflammation (52).
The initial stimulus for the inflammatory process is still unknown, however several have been proposed. They include; bacterial (E.coli) or viral (HPV, herpes simplex) infections, hormone changes, dietary factors, autoimmune responses and urinary reflux into prostate collecting ducts (53).
The initial stimulus causes the activated T cells in particular to release cytokines and interleukins(IL) responsible for cell damage, such as an increase in expression of IL-15 in stromal cells (54), IL-17 from T cells (52), interferon-gamma in basal and stromal cells (55) and IL-8 in epithelial cells. IL-8 is thought to be key, as it induces the expression of FGF-2, which has been shown to be a potent growth factor for both stromal and epithelial cells (47).

This process of lymphocyte activation, cytokine release and growth factor -induced hyperplasia acts as a self-perpetuating cycle, leading to chronic inflammation and a progressive increase in prostate volume (45).
Added to this, the constant remodelling process causes a localised hypoxic environment, which stimulates the release of reactive oxygen species (ROS). Such ROS can promote

the release of growth factors (FGF-2, FGF-7, TGFb1) and the creation of a new vascular supply (via vascular endothelial growth factors)(56).

This "vicious cycle" is illustrated in figure 2 and also demonstrates that, in the presence of inflammation, 5a reductase inhibitors may not lead to symptom resolution.

The presence of chronic inflammation doesn't just seem to be a cause of BPH, but can lead to disease progression, with larger prostate size and increased clinical symptoms. In BPH cases, those found to have chronic inflammation had larger prostate volumes, higher IPSS scores, while developing urinary retention, and were more likely to require surgical intervention (50, 57).

The role of anti-inflammatory cytokines (such as IL-4) in BPH is not fully understood. In early BPH disease they appear to lose their inhibitory effect, but once a mature disease state is reached (presence of nodules), IL-4 and IL-13 levels increase, suggesting that the initial inflammatory process may have been scaled back (58).

With strong evidence that inflammation plays a role in BPH progression, treatment with anti-inflammatory therapy has been investigated.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used and available in medicine. They inhibit to varying degrees COX1 & 2 enzymes, which are expressed and elevated in BPH (59). *In vitro* studies have demonstrated inhibitory effects of NSAIDs on BPH cell proliferation (60) and clinical trials have demonstrated improved IPSS scores when NSAIDs are used in combination with either alpha adrenoreceptor blockers or 5 alpha reductase inhibitors (5ARI) to single therapy alone, butover a short treatment duration(61). However over longer treatment periods, other studies have demonstrated no improvement of symptoms with stand-alone or combination NSAID use and in some cases, a worsening of LUTS (61).

Other anti-inflammatory therapies such as dietary polyphenols and vitamin D receptor (VDR) agonists have also been shown to reduced BPH symptoms and progression via a number of pathways (COX-2, reactive oxidative species and VDR activation). These are an organic alternative therapy, with *in vitro* and animal studies demonstrating BPH

regression (62, 63). Clinical trials for polyphenols including a RCTs, have shown improved IPSS scores (64), however these studies are of low numbers and at too low power to draw meaningful conclusions.

Despite the apparent key role inflammation plays within BPH and the evidence of in vitro studies demonstrating BPH regression, the success of anti-inflammatory therapies remains to be confirmed in the clinical setting.

Reawakening hypothesis

In 1978 McNeal (65) suggested that BPH was an "embryonic reawakening" process, similar to when the basal epithelial cells in the embryonic prostate proliferate in response to stromal signalling factors. These factors were associated with age and caused new glandular formation and budding, eventually resulting in hyperplastic nodules (65). As mentioned above, the "factors" are most likely to be growth factors which may reawaken embryonic growth potential (66). The question is what cells then harbour the capability for this growth potential?

Stem cells

The role of tissue stem cells in prostate disease is both an old and revised concept. Prostate stem cells are believed to be able to differentiate and re-supply the different cell sub-populations within the epithelial layers. Their location is most likely to be in the basal layer, often at the base of a budding region or branching point (67). However, the most recent single cell expression data (68) implies a common stem-like role for various populations of luminal cells, based initially on biological studies in mice, but latterly extended to autopsy material from human prostates. The role of stem cells in prostate cancer has been extensively researched, and in BPH their importance was first proposed as long ago as 1989. Isaacs and Coffey suggested that BPH may be explained by an increase in the overall number of stem cells or an increase in the proportion of them which differentiated into transit-amplifying cells, leading to hyperplasia of the prostate (69). A recent hypothesis to link these mechanisms involves the recruitment of

bone marrow derived mesenchymal stem cells into the prostate transition zone (TZ). When exposed to urinary components and antigens, an inflammation state develops in the TZ microenvironment, leading to an infiltration of these stem cells. These MSC cells, under the influence of inflammatory growth factors and cytokines, differentiate into smooth muscle cells within the prostate stroma. The new smooth muscle cells replace the native smooth muscle cells of the periurethral area, which suppress the epithelial stem cells located in niches of the basal layer of prostatic glands of the transition zone. This initiates a paracrine stroma induced epithelial benign hyperplastic process, where the epithelial stem cells undergo neoplastic benign expansion, leading to nodular BPH (70), i.e. a reawakening of such of the process seen in the embryonic prostate. Added to this, stem cell-like properties have been found within the stroma of BPH tissues (71). Single cell sequencing has recently confirmed the essential role to be played by stromally encoded factors in the hyperproliferation in both prostate gland regeneration after reversal of castration, and indeed in a distinct luminal population in BPH (68). However, no follow up studies have been able to show whether these cells cause BPH, until recent work on telomerase in different prostate cell subpopulations has revealed details of epithelial cell lineages in BPH.

Role of telomerase

The enzyme complex Telomerase adds “TTAGGG” DNA base repeats onto telomere regions to maintain them above a critical size limit for mitotic division. An increase in Telomerase activity has been detected within 70-90% of human cancers, including prostate cancer (72).

Telomere length and telomerase activity are both higher in prostate cancer than normal tissue (73). However in BPH, whilst there is a higher proliferative index (74) (compared to normal), telomere length has been found to be normal or slightly longer than normal matched controls, and total telomerase activity is absent or very weak (72, 73). This paradox could be explained by the heterogeneity of telomerase activity in different cell subpopulations. Telomerase activity is generally considered to reside principally in

stem cells and the transient amplifying cells, rather than the more differentiated basal and luminal cells of the prostate. Rane et al argued that previous studies were only able to demonstrate variable and low telomerase activity within BPH, as heterogeneous BPH "whole" tissue samples consist mostly of differentiated basal and luminal cells (>95%)(75).

When telomere length and activity levels of telomerase in each of these different subpopulations were quantified, in normal prostate tissue, no telomerase activity was seen in any of the subpopulation types. In the prostate, it is hypothesised that a small population of stem cells act as reservoir to re-supply more differentiated cells that have died or been lost to injury. The stem cells lie at the base of a hierarchy where they divide asymmetrically to produce a new stem cell and a tissue regenerating transient amplifying cell (TA). TA cells in turn differentiate into committed basal (CB) cells, which then replace luminal (L) cells when they are lost (76). However, in BPH, significantly higher levels of telomerase were seen in both stem and TA cells compared to CB and luminal cells (75), whilst no telomerase activity was seen in stromal cells. This implies that the "driver' cells behind the hyperplasia could be the stem and TA cells and that telomerase activity is not essential for stromal hyperproliferation in BPH, although no attempt was made to identify a telomerase phenotype of the mesenchymal stem cells from which the stromal population is derived.

When telomere length was measured in the different subpopulations, as expected the stem and TA cells had longer telomeres compared to their immediate differentiated progeny, the telomerase-negative CB cells. However the telomerase negative luminal cells also had longer telomere lengths, similar to those of the stem and TA cells and were always longer than those in patient matched CB cells (75).

However, these luminal cells are believed to be derived from CB cells, but as telomere lengths in luminal cells are longer than CBs where there is no telomerase activity, this has led to the proposal that luminal and CBs may derive from distinct progenitors. The proposed existence of luminal precursors (68, 77) provides a further explanation for this, but cannot resolve the absence of telomere maintenance mechanisms in the

luminal cells, unless an alternative mechanism is invoked (ALT - as seen in some prostate cancer cell lines (78), in the luminal precursor populations.

To test this hypothesis, Rane et al performed an immunohistochemical analysis of the different cell types in BPH tissue. Figure 3 shows distinct areas of basal and luminal hyperproliferation occurring independently and even together (75), which supports their statement that two distinct progenitors may exist in the prostate.

This data agrees with studies from the 1990's by Bonkoff and McNeal, which showed that the basal layer was the only layer in which proliferation took place in BPH and that the luminal progenitors derived from stem cells in this layer displayed characteristics of both luminal and basal phenotypes.

A cellular population with these properties was recently identified by Karthaus et al, linking the theories of distinct progenitor lineages and stem/mesenchymal cells, using single cell RNA sequencing to demonstrate that after androgen ablation and then restoration, prostate regeneration was driven by subpopulations with distinct stem cell and more differentiated luminal cell phenotypes. *In vitro,* this process occurred via growth factor expression from mesenchymal cells acting on luminal cells in a paracrine fashion (68), as discussed earlier.

Thus in BPH, mesenchymal induced stem cells may be recruited to the prostate by basal and luminal progenitors under the influence of these growth factors, resulting in proliferation of both or either of the stromal and epithelial cell layers.

Since such excessive proliferation would ultimately exhaust telomeres in the absence of detectable renewal mechanisms, local inhibition of telomerase may be an alternative therapeutic BPH target, as it would limit the proliferation of both luminal and basal progenitors.

Implications for current treatment modalities

A surgical approach via prostate tissue resection, vaporisation or enucleation remains the gold standard of treatment for the benign prostatic obstruction of the urethra, normally for severe symptoms or disease complications. Surgery is not without risk,

with the main problems being infection, incontinence, ejaculatory dysfunction and impotence. Minimal invasive procedures are an emerging treatment arm for BPH. Patients within this arm normally have symptoms that are not responding to medical therapies but do not wish to undergo invasive surgical procedures or are not medically fit to undergo them, however not completely risk free, with reports of urinary retention, urge incontinence and pelvic pain post procedure for all methods (79).

Due to these risks, with milder symptoms, medical therapy is the first option. The treatment involves either as a monotherapy or as a combination of alpha-blockers and 5ARIs. Both these treatments have been recommended for over 20 years (80).

Alpha blockers such Tamsulosin and Alfuzosin, act on the smooth muscle within the prostatic urethra, relaxing it, enabling better flow of urine. 5-ARIs such as Finasteride and Dutasteride, inhibit the conversion of testosterone to dihydrotestosterone and decrease the impact of androgen receptor (AR) on cell proliferation. The combination of these two groups together has been shown to improve overall symptoms (81).

There are however problems with both treatments. Alpha-blockers do not treat any area of disease initiation/causation, so after 2 years of treatment their efficacy can be seen to decrease (82). They also have side effects such as postural hypertension and retrograde ejaculation.

5-Alpha reductase inhibitors clinically take a substantial time to show effect, normally 6 to 9 months. The reasons for this are discussed above, which include; the overall dependence of BPH on androgens, the targeting of the wrong “driver” cell population and the independence of growth factor release in chronic inflammation seen in BPH (figure 1). Furthermore, the activation of the nuclear factor-kappa B pathway by inflammation, induces overexpression of androgen receptor variant type 7. This AR variant is associated with increased disease severity and provides a mechanism for patient resistance to 5-ARI treatment (83).
Added to this, they have a significant side effect profile of erectile dysfunction, decreased libido and decreased ejaculate volume (84). Also, their use in men with BPH with undetectable cancers has been brought into perspective by some negative

outcomes in the REDUCE and PCPT trials in the USA (85). Based on this data, any underlying high-grade prostate cancer (in addition to BPH) would be likely to progress faster to malignant and fatal disease, as a result of this treatment for non-fatal BPH by 5ARIs. There is also some evidence that long-term use of 5aR inhibitors can have significant side effects for men. These include the loss of sexual function, neurological and psychological problems, sometimes persisting even after the treatment has been stopped (86).

Conclusion

With years of research into the pathological process of BPH, we are still far from having a definite answer for the initiating and maintaining factor(s) for this disease. Current treatment has not changed for a number of years, despite the fact that the mechanism of the disease has yet to be proven and there is lengthy delay seen in clinical benefit from treatment. As highlighted above, this disease will most likely impose a significant burden on patients and healthcare services in the future, so new research into finding the driving factor(s) behind this common and neglected disease to discover new treatment avenues is imperative.

Author Contributions

Each named author has substantially contributed to conducting the underlying research and drafting this manuscript.

Conflicts of Interest

To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

References:

1. Bostwick D. The Pathology of Benign Prostatic Hyperplasia. Kirby P, McConnell J, Fitzpatrick J, editors. London Isis Medical Media 2002.

2. Uson A, Paez A, Uson-Jaeger J. The natural history and course of untreateed benign prostatic hyperplasia Eur Urol. 1991;20(1):22-6.

3. Berry S, Coffey D, Walsh P, Ewing L. The development of human benign prostatic hyperplasia with age. J Urol. 1984;132:474-9.

4. Speakman M, Kirby R, Doyle S, Ioannou C. Burden of male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH)- focus on the UK. BJU Int. 2015;115:508-19.

5. Logie J, Clifford G, Farmer R. Incidence, prevalance and management of lower urinary tract symptoms in men in the UK. BJU Int. 2005;95:557-62.

6. Lee S, Chan E, Lai Y. The global burden of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: A systematic review and meta-analysis. . Sci Rep. 2017;7(1):7984.

7. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224-60.

8. Johnson T, Abbasi A, Ehrlich S, et a. Major depression drives severity of American Urological Assocation Symptom Index. Urology. 2010;76:1317-20.

9. Hernandez C, Estivill E, Prieto M, Badia X. Noctuira in spanish patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). Curr Med Res Opin. 2008;24:1033-8.

10. Roehrborn C, Marks L, Harkaway R. Enlarged prostate: a landmark national survery of its prevalence and impact on US men and their partners. . Prostate Cancer Prostatic Dis. 2006;9:30-4.

11. Pesonen JS, Vernooij RWM, Cartwright R, Aoki Y, Agarwal A, Mangera A, et al. The Impact of Nocturia on Falls and Fractures: A Systematic Review and Meta-Analysis. J Urol. 2020;203(4):674-83.

12. vanExcel N, Koopmanschap M, Mcdonnell J, Chapple C, Berges R, Rutten F. Medical consumption and costs during one-year follow-up of patients with LUTS

suggestive of BPH in six european countries:report of the TRIUMPH study. Eur Urol. 2006;49:92-102.
13. Nash J. Benign prostatic hyperplasia: prevalence and diagnosis. GM Journal. 2010;40(June):321-4.
14. Partin AW, Page WF, Lee BR, Sanda MG, Miller RN, Walsh PC. Concordance rates for benign prostatic disease among twins suggest hereditary influence. Urology. 1994;44(5):646-50.
15. Sanda MG, Beaty TH, Stutzman RE, Childs B, Walsh PC. Genetic susceptibility of benign prostatic hyperplasia. J Urol. 1994;152(1):115-9.
16. Aly MS, Dal Cin P, Van de Voorde W, van Poppel H, Ameye F, Baert L, et al. Chromosome abnormalities in benign prostatic hyperplasia. Genes Chromosomes Cancer. 1994;9(4):227-33.
17. Salam MT, Ursin G, Skinner EC, Dessissa T, Reichardt JK. Associations between polymorphisms in the steroid 5-alpha reductase type II (SRD5A2) gene and benign prostatic hyperplasia and prostate cancer. Urol Oncol. 2005;23(4):246-53.
18. Qi J, Tian L, Chen Z, Wang L, Tao S, Gu X, et al. Genetic variants in 2q31 and 5p15 are associated with aggressive benign prostatic hyperplasia in a Chinese population. Prostate. 2013;73(11):1182-90.
19. Giri A, Edwards TL, Motley SS, Byerly SH, Fowke JH. Genetic Determinants of Metabolism and Benign Prostate Enlargement: Associations with Prostate Volume. PLoS One. 2015;10(7):e0132028.
20. Hellwege JN, Stallings S, Torstenson ES, Carroll R, Borthwick KM, Brilliant MH, et al. Heritability and genome-wide association study of benign prostatic hyperplasia (BPH) in the eMERGE network. Sci Rep. 2019;9(1):6077.
21. Masai M, et-al. Immunohistochemical study of androgen receptor in benign hyperplastic and canerous human prostate. Prostate 1990;17:293-300.
22. Song L, Shen W, Zhang H, Wang Q, Wang Y, Zhou Z. Differential expression of androgen, estrogen and progesterone receptors in benign prostatic hyperplasia. . Bosn J Basic Med Sci. 2016;16:201-8.
23. Ho C, Habib F. Estrogen and androgen signaling in the pathogenesis of BPH Nat Rev Urol. 2011;8:29-41.

24. Imperato-McGinely J, et-al. Prostate visualisation studies in males homozygous and heterozygous for 5 alpha reductase deficiency. J Clin Endocrinol Metab. 1992;75:1022-6.
25. Lenzi A. Epidemiology, diagnosis and treatment of male hypogonadotrophic hypogonadism. J Endocrinol Invest. 2009;32:934-8.
26. Vignozzi L, et-al. Benign prostatic hyperplasia new metabolic disease? J Endrocrinol Invest. 2014;37:313-22.
27. Siiteri P, Wilson J. Dihydrotestosterone in prostatic hypertrophy. The formation and content of dihydrotestosterone in the hypertrophic prostate of man. . J Clin Invest. 1970;49:1737-45.
28. Morgentaler A, Traish A. Shifting the paradigm of testosterone and prostae cancer: the saturation model and the limits of androgen-dependant growth. Eur Urol. 2009;55:310-20.
29. Thorson P, et-al. Basal cell hyperplasia in the peripheral zone of the prostate. Mod Pathol. 2003;16(6):598-606.
30. Edwards J, Moore R. Finasteride in the treatment of clinical benign prostatic hyperplasia:a systematic review of randomised trials. BMC Urol. 2002;2:14.
31. McPherson S, et-al. Estrogen receptor-beta activated apoptosis in bengin hyperplasia and cancer of the prostate is androgen independant and TNFaplha mediated. Proc Natl Acad Sci USA. 2010;107(3123-3128).
32. Simpson E, et-al. Aromatase cytochrome P450, the enzyme responsible for estrogen biosyntheis. Endocr Rev. 1994;15:342-55.
33. Muraleedharan V, Jones TH. Testosterone and the metabolic syndrome. Ther Adv Endocrinol Metab. 2010;1(5):207-23.
34. Chen Z, Miao l, Gao X, wang G, Xu Y. Effect of obesity and hyperglycemia on benign prostatic hyperplasia in elderly patients with newly diagnosed type 2 diabetes. . International journal of clinical and experimental medicine. 2015;8(7):11289-94.
35. Roberts R, et-al. Serum sex hormones and measures of benign prostatic hyperplasia. Prostate 2004;61(124-131).
36. Nicholson T, Ricke W. Androgens and estrogens in benign prostatic hyperplasia: past, present and future Differentiation. 2011;82:184-99.

37. Shao R. Epithelial-to-mesenchymal transition and estrogen receptor aplha mediated epithelial dedifferentation mark the development of benign prostatic hyperplasia. Prostate. 2014;74:970-82.
38. Hiramatsu M, et-al. Aromatase in hyperplasia and carcinoma of the human prostate Prostate. 1997;31:118-24.
39. Nomura H, et-al. Effect of selective estorgen receptor modulators on cell proliferation and estrogen receptor activities in normal human prostate stromal and epithelial cells. . Prostate Cancer Prostatic Dis. 2009;12:375-81.
40. Nandeesha H, Koner B, Dorairajan L, Sen S. Hyperinsulinema and dyslipidermia in non-diabetic beign prostatic hyperplasia Clin Chim Acta. 2006;370:89-93.
41. Celmmons D, Malie L. Interaction between insulin-like growth factor-1 receptor and aplhaVbeta 3 intergrin linked signaling pathways:cellualr responses to changes in multiple signaling inputs. Mol Endocrinol. 2005;19(1):1-11.
42. Li W, Wu C, Febbo P, Olumi A. Stromally expressed c-Jun regulates proliferation of prostate epithelial cells. . Am J Pathol. 2007;171(4):1189-98.
43. Sreenivasulu K, et-al. Elevated insulin and reduced insulin like growth factor binding protein-3/ prostate specific antigen ration with increase in prostate size in benign prostatic hyperplasia Clinca Chimica Acta. 2017;469:37-41.
44. Wang Z. Meformin inhibits the proliferation of benign prostatic epithelial cells. . Plos one. 2017 Mar 2;12(3):e0173335.
45. Ficarra V, et-al. The role of inflammation in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and its potential impact on medical therapy. Curr Urol Rep. 2014;15(12):463-9.
46. LaVignera S, Condorelli RA, Russo GI, Morgia G, Calogero A. Endocrine control of benign prostatic hyperplasia. Andrology. 2016;4:404-11.
47. Giri D, Ittmann M. Interleukin-1alpha is a paracrine inducer of FGF7, a key epithelial growth factor in benign prostatic hyperplasia. Am J Pathol. 2000;157:249-55.
48. Sampson N, et-al. Stromal insulin-like growth factor binding protein 3 (IGFBP£) is elevated in the diseased human prostate and promotes ex vivo fibroblast-to-myofibroblast differentiation. Endocrinology. 2013;154:2586-99.
49. Xu D, Wang X, Jiang C, Ruan Y, Xia S, Wang X. The adrogen recpeptor plays different roles in the macrophage-induced proliferation in prostate stromal cells

between transitional and peripheral zones of benign prostatic hypertrophy EXCLI Journal. 2017;16:939-48.

50. Nickel J, et-al. The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial. Eur Urol. 2008;54:1379-84.

51. DeNunzio C, et-al. The controverial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation. . Eur Urol. 2011;60:106-17.

52. Steiner G, et-al. Expressiomn and function of pro-inflammatory interleukin IL-17 and IL-17 receptor in normal, benign hyperplastic and malignant prostate. Prostate 2003;56:171-82.

53. Ficarra V, et-al. Why and how to evaluate chronic prostatic inflammation Eur Urol Suppl. 2013;12:110-5.

54. Handisurya A, et-al. Differential expression of interleukin-15, pro-inflammatory cytokine and T-cell growth factor and it's receptor in human prostate. Prostate. 2001;49:251-62.

55. Royuela M, et-al. Interferon- gamma and its functional receptors overexpression in benign prostatic hyperplasia and prostatic carcinoma: parallelism with c-myc and p53 expression Eur Cytokine Netw 2000(11):119-27.

56. Wang L, et-al. Chronic inflammation in benign prostatic hyperplasia: implications for thearpy. Med Hypotheses. 2008;70:1021-3.

57. Robert G, et-al. Inflammation in benign prostatic hyperplasia: a 282 patients' immunohistochemical analysis. . Prostate. 2009;69:1774-80.

58. Kramer G, Mitteregger D, Marberger M. Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? European Urology. 2007;51(5):1202-16.

59. Wang W, Bergh A, Damber JE. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2, and cell proliferation in the glandular epithelium. Prostate. 2004;61(1):60-72.

60. Minnery CH, Getzenberg RH. Benign prostatic hyperplasia cell line viability and modulation of jm-27 by doxazosin and Ibuprofen. J Urol. 2005;174(1):375-9.

61. Ishiguro H, Kawahara T. Nonsteroidal anti-inflammatory drugs and prostatic diseases. Biomed Res Int. 2014;2014:436123.

62. Eleazu C, Eleazu K, Kalu W. Management of Benign Prostatic Hyperplasia: Could Dietary Polyphenols Be an Alternative to Existing Therapies? Front Pharmacol. 2017;8:234.

63. Chughtai B, Lee R, Te A, Kaplan S. Role of inflammation in benign prostatic hyperplasia. Rev Urol. 2011;13(3):147-50.

64. Schwarz S, Obermuller-Jevic UC, Hellmis E, Koch W, Jacobi G, Biesalski HK. Lycopene inhibits disease progression in patients with benign prostate hyperplasia. J Nutr. 2008;138(1):49-53.

65. McNeal J. Origin and evolution of benign prostatic enlargement Invest Urol 1978;15:340-5.

66. Habib F. Benign prostatic hyperplasia Chisholm G, editor. New York: Raven press; 1994.

67. Maitland N. Stem cells in the normal and malignant prostate In: Tindall D, editor. Prostate cancer: biochemistry, molecular biology and genetics: Mayo clinic; 2013.

68. Karthaus WR, Hofree M, Choi D, Linton EL, Turkekul M, Bejnood A, et al. Regenerative potential of prostate luminal cells revealed by single-cell analysis. Science. 2020;368(6490):497-505.

69. Isaacs J, Coffey D. Etiology and disease process of benign prostatic hyperplasia. Prostate Suppl. 1989;2:33-50.

70. Brennen WN, Isaacs JT. Mesenchymal stem cells and the embryonic reawakening theory of BPH. Nat Rev Urol. 2018;15(11):703-15.

71. Lin V, et-al. Prostatic stromal cells derived from benign prostatic hyperplasia specimens possess stem cell like property. Prostate. 2007;267(12):1265-76.

72. Meeker A. Telomeres and telomerase in prostatic intraepithelial neoplasia and prostate cancer biology. . Urol Oncol. 2006;24:122-30.

73. Zhang W, et-al. Telomerase activity in prostate cancer, prostatic intraepithelial neoplasia and benign prostatic epithelium. Cancer Res. 1998;58(619-621).

74. Kyprianou N, Tu H, Jacobs S. Apoptotic versus proliferative activites in human benign prostatic hyperplasia Hum Pathol. 1996;27:668-75.

75. Rane J, et-al. Telomerase activity and telomere length in human benign prostatic hyperplasia Stem-like cells and their progeny implies the existence of distinct basal and luminal cell lineages. Eur Urol. 2016;69(4):551-4.

76. Richardson G, et-al. CD133, a novel marker for human prostatic epithelial stem cells. Journal of Cell Science. 2004;177:3539-45.
77. Ousset M, Van Keymeulen A, Bouvencourt G, Sharma N, Achouri Y, Simons BD, et al. Multipotent and unipotent progenitors contribute to prostate postnatal development. Nat Cell Biol. 2012;14(11):1131-8.
78. Graham MK, Kim J, Da J, Brosnan-Cashman JA, Rizzo A, Baena Del Valle JA, et al. Functional Loss of ATRX and TERC Activates Alternative Lengthening of Telomeres (ALT) in LAPC4 Prostate Cancer Cells. Mol Cancer Res. 2019;17(12):2480-91.
79. Pham H, Sharma P. Emerging, newly-approved treatments for lower urinary tract symptoms secondary to benign prostatic hypertrophy. . Can J Urol. 2018;25(2):9228-37.
80. Vela-Navarrete R, et-al. The impact of medical therapy on surgery for benign prostatic hyperplasia: a study comparing changes in a decade (1992-2002). BJU Int. 2005;96(7):1045-8.
81. Oelke M, et-al. Guidelines in the mamagement of male lower urinary tract symptoms (LUTS) incl. benign prostatic obstruction (BPO) http://www.uroweb.org [
82. Madersbacher S, et-al. The longterm outcome of medical therapy for BPH. Eur Urol. 2007;51:1522-33.
83. Austin DC, Strand DW, Love HL, Franco OE, Jang A, Grabowska MM, et al. NF-kappaB and androgen receptor variant expression correlate with human BPH progression. Prostate. 2016;76(5):491-511.
84. Fullhase C, et-al. Systematic review of combination drug therapy for nonneurogenic male lower urinary tract symptoms. . Eur Urol. 2013;64:228-43.
85. Pinsky P, Black A, et-al. Projecting prostate cancer mortaility in the PCPT and REDUCE chemoprevention trials. Cancer Res. 2013;119(3):593-601.
86. Traish A. The impact of the 5-alpha-reductase inhibitors on male sexual function and psychological wellbeing. . Current sexual health reports 2015;7(4):2010-9.

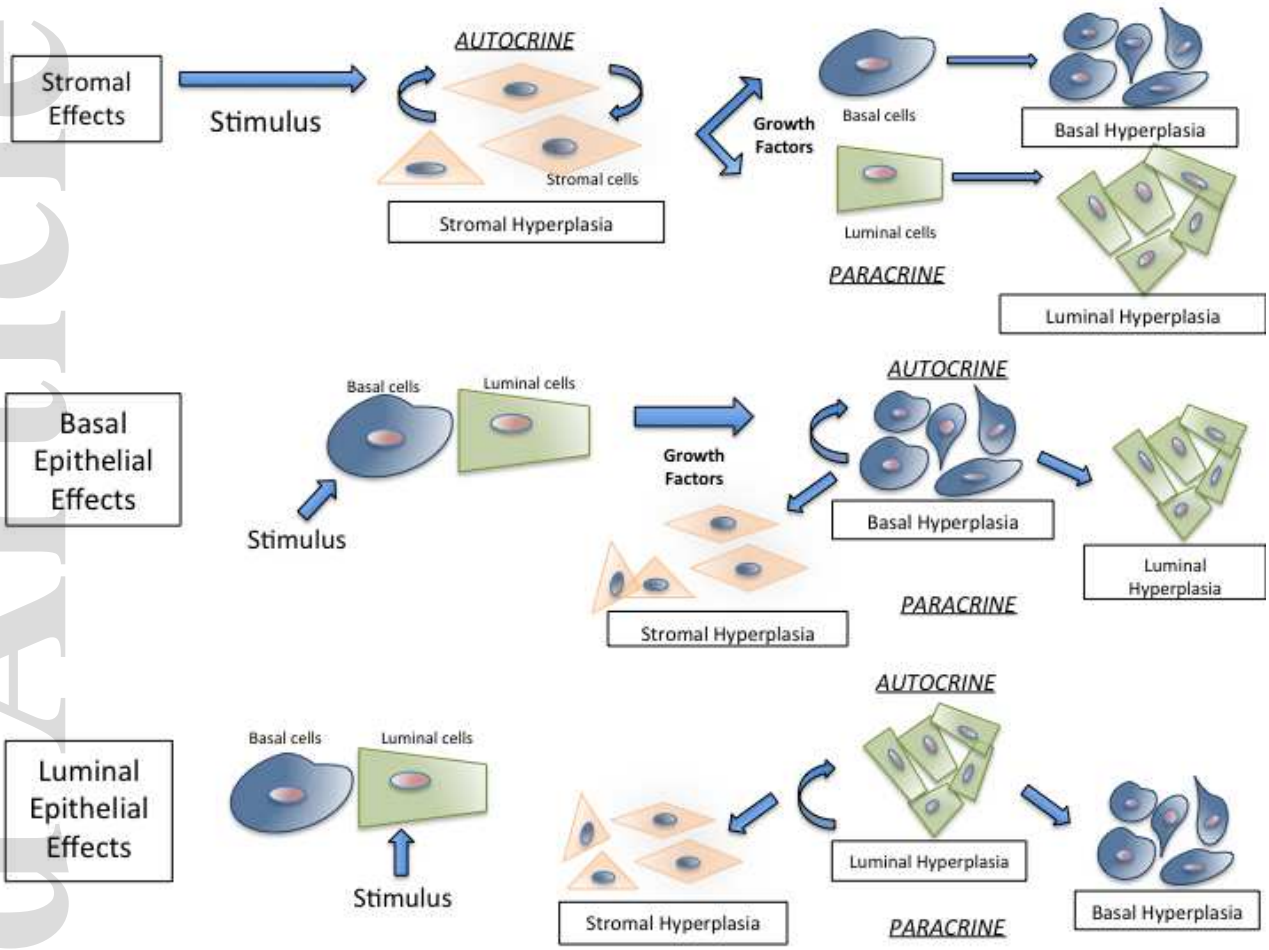

Figure 1: Multiple consequences of an external Growth stimulus on pre-hyperplastic tissues in the prostate.

Inhibition of either the original stimulus, or the secondary messenger growth factors (or hormones) would provide a novel and effective treatment for BPH.

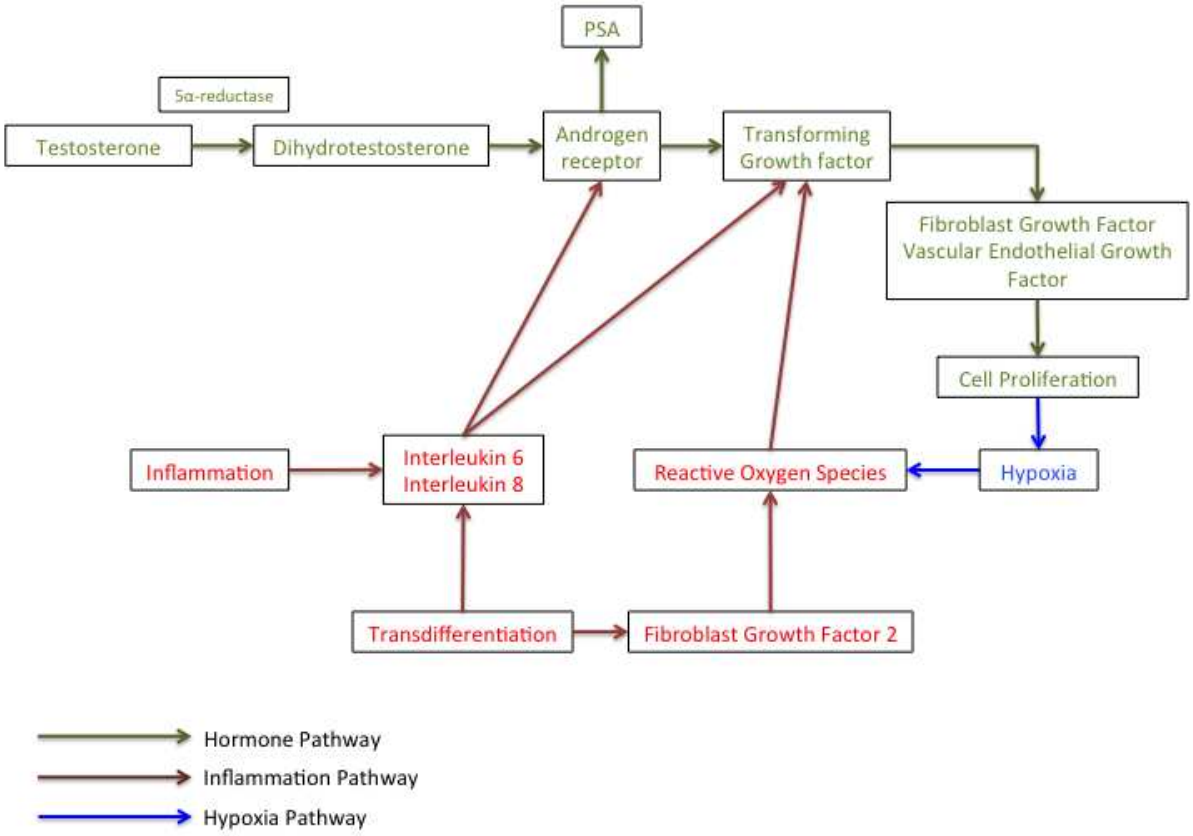

Figure 2: Adpated from Ficarra et al 2014. The self-perpetuating cycle of inflammation and how it can lead to hyperplasia and BPH (47).

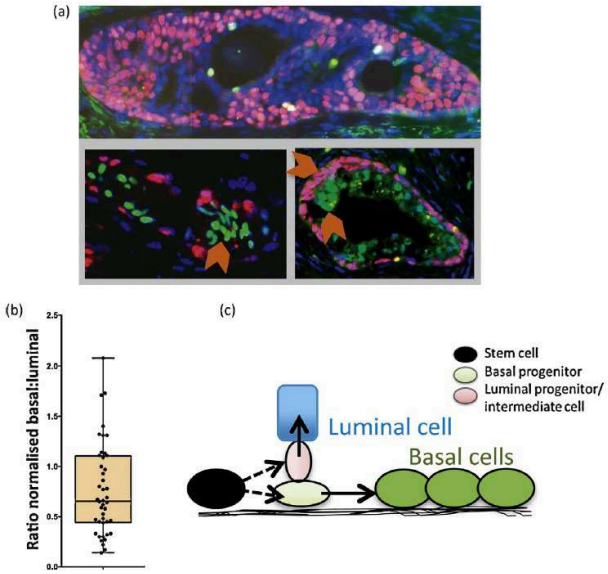

Figure 3: The heterogeneity of human BPH tissues, showing overgrowth of basal and luminal cells (figures A and B) and the hypothesis from this study: the presence of separate basal and luminal progenitors in BPH (62) (Used with permission from Rane et al, 2016)