9

Review Article

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Mechanistic targets for BPH and prostate cancer—a review

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Abstract: All men, almost, suffer from prostatic disorders in average life expectancy. In the year of 1950s, the first autopsy of prostate gland discovered the link between Benign prostatic hyperplasia (BPH) and Prostate Cancer (PCa). After that, many histology, biochemistry, epidemiology studies explained the association and associated risk factor for the same. From the various scientific evidence, it is proved that both diseases share some common transcription factors and signalling pathways. Still, BPH cannot be considered as the first step of PCa progression. To define, the relationship between both of the diseases, a well-defined large epidemiological study is needed. Along with androgen signalling, imbalanced apoptosis, oxidative stress, and microbial infection also crucial factors that significantly affect the pathogenesis of BPH. Various signalling pathways are involved in the progression of BPH. Androgen signalling is the driving force for the progress of PCa. In PCa androgen signalling is upregulated as compared to a healthy prostate. Some dominant Androgen-regulated genes and their functions have been discussed in this work.

Keywords: androgen signalling; BPH; FKBP5; prostate cancer; TGF β signalling.

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Introduction

In the year of 1950s, the first autopsy of prostate gland discovered the link between BPH and PCa [1]. After that, many histology, biochemistry, epidemiology studies explained the association and associated risk factor for the same [2]. Till date, it remains a controversial issue and remains uncertain whether this association is due to common risk factors or pathophysiological mechanisms. In the new scenario, it is broadly accepted that, even though both the diseases exist together generally, BPH is proven to be not a non-cancerous lesion [3]. BPH is histologically characterized by stromal hyperplasia with subsequent nodule formation. PCa is an adenocarcinoma mainly arise in prostate gland from epithelial cells; localized in the peripheral zone [4]. Although BPH and PCa have some common characteristics like hormone dependency and pharmacological effect to androgen antagonist agents (Table 1) [5]. Chronic inflammation, metabolic disruption, and genetic variation have an impact in both conditions.

Associated risks with BPH and PCa [5]

- BPH and PCa both are arising due to chronic inflammation. However, anti-inflammatory drugs are ineffective to reduce the risk of either disease
- Metabolic factor-like Insulin growth factors and high content of triglyceride—are associated with the development of BPH and PCa. However, several studies proposed that the two ailments can be said to belong to metabolic syndrome.
- Androgens are required for the BPH and PCa. Antiandrogens are one of the best therapeutic options to reduces lower urinary tract syndrome (LUTS) and PCa.
- Even though genetic variants are believed to be linked with BPH and PCa, the genetic markers of ailments are not available in practical clinical aspect.

From the various scientific evidence, it is proved that both diseases share some common transcription factors and

Table 1: Comparison of general characteristics of BPH and Prostate Cancer.

Sr. No.	ВРН	Prostate cancer
1	Non-malignant type - cells are localized with increased size	May be malignant type – Cancer cells with multiplication and spreading ability can be observed
2	Prostate central area shows maximum affected zone	The affected zone observed is at sides of prostate
3	PSA elevated	PSA and alkaline phosphatase elevated
4	Symptomatic treatments with many options are available	Patients health and stage of cancer decides the treatment
5	Inflammation present in majority of cases in biopsies	Here also inflammation present in majority of cases in biopsies
6	Part of the metabolic syndrome	Part of metabolic syndrome
7	Antiandrogens used to pre- vent lower urinary tract symptoms	Antiandrogens used to prevent risk of prostate cancer

signalling pathways. Still, BPH cannot be considered as the first step of PCa progression. To define, the relationship between both of the disease, a well-defined large epidemiological study is needed. The precise contribution of each factor like prostate-specific antigen (PSA) analysis, evaluation of biopsies, staging, and risk of PCa is recommended to understand the intricate pathways connecting BPH and PCa (Table 2) [6].

There is limited evidence on the possible effect on blood cells count in prostate cancer and Benign Prostate Hyperplasia patients. However, Kazutoshi Fujita; et al. (2014) reported that, WBC count and neutrophil count are positively associated with prostate enlargement and BPH [11]. An increased WBC count reveals the systemic inflammations associated with prostate enlargement and lower urinary tract symptoms. In another investigation, Yasemin Benderli Cihan et al. (2014) examined the haematological parameters in 160 PCa patients and 285 patients with pathological BPH. PCa patients shown lower level of lymphocytes, neutrophils and WBCs and a higher level of monocytes with a significant difference in lymphocyte count, compared to healthy and BPH patients [12].

The development of metastatic prostate cancer is dependent on the macrophages and tumor cell interactions. This leads to androgen resistance and invasion of cancerous cells to other organs. Another study, on aged mice proved the role of macrophages, the known immune cells involved in PCa development [13].

Table 2: Common genetic Functions shared between BPH and PCa.

Sr. No.	Functions	Remarks
1	Androgen conversion genes (SRDAR2)	It gives a strong rational to use 5α-reductase inhibitors as a regimen against BPH [7].
2	Synthesis of andro- gens (CYP 17)	The correlation does not exists between PCa, BPH and normal prostate for CYP17 gene polymorphism [8].
3	Degradation of andro- gens (CYP 19)	The study conducted in african population revealed that CYP 19 and prostate cancer has no correlation. Different type of modelling have been used to prove the same [9].
4	Cell cycle and apoptosis genes (14-3-3α)	The genes involved in cell cycle and apoptosis are hypermethylated in BPH and PCa. This finding suggest that there is link of epigenetics in BPH and PCa [6].
5	Tumour suppressor gene (RASSF1A)	The iranian men study on prostate cancer had the genes involved like GSTP1, RASSF1, DNMT3B and DNMT3A. These genes are targets for cancer hormone therapy as studied in other population [10].

Tim-3 (T-cell immunoglobulin domain and mucin domain-containing molecule 3) is a newly discovered immunomodulatory protein. Tim-3 is key player for immunity. A study conducted on PCa and BPH prostate samples showed that Tim-3 staining was observed in PCa but not in BPH, in immunohistochemistry experiments. Tim-3 is said to be responsible for progression of PCa but experimental evidence is lacking for same. If it is true, then Tim-3 can be a novel target for treatment of PCa [14].

Benign prostatic hyperplasia (BPH)

In ageing males, the lower urinary tract symptoms (LUTS) develops as a significant symptom of BPH. LUTS involves mal-adaptive storage and emptying stage and incomplete bladder emptying as the post micturition signs. LUTS is a progressive and age-related pathophysiological condition with nonspecific symptoms and impairs quality of life [15]. Traditionally, LUTS arises due to bladder outlet obstruction (BOO), which leads to benign prostatic obstruction (BPO) and further result in the histological condition of BPH. Hyperplasia is different from hypertrophy; in hypertrophy, the size of cells gets increased while in hyperplasia cells count increases. The pathophysiological origin involves enhanced cell proliferation along with a reduction in cell death [16].

Hormonal regulation in BPH

Androgen-signalling cascade includes four primary steps as (1) testes and adrenal glands synthesis testosterone (T); (2) Dihydrotestosterone (DHT) formation from testosterone; (3) DHT is transferred to specific tissues of choice; and (4) interaction of DHT to AR receptors affecting gene expression [17]. Testosterone is converted to DHT under the influence of the 5- α -reductase enzyme. There are two different forms of 5-α-reductase isoenzymes as I and II. As per reported experimental results, type 1isoenzyme was predominant in epithelial cells and type 2 isoform found in stromal and epithelial cells [18].

There are organ-specific differences in the expression I and II isoenzyme. Type - I isoenzyme is present in sebaceous glands. Whereas, type II isoenzyme is localized in the prostate, epididymis, testes, gubernaculum and corpus cavernosum [19], five α -Reductase enzyme, DHT, and AR are found in epithelial and stromal cells of the gland [20]. DHT possesses a different mode of action on prostate cells and works by an endocrine, paracrine, or autocrine mechanism(Figure 1) [21, 22].

- In the endocrine mechanism, a hormone-like DHT synthesized by organs other than prostate reaches to AR in the stroma via circulation.
- In the paracrine mechanism, DHT formed in the stroma region can diffuse into neighbouring stromal and epithelial cells to perform their action.
- In the autocrine mechanism, the hormone-releasing and target cells both are same. In the case of DHT and its mediators like growth factors, impact their cellular function by the paracrine or autocrine pathway.

Role of androgen in BPH

It is well-known that BPH arises due to stromal and epithelial interactions, under the influence of androgens. Several experimental results reveal, that, BPH originated from the prostatic cell imbalance, i.e. cellular propagation and death. Due to fibroblast growth factor (bFGF/FGF), Insulin-like growth factors (IGFs), Epidermal Growth Factor (EGF), Transforming growth factor (TGF-b), Vascular Endothelial Growth Factor (VEGF) and release of inflammatory mediators such as interleukin 1 (IL-1), IL-6, and tumour necrosis factor-a (TNF-a), growth factors, and chemotactic factors. Along with it, imbalanced apoptosis, oxidative stress, and microbial infection also key factors that significantly affect the pathogenesis of BPH. Various signalling pathways, as mentioned below:

Fibroblast growth factor signalling

The basic Fibroblast Growth Factor (bFGF/FGF) was isolated from the prostate. It was the first growth factor to be isolated [23]. Fibroblast growth factors (FGFs) and associated receptors (FGFRs) are responsible for the development of the prostate gland and overexpressed in BPH.FGFs interact with the tyrosine kinases receptors from FGFR1 to FGFR4 to perform various cellular responses [24]. In the human prostate, FGFR1-3 profusely found to be expressed in the stromal and epithelial cells of gland, and FGFR4 has moderately expressed in the epithelial cells [25]. The large number of FGF are involved in the benign and malignant growth of prostates like FGF1, 2, 3, 7 (KGF), and 8. FGFs is responsible for the mitosis in epithelium and stroma, except KGF, that synthesized by cells of stroma and excites epithelium. In BPH, bFGF expression enhanced by 2-3-fold in comparison to normal prostate [26-28].

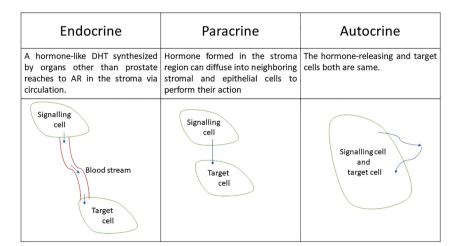


Figure 1: Different hormonal signalling mechanism.

Insulin-like growth factors (IGFs) signalling mechanism

IGF-I and IGF-II act in an either autocrine or paracrine fashion. This process maintains prostate homeostasis. The liver synthesizes IGFs via growth hormone (GH) signalling. It mediates cellular responses by interacting with two types of receptors, like, type 1 (IGFR1) and type 2 (IGFR2) IGF receptors. However, IGFR1 is involved in mitogenic and antiapoptotic effects, with intrinsic tyrosine activity. Hyperinsulinemia, it excites the liver for more production of IGF-I and subsequently leads to the hyperproliferation of stroma and epithelium and hence, prostate gland increase in size [29]. However, in some studies, DHT may increase gene and protein expression of IGF-II, particularly the region of periurethral. The place from which the BPH originates. Therefore IGF-II may be one of the mediators responsible for BPH [30].

Epidermal growth factor (EGF) signalling mechanism

The seminal plasma secreted by prostate gland contains high levels of epidermal growth factor (EGF). The diseases like hypogonadism or inflammation of prostate indicate reduced content of EGF in the seminal plasma. Therefore EGF levels found in seminal plasma is one of the significant biomarkers in prostate-related disorders [31]. Transforming growth factor-α (TGF-α) belongs to the EGFs class and reported to be found in the prostate. Both are mitogenic on rat prostate epithelial cells culture by binding to the basal cells surface EGF receptor (EGFR) present in the prostate [32].

Transforming growth factor (TGF-β) signalling mechanism

TGF-β is the crucial factor for the inhibitions of proliferation and alteration of apoptosis mechanism. TGF-β is an essential cytokine which performs various functions. There are three different isoforms of TGF as TGF-β 1, TGF-β 2, TGF- β 3, which performs their functions by interacting I and type II receptors (TbRI and TbRII). TGF-β-1 secreted by basal epithelial cells and possess type I and I1 receptors. It inhibits basal cell proliferation by an autocrine mechanism. In the prostate, smooth muscles release TGF-β While epithelium has receptors, modulation found here is paracrine. In normal as well as pathophysiological conditions like BPH and PCa, TGF-β I help in the regulation of basal cell in a paracrine way in the prostate gland [33, 34] TGF-β Hinders propagation of cells found in the epithelium of prostate and induces apoptosis [35, 36]. On cells of stroma, TGF-β shows dual potential. At low doses, it stimulates cell

proliferation while at higher doses, inhibition takes place [37]. It leads to the distinction of cells of stroma to cells of smooth muscle (SMCs) and favours the aggregation of SMCs in muscular nodules [38].

Vascular Endothelial Growth Factor (VEGF) signaling mechanism

Another vital aspect is the microvascularity involved in BPH. The bFGF and VEGF are responsible for angiogenesis in the gland. These are released by epithelial cells under the influence of androgens and contribute to hyperplasic growth to induce BPH [39].

Inflammatory signalling mechanism

Apart from the androgens, various inflammatory mediators are involved in the prostatic angiogenesis and an essential part of the definition related to the pathogenesis of BPH [40]. Inflammation is the primary cause of BPH affected in 70% of elderly males. The BPH nodules mainly made up of inflammatory infiltrate. Cytokines are being secreted by these cells, which is said to be promoting fibromuscular development. The mobilization of cells from inflammatory sneak into the affected part leads to enhancement in the process of cytokines production, which results in inflammation like IL-6, 8 and 15. The unknown mechanisms kill surrounding cells in the inflamed area, and fibromuscular nodules fill the spaces with Th0/Th3 type of immune response [41]. The prostate is an immunocompetent organ due to the localization of inflammatory cells, including T- and B-lymphocytes, macrophages. Mast cells and prostatic stromal cells can secrete various proinflammatory cytokines and activate CD4C cells in inflamed prostate. In most of the conditions, the immune competence of the prostate would be beneficial to the host. On the other hand, Th1/Th17 cytokine regulation is responsible for the killing of tissue seen in the BPH. AR signaling also inhibits prostate inflammation [42].

Apoptosis

Apoptosis and inflammation are the key players in the regulation of cell growth. Dysregulation of apoptosis directly linked to BPH [43]. In pathophysiological conditions of BPH increased levels of Dickkopf-related protein 3, which reduces main apoptotic proteins like B cell lymphoma (Bcl)-2 associated X protein (Bax). It further inhibits caspases activity and affects cell death by modulating nuclear factor-κΒ [44]. Pharmacotherapy and phototherapy, significantly interfere with the apoptosis can be an alternate therapy for BPH [45].

Shah et al.: BPH v/s. PCa - Targets — 265

Oxidative stress

Oxidative stress leads to impaired cellular proliferation and hyperplasic cell growth. In BPH patients, free radical generation is reflected by increased Glutathione S-transferases (GST) activity while tissue damage due to impaired oxidant-antioxidant balance causes increases malondialdehyde (MDA) levels. High level of glutathione peroxidase (GPx) and conjugating glutathione (GSH) can be used as important biomarkers in BPH patients. In BPH, there was an increase in tumour necrosis factoractivator protein-1 (TNF-α/AP-1) pathway, which lead to enhancing apoptosis. Nitric oxide synthase (NOS) [46] found raised in BPH patients in comparison of controls. The diminished activity of superoxide dismutase (SOD) and catalase (CAT) found in BPH patients [47, 48]. Thus, these studies showed evidence of the association of oxidative stress in BPH patients.

Microbial infection medicated BPH

The micro-organisms can cause prostatitis and can trigger the proinflammatory reaction [49, 50]. These micro-organisms are sexually transmitted organisms (e.g. *Neisseria gonorrhea, Chlamydia trachomatis, Trichomonas vaginalis* and *Treponema pallidum*), human papillomavirus, herpes simplex virus type 2, and cytomegalovirus; and Escherichia coli [49, 50].

Prostate cancer (PCa)

Overview of molecular pathways involved in PCa and associated genes (Figure 2) [51-53]

Androgen signalling and need for high-throughput screening

Androgen signalling is the driving force for the progression of PCa. In PCa androgen signalling is upregulated as compared to a healthy prostate. It regulates its action under the influence of circulating androgens, enhanced AR activity related to transcription and expression of various genes regulated by AR [54]. AR interacts transiently with its regulatory element. The FRAP (fluorescence recovery after photobleaching) analysis suggest that the interaction of the AR– chromatin is deepened on the nature of the ligand. FRAP recovery kinetics of antagonist-bound AR is 10 folds faster than agonist-bound AR [55]. The FRAP studies suggest the regulation of gene expression by androgen signalling and the

importance of antiandrogens in prostate cancer therapy. Thus, rational drug design leads to the discovery of antiandrogens with high accuracy of antagonistic activity for AR, with least adverse events. The ligand- AR interaction can potentially use as a basis for the designing of the innovative ligand with androgen antagonist. Due to the unavailability of a standard treatment regimen for PCa, nowadays, more attention has been given to developing prostate-specific molecules and therapeutic targets as a treatment modality. Therefore, identification of AR-regulated genes and molecular pathway correlated with the PCa is of particular interest [56].

Some significant androgen-regulated genes and their functions

Caspase-2 (The apoptotic enzyme)

The caspase two enzyme is well known important enzyme involved apoptosis of cells. The caspase-2 expression is androgen-regulated marker interacts with AR to express caspase-2 gene. DHT inhibited caspase activity via Akt and p53 pathways. Molecular mechanistic studies suggest that caspase -2 is responsible for androgen-mediated apoptosis in LNCaP androgen-sensitive PCa cell line [57].

CYP3A5

CYP3A5 belongs to the drug-metabolizing enzyme family of cytochrome P450. It converts T to the inert component, that is 6b-hydroxylated. It expressed by lumen and base epithelium gland. Androgen binds to the CYP3A5 and regulates AR-mediated mechanism. CYP3A5 is testosterone- inactivating enzyme can partly control T contact to prostatic cells. Therefore, CYP3A5 as a novel target that can affect prostatic syndromes [58].

TMPRSS2

TMPRSS2 is a serine protease enzyme, and androgenregulated marker explicitly expressed in normal and neoplastic prostate epithelium. TMPRSS2 is cell surface biomarker involved in prostate carcinogenesis and serves as a diagnostic and treatment tool in disease progression [59]. Recently, gene fusion transcripts of transmembrane protease serine 2 (TMPRSS2): erythroblastosis virus E26 oncogene homolog (ERG), also termed TMPRSS2: ERG or T2E, have been identified as promising urinary novel biomarkers in prostate cancer. The normal function of

PROSTATE CANCER

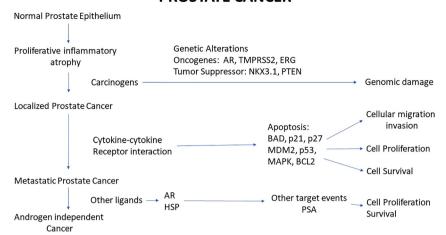


Figure 2: Prostate Cancer Pathway from KEGG pathway.

The Immunohistochemistry confirmed the expression of AR in benign and malignant prostate diseases. The AR number found to be more in PCa as compared to BPH [75].

TMPRSS2 is not clearly understood. It believed, TMPRSS2 might be a natural enhancer of PSA and hK2. PSA process the tumour cell invasion and metastasis by degrading extracellular matrix. hK2 can activate the proteolytic enzyme uPA, which is a crucial marker for tumour invasion and metastasis. The activity of TMPRSS2 on these and other substrates are still under investigation in laboratory scale [60].

FK506-binding protein 51 (FKBP51)

FKBP51 are from the class of receptors that are intracellular and targeting drugs. These are immunosuppressants (FK506 and rapamycin). These proteins generally considered as a co-worker protein. The endogenous androgens {DHT and R1881 (synthetic)} influences FKBP51's production. They regulate the synthesis of FKBP51 and monitors its level. FKBP51 expressions at the protein level observed to be more at significant levels in PCa in comparison to BPH. Thus, it can be said that FKBP51 is a potential and novel marker for diagnosis and can be a target for PCa treatment [61].

PSA/Kallikrein

This gene is composed of three associates as the prostatespecific antigen (PSA; human kallikrein-3 protein), glandular kallikrein (hGK-l; hK2; human kallikrein 2), and pancreatic/renal kallikrein (hPRK). The hGK-1 and PSA are found explicitly in gland while hPRK is detected in nonprostate tissues, for example, pancreas. Androgens are the critical players in progression and secretion potentials of the gland. The concentration of hGK-1 in human prostates

is approximately 10-50% of the PSA level. The mRNA of hGK-1 in comparison to mRNA of PSA is half in levels observed in human BPH. The expression of the hGK-1 mRNA is regulated by androgens in cells of LNCaP and increased by dihydrotestosterone via the androgen receptor-mediated pathway [62]. Novel agents targeting androgen signalling like CYP17 inhibitor Abiraterone acetate and AR inhibitor MDV3100 are in Phase II and I clinical trials, respectively [63].

Apart from Androgen signalling, various other pathways as Hedgehog, Src family kinases, Integrins mediates pathways and few more are responsible for the development of PCa [64].

Hedgehog (Hh) signaling

In prostatic development, Hh signalling is essential for duct development and propagation. Sonic hedgehog (SHH) leads to activation of prostate tumour progression and survival. By autocrine and paracrine mechanisms. Autocrine cancers which are ligand-dependent release SHH causing activation of the cell-autonomous pathway. On the other hand paracrine cancers which are ligand-dependent also release SHH that binds on stromal cells, causing activation of pathway and feedback of other growth or survival signals [64]. The newer molecule, GDC-0449 Inhibits Hh pathway is under phase II clinical trials investigation [63].

Fibroblast growth factors (FGFs) signalling

In the prostate gland, FGFs are secreted by stroma while its receptors localized on the membrane of epithelium cells. In

Shah et al.: BPH v/s. PCa - Targets — 267

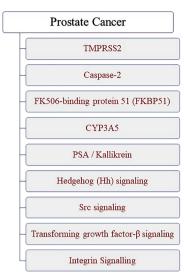


Figure 3: The targets of BPH and prostate cancer.

The general trend observed for PCa is that it initiates in the peripheral zone usually. But, in a few cases, it is also found to initiate in the transition zone. The trend is vice versa for BPH. BPH initiates in the transition zone mostly and in few cases observed in the peripheral zone [3]. A study genome-wide association conducted and found little or no overlap among BPH variants and PCa variants published earlier. A few variants related to serum PSA observed in BPH [76, 77].

PCa cells, there is increased expression of FGF1, 2, 6 and 8. Upon binding to its receptors, it down-regulates four critical pathways as phosphoinositide-3-kinase; PI3K-Akt, mitogen-activated protein kinase (MAPK), protein kinase (PKC) and signal transducer and activator of transcription (STAT). These pathways majorly regulate the cell growth and process of apoptotic inhibition in PCa [65, 66]. The inhibitors of FGF/FGFR signalling and tyrosine kinase are numerous. Some TKIs that act through FGFRs are dovitinib, brivanib, nintedanib, masitinib, orantinib, lenvatinib, and PD173074. The various inhibitors are under development that targets FGF and FGFR [67, 68].

Src signaling

Src signalling induces androgen-dependent proliferation and imparts androgen-independent growth. Src, interact with GF receptors that result in an increase of cell, invasion, survival, and angiogenesis via the MAPK pathway. Src targets focal adhesion kinase (FAK) promotes prostate cell invasion while PI3K maintain cell survival [69]. Src family kinase inhibitor as Dasatinib, Sunitinib small molecule, are under clinical trials for PCa treatment [70].

TGF-B signalling

TGF- β mainly released from epithelial cells. TGF- β down-regulates autocrine signalling in the prostate tumour microenvironment. TGF- β acts upon TGF- β (type II) receptor and controls the transcription of the genes of choice by receptor-related Smad (R-Smad) pathway. R-Smad interacts with TGF- β -Responsive elements, directly or indirectly and helps to control the genetic expression of targets to regulate stroma formation and angiogenesis [71]. There is increasing evidence

of the development of Anti-TGF- β agents for prostate cancer under preclinical and clinical investigation. Antisense Pharma is targeting to develop an oligonucleotide specific for TGF- β (AP 11014) for the advanced stage of PCa [71].

Integrin signalling

Integrins are cell adhesion receptors which support the adhesion of cells of the epithelium to the membrane, called basement membrane. Only basal epithelial cells express integrins and lost in PCa conditions. Therefore, the expression of integrin varies in PCa progression. The regulation of integrin subunits α and β have been proven to be downregulated in PCa. The β4 integrin expression lost at all stages of PCa. Integrin is key players in metastatic PCa. The upregulated avB3 found on the surface of the endothelial cells supports in migration, proliferation, and invasion of these cells to the tumour [72, 73]. Agents that antagonize integrins such as an antibody, like, a human monoclonal drug targeted contrary to the human ανβ3 integrin; CNTO 95 (in combination with docetaxel), MEDI-522 (in combination with docetaxel, prednisone and zoledronic acid) and inhibitor of ανβ3 and ανβ5 integrins as Cilengitide is under phase II clinical trials [74].

Conclusion

As we know now, BPH cannot call as the first step of PCa, and it is time to take up the study on a large scale to give clarity to develop the relationship between both. This work has highlighted significant pathways and targets

associated with BPH and PCa (Figure 3). Hence, this will be helpful for researchers and clinicians to establish a correlation between both the aliments and develop new novel molecules for set targets.

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