Journal of Advanced Biomedical and Pharmaceutical Sciences

Journal Homepage: http://jabps.journals.ekb.eg

Potential Role of Fibroblast Growth Factors (FGFs) in Benign Prostatic Hyperplasia

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Received: February 17, 2025; revised: March 18, 2025; accepted: March 23, 2025

Abstract

Benign prostatic hyperplasia (BPH) is a nonmalignant overgrowth of the prostate gland that is associated with lower urinary tract symptoms which deteriorate the patient's quality of life. Although the high prevalence of BPH among aged men, its pathophysiology is not completely understood. Both androgenic and non-androgenic factors mediate the pathophysiology of prostatic hyperplasia. However, inflammation plays a crucial role in BPH pathophysiology. The inflammatory injury stimulates the production of variant cytokines and local growth factors that induce tissue remodeling and stromal hyperproliferation. Fibroblast growth factors (FGFs) are the most versatile in their ability to regulate cellular proliferation and differentiation. This review will discuss evidence that support the role of FGFs in BPH and their signaling pathways involved in stromal hyperplasia.

Keywords

BPH, Inflammation, FGF-2, FGF-7, FGF-9

1. Introduction

Benign prostatic hyperplasia (BPH) is a noncancerous growth of the prostate gland arising from stromal and epithelial proliferation. It is one of the most common diseases among aging men with increasing prevalence. In 2019, there were about 94 million prevalent cases of BPH in comparison to 51.1 million cases in 2000 [1]. In the fourth decade of life, the prevalence of BPH is about eight percent but fifty percent of men above eighty years and nearly ninety percent of males in their ninth decade of life progress BPH.

Symptoms associated with BPH usually interfere with the patient's quality of life. Lower urinary tract symptoms (LUTS) as storage symptoms (urgency, nocturia, frequency and urinary incontinence), voiding symptoms (feeling of incomplete emptying and reduced peak flow) and post-void dribbling are secondary to prostatic enlargement. They are usually quantified by the American Urological Association (AUA) symptom score or the International Prostate Symptom Score (IPSS) [2, 3]. The IPSS is elevated approximately by 0.18 points per year. Further, the prostate growth is increased by 1.9% per year and the maximal urinary flow rate is decreased by 2 % per year [4].

Surgical intervention, such as transurethral resection of the prostate (TURP) and transurethral incision of the prostate (TUIP), is one of the available options for treatment [5]. Moreover, several forms of medical and minimally invasive treatments have been identified. Alpha-1 blockers such as tamsulosin and alfuzosin and five alpha-reductase inhibitors such as finasteride and dutasteride are the most effective approved drugs for BPH. They reduce prostate size, improve LUTS and reduce the risk of acute urinary retention and the need for BPH-related surgery [6,7].

As mentioned before, both androgen-dependent and non androgen-dependent pathways are involved in stromal hyperproliferation but androgen is considered the mainstay in BPH pathophysiology (Fig.1) [8]. Understanding the signaling pathways and identification of mediators that participate in BPH have been useful for discovering several therapeutic agents effective in prostatic hyperplasia.

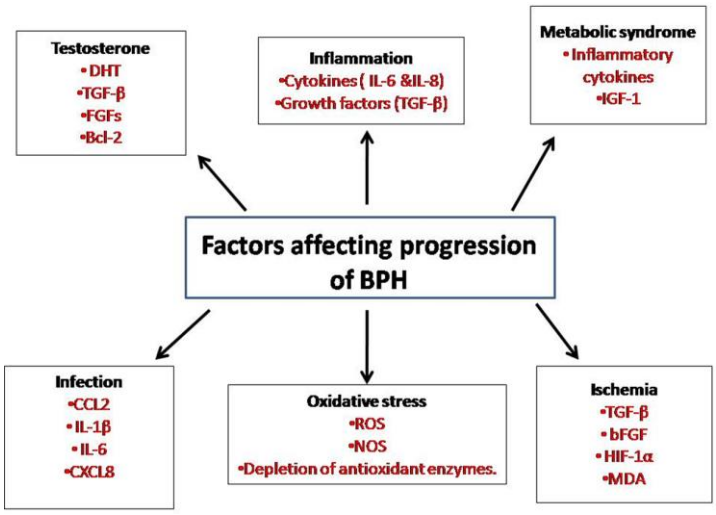

Figure 1. Summary of factors affecting the progression of benign prostatic hyperplasia

2. Role of androgen in BPH

Although BPH manifests at the age of life when androgen levels decline, testosterone is a major contributor to its pathophysiology [9]. Androgens are mainly secreted from testes and testosterone

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is the principal one [10]. It is essential for Wolffian duct differentiation into epididymides, seminal vesicles and vas deferens. Testosterone is converted to the most active form dihydrotestosterone (DHT), which is responsible for prostate development, virilization during fetal growth, and sexual maturation during puberty, by the action of the 5α reductase enzyme. Two isozymes of 5α reductase have been identified 5α R_1 and 5α R2 with the latter being more predominant isozyme in the prostate [11]. Both isoforms of androgen receptors (AR1 and AR2) are mainly expressed in the prostate and seminal vesicles [12]. Several studies support the role of androgen in BPH etiology. The androgen receptors were found to be overexpressed in prostatic tissues isolated from BPH patients compared to the normal ones [12, 13].

Moreover, treatment of patients with finasteride or dutasteride, 5α reductase inhibitors, reduces prostate volume, alleviates LUTS-associated symptoms and diminishes serum DHT levels [12, 14]. In the testosterone-induced BPH model, the antiapoptotic gene Bcl-2 was overexpressed in the prostates while the apoptosis-related genes, such as p53, Bax and caspase-3, were downregulated which induced stromal hyperproliferation [15]. The concentration of DHT in the prostate is the most accurate tool that reflects the effect of androgens on prostate hyperproliferation. Several studies showed that there is no correlation between testosterone or DHT levels in the serum and the prostate. DHT may be efficiently formed and retained stably in the prostate; this may explain the occurrence of BPH in the phase of life when testosterone levels decline [16, 17].

3. Role of androgen-independent pathway in BPH

Although sex steroid hormones, especially androgens, play a crucial role in BPH development and cellular proliferation, other androgen-independent factors including; inflammation, ischemia, infection, autoimmune reaction and oxidative stress may be involved in the disease pathogenesis [8].

3.1 Metabolic syndrome

Metabolic syndrome is a group of conditions that occur together and increase a risk of heart diseases, type-II diabetes and stroke. It includes dyslipidemia, insulin resistance, central obesity, glucose intolerance and hyperinsulinemia and it is associated with chronic inflammation [18]. Several studies have shown the correlation between metabolic syndrome and prostatic diseases such as BPH and prostate cancer [18].[19] reported that obese and diabetic men have higher incidence for the development of enlarged prostates compared to normal subjects. A recent study has shown that simvastatin, a peroxisome-proliferator-activated receptor-gamma activator and antihyperlipidemic agent, had a permissive role in alleviating BPH. Simvastatin modulated the prostate tissue fibrosis, proliferation and apoptosis and consequently reduced the prostate volume and improved the BPH-associated symptoms [20]. Moreover, the insulin-like growth factor-1 (IGF-1), was found to have a major role in prostate growth in both normal and pathological conditions. It binds to IGF-1receptors in prostate tissue, activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway and induces cellular proliferation [21]. Soulitzis, Karyotis [22] also reported that IGF-1 was overexpressed in BPH patients. This result confirmed its potential role in stromal proliferation.

3.2 Ischemia

Another contributor to prostate proliferation is the chronic tissue hypoperfusion that is induced by arterial endothelial injury and a high cholesterol diet [23]. In spontaneous hypertensive rats, the blood flow of the prostate was found to be reduced causing a hyperplastic morphological change in the prostatic structure. Those rats showed an elevation of HIF-1α and MDA (a marker for lipid peroxidation) as well as bFGF and TGF-β1 (markers of cell proliferation). The use of Terazosin, an alpha-1 blocker, restored the blood flow and reduced the prostatic hyperplasia [24] indicating the role of hypoxia in cell proliferation and BPH development.

3.3 Microbiome

Infection initiates the inflammation process in BPH. infection may promote autoantigen exposure of prostatic tissue thus activate the complement pathway and induce prostatic hyperplasia [25]. Different viruses, bacteria and fungi have been reported to be involved in prostate proliferation [8, 26]. Exposure of the BPH-1 cell line to trichomonas vaginalis initiates the release of several inflammatory mediators such as CCL2, IL-1β, IL-6, and CXCL8, and in turn stromal and epithelial cell proliferation via stromal-epithelial interaction [27]. It was also reported that ninety percent of BPH patients had pathogens as porphyromonas gingivalis and treponema denticola, the main causative agents of periodontitis, in their prostatic secretion samples [28].

3.4 Oxidative stress

Several reports have studied the role of oxidative stress in BPH. Serum samples of BPH patients showed a higher level of MDA and reduced levels of antioxidant enzymes as GSH, SOD and catalase compared to normal patients [29]. Transgenic mice with a specific expression of NADPH oxidase 4 (Nox4) in the prostate have shown increased levels of Nox-4 and 8-OH deoxyguanosine (8-OH dG), a marker of oxidative DNA damage. This resulted in enlarged weight of the prostate with epithelial and stromal proliferation as well as fibrosis of prostate tissues [30].Inducible nitric oxide synthase (iNOS), responsible for NO production, was found to be highly expressed in the BPH samples. It was detected in the basal epithelial cells and the secretory cells of the glandular epithelium [31].

3.5 Inflammation

As mentioned before, inflammation is responsible for prostatic hyperplasia and cellular proliferation. It is associated with LUTS and a high risk of acute urinary retention [32]. Robert, Descazeaud [33] reported that patients with a low degree of inflammation had smaller prostates while those with a higher degree of inflammation, had larger ones.The inflammatory injury within the prostatic tissues induces overproduction of variant cytokines and local growth factors that induce tissue remodeling and stromal hyperproliferation. Several reports confirmed the presence of inflammatory infiltrate within the prostatic specimen of BPH patients. This infiltrate contained T-cells, B-cells, mast cells and macrophages. Besides, various cytokines such as IL-4, IL-6, IL-8 and IL-13 and growth factors as TGF-β were upregulated in the inflammatory infiltrate. Accumulation of ROS contributes majorly to the increased secretion of tumor necrosis

factor-alpha (TNF-α) and multiple inflammatory interleukins such as IL-8 and IL-1α [30, 34-37].

4. Fibroblast Growth Factors (FGFs)

Fibroblast Growth Factors (FGFs) are group of twenty proteins that mediate endocrine functions in several biological processes such as; angiogenesis, embryonic development, tissue homeostasis and cancer. They mediate their activity via binding to their receptors, transmembrane tyrosine kinase FGF receptors (FGFRs 1-4). FGF-FGFR interaction initiates intracellular signaling cascades including; activation of the phosphatidylinositol 3-kinase (PI3K)/AKT, mitogen-activated kinase, phospholipase Cγ (PLCγ) and signal transducers and activators of transcription signaling pathways [38, 39]. It was reported that FGFs, especially FGF-2, FGF-7 and FGF-9, regulate the interaction between prostatic epithelial and mesenchymal compartments, essential for organogenesis.They are responsible for normal embryonic development of the prostatic gland [38, 40]. However, in adults, they control its homeostasis and function. FGFs are secreted in the mesenchyme while their receptors are mainly expressed in epithelial cells. Disruption of the FGF/FGFR signaling axis contributes to prostatic cancer progression and stromal hyperplasia (Fig.2) [38].

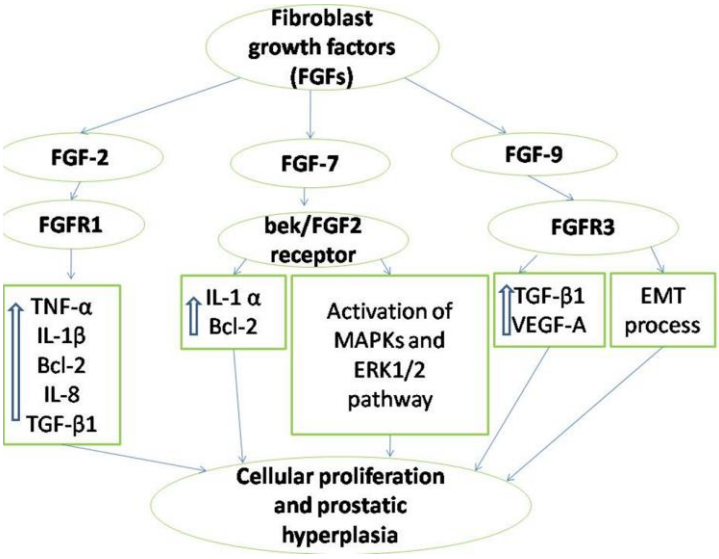

Figure 2. Role of fibroblast growth factors in benign prostatic hyperplasia.

4.1 Fibroblast growth factor-2 (basic fibroblast growth factor)

FGF-2 acts in an autocrine mode on the prostatic stromal cell. It is secreted in stromal cells and induces its proliferation. However, it acts in a paracrine mode on the epithelial cells where it is synthesized in stromal cells and stimulates the mitogenic action of epithelial cells [41]. It plays a crucial role in the development of BPH. Compared to normal prostatic tissues, hyperplastic tissues had a 2-3 fold increase in FGF-2 levels as well as an overexpression of FGFR1, the main receptor for FGF-2 [42]. In a model of prostate cancer, the FGF-2 knockout mice showed an increase in survival rate with a significant reduction in cancer metastasis. This confirmed its role in prostatic proliferation [43]. Additionally, in a testosterone-induced BPH animal model in which testosterone is given (3 mg/kg) for 6 weeks, the levels of FGF-2 were increased by 2-3 folds [44, 45]. This may suggest that FGF-2 expression is androgen-dependent. Stimulation of FGFR upregulates proinflammatory mediators; TNF-α and IL-1β as well as anti-apoptotic proteins resulting in cellular proliferation [46]. Moreover, activation of ARs stimulates the release of FGF-2, FGF-binding protein as well as FGF-receptors overexpression. It also upregulates Bcl-2 expression, an antiapoptotic protein, in prostate carcinoma cells [47].
[48] mentioned the strong correlation of IL-8 with FGF-2 in BPH. After transurethral resection of the prostate, immunohistochemical detection of FGF-2, bcl-2 and IL-8 showed upregulation of their levels in the prostate samples of BPH patients. Interestingly, the addition of anti-interleukin (IL)-8 antibodies to the epithelial and stromal cell cultures downregulated the expression of FGF-2 and suppressed the abnormal proliferation [34]. A relation between TGF-β1 and FGF-2 was also noticed in several studies. TGF-β1 upregulated FGF-2 mRNA expression about 3 fold in the cultured human prostate stromal cells through TGF-β/Smad3 and TGF-β /MAPK dependent pathways. Inhibition of MAPK activity blocked TGF-β-induced FGF-2 expression. Dysregulation and imbalance of these signaling pathways may exacerbate BPH [49, 50].

4.2 Fibroblast growth factor-7 (keratinocyte growth factor)

FGF-7 is a potent mitogen for prostatic cells that is highly expressed in stromal cells and acts on (bek/FGF2) receptors expressed on the prostate epithelial cells. Interestingly, FGF-7 production is androgen-dependent and androgen-independent. Several reports showed that testosterone administration in human and rat-cultured prostatic stromal cells induced FGF-7 production [51, 52]. On the other hand, FGF-7 levels were found to be elevated in castrated rats. Its levels remain high through 21 days after castration [53]. Huang, Wang [54] reported that FGF-7 concentration is correlated with increased expression of the Bcl-2 in the prostatic tissue. Exposure of primary cultured human prostate cancer stromal cells to FGF-7 for different periods phosphorylates Akt and in turn, upregulates Bcl-2. Interestingly, inhibition of FGF-7 suppressed Bcl-2 levels and hindered cellular proliferation of the stromal cells. Scott Lucia and Lambert [42] also mentioned that FGF-7 expression is upregulated by PAR-1 activation in cultured stromal cells and downregulated by small interfering RNAs against PAR-1. PAR-1 is a G-protein coupled receptor located in the human prostate. Its activation stimulates mitogen-activated protein kinases (MAPKs) and extracellular-signal-regulated kinase 1&2 (ERK1/2) and initiates cellular proliferation [55].
On the other side, a strong correlation was established between IL-1α production and FGF-7 levels in the BPH tissue samples. IL-1α is an inflammatory cytokine that is produced by prostatic epithelial cells and presented in higher levels in the hyperplastic prostate tissues. It upregulates several growth factors including FGF-7. FGF-7 itself leads to increased IL-1α secretion and further epithelial growth. Anti-interleukin-1α (Il-1α) antibodies and an IL-1α receptor antagonist added to the cultured prostatic cells hindered the upregulation of FGF-7 suggesting that FGF-7 is an (IL-1α)-dependent [56, 57].

4.3 Fibroblast growth factor-9

FGF-9 is secreted by stromal cells, independent of androgens, and acts on its receptors (FGFR3). The FGF-9/FGFR3 interaction strongly correlates with DNA synthesis and in turn cellular proliferation. FGF-9 is more potent than FGF-2 and FGF-7 in initiating prostatic hyperproliferation. Analogous to other FGFs,

FGF-9 levels in the prostatic transition zone of BPH patients were significantly higher compared to normal subjects [58]. FGFR3 was found to be highly expressed in the prostatic tumor cells and expressed only in functionally significant levels in normal prostatic cells [59]. It was reported that FGF9 participates in the epithelial-mesenchymal transition (EMT) process, a process in which the immotile epithelial cells transform into motile mesenchymal cells and cause stromal hyperproliferation, by induction of vascular endothelial growth factor (VEGF-A). The immunohistochemical staining of prostate cells incubated in FGF9-containing media displayed the upregulation of VEGF-A as well as N-cadherin, an angiogenesis promoter through the P13K/Akt signaling pathway, by FGF-9 in prostatic tissues [60]. Moreover, FGF-9 activates androgen receptors via its downstream signaling pathways. Circulating cytokines stimulated the release of FGF-9 which further phosphorylates STAT-3, ERK1/2 and AKT. This leads to the stimulation of ARs and finally induction of cellular proliferation [61]. FGF-9 also promoted TGF-β1expression via a cJun-mediated signaling pathway that initiated cellular proliferation. Transgenic mice, forced to express FGF9 in the prostatic epithelial cells, developed a high degree of prostatic tumor in a level-dependent manner. Increased levels of TGF-β1 were also observed in the isolated prostatic stromal cells [62].

5. Inhibition of FGFs as a potential target of BPH treatment

Several drugs exert their protective role in BPH by downregulating FGFs expression. Many clinical reports as well as experimental animal studies confirmed that suppression of FGF levels hinders stromal and epithelial hyperproliferation. After prostate resection in finasteride-treated patients and untreated patients, it was found that finasteride treatment reduced the prostatic levels of FGF-2 as well as prostate size compared tountreated patients [38]. L.cuneata, a traditional herbal medicine used in several diseases including asthma and breast cancer, showed a protective role in BPH. It reduced the prostate size as well as downregulated FGF-2, 5αR and ARs expression in the BPH animal model where testosterone was subcutaneously injected in a dose of 3mg/kg for six weeks. [63]. Also, Cornus alba, a Chinese herbal medicine, proved its effectiveness in both human prostate cell culture and testosterone-induced BPH animal model. It significantly hinders the expression of FGF-2, epidermal growth factor (EGF), Bcl-2 and 5αR and finally arrests cell growth [64]. The luteinizing hormone-releasing hormone (LHRH) inhibitor, cetrorelix, suppressed higher prostatic proliferation rate in the human BPH-1 cell line [65] as well as in a BPH rat model [66]. It reduced the prostatic levels of FGF-2, FGF-7 and EFG and inhibited STAT-3 activation. In the testosterone-induced BPH model, Guizhi Fuling capsule reduced the prostate size and inhibited cell proliferation through downregulation of FGF-7, TGF-β and VEGF[67]. In prostate-derived fibroblast cell culture, tadalafil, a PDE inhibitor, inhibited TGF-β and consequently suppressed the expression of FGF-9. In turn, it hindered the EMT process and the hyperproliferation of stromal culture [68].

6. Conclusion

All previously mentioned evidence confirmed the role of FGFs in BPH pathophysiology. FGFs are highly expressed in the hyperplastic tissues. They participate in the EMT process and upregulate the release of several proinflammatory mediators as IL-1 and IL-8. Besides, FGFs increase the expression of the antiapoptotic Bcl2, TGF-β and VEGF in the prostatic tissues which induce abnormal stromal hyperproliferation. To conclude, further preclinical and clinical studies using monoclonal antibodies against the FGFs 2, 7, and 9 are required to dissect their importance in BPH pathophysiology. These studies might be helpful to elicit FGF inhibitors as an effective option for the management of BPH and its associated symptoms.

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