

## **Molecular Mechanism of Traditional Chinese Medicine Treatment of BPH Based on BFGF/ERK and TGF- $\beta$ /Smad Pathway**

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**Keyword:** BFGF/ERK, TGF- $\beta$ /Smad Pathway, Traditional Chinese Medicine, BPH.

**Abstract:** Objective: To investigate the molecular mechanism of benign prostatic hyperplasia (BPH) and the characteristics of traditional Chinese medicine in the treatment of BPH. **Method:** Around bFGF/ERK, TGF- $\beta$ /Smad pathway and related apoptosis gene expression, By analyzing the expression of TGF- $\beta$ , bFGF and their respective mRNA, ERK enzyme, Smad protein level, combined with the mechanism of traditional Chinese medicine in the treatment of BPH, to explore the rule of the occurrence of BPH.. **Result:** Growth factor theory, hormone endocrine theory, apoptosis theory is the main mechanism of prostatic hyperplasia, BFGF/ERK, TGF- $\beta$ /Smad pathway and related apoptosis gene expression were the most important in growth factor theory, Chinese medicine has obvious advantages in the treatment of BPH. **Conclusion:** BFGF/ERK, TGF- $\beta$ /Smad pathway and the expression of related apoptotic genes on the occurrence of BPH, the development of great significance, for the treatment of BPH in traditional Chinese medicine pharmacological research and clinical treatment to provide new ideas and new methods.

Benign prostatic hyperplasia (BPH) is one of the common urinary tract diseases causing urinary dysfunction in elderly men. It has performance of urgency, frequent urination, dysuria and urinary endless and other symptoms. Two necessary conditions for the occurrence of benign prostatic hyperplasia are Relative to the elderly and the body has the function of the existence of the testis [1]. Its incidence increased with age, the incidence of 50 years old was 30% ~ 50%, to 80 years of age up to 90% [2]. With the accelerated process of China's population aging, the incidence of BPH is increasing year by year, the research and breakthrough for the treatment of BPH is particularly urgent.

### **Molecular Mechanisms of Prostatic Hyperplasia**

At present, the incidence of BPH theory has the growth factor theory, hormone endocrine theory [4-5], the theory of apoptosis [6-7]. The three theories are cross, revealing the characteristics of BPH from different angles. Among them, male and female hormone disorders is the source of BPH; disorder of apoptosis can be induced by the change of growth factors and hormones. And the growth factor is the direct main factor that regulates the prostate hyperplasia, and plays the role of bridge.

#### **Growth Factor Theory:**

Growth factor theory [8-10] thinks that the pathogenesis of BPH is closely related to the 4 kinds of peptide growth factors: Bfgf [3], TGF- $\beta$ , EGF, IGF-I. In these 4 growth factors, the precise regulation of TGF- $\beta$  and bFGF is an important mechanism for maintaining the balance of proliferation and apoptosis. And BFGF/ERK and TGF-

$\beta$ /Smad is an important pathway leading to prostate hyperplasia, which can be used to study the molecular mechanism of BPH.

### TGF- $\beta$ /Smad Pathway

In the TGF-  $\beta$  signal transduction, TGF- $\beta$  regulates c-myc expression through classical Smads signaling pathway, and regulates cell proliferation [13]. I-Smads can be firmly combined with T $\beta$ RI, so that it can not be Smad2/3 phosphorylation to block the signal transduction process, which constitute a negative feedback regulation loop in the TGF-  $\beta$  signal transduction; R-Smads protein is activated by type I receptor activation, and Smad4 protein formation complex, together with the nucleus, where to guide the transcription of the gene. DNA and Smad affinity is relatively low, and need to be combined with other transcription factors to form a stable protein [11-12]. In addition, the literature indicates that TGF- $\beta$  can inhibit the transcription of c-myc gene so that the cells stop in the late G1, while bFGF can make c-myc gene activation, antagonistic TGF-  $\beta$ .

### BFGF/ERK Access

BFGF can induce ERK and promote the proliferation and differentiation of prostate cells to cause BPH. ERK involved in BFGF induced mitosis. BFGF receptor can activate the ERK1/2 [14] signaling pathway through the Ras/Raf-1/MEKs pathway, and induce the activation of ERK signaling pathway in epithelial cells, which promotes the proliferation and differentiation of muscle satellite cells. The inactive ERK1/2 is located in the cytoplasm, which is activated by the rapid entry into the nucleus, and its substrates include c-fos, c-myc, c-myb. And by adjusting the respective target gene mRNA transcription and translation process, BFGF/ERK access caused changes in the expression or activity of a specific protein, on the cell growth, proliferation, differentiation, migration and anti apoptotic process plays an important role in the regulation.

In the prostatic stroma and epithelial cells, the enhanced negative regulation of TGF- $\beta$  and the positive regulation of bFGF decreased, which could accelerate the apoptosis of prostate cells and prostate tissue atrophy [15]. Molecular mechanisms of prostate hyperplasia in the bFGF/ERK and TGF-  $\beta$  /Smad pathway as shown in figure 1:

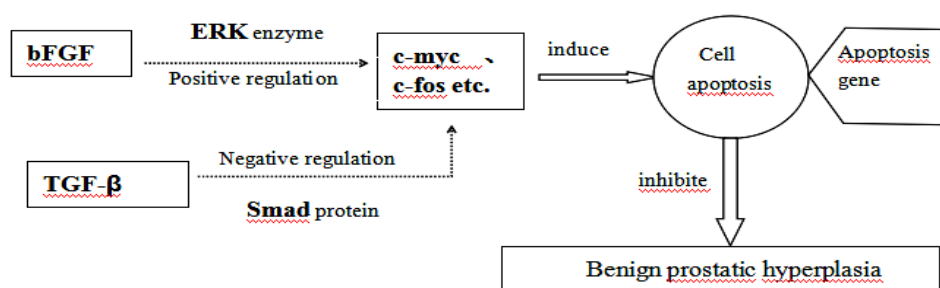


Figure.1 Molecular mechanisms of BPH in the bFGF/ERK and TGF-  $\beta$  /Smad pathway

### Traditional Chinese Medicine in the Treatment of BPH and its Mechanism

In modern medical treatment BPH prostate resection [16] is still the main treatment for BPH, because it will produce a lot of complications and sequelae, drug therapy [17]

has gradually become the main treatment. But the side effects are greater, and most of the price of drugs is more expensive, often make it subject to many restrictions.

In traditional Chinese medicine prostatic hyperplasia classified as "Longbi" "Stranguria syndrome" category, with dysuria, drip and lack of clinical features; The common syndromes of The decline of kidney yang and Kidney deficiency and blood stasis, Lung heat congestion, gas in body subsidence, which is the basic pathogenesis of benign prostatic hyperplasia, and blood stasis, phlegm with turbid, damp heat is the basic pathological factors. Under the guidance of traditional Chinese medicine theory, the treatment of traditional Chinese medicine, which has the functions of reinforcing spleen and kidney, promoting blood circulation, removing blood stasis, diuretic, clearing away heat and toxic materials, and so on, Such as Aphrodisiac medicine: It can improve the function of endocrine regulation, improve the function of hypothalamus pituitary gonadal axis, and promote the improvement of sex hormone balance disorders. Blood activating and stasis eliminating drugs: Improve the circulation, to achieve the effect of blood stasis, anti-inflammatory, promoting tissue repair and inhibit the proliferation of tissue.

Traditional Chinese medicine in the prevention and treatment of BPH, especially the symptoms of BPH has a stable effect, lasting effect, adverse reactions, low recurrence rate and low recurrence rate, can be from many aspects, multi target for treatment of BPH. Clinical practice of traditional Chinese medicine to the kidney, lung, spleen, BPH commonly used in the treatment of single medication with epimedium, zedoary, liquorice etc (see Table 1). Because the BPH disease involves many kinds of pathogenesis, the clinical symptom of simple syndrome is not much, the multiple primary and secondary or multi syndrome, Therefore, the use of traditional Chinese medicine and preparations for treatment (see Table 1), showing the advantages of traditional Chinese medicine treatment of the disease [18].

Table 1 Traditional Chinese medicine for treating BPH and its active components

Traditional Chinese medicine or active ingredients			pharmacological action
Soybean isoflavone			To reduce secretion of IGF-1, EGF and bFGF inhibited the proliferation of prostate cells through its estrogen like effect.
Ethanol extract from		peanut root [19]	The expression rate of Bcl-2 was decreased, the expression rate of Bax was significantly increased, and the balance of apoptosis gene was inhibited.
Linariifolioside	total	flavonoids [20]	The wet weight of prostate and the prostate index were significantly decreased, and the levels of testosterone and epidermal growth factor (EGF) were significantly decreased.
Leonurine	Total	alkaloids [21]	The wet weight and index of the prostate were significantly reduced, and the pathological changes induced by the model were reduced.
Compound capsule of		Lysimachia christinae [22]	It can reduce the rat prostate volume, reduce the prostate index; The BPH model has obvious protective effect, which may be related to inhibiting the expression of epithelial cell proliferation and growth factor and promoting apoptosis.
Guizhi Fuling granules		[23]	By decreasing the expression level of VEGF and bFGF in rat prostatic hyperplasia gland tissue, and then reducing the volume and index of prostate.
Qianlongtong	capsule	[24]	By decreasing the expression of 1m beta RNA TGF- in stromal cells and TGF-β1 to treat Benign prostatic hyperplasia.

## Outlook

Benign prostatic hyperplasia is a chronic progressive disease, the pathogenesis is a very complex pathological process, involving many factors. As the final executor of biological function, growth factor plays a key role in the pathogenesis of prostatic hyperplasia. In this paper, the molecular mechanism of prostatic hyperplasia was discussed from the bFGF/ERK and TGF- $\beta$ /Smad signaling pathway, and the mechanism of the treatment of BPH was summarized [25], will provide a new direction for the pathogenesis of BPH.

At present, Chinese medicine from the body as a whole, according to the diversity of the etiology and pathogenesis, syndrome differentiation; The use of detoxification and gynecological common blood circulation oral compound and single herb preparations such as Herba Leonuri, Wujibaifeng pills [26]. It has the characteristics of multiple targets, which is safe and effective. However, because of the diversity of the composition of Chinese traditional medicine, its mechanism of action still needs to be further explored. Based on the current commonly used in gynecology of traditional Chinese medicine on benign prostatic hyperplasia remarkable curative effect, in future research, the molecular mechanism of its correlation is studied, will further clarify the pathogenesis of benign prostatic hyperplasia and the mechanism of traditional Chinese medicine treatment of benign prostatic hyperplasia, to provide new ideas and new methods for the treatment of benign prostatic hyperplasia.

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