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Advances in Research of Traditional Chinese Medicine in the Treatment of Prostatitis through p38MAPK Signaling Pathway

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Abstract Prostatitis is a common genitourinary disease characterized by a complex pathogenesis involving infection, inflammation, oxidative stress, and immune dysfunction. The p38MAPK signaling pathway plays a key role in inflammation and stress response, and inhibition of this pathway can reduce the expression of inflammatory factors, thereby alleviating prostatitis. Studies have shown that traditional Chinese medicine can effectively treat prostatitis by regulating p38MAPK pathway. In this study, the role of p38MAPK in prostatitis is discussed through literature review, which provides a new scientific basis for the treatment of traditional Chinese medicine.

Key words Prostatitis, Traditional Chinese medicine, p38MAPK, Inflammation, Mechanism

1 Introduction

Prostatitis is a prevalent genitourinary disorder worldwide, predominantly affecting males under the age of 50. The reported prevalence ranges from 3% to 16% across North America, Europe, and Asia[1]. Clinical manifestations typically include localized pain (particularly in the perineal region), urinary dysfunction, sexual impairment, and systemic presentations that may encompass psychological disturbances. Notably, chronic cases have been associated with potential reproductive complications including infertility[2]. The disease pathogenesis remains multifactorial and poorly understood, characterized by heterogeneous symptom profiles and high recurrence rates. These clinical challenges contribute to the current limitations in establishing standardized diagnostic criteria and developing universally effective therapeutic protocols.

Current pathophysiological models propose that prostatitis may originate from primary pathologies or secondary complications involving the prostate gland and adjacent anatomical structures, including peri-prostatic tissues, musculature, and neural networks. Notably, persistent pathophysiological alterations may persist as self-sustaining pathological processes, even following resolution of initial etiological factors[3]. The disease etiology involves multifactorial interactions among infectious agents, inflammatory cascades, oxidative stress responses, immune dysregulation, and pelvic floor neuromuscular dysfunction. At the molecular level, a cytokine network comprising TNF-α, IL-1β, IL-6, and IL-8 forms an integrated pathophysiological axis through synergistic interactions. These mediators collectively drive inflammatory amplification cycles, ultimately mediating both disease initiation and chronicity[4].

2 The p38MAPK signaling pathway

P38 mitogen-activated protein kinase (p38 mitogen activated protein kinase, p38MAPK) signaling pathway is an important member of MAPK family, which is an important molecule in intracellular signal transduction and mainly involved in cellular reactions. It participates in many physiological processes such as cell growth and development and functional synchronization between cells, and is closely related to the regulation of inflammation, stress and apoptosis. It is considered to be the intersection and common pathway of cell information transmission. MAPK signaling pathway is divided into four subfamilies: EPK, JNK, p38MAPK and EPK5. The p38MAPK signaling pathway plays an important role in inflammation, cell development and apoptosis, and is the central pathway of cell signaling. p38MAPK is composed of five subtypes encoded by different genes: p38a, p38β1, p38β2, p38y and p386. The distribution of each subtype in human tissue structure has obvious tissue distribution difference[5]. p38MAPK can be activated by the stimulation of IL, physiological stress, TNF, inflammatory cytokines, LPS and so on. At present, many studies have found that inflammation, oxidative stress and immunity may be important factors leading to prostatitis. The activation of p38MAPK signaling pathway is involved in the occurrence and development of prostatitis, and inhibition of p38MAPK signaling pathway can inhibit the expression of inflammatory factors, thereby inhibiting the occurrence of prostatitis[6].

When p38MAPK is activated by phosphorylation, there are three ways: (i) in the cytoplasm, it activates a series of other protein kinases to play its regulatory role; (ii) in the cytoplasm, it phosphorylates cytoskeletal components; (iii) It enters the nucleus and regulates the expression of genes by phosphorylating transcription factors. p38MAPK is widely distributed in the body, and many factors can become the activator of p38MAPK. Cellular stress including osmotic stress, inflammatory cytokines such as TNF-α, IL-1, LPS, UV, growth factors, and PMA, a specific activator of protein kinase C, can activate p38MAPK signaling pathway[7]. p38MAPK transduces signals through a highly conserved cascade of tertiary kinases. When cells are stimulated, MAP-KKK is activated through an intermediate link, which in turn activates

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MAPKK, which regulates the activity of p38MAPK through two-site phosphorylation. MKK3 and MKK6 are putative upstream kinases of p38MAPK. The downstream kinases of p38MAPK include MAP-KAPK-2 (MAPK activated protein 2) and MAPKAPK-3, Mnk-1 (MAPK interacting kinase 1) and Mnk-2, MSK-1 (mitogen and stress activated kinase 1), *etc.* Activation of MAPKAPK-2 activates the small heat shock protein HSP27 and the transcription factor cAMP response element binding protein CREB (Cyclic AMP response elementbinding protein), ATF-1 (activating transcription factor 1)[8]. The substrates of p38MAPK include ATF-2 (activating transcription factor 2), ELK-1 (ets-like gene 1), MEF-2 (myocyte enhancer factor), CHOP (C/EBPhomologous protein), c-jun, c-fos, *etc.* A variety of substrates directly or indirectly affect the activity of a variety of transcription factors, specifically regulate the transcription and expression of TNF, c-myc, Fas/FasL and other genes, regulate cell differentiation and apoptosis, and regulate a variety of cellular responses[9].

3 The relationship between p38MAPK signal pathway and prostatitis

p38MAPK signaling pathway plays an important role in inflammatory response, and inflammation is an important factor in the development of prostatitis. The acute inflammatory response begins with the secretion of various cytokines (TNF-α and IL-1) and chemokines (IL-8, MCP-1, and MIP-1-α), all of which stimulate the recruitment of inflammatory cells in the prostate. MIP-1-α is a chemotactic agent for neutrophils, monocytes, and macrophages. MCP-1 is a powerful chemotactic agent for circulating monocytes, regulating monocyte recruitment and macrophage infiltration formation. MCP-1 can be produced by a variety of cell types through natural gene expression, growth factors, cytokines, and oxidative stress. Acute inflammation is usually caused by bacteria, and if the bacteria are not eliminated, the inflammatory process will become chronic. Since the inflammatory process is not interrupted and the regulatory mechanisms for production and release are not activated, the production of cytokines, ROS, and RNS persists and prostatic inflammation becomes a chronic disease. Histopathological features of chronic prostatitis show that macrophages and lymphocytes are widely present in the stroma adjacent to the prostatic acini, but rarely in the epithelial cells[10]. Macrophages, on the other hand, can promote the inflammatory response by secreting cytokines and growth factors and activating other cells, particularly T cells; in addition, high expression of the cytokine TNF-α[11-12] has also been observed in patients with prostate calcification.

Activated p38 MAPK (p-p38 MAPK) regulates the active expression of some transcription factors, promotes the production of MCP-1, TGF-β, TNF-α, IL-6 and other related inflammatory cytokines, thereby increasing the inflammatory infiltration of tissue cells[13]. MCP-1 can up-regulate the expression of some adhesion molecules such as ICAM-1 and VCAM-1, and promote the aggregation of inflammatory cells such as monocytes and macrophages to inflammatory sites. Studies have shown that under the influence of chemotaxis and adhesion molecules, the recruitment of macrophages at the site of tissue inflammation will adaptively secrete a large number of pro-inflammatory, pro-fibrotic and connective tissue factors to participate in the excessive repair process of tissues, and their aggregation and activation can also directly differentiate into fibroblasts, thus accelerating the formation of tissue fibrosis[14]. Studies have shown that inhibition of p38MAPK signaling pathway can reduce the expression of TNF-α mRNA, IL-6 mRNA and TNF-α, IL-6, p-P38 MAPK protein in prostate tissue of rats with prostatitis, and inhibit inflammatory response[15]. Cheng Liyan *et al.* found that compared with the blank group, the expression of MMP-9, p38MAPK and p-p38MAPK in the chronic abacterial prostatitis model group was significantly increased[16]. In addition, some studies have shown that p38MAPK signaling pathway is also related to prostatitis pain, specifically related to the expression of TNF-α mediated by p38MAPK. In this study, using a rat model of central nervous system pain produced by transverse hemisection of the spinal cord, it was found that lumbar spinal microglial activation and high TNF-α expression were associated with mechanical allodynia in the hindfoot of rats, and that p-p38MAPK and membranous TNF-α expression were also reduced when pain behavior was reduced[17].

It has been found that in the prostatic fluid and serum of prostatitis patients, chemokines CXCL5, CXCL8, CXCL10 and inflammatory cytokines TNF-α, IL-2, IL-1β, *etc.* Are all increased. Because of aging and/or inflammatory response, the normal tissue homeostasis of the prostate is destroyed, and various chemokines are secreted in the prostatic microenvironment. The p38MAPK signaling pathway is activated by inflammatory cytokines to induce the targeted aggregation of macrophages and T lymphocytes and the secretion of proinflammatory mediators, which proves that p38MAPK is an important pathway involved in prostatic inflammatory infiltration and pain symptoms[18].

4 Traditional Chinese medicine treatment of prostatitis

Xu Fusong posits that the etiology of prostatitis involves internal deficiency and external invasion of damp-turbidity. The pathogenesis can be summarized as damp-turbidity manifesting as the secondary aspect, stasis representing the pathological transformation, and kidney deficiency constituting the root cause. Clinically, it manifests in various patterns including damp-heat, blood stasis, spleen deficiency, and kidney deficiency[19]. Professor Cui Xuejiao proposes that the prostate should be categorized within the Sanjiao (triple energizer) system among the six internal organs. Its primary physiological characteristic lies in regulated opening-closing mechanisms and separation of clear from turbid, while its main pathological feature manifests as stasis accumulation in the

lower energizer[20]. From the perspective of TCM theory, the prostate should be classified as part of the "essence chamber", functioning in both storage and discharge, thus belonging to the "extraordinary organs". Located in the lower energizer, once damp-heat toxins accumulate and congeal in this region, they tend to persist and easily recur when triggered by predisposing factors. Prolonged illness with improper treatment leads to chronic pathological changes entering the collaterals, resulting in blood stasis within the essence chamber's vessels and the mutual binding of defective essence with damp-heat pathogens. Therefore, blood stasis permeates the entire disease progression. The pathogenesis fundamentally involves spleen-kidney deficiency with concurrent manifestations of damp-heat turbid toxin stasis, forming an interdependent relationship between root and secondary factors[21]. Consequently, the therapeutic principles primarily focus on clearing heat-dampness and activating blood circulation to resolve stasis.

Bazheng Powder, the representative prescription of traditional Chinese medicine for the treatment of prostatitis, is from *Prescriptions of the Bureau of Taiping People's Welfare Pharmacy* (*Taiping Huimin Heji Ju Fang*) of the Song Dynasty. It is composed of Caulis Akebiae, Herba Dianthi, Herba Polygoni Avicularis, Talcum, Fructus Gardeniae, Radix Glycyrrhizae Uralensis, Semen Plantaginis, and Radix et Rhizoma Rhei. It is a heat-clearing and dampness-dispelling agent, and has the effects of clearing heat, purging fire, inducing diuresis, and treating stranguria[22]. It can be used for treating damp-heat stranguria. Symptoms include frequent urination, urgent urination, painful urination, unsmooth urination, red urine, even obstruction of urine, fullness in the lower abdomen, dry mouth and throat, yellow and greasy tongue coating, and slippery and rapid pulse. Clinically, it is often used to treat cystitis, urethritis, prostatitis, urinary calculi, pyelonephritis and other patients with downward flow of damp-heat. The downward flow of damp-heat accumulates in the bladder, causing difficulty in the water channel, resulting in frequent and urgent urination, painful drowning, unsmooth dripping, and even obstruction; the accumulation of damp-heat causes the urine to be red; the stagnation of damp-heat causes the obstruction of qi movement, resulting in urgent fullness in the lower abdomen. In Bazheng Powder, Herba Dianthi and Herba Polygoni Avicularis are used to induce diuresis and treat stranguria, clear heat and cool blood, and Caulis Akebiae is used to induce diuresis and reduce fire; Semen Plantaginis and Talcum are used to clear heat and promote diuresis, and relieve stranguria; Fructus Gardeniae and Radix Et Rhizoma Rhei are used to clear heat and purge fire, and induce heat to descend; Radix Glycyrrhizae is used to relieve urgency and relieve urethral pain. The combination of the medicines has the effects of clearing heat, purging fire, inducing diuresis and treating stranguria. At present, it is widely used in clinic to treat prostatitis due to downward flow of damp-heat, and has achieved good curative effect.

Combined with animal experiments and network pharmacology, Chen *et al.* believed that Cornu Bubali, Radix Rehmanniae, Radix Paeoniae Rubra and Cortex Moutan in Rhinoceros Horn and Rehmannia Decoction could regulate inflammation, coagulation and other biological processes by regulating 38MAPK signaling pathway[23]. Shi Xue *et al.* conducted a systematic meta-analysis by screening the literature on the intervention effects of Salvia miltiorrhiza, giant knotweed, Ligusticum wallichii and red peony root on inflammatory factors related to autoimmune prostatitis (EAP) model, which showed that heat-clearing and blood-activating herbs could reduce the expression of IL-1, IL-6, TNF-α and other inflammatory factors. NF-κB and MAPK/p38MAPK may participate in the regulation of inflammation[24]. Fan Hongbo *et al.* analyzed the mechanism of action of Cortex Phellodendri, Cortex Moutan, Semen Plantaginis and Rhizoma Alismatis in the treatment of prostatitis through network pharmacology. Jinze Qingzhuo Tongluo Prescription is mainly used to clear heat and eliminate dampness, and promote blood circulation and diuresis. It is found that Kanazawa Qingzhuo Tongluo Prescription plays an anti-inflammatory role mainly through NF-κB pathway, inflammatory factor injury and MAPK signaling pathway, and the main active components such as quercetin, luteolin and kaempferol have high contents in Semen Plantaginis, Flos Lonicerae and Cortex Moutan[25]. Dai Jianye *et al.* observed the effect of Yao herbal medicine wild pineapple, Bidens bipinnata and Mallotus apeltatus on chronic nonbacterial prostatitis rats, and the results showed that it could inhibit the expression of p-p38MAPK, reduce the levels of inflammatory cytokines and MMP-9 protein, and alleviate the inflammatory changes of chronic nonbacterial prostatitis rats[26].

5 Conclusions

The p38 mitogen-activated protein kinase (MAPK) signaling pathway represents a pivotal intracellular transduction system that has emerged as a promising therapeutic target for prostatitis management. Current evidence indicates that phytotherapeutic agents exert multi-target modulation of this pathway, demonstrating therapeutic efficacy through three principal mechanisms: (i) attenuation of prostatic inflammatory cascades, (ii) amelioration of lower urinary tract symptoms, and (iii) mitigation of chronic pelvic pain syndrome. Although research on botanical interventions targeting p38MAPK in prostatitis remains in its nascent stages, with numerous mechanistic intricacies requiring further elucidation, accumulating data reveal its dual regulatory role in both pain pathogenesis and maintenance. Specifically, p38MAPK not only modulates nociceptive processing through cytokine network interactions (*e.g.*, IL-1β/TNF-α axis) but also sustains chronic pain states via epigenetic regulation of nuclear transcription factors and translational control of pain-associated proteins[27].

These findings underscore the necessity for systematic investigation into the spatiotemporal dynamics of p38MAPK activation patterns throughout disease progression. Such research may unveil

novel therapeutic windows for precision interventions while providing pharmacological foundations for developing next-generation phytomedicines. Consequently, integrating p38MAPK-targeted strategies with traditional Chinese medicine formulations presents a transformative approach for advancing evidence-based prostatitis therapeutics, particularly through the lens of systems biology and network pharmacology.

References

[1] WATSON HI, SHEPHERD AA, RHODES J. Revisited: A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury[J]. Critical Care Medicine, 2018, 46(6): 972 – 979.

[2] XU WL, MA WM, LIANG CC. Research progress on changes of seminal plasma composition and corresponding sperm quality in patients with chronic prostatitis/chronic pelvic pain syndrome[J]. Chinese Journal of Andrology, 2024, 30(5): 444 – 449. (in Chinese).

[3] PAULIS G. Inflammatory mechanisms and oxidative stress in prostatitis: The possible role of antioxidant therapy[J]. Research and Reports in Urology, 2018, 10: 75 – 87.

[4] KOVAL'CHUK LV, GANKOVSKAIA LV, MAZO EB, *et al.* Analysis of cytokines in seminal plasma and blood sera of patients with chronic prostatitis during immunotherapy with natural complex of cytokines and antimicrobial peptides[J]. Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii, 2007(5): 57 – 61.

[5] KCIUK M, GIELECISKA A, BUDZINSKA A, *et al.* Metastasis and MAPK pathways[J]. International Journal of Molecular Sciences, 2022, 23(7): 3847.

[6] YAN ZR, YIN HW, PAN JQ, *et al.* Mechanism of Jiedu Huoxue Decoction in the treatment of type III prostatitis based on ERK/p38 MAPK signaling pathway[J]. Journal of Yunnan University of Traditional Chinese Medicine, 2024, 47(1): 67 – 78. (in Chinese).

[7] STUDER RK, GILBERTSON LG, GEORGESCU H, *et al.* p38 MAPK inhibition modulates rabbit nucleus pulposus cell response to IL-1[J]. Journal of Orthopaedic Research, 2008, 26(7): 991 – 998.

[8] MAO Q, XU JN, WEN XY, *et al.* Effect of p38MAPK on CREB expression in microglial cells intervened by nutmeg extract[J]. Shandong Medical Journal, 2011, 51(12): 35 – 36. (in Chinese).

[9] HISATSUNE J, NAKAYAMA M, ISOMOTO H, *et al.* Molecular characterization of Helicobacter pylori VacA induction of IL-8 in U937 cells reveals a prominent role for p38MAPK in activating transcription factor-2, cAMP response element binding protein, and NF-kappaB activation[J]. Journal of Immunology, 2008, 180(7): 5017 – 5027.

[10] PAULIS G. Inflammatory mechanisms and oxidative stress in prostatitis: The possible role of antioxidant therapy[J]. Research and Reports in Urology, 2018, 10: 75 – 87.

[11] GANDAGLIA G, BRIGANTI A, GONTERO P, *et al.* The role of chronic prostatic inflammation in the pathogenesis and progression of benign prostatic hyperplasia (BPH)[J]. BJU International, 2013, 112(4): 432 – 441.

[12] ENGELHARDT PF, SEKLEHNER S, BRUSTMANN H, *et al.* Tumor necrosis factor-alpha expression in patients with obstructive benign prostatic hyperplasia is associated with a higher incidence of asymptomatic inflammatory prostatitis NIH category IV and prostatic calcification[J]. Scandinavian Journal of Urology, 2015, 49(6): 472 – 478.

[13] HUANG YR, WAN YG, SUN W, *et al.* Effect and mechanism of Tripterygium wilfordii polyglycoside on regulating p38MAPK signaling pathway in renal tissue and improving glomerular inflammatory injury in diabetic nephropathy[J]. Chinese Journal of Traditional Chinese Medicine, 2014, 39(21): 4102 – 4109. (in Chinese).

[14] XU L, SHEN P, BI Y, *et al.* Danshen injection ameliorates STZ-induced diabetic nephropathy in association with suppression of oxidative stress, pro-inflammatory factors and fibrosis[J]. International Immunopharmacology, 2016, 38: 385 – 394.

[15] LI XS, HUANG B, WU WQ, *et al.* Effects of sinomenine on inflammatory response and p38MAPK signaling pathway in rats with chronic abacterial prostatitis[J]. Advances in Modern Biomedicine, 2011, 11(22): 4244 – 4246. (in Chinese).

[16] CHENG LY, TU LL, SHI H. Effect of p38MAPK on pain of chronic prostatitis and intervention of quercetin[J]. China Modern Applied Pharmacy, 2016, 33(8): 984 – 988. (in Chinese).

[17] CHENG C, QIN Y, SHAO X, *et al.* Induction of TNF-alpha by LPS in Schwann cell is regulated by MAPK activation signals[J]. Cellular and Molecular Neurobiology, 2007, 27(7): 909 – 921.

[18] DENG M, ZHAO HF. Effect of immunoglobulin levels in serum and prostatic secretion on the progression of chronic prostatitis[J]. Journal of Hebei Medical University, 2019, 40(8): 960 – 963. (in Chinese).

[19] BIAN TS, XU FS. Xu Fusong's experience in diagnosis and treatment of chronic prostatitis[J]. Liaoning Journal of Traditional Chinese Medicine, 2009, 36(5): 729 – 730. (in Chinese).

[20] WANG J, CHEN M. Professor Cui Xuejiao's view on etiology, syndrome differentiation and treatment of chronic prostatitis[J]. Sichuan Traditional Chinese Medicine, 2006(4): 2 – 4. (in Chinese).

[21] WANG JS, ZENG QQ, XU FS. Research on syndrome differentiation and treatment of chronic prostatitis[J]. Modern Chinese Medicine, 2004(2): 46 – 47. (in Chinese).

[22] HUANG MY, XU RZ, CAI XJ. Research progress of clinical application of Bazheng Powder[J]. Journal of Practical Traditional Chinese Medicine, 2019, 35(10): 1295 – 1296. (in Chinese).

[23] CHEN Y, DAI Y, XIA J, *et al.* Serum pharmacochemistry combining network pharmacology to discover the active constituents and effect of Xijiao Dihuang Tang prescription for treatment of blood-heat and blood-stasis syndrome-related disease[J]. Oxidative Medicine and Cellular Longevity, 2022: 6934812.

[24] SHI X, ZHU M, DAI F, *et al.* Systematic review of intervention effect of heat-clearing and blood-activating herbs on inflammatory factors in autoimmune prostatitis (EAP) model[J]. Shandong Journal of Traditional Chinese Medicine, 2020, 39(7): 719 – 725. (in Chinese).

[25] FAN HB, GUO J, ZHANG GM, *et al.* Analysis of the mechanism of Jinze Qingzhuo Tongluo Fang in the treatment of chronic prostatitis based on network pharmacology and molecular docking[J]. Clinical Research of Traditional Chinese Medicine, 2021, 13(31): 1 – 5. (in Chinese).

[26] DAI JY, ZHANG M. Intervention mechanism of Yao medicine Fudingtang on p38MAPK signal transduction pathway in rats with chronic abacterial prostatitis[J]. World Latest Medical Information Digest, 2019, 19(42): 173 – 174. (in Chinese).

[27] WANG Q, CHEN YD, LIU YR, *et al.* Research progress on the relationship between p38MAPK signaling pathway and prostatitis pain[J]. Journal of Bethune Military Medical College, 2012, 10(4): 319 – 322. (in Chinese).