



The Therapeutic Potential of Acupuncture in Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Yang Yu¹ Xunchao Peng¹ Chenglin Tang²

¹Acupuncture Department, Yongchuan Traditional Chinese Medicine Hospital Affiliated to Chongqing Medical University, Chongqing, China
²College of Traditional Chinese Medicine, Chongqing Medical University, Chongqing, China

Address for correspondence Xunchao Peng, Professor, Chief Physician, Acupuncture Department, Yongchuan Traditional Chinese Medicine Hospital Affiliated to Chongqing Medical University, No.2 Yingbin Avenue, Yongchuan District, Chongqing 400016, China (e-mail: 13983666722@163.com).

CMNP 2023;3:e117–e125.

Abstract

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) represents the most common type of CP, characterized by complex pathogenesis and a wide array of symptoms, making diagnosis and treatment challenging. Acupuncture, a widely used treatment for chronic and painful conditions, has demonstrated clinical efficacy in restoring prostate function and enhancing the quality of life for affected patients. This article critically examines the intricate pathogenesis of CP/CPPS and explores the related therapeutic mechanisms of acupuncture. Additionally, it summarizes the advancements made in the last decades regarding the use of acupuncture for treating CP/CPPS and elucidates potential effect pathways, laying the groundwork for further fundamental research.

Keywords

- ▶ chronic prostatitis
- ▶ chronic pelvic pain syndrome
- ▶ acupuncture
- ▶ mechanism

Introduction

The National Institutes of Health (NIH) has conducted extensive basic and clinical research on prostatitis. Based on factors such as the speed of onset, prostatic massage fluid, and semen or according to the routine microscopic examination of the third urine specimen during bladder function testing, patients were divided into two groups. Prostatitis was classified into four types: acute bacterial prostatitis (type I), chronic bacterial prostatitis (type II), chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (type III), and asymptomatic prostatitis (type IV). According to the increase of white blood cells and (or) lecithin bodies under the microscope, type III prostatitis is divided into two subtypes: type IIIA with positive under the microscope and type IIIB with negative under the microscope.¹ The main symptoms of CP include pelvic pain, lower urinary tract manifestations, mental and psychological manifestations, and sexual dysfunction. Notably, somatization symptoms such as pain in urogenital parts, ejaculation pain, urination pain, and lower abdominal or pelvic floor muscle tenderness are prevalent. It also includes lower urinary tract

symptoms such as urgent urination, frequent urination, nocturia and urge urinary incontinence, prolonged urination time, thinning urine stream, difficult urination or urethral incontinence, and posturination dribbling. It may also be accompanied by impotence, lack of libido, abnormal ejaculation function, etc. In addition, psychological symptoms are also the main symptoms of CP, including restlessness and depression, cognitive and behavioral abnormalities, and reduced quality of life.^{2,3}

In traditional Chinese medicine (TCM), CP/CPPS is categorized into different syndrome types based on its pathogenic factors and pathogenesis processes, such as dampness, heat, qi stagnation, blood stasis, deficiency of the liver, spleen, and kidney, and other combinations of deficiency and excess.^{1,4} The causes of dampness and heat may stem from improper diet, indulgence in fat, sweet, wine, and greasy foods, the accumulation of dampness and heat in the lower energizer, or the disorderly movement of ministerial fire due to unmet desires, leading to the accumulation of white turbidity or invasion from dampness and heat stagnation and qi and blood stasis.⁵

received

April 2, 2023

accepted after revision

May 22, 2023

DOI <https://doi.org/>

10.1055/s-0043-1774412.

ISSN 2096-918X.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Acupuncture, as a kind of TCM treatment, has demonstrated effectiveness in treating CP/CPPS, supported by substantial evidence. It has also been recommended by urologists in China and other countries.⁶⁻⁸ Based on the feasibility of acupuncture treatment and a large amount of clinical experience, this article will delve into the pathogenesis of CP/CPPS and the mechanism of action of acupuncture, highlighting the advantages of acupuncture and moxibustion in its treatment from a pathological perspective, drawing from the feasibility of acupuncture treatment and extensive clinical experience.

Pathogenesis of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

The pathogenesis of CP/CPPS is intricately linked to male lifestyle factors, encompassing eating habits, occupational habits, sexual habits, and more.⁹ Among these abnormal urination function, fluctuation of sex hormone levels, neuroendocrine factors, and immune responses are the main causes of inflammation and pain.

Immunology

Prostatitis is characterized by the infiltration of multinucleated and mononuclear cells (such as neutrophils, lymphocytes, macrophages, and plasma cells) in the stromal connective tissue surrounding the acinar or duct.¹⁰ Relevant studies have shown that CD4⁺T cells play a major role in the occurrence of the disease and the production of pain response, and the infiltration of CD4⁺T cells in the prostate can be observed in animal experiments related to CP.¹¹ After activation, early CD4⁺T cells can be divided into Th1, Th2, Th17, Treg, and other cells according to their activity. These cells jointly affect the local inflammatory process in different ways.

In the process of research on autoimmune prostatitis (AIP), it is found that the immune response is mainly mediated by Th1 cells, accompanied by an increase in interferon (IFN)- γ secretion.¹² Haverkamp et al¹¹ found that in the rat CP model, IL-12 and IFN- γ in the prostate tissue increased, while IL-4 and IL-10 decreased significantly when the immune mechanism was activated, indicating that the activity of Th2 cells was inhibited during this process and was involved in the related immune process. In addition, in the experiment on the induction of prostatitis by *Escherichia coli* strain CP1, the cell concentration of Th17 was significantly increased and the cytokine IL-17 was also significantly increased after subsequent activation; hence, it can be concluded that Th17 is involved in the occurrence and progression of CP.¹³ Murphy et al¹⁴ found in the rat model of AIP that when CD4⁺T cells increased, the symptoms of CP were inhibited by inhibiting the function of IL-17. It can be concluded that cytokine IL-17 can induce the appearance of CP. Not only that but suppressor cells called Treg cells are also involved in this process. Breser et al¹⁵ showed that after reducing the activity of Treg cells, the prevalence of mice was reduced. Further studies found that CD25⁺Treg cells could inhibit Th1 or Tc1 autoimmune responses and activate IFN- γ in a mouse model of AIP. Under these conditions, the

expression of the CXCR3 receptor on T effector cells was controlled, thereby alleviating the pathological changes of CP. Quick et al¹⁶ studied the function of Treg in AIP. The results showed that when the function of Treg was inhibited, the transcriptional expression of IFN- γ and IL-17 was increased, and the secreted Th1 and Th17 cells could cause pelvic pain in autoimmune mice. This suggests that the suppressive effect of Treg cells combined with their secreted Th1 and Th17 cell activation contributes to the occurrence of pelvic pain. After reducing the level of IL-17 in mice with AIP, the number of CD25 and FoxP3 cells expressed by CD4⁺T increased,¹⁴ indicating that the synergistic effect of Th17 cells and Treg cells leads to the occurrence of CP. In addition, Ye et al¹⁷ used radioimmunoassay to measure the levels of cytokines IL-6 and IL-8 in the prostatic fluid of CP patients and found that the content of inflammatory cytokine IL-8 and anti-inflammatory cytokine IL-6 increased after the disease, which indicated that the immune activity of the prostate was active. At the same time, many immune antibodies such as IgG and IgA appear,¹⁸ which indicates that the pathogenesis of CP is related to the secretion of IL-6 and IL-8, and their secretion activates the body's immune response. In Murphy et al¹⁹ study, gram-positive strains from CPPS patients showed an enhanced ability to induce haptic allodynia. PI strains (*Staphylococcus haemolyticus* 2551, *Enterococcus faecalis* 427, and *Staphylococcus epidermidis* 7244) induced and maintained haptic allodynia responses (200% increase from baseline) in NOD/ShiLtJ mice for up to 28 days. Exploring the mechanism in depth, they suggested that prostatitis induced by the patient isolate specifically involved T cells and monocytes. Nuclear factor-activated B cell κ -light chain enhancement (NF- κ B) is a protein complex that controls the transcription of DNA, cytokine production, and cell survival. NF- κ B plays a key role in regulating the immune response to infection. In Zhang et al²⁰ study, using the experimental autoimmune prostatitis (EAP) model mouse to study the effects of the NF- κ B inhibitor SC75741 on prostatitis and pelvic pain after daily intraperitoneal injections of Eriocalyxin B (EriB) in mice, they found that the development of chronic pain, histological manifestations, and cytokine levels indicated that EriB could alleviate the severity pathway of EAP in a dose-dependent manner by down-regulating NF- κ B. The results indicate that the development of pain in CP is closely related to NF- κ B.

In conclusion, the immune response plays a key role in the pathogenesis of CP. The suppression of immunosuppressive cell activity, the imbalance of immune tolerance, and the imbalance of proinflammatory and anti-inflammatory mediators jointly promote the occurrence of the disease.¹² The increase of Th1 cells, the decrease of Th2 cells, the increase of Th17 cells, and the decrease of Treg cells that suppress inflammation jointly promote the occurrence of CP pain symptoms. Controlling the function of Treg cells and increasing the ratio of Th17/Treg cells can significantly increase the pain symptoms of prostatitis.²¹ The level of IL-8 in the prostatic fluid is positively correlated with the white blood cell count in prostatic fluid. Under the induction of chemotactic cytokines, a mass of white blood cells gathers in the

prostate, thereby forming an inflammatory response. IL-6 and other anti-inflammatory cytokines can inhibit the inflammatory response. The role of IL-8 is more prominent in the early stage of CP, while IL-6 increases more significantly in the middle and late stages of prostatitis.¹⁷

Urodynamic Changes

Urodynamic changes refer to changes in the secretory capacity of prostate cells caused by various factors directly or indirectly, and abnormal contraction of prostate smooth muscle, urethra, or bladder, resulting in abnormal urine storage or voiding process. These changes can lead to voiding dysfunction, pain in the lower abdomen and pelvic area, and bladder irritation (+).²²

During the disease course, the frequent contraction of the urethral sphincter in patients with CP/CPPS leads to bladder outlet obstruction and a large amount of residual urine production, or the simultaneous contraction of the detrusor and urethral sphincter leads to increased urethral pressure in the prostate, forcing a large amount of urine into the prostate in the opposite direction. Uric acid produces chemical stimulation in the prostate or urethra. Further inducing the occurrence of this disease, resulting in abnormal urination or pain and discomfort in the pelvic area.^{23,24} Moreover, the rat experiments of Bernoulli et al²⁵ proved that prostatic blood vessels are one of the sites of estrogen action from the distribution and location of inflammatory cells, and the increase of estrogen concentration has a high correlation with the development of prostate inflammation. The study of urodynamic changes related to gland inflammation shows that bladder function is abnormal and reflects obvious obstruction. The CP/CPPS rat model of Sugimoto et al²⁶ also induced the increase of cytokines IL-1 β , tumor necrosis factor (TNF- α), and chemokines in the prostate and urine of male rats by injection of estradiol. It is suggested that the related changes in sex hormone levels can induce the development of CP/CPPS. Neuroendocrine factors are also relevant. Neuroendocrine cells (NECs) of the prostate are a very special type of cells in the human body, which are multifunctional proteins composed of central nervous cells and epithelial cells with the functions of the two cells, respectively.²² Helle²⁷ found that chromogranin A (CgA), a major marker of neuroendocrine tumors and a mediator of inflammation, can be converted into vasostatin and catestatin (a cardiovascular regulatory protein), which can improve the permeability of endothelial cells. In turn, it promotes the extravasation of prostatic fluid. In addition, vasostatin-I and catestatin derived from CgA and its transformation can promote peripheral nerve endings to cause pain response and increase the concentration of CgA in inflammatory interstitial smooth muscle.²² Huang et al²⁸ showed that IL-8 and CXCR-2 are expressed by NECs in normal prostate tissue, which is positively correlated with the localized inflammatory sites of the prostate and the response of inflammatory cells. NECs produce IL-8 and regulate the function of NECs through autocrine mechanisms and can also promote the development of inflammation through IL-8. Conversely, inflammatory cells can also regulate the function of NECs.

Oxidative Stress

Increased production of lipid peroxidation products (reactive oxygen species and malondialdehyde) and decreased activities of antioxidant enzymes (superoxide dismutase and catalase) in Lin et al²⁹ EAP indicate an abnormal oxidative stress state in CP/CPPS. Elevated iron concentrations were also observed, and important biological properties associated with ferroptosis were identified, including downregulation of the systemic Xc-/GPX4 axis and up-regulation of the ACSL4/LPCAT3 axis. In addition, the reduction of NRF2/HO-1 indicates the vulnerability of EAP to the ferroptosis response.

Other Factors

It is also hypothesized that changes in ion concentrations play a role. Patients with chronic prostatitis (CP) often exhibit varying degrees of alterations in prostatic secretory function, resulting in notable modifications in prostatic fluid composition, particularly affecting the concentrations of K⁺ and Ca²⁺. These ion concentration shifts are considered one of the underlying mechanisms contributing to prostatitis. Liang et al³⁰ used the streptavidin/peroxidase immunohistochemical technique to detect streptavidin/peroxidase immunohistochemistry in tissue samples of men with benign prostatic hyperplasia and found that the KV1.3K⁺ pathway of prostatic epithelial cells in CP patients was shortened, which led to a significant increase in the content of K⁺ in the prostatic cavity. K⁺ penetrates the stroma through the gap between epithelial cells, stimulating peripheral nerves and causing clinical symptoms such as pain. The increase in intracellular Ca²⁺ concentration leads to the increased expression of the new calcium channel TRPV5 in epithelial cells, and calcium overload can also cause pain in CP.³¹ Similarly, newer studies have demonstrated that ferroptosis may be a key factor in the progression of CP. Mast cells are closely related to the development of chronic pelvic pain in a mouse model of EAP. Roman et al³² found that mast cell degranulation products were detected in the prostatic secretions and urine of CP/CPPS patients, and the expression of mast cell mediators tryptase- β and PAR2 was detected. Tryptase- β can induce pelvic pain and increase together with its receptor PAR2, which promotes the occurrence of CP/CPPS. PAR2 signaling in the dorsal root ganglion (DRG) leads to extracellular signal-regulated kinase 1/2 phosphorylation and calcium influx. A further study by Pattabiraman et al³³ showed that mMCP7 induced acute pelvic allodynia in C57BL/6J mice. In vitro studies of mMCP7 on mast cells in culture and isolated primary neurons demonstrated its ability to induce differential activation of pain- and inflammation-related molecules. mMCP7 and its human ortho δ -tryptase may play an important role in mediating the development of pelvic haptic allodynia in mouse models of pelvic pain and in CP/CPPS patients.

Mechanism of Acupuncture Effect

Acupuncture, as a traditional treatment method of TCM, boasts a long history and is known for its simplicity and effectiveness. Numerous high-quality modern studies have

further confirmed the definite analgesia and anti-inflammatory effects of acupuncture. Considering that the most prominent symptom of CP/CPPS is pain, which is closely related to inflammation, acupuncture's potential to address both inflammation and pain is particularly relevant.³⁴

The generation of pain involves the ascending conduction system and the descending regulatory system. During acute pain, acupuncture can stimulate the regulation of analgesia by μ -, δ -, and κ -opioid peptide receptors in the dorsal horn³⁵ and stimulate the projections of serotonin-containing macronuclear and noradrenaline-containing neurons to the spinal cord,³⁶ thereby inhibiting the activation of the pain-causing N-methyl-D-aspartate receptor and effectively inhibiting pain. It also mediates changes in the concentration of cholecystikinin octapeptide for central analgesia.³⁷ In addition, a variety of transmitters and modulators, including endogenous opioids, serotonin, glutamate, norepinephrine (NE), dopamine, gamma-aminobutyric acid, acetylcholine, and octreotide A, are involved in central analgesia with acupuncture.³⁸ At the same time, acupuncture can enhance the medial medulla oblongata of the descending regulatory system and the expression of endorphins, thereby alleviating hyperalgesia in patients with cancer bone pain.³⁹ Electroacupuncture also reduces neuropathic pain by increasing the content of gabaergic receptors in the spinal cord.⁴⁰ In addition, acupuncture can inhibit the upstream excitatory system and neuronal conduction efficiency by down-regulating glutamate, NMDA receptor, P2XR, SP, CGRP, and other neurotransmitters and receptors in the spinal cord, as well as the serum channels such as TRPV1 and HCN. It can also stimulate hypothalamic appetite-regulating neurons through up-regulation of opioid peptides (β -endorphin), MOR receptors, and bidirectional regulation of serotonin (5-HT) and its receptors (up-regulation of 5-HT 1A and down-regulation of 5-HT7R), thereby activating downstream pain-inhibitory pathways.⁴¹

Acupuncture can also relieve pain by inhibiting peripheral and central inflammatory responses to reduce peripheral and central sensitization, and anti-inflammation is the basic mechanism of acupuncture analgesia.⁴² Opioids released from peripheral inflammatory cells are involved in the suppression of inflammatory pain by electric acupuncture (EA).⁴³ Rittner et al⁴⁴ found that the degree of endogenous pain suppression was proportional to the number of cells producing opioid peptides. EA induces lymphocytes, monocytes/macrophages, and granulocytes to release endogenous opioids into inflamed skin, activate peripheral nerve endings, and suppress pain perception. In addition, many ion channels, including TRPV1, ASIC3, and NaV play important roles in inflammatory pain.⁴⁵ Upregulation of acid-sensing ion channel 3 (ASIC3) induced by nerve growth factor through phosphoserine 3-kinase/protein kinase B signaling induces pain. EA can rescue mechanical hypoalgesia by reducing ASIC3 overexpression in carrageenin and CPA-induced inflammation.⁴⁶ EA also reduced the noxious Nav sodium current in DRG neurons, while significantly increasing the expression of TRPV1 and related signaling pathways under this model, which could be further signifi-

cantly attenuated by EA treatment.⁴⁷ Among them, TRPV1, TRPV2, TRPV4 receptors, and chloride channels are mechanosensitive channels expressed by mast cells, and acupuncture can indirectly activate mast cells through the collagen network. Subsequently, mediators such as histamine, serotonin, adenosine triphosphate, and adenosine are released into intercellular material, thereby relieving pain caused by inflammation.⁴⁸ Wu et al⁴⁹ found large amounts of TRPV1, TRPV4, and ASIC3 in the anatomical layers of ST36, which may be involved in acupuncture-related analgesia. At the same time, acupuncture can also directly promote the expression of inflammatory mediators, thereby anti-inflammatory. Wang et al⁵⁰ found that EA could reduce TNF- α levels and increase IL-4 and IL-10 levels. In addition, EA could regulate the expression of proinflammatory factors TNF- α , IL-1 β , and IL-6 through the phosphorylation of extracellular signal-regulated protein kinase (ERK), thereby reducing the inflammatory response of bone and joint.⁵¹ This was also confirmed by the group of Chen et al,⁵² who also found that EA inhibited the levels of the proinflammatory cytokines TNF- α , IL-1 β , and IL-6 and increased the levels of the sympathetic neurotransmitter NE. EA-induced increase in synovial NE inhibits CXCL1-CXCR2-dependent overexpression of IL-6 in synovial macrophages in a β 2-adrenergic receptor-mediated manner. This indicates that EA can regulate inflammatory response and macrophage differentiation. In addition, acupuncture can inhibit neuroinflammation by inhibiting the JAK2/STAT3 and PI3K/mTOR pathways, down-regulating the chemokine receptor CX3CR1 on microglia, up-regulating the adenosine receptor A1R on astrocytes, inhibiting the activation of glial cells, and reducing TNF- α and other inflammatory substances.⁴¹ At the same time, these chemokines and their receptors, such as CX3CL1/CX3CR1, CXCL12/CXCR4, CCL2/CCR2, CXCL1/CXCR2, etc., can also produce analgesic effects through anti-inflammation under the action of acupuncture.⁵³

Moreover, immune regulation is also an important effector pathway. Chen et al⁵⁴ found that EA could promote Ca²⁺ influx through TRPV1, thereby stimulating the release of IL-17, IL-2, and IFN- γ from CD4⁺T cells, indicating that TRPV1 has a role in T cell activation. At the same time, Xu et al³⁴ found that acupuncture can effectively stimulate innate immune cytokines IL-1, IL-1 β , IL-6, IL-7, IL-18, TNF- α and adaptive immune cytokines IL-2, IL-12, IFN- γ , IL-4, IL-5, IL-10, IL-13, IL-17 as the immune response to alleviate inflammation and the pain. Zhao et al⁵⁵ found that acupuncture reduced autophagosome formation in lung tissue and increased IFN- γ content and decreased IL-4, IL-17, and TGF- β content. At the same time, the imbalance of Th1/Th2 and Treg/Th17 subsets of CD4⁺T lymphocytes was corrected. Dong et al⁵⁶ also demonstrated that acupuncture increased the number of CD4⁺IFN- γ ⁺ and CD4⁺Foxp3⁺ cells and the levels of Treg-type cytokine IL-10 in serum. At the same time, the number of CD4⁺IL-17A⁺ cells and the contents of IL-5, IL-13, and IL-17A in serum were reduced. More importantly, Ren et al⁵⁷ found that acupuncture and targeted delivery could alleviate pain through the targeted delivery of anti-inflammatory agents and an acupoint delivery system that mimics acupuncture, thereby regulating

inflammatory factors and restoring the Th17 / Treg cell balance. Wang et al⁵⁸ similarly pointed out that EA could modulate Tregs and $\gamma\delta$ T cells. In addition, in the study by Xue et al,⁵⁹ EA reduced inflammation and pain by reducing TLR4 expression, inhibiting NF- κ B activation, and down-regulating IL-1 β and IL-18 levels.

Potential Mechanism of Acupuncture Treatment for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

In summary, the pathogenesis of CP/CPPS is complicated and current research on the mechanism of acupuncture treatment for CP/CPPS has its limitations. However, by considering the effect mechanism of acupuncture and the pathogenesis of this disease, we aim to summarize and analyze the potential effect mechanism of acupuncture in the treatment of CP/CPPS.

The primary and most significant symptom of CP/CPPS is pain.^{8,60} In the pathogenesis of CP/CPPS, factors such as infection, inflammation, immune response, and oxidative stress can directly or indirectly affect patients' pain symptoms.⁶¹ Acupuncture therapy exerts its effects primarily through anti-inflammatory, analgesic, and immune function mechanisms, and these three aspects also complement and reinforce each other.

Immunologic Mechanism

Acupuncture in the treatment of CP/CPPS can achieve anti-inflammatory and analgesic effects through the immune mechanism. Chang et al⁶² found that, through the establishment of the CFA rat model, the morphological structure of rat prostate tissue was seriously damaged, and a large number of inflammatory cells were infiltrated. TNF- α , IL-1 β , and PGE2 levels were higher than those of the control group, and the expression of P2 \times 7R, NLRP3, caspase-1, and IL-18 mRNA was higher than those of the control group. EA at Guanyuan (CV 4), Zhongji (CV 3), Huiyang (BL 35), and Sanyinjiao (SP 6) can improve inflammation and pain symptoms in CPPS rats induced by CFA. EA at Guanyuan (CV 4), Zhongji (CV 3), Huiyang (BL 35), and Sanyinjiao (SP 6) can inhibit the release of inflammatory cytokines in CPPS by blocking the activation of P2 \times 7R/NLRP3 signaling pathway and produce anti-inflammatory and analgesic effects. In the rat model of CP, EA stimulation of bilateral "Jiayin" and "Zhongyin" points was found to be beneficial to the relief of chronic abacterial prostatitis, which may be related to the enhancement of cellular immune function by up-regulating the levels of plasma CD4⁺ and CD4⁺/CD8⁺.⁶³ Similarly, Yan et al⁶⁴ studies also confirmed that electroacupuncture at Sanyin acupoint could protect the prostate tissue from morphological damage and reduce the inflammatory response in AIP rats by reducing the activity of pro-inflammatory cytokines, vascular permeability, and inflammatory cell infiltration, and increasing the activity of antioxidant defense system.

Analgesic Mechanisms

Cyclooxygenase-2 (COX-2) is a membrane-bound protein that induces stimuli including proinflammatory cytokines

and growth factors, implying that COX-2 plays a role in both inflammation and cell growth control while being involved in neurotransmission, particularly for pain and fever.⁶⁵ In Wu et al⁶⁶ studies, they found that EA can effectively relieve pain in rats with CPPS, which may be related to the down-regulation of COX-2 and PGE2 and the up-regulation of β -EP. In addition, the above-mentioned role of the spinal cord pathway in analgesia was further confirmed. Xu et al⁶⁷ found that EA could exert anti-inflammatory and analgesic effects by regulating the expression of related genes in the PI3K-AKT/JAK-STAT signaling pathway in the spinal cord dorsal horn, and they believe that this study provides a putative new target of EA, which may have the anti-inflammatory and analgesic effects of CPPS. Capsaicin transmits information about noxious stimuli to the sensory neurons of the central nervous system through selective activation, triggering a burning sensation. TRPV1 is a key molecule in peripheral nociception.⁶⁸ Wu et al⁶⁹ believe that the analgesic mechanism of EA on CP/CPPS may be achieved by regulating the cAMP-PKA-TRPV1/PLC-PKC-TRPV1 signaling pathway.

Anti-inflammatory Mechanisms

Mast cells may synthesize chemokines and cytokines after activation. Cytokine and chemokine secretion that occurs after several hours may lead to chronic inflammation.⁷⁰ The release of particles and the material in the particles by cell breakdown can cause an immediate allergic reaction (inflammation) in the tissue.⁷¹ Li et al⁷² found that EA can alleviate prostate pain, inflammation, and fibrosis in chronic nonbacterial prostatitis rats, which may be related to inhibiting prostate mast cell degranulation and down-regulating the expression of inflammatory factors and TGF- β 1.

In summary, according to the pathogenesis and pathogenic targets of CP/CPPS, the mechanism of acupuncture in the treatment of CP/CPPS can also be explained from the three aspects of immunity, anti-inflammation, and analgesia, and there is also a cross and mutual influence among the three at the pathological level.

Potential Mechanisms

In addition to the mechanisms mentioned above, certain potential specific targets or effector pathways remain blind spots. To address this, we focused on the specific pathogenic factors involved in the pathogenesis of CP/CPPS and identified potential target points for acupuncture action. By analyzing the overlapping aspects, we created a Venn diagram to classify and illustrate these potential targets. See **Fig. 1**.

Early CD4⁺T cells can be divided into Th1, Th2, Th17, Treg, and other cells according to their activity, and these cells jointly affect the local inflammatory process of the prostate in different ways. At the same time, acupuncture can correct the imbalance of CD4⁺T lymphocyte subsets Th1/Th2 and Treg/Th17, thereby alleviating the local inflammation of the prostate. IFN- γ is the most important cytokine involved in anti-tumor immunity. IFN- γ plays a central role in the recognition and elimination of transformed cells by its growth-inhibiting, apoptosis-promoting, and immune-elicitation effects.⁷³ In AIP, the immune response is mainly mediated by Th1 cells accompanied by increased secretion of

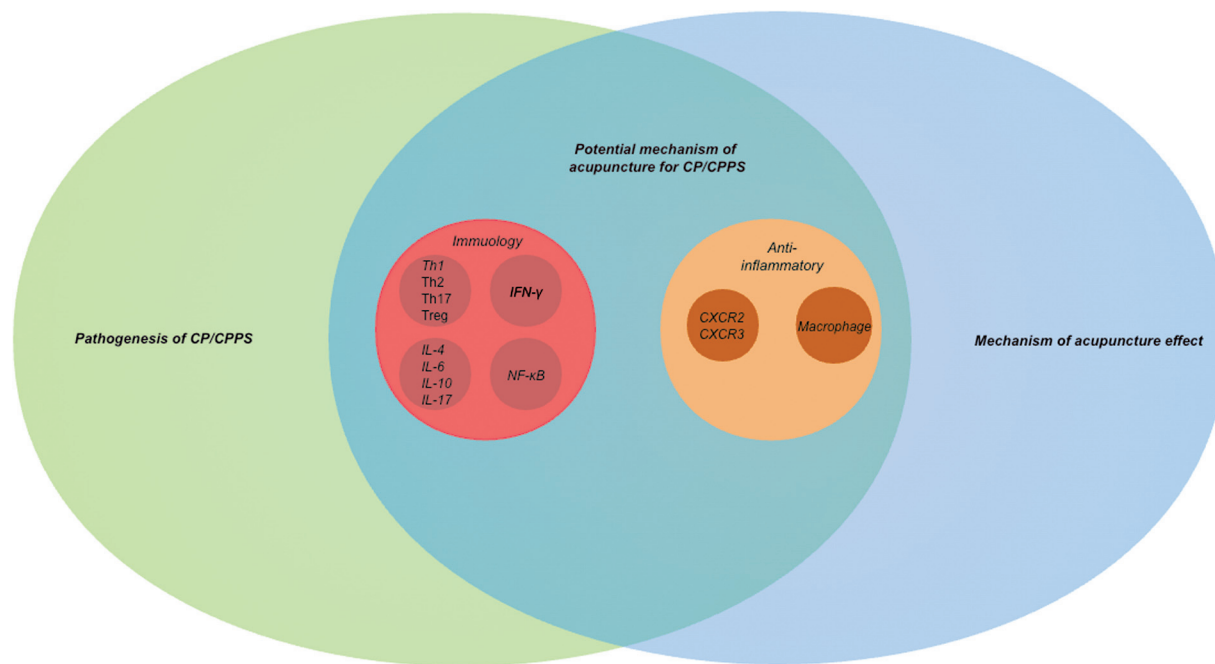


Fig. 1 Potential beneficial targets of acupuncture for CP/CPPS.

IFN- γ , while acupuncture can correct the number of CD4⁺IFN- γ ⁺ and CD4⁺Foxp3⁺ cells in the tissues. Meanwhile, another piece of evidence that the activity of Th2 cells was inhibited in the pathogenesis of CP was that IL-4 and IL-10 were significantly decreased, while manual acupuncture could effectively stimulate the adaptive immune cytokines IFN- γ , IL-4, IL-10, and IL-17 as an immune response. The level of anti-inflammatory cytokine IL-6 in the prostatic fluid of the patient increased after the disease, indicating that the immune activity of the prostate was active. Manual acupuncture could stimulate the immune response of innate immune cytokine IL-6. In addition, the development of pain in CP/CPPS is closely related to NF- κ B, and EA can alleviate inflammation and pain through NF- κ B inhibition.

The CXC chemokine family plays an important role in the mechanism of neuropathic pain. CXCR2 and CXCR3 play an important role in nociceptive transmission during the occurrence of neuropathic pain.⁷⁴ CD25⁺Treg cells can inhibit Th1 or Tc1 self-immune response and activate IFN- γ in a mouse model of AIP. Under this premise, the expression of the CXCR3 receptor on T effector cells was controlled. Acupuncture can mediate chemokines such as CX3CL1/CX3CR1, CXCL12/CXCR4, CCL2/CCR2, and CXCL1/CXCR2 and their receptors, thereby producing anti-inflammatory and analgesic effects. Lastly, it is noteworthy that macrophages, as previously discussed, infiltrate the prostatic stroma surrounding acini or ducts, consequently leading to the generation of inflammation and pain. EA can induce the release of endogenous opioids, activate peripheral nerve endings, and inhibit pain perception.

Discussion

Due to the complex characteristics and unclear pathogenesis of CP/CPPS, this condition has become a significant challenge

for many patients and specialists. Acupuncture, as essential therapy in TCM, has been proven to be an effective alternative. Presently, the efficacy of acupuncture in treating CP/CPPS is supported by substantial evidence. A systematic review and meta-analysis⁷⁵ pointed out that the current evidence supports acupuncture as an effective method to treat the symptoms induced by CP/CPPS, especially in relieving pain. A multicenter randomized controlled trial⁷⁶ demonstrated that 20 acupuncture sessions over 8 weeks resulted in greater improvement in symptoms of moderate-to-severe CP/CPPS, with durable effects up to 24 weeks after treatment.

The mechanism underlying acupuncture's effectiveness in treating CP/CPPS is closely related to the pathogenesis of the disease. Through immune regulation, acupuncture helps balance various cytokines, thereby inhibiting local inflammation and producing indirect or direct analgesic effects. TNF- α , lymphocytes, cytokines, and nerve growth factor play different roles in the treatment of the disease. Moreover, helper T cells, regulatory T cells, interleukins, interferons, nuclear transcription factors, chemokine receptors, and macrophages may also be involved in mediating the relief of CP/CPPS symptoms through acupuncture.

There is still considerable scope for exploring the specific targets or pathways of acupuncture for the treatment of this disease. Various helper cells, which belong to the subset of T cells, play certain roles in the pathogenesis of CP/CPPS. Acupuncture stimulation may be involved in the secretion of these cytokines, the maintenance, and inhibition of cell proliferation, and can indirectly activate interleukins and produce anti-inflammatory effects. In addition, acupuncture may also potentially mediate macrophages and lymphokines in lymphocytes, which are involved in the pathogenesis of CP/CPPS, and further regulate immune function. At the same

time, in the process of immune response, it can activate some chemokines and inhibit some signal transduction pathways. These corresponding targets or pathways are involved in the pathogenesis and pathogenesis of CP/CPSPS. Although acupuncture has been shown to impact these specific targets and pathways in some diseases, there are still gaps in animal experiments for CP/CPSPS models.

Extensive evidence supports the notion that acupuncture can modulate the immune process and contribute to symptom improvement. Currently, the application of acupuncture in the treatment of CP/CPSPS is still limited to the anti-inflammatory and analgesic aspects, with clinical acupoints selection often based on this function. However, it is essential to acknowledge that patients with CP/CPSPS frequently experience mental and emotional changes. While acupuncture treatment shows promise in improving brain function, the lack of support from basic experiments poses challenges in establishing a basis to guide clinical treatment for psychiatric symptoms.

Conclusion

Despite the substantial clinical evidence demonstrating the effectiveness of acupuncture in treating CP/CPSPS, there remains an urgent need to explore its therapeutic mechanism due to the limited availability of basic research. In addition to its anti-inflammatory and analgesic effects, the impact of CP/CPSPS on patients' mental and brain functions should also be taken into account to delve into deeper effect pathways. Expanding our understanding of acupuncture's mechanisms in addressing both physical and psychological aspects of CP/CPSPS can pave the way for more comprehensive and effective treatment strategies.

CRedit Authorship Contribution Statement

Y.Y. was responsible for conceptualization, formal analysis, investigation, visualization, and writing the original draft. X.P. was responsible for funding acquisition, supervision, writing review & editing. C.T. was responsible for methodology, validation, writing review and editing.

Funding

This work was supported by Chongqing Municipal Famous TCM Department Construction Project (Chongqing Traditional Chinese Medicine (2022) No. 2).

Conflict of Interest

The authors declare no conflict of interest.

References

- Zhang MJ, Bin B, Shang XJ, et al. Expert consensus on the diagnosis and treatment of chronic prostatitis. *Chin J Integr Tradit Wes Med* 2015;35(08):933–941
- Rees J, Abrahams M, Doble A, Cooper A. Prostatitis Expert Reference Group (PERG) Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline. *BJU Int* 2015;116(04):509–525
- Murphy AB, Macejko A, Taylor A, Nadler RB. Chronic prostatitis: management strategies. *Drugs* 2009;69(01):71–84
- Mao DD. Study on TCM Constitution, Syndrome Types of Chronic Prostatitis and Influencing Factors of NIH-CPSI. Huzhou: Huzhou Teachers College; 2020
- Wan S. 60 cases of type III chronic prostatitis treated with chinese medicine by ultrasonic electric conductive drug delivery instrument. *Henan Tradit Chin Med* 2014;34(11):2228–2229
- Yu XJ, Gao QH. Guideline for the multidisciplinary diagnosis and treatment of chronic prostatitis with integrated traditional chinese and western medicine. *Nat J Andr* 2020;26(04):369–376
- Pena VN, Engel N, Gabrielson AT, Rabinowitz MJ, Herati AS. Diagnostic and management strategies for patients with chronic prostatitis and chronic pelvic pain syndrome. *Drugs Aging* 2021;38(10):845–886
- Zaidi N, Thomas D, Chughtai B. Management of chronic prostatitis (CP). *Curr Urol Rep* 2018;19(11):88
- Zheng XT, Chen SH, Yao WL, et al. Research progress on the etiology and pathogenesis of chronic prostatitis. *Mod Diag Treat* 2019;30(11):1810–1814
- Vykhovanets EV, Resnick MI, MacLennan GT, Gupta S. Experimental rodent models of prostatitis: limitations and potential. *Prostate Cancer Prostatic Dis* 2007;10(01):15–29
- Haverkamp JM, Charbonneau B, Crist SA, et al. An inducible model of abacterial prostatitis induces antigen specific inflammatory and proliferative changes in the murine prostate. *Prostate* 2011;71(11):1139–1150
- Liu Y, Chen XG, Liang CZ. Research progress on the immune mechanism of chronic prostatitis. *Nati J Andr* 2017;23(07):652–655
- Simons BW, Durham NM, Bruno TC, et al. A human prostatic bacterial isolate alters the prostatic microenvironment and accelerates prostate cancer progression. *J Pathol* 2015;235(03):478–489
- Murphy SF, Schaeffer AJ, Done J, et al. IL17 mediates pelvic pain in experimental autoimmune prostatitis (EAP). *PLoS One* 2015;10(05):e0125623
- Bresler ML, Lino AC, Motrich RD, Godoy GJ, Demengeot J, Rivero VE. Regulatory T cells control strain specific resistance to experimental autoimmune prostatitis. *Sci Rep* 2016;6:33097
- Quick ML, Wong L, Mukherjee S, Done JD, Schaeffer AJ, Thumbikat P. Th1-Th17 cells contribute to the development of uropathogenic *Escherichia coli*-induced chronic pelvic pain. *PLoS One* 2013;8(04):e60987
- Ye HY, Hou SK, Bai WJ, Deng QP. Expression and significance of IL-6 and IL-8 in prostatic fluid of patients with chronic prostatitis. *Chin J Urol* 2003;(04):62–64
- Hu XP, Bai WJ, Zhu JC, Wang XF. Bacterial and immunological study of chronic prostatitis. *Chin J Urol* 2002;(01):29–31
- Murphy SF, Anker JF, Mazur DJ, Hall C, Schaeffer AJ, Thumbikat P. Role of gram-positive bacteria in chronic pelvic pain syndrome (CPPS). *Prostate* 2019;79(02):160–167
- Zhang LG, Yu ZQ, Yang C, et al. Effect of Eriocalyxin B on prostatic inflammation and pelvic pain in a mouse model of experimental autoimmune prostatitis. *Prostate* 2020;80(16):1394–1404
- Done JD, Rudick CN, Quick ML, Schaeffer AJ, Thumbikat P. Role of mast cells in male chronic pelvic pain. *J Urol* 2012;187(04):1473–1482
- Su Y, Liang CZ. Research progress on the relationship between prostatic neuroendocrine cells and chronic prostatitis. *Nat J Andr* 2012;18(07):631–634
- Zheng XT, Chen D, Ying S, Ma L, Wang JH. Effect of white blood cell count in prostatic fluid on the degree of chronic prostatitis symptoms. *Zhonghua Zhongyiyao Xuekan* 2016;34(08):1914–1916
- Zhang BB, Bai AS. Progress in pathogenesis and treatment of chronic prostatitis. *Chin J Diff Comp Cases* 2014;13(03):326–329
- Bernoulli J, Yatkin E, Talvitie EM, Santti R, Streng T. Urodynamic changes in a noble rat model for nonbacterial prostatic inflammation. *Prostate* 2007;67(08):888–899
- Sugimoto M, Oka M, Tsunemori H, Yamashita M, Kakehi Y. Effect of a phytotherapeutic agent, Eviprost®, on prostatic and urinary cytokines/chemokines in a rat model of nonbacterial prostatitis. *Prostate* 2011;71(04):438–444

- 27 Helle KB. Regulatory peptides from chromogranin A and secretogranin II. *Cell Mol Neurobiol* 2010;30(08):1145–1146
- 28 Huang J, Yao JL, Zhang L, et al. Differential expression of interleukin-8 and its receptors in the neuroendocrine and non-neuroendocrine compartments of prostate cancer. *Am J Pathol* 2005;166(06):1807–1815
- 29 Lin D, Zhang M, Luo C, Wei P, Cui K, Chen Z. Targeting ferroptosis attenuates inflammation, fibrosis, and mast cell activation in chronic prostatitis. *J Immunol Res* 2022;2022:6833867
- 30 Liang CZ, Guo QK, Hao ZY, et al. K channel expression in prostatic epithelium and its implications in men with chronic prostatitis. *BJU Int* 2006;97(01):190–192
- 31 Fan S, Liang CZ, Hao ZY, et al. Expression and significance of TRPV5 in prostatic epithelial cells of patients with chronic prostatitis. *Chin J Andr* 2007;(10):12–15
- 32 Roman K, Done JD, Schaeffer AJ, Murphy SF, Thumbikat P. Trypsinase-PAR2 axis in experimental autoimmune prostatitis, a model for chronic pelvic pain syndrome. *Pain* 2014;155(07):1328–1338
- 33 Pattabiraman G, Liu Z, Paul M, Schaeffer AJ, Thumbikat P. mMCP7, a mouse ortholog of δ trypsinase, mediates pelvic tactile allodynia in a model of chronic pelvic pain. *Front Pain Res (Lausanne)* 2022;2:805136
- 34 Xu Y, Hong S, Zhao X, et al. Acupuncture alleviates rheumatoid arthritis by immune-network modulation. *Am J Chin Med* 2018;46(05):997–1019
- 35 Li JJ, Chen RM, Liu L, et al. Effects of electroacupuncture on the immunoreactivity of focal cutaneous CB2Receptor Positive Cells In Arthritis Rats. *Acup Res* 2007;(01):9–15
- 36 Li A, Wang Y, Xin J, et al. Electroacupuncture suppresses hyperalgesia and spinal Fos expression by activating the descending inhibitory system. *Brain Res* 2007;1186:171–179
- 37 Huang C, Hu ZP, Jiang SZ, Li HT, Han JS, Wan Y. CCK(B) receptor antagonist L365,260 potentiates the efficacy to and reverses chronic tolerance to electroacupuncture-induced analgesia in mice. *Brain Res Bull* 2007;71(05):447–451
- 38 Chen T, Zhang WW, Chu YX, Wang YQ. Acupuncture for pain management: molecular mechanisms of action. *Am J Chin Med* 2020;48(04):793–811
- 39 Zhang C, Xia C, Zhang X, Li W, Miao X, Zhou Q. Wrist-ankle acupuncture attenuates cancer-induced bone pain by regulating descending pain-modulating system in a rat model. *Chin Med* 2020;15(01):13
- 40 Jiang SW, Lin YW, Hsieh CL. Electroacupuncture at Hua Tuo Jia ji acupoints reduced neuropathic pain and increased GABAA receptors in rat spinal cord. *Evid Based Complement Alternat Med* 2018;2018:8041820
- 41 Chen Y, Li D, Li N, et al. Role of nerve signal transduction and neuroimmune crosstalk in mediating the analgesic effects of acupuncture for neuropathic pain. *Front Neurol* 2023;14:1093849
- 42 Lu SS, Wang JQ, Huang J, et al. Study on the anti-inflammatory and analgesic mechanism of acupuncture. *J Clin Acup Moxib* 2021;37(05):1–4
- 43 Zhang R, Lao L, Ren K, Berman BM. Mechanisms of acupuncture-electroacupuncture on persistent pain. *Anesthesiology* 2014;120(02):482–503
- 44 Rittner HL, Brack A, Machelska H, et al. Opioid peptide-expressing leukocytes: identification, recruitment, and simultaneously increasing inhibition of inflammatory pain. *Anesthesiology* 2001;95(02):500–508
- 45 Linley JE, Rose K, Ooi L, Gamper N. Understanding inflammatory pain: ion channels contributing to acute and chronic nociception. *Pflügers Arch* 2010;459(05):657–669
- 46 Chen WH, Hsieh CL, Huang CP, et al. Acid-sensing ion channel 3 mediates peripheral anti-hyperalgesia effects of acupuncture in mice inflammatory pain. *J Biomed Sci* 2011;18(01):82
- 47 Lu KW, Hsu CK, Hsieh CL, Yang J, Lin YW. Probing the effects and mechanisms of electroacupuncture at ipsilateral or contralateral ST36–ST37 acupoints on CFA-induced inflammatory pain. *Sci Rep* 2016;6:22123
- 48 Wang LN, Wang XZ, Li YJ, et al. Activation of subcutaneous mast cells in acupuncture points triggers analgesia. *Cells* 2022;11(05):809
- 49 Wu SY, Chen WH, Hsieh CL, Lin YW. Abundant expression and functional participation of TRPV1 at Zusanli acupoint (ST36) in mice: mechanosensitive TRPV1 as an “acupuncture-responding channel”. *BMC Complement Altern Med* 2014;14:96
- 50 Wang HF, Chen L, Xie Y, et al. Electroacupuncture facilitates M2 macrophage polarization and its potential role in the regulation of inflammatory response. *Biomed Pharmacother* 2021;140:111655
- 51 Chen H, Shao X, Li L, et al. Electroacupuncture serum inhibits TNF- α -mediated chondrocyte inflammation via the Ras–Raf–MEK1/2–ERK1/2 signaling pathway. *Mol Med Rep* 2017;16(05):5807–5814
- 52 Chen W, Zhang XN, Su YS, et al. Electroacupuncture activated local sympathetic noradrenergic signaling to relieve synovitis and referred pain behaviors in knee osteoarthritis rats. *Front Mol Neurosci* 2023;16:1069965
- 53 Lyu Z, Guo Y, Gong Y, et al. The role of neuroglial crosstalk and synaptic plasticity-mediated central sensitization in acupuncture analgesia. *Neural Plast* 2021;2021:8881557
- 54 Chen L, Xu A, Yin N, et al. Enhancement of immune cytokines and splenic CD4⁺ T cells by electroacupuncture at ST36 acupoint of SD rats. *PLoS One* 2017;12(04):e0175568
- 55 Zhao H, Dong F, Li Y, et al. Inhibiting ATG5 mediated autophagy to regulate endoplasmic reticulum stress and CD4⁺ T lymphocyte differentiation: Mechanisms of acupuncture's effects on asthma. *Biomed Pharmacother* 2021;142:112045
- 56 Dong M, Wang WQ, Chen J, et al. Acupuncture regulates the balance of CD4⁺ T cell subtypes in experimental asthma mice. *Chin J Integr Med* 2019;25(08):617–624
- 57 Ren S, Liu H, Wang X, et al. Acupoint nanocomposite hydrogel for simulation of acupuncture and targeted delivery of triptolide against rheumatoid arthritis. *J Nanobiotechnology* 2021;19(01):409
- 58 Wang Y, Chen Y, Meng L, et al. Electro-acupuncture treatment inhibits the inflammatory response by regulating $\gamma\delta$ T and Treg cells in ischemic stroke. *Exp Neurol* 2023;362:114324
- 59 Xue X, Liu Y, Wang SH, et al. [Effect of electroacupuncture intervention on relieving pain and inflammation by suppressing TLR4/NF- κ B signaling in rats with primary dysmenorrhea]. *Zhen Ci Yan Jiu* 2023;48(01):63–70
- 60 Zhang MJ, Chang DG, Bin B, et al. Diagnosis and treatment guide of integrated Chinese and western medicine for chronic prostatitis. *Chin J Andr* 2023;37(01):3–17
- 61 Guideline for the diagnosis and treatment of chronic prostatitis/chronic pelvic pain syndrome. *Nat J Andr* 2022;28(06):544–559
- 62 Chang XU, Na LI, Xiaoling WU, et al. Effect of electroacupuncture on inflammatory signal expression in local tissues of rats with chronic pelvic pain syndrome based on purinergic 2 \times 7 receptor/NOD-like receptor pyrin domain-containing 3 signal pathway. *J Tradit Chin Med* 2022;42(06):965–971
- 63 Liu AG, Li HZ, Yan XK, et al. [Effect of electroacupuncture at “Sanyin” acupoints on cellular immune function in rats with chronic abacterial prostatitis]. *Zhen Ci Yan Jiu* 2013;38(03):192–197
- 64 Yan XK, Liu AG, He TY, et al. [Decreasing effect of electroacupuncture on inflammatory cytokines in autoimmune prostatitis rats]. *Zhonghua Nan Ke Xue* 2013;19(05):451–455
- 65 Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol* 1998;38(01):97–120
- 66 Wu XL, Li N, Xu C, et al. [Effect of electroacupuncture on pain threshold and expression of pain-related factors cyclooxygenase-2, prostaglandin E2 and β -endorphin in rats with chronic pelvic pain syndrome]. *Zhen Ci Yan Jiu* 2022;47(06):531–536

- 67 Xu C, Cheng K, Wu XL, et al. Expression profiling of L5–S2 spinal cord dorsal horn in a rat model of chronic pelvic pain syndrome uncovers potential mechanism of electroacupuncture mediated inflammation and pain responses. *J Pain Res* 2022;15:2067–2084
- 68 Tominaga M, Tominaga T. Structure and function of TRPV1. *Pflugers Arch* 2005;451(01):143–150
- 69 Wu XL, Cheng K, Xu C, et al. Effect of electroacupuncture on cyclic adenosine monophosphate-protein kinase A-vanillic acid receptor subtype 1 of the transient receptor potential/PLK-protein kinase C-vanillic acid receptor subtype 1 of the transient receptor potential pathway based on RNA-seq analysis in prostate tissue in rats with chronic prostatitis/chronic pelvic pain syndrome. *Front Neurosci* 2022;16:938200
- 70 Metcalfe DD, Baram D, Mekori YA. Mast cells. *Physiol Rev* 1997;77(04):1033–1079
- 71 Breedveld A, Groot Kormelink T, van Egmond M, de Jong EC. Granulocytes as modulators of dendritic cell function. *J Leukoc Biol* 2017;102(04):1003–1016
- 72 Li ZH, Zhao XD, Ming SR, Li X, Hu JW, Chen YL. [Effect of electroacupuncture on the morphology of prostate and degranulation of mast cells in rats with chronic nonbacterial prostatitis]. *Zhen Ci Yan Jiu* 2023;48(01):56–62
- 73 Kursunel MA, Esendagli G. The untold story of IFN- γ in cancer biology. *Cytokine Growth Factor Rev* 2016;31:73–81
- 74 Piotrowska A, Ciapała K, Pawlik K, Kwiatkowski K, Rojewska E, Mika J. Comparison of the effects of chemokine receptors CXCR2 and CXCR3 pharmacological modulation in neuropathic pain model—in vivo and in vitro study. *Int J Mol Sci* 2021;22(20):11074
- 75 Qin Z, Guo J, Chen H, Wu J. Acupuncture for chronic prostatitis/chronic pelvic pain syndrome: a GRADE-assessed systematic review and meta-analysis. *Eur Urol Open Sci* 2022;46:55–67
- 76 Sun Y, Liu Y, Liu B, et al. Efficacy of acupuncture for chronic prostatitis/chronic pelvic pain syndrome: a randomized trial. *Ann Intern Med* 2021;174(10):1357–1366