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REVIEW ARTICLE

The Effect of Immune Cell Abnormalities in the Pathogenesis of Chronic Prostatitis / Chronic Pelvic Pain Syndrome

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ABSTRACT
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a prevalent urological condition with high incidence, complicated etiology, and unsatisfactory treatment. It seriously affects the quality of life of patients, and the pathogenesis of the disease is still not clear. This paper reviews the recent progress of research on the effect of immune cell abnormalities in CP/CPPS.

KEYWORDS: Chronic prostatitis/chronic pelvic pain syndrome(CP/CPPS); immune cells; cytokines; Pelvic Pain; inflammation

INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a prevalent disease in adult men, with almost 50% of men experiencing symptoms of prostatitis at some point in their lives. However, the pathogenesis of this disease is currently unclear. However, there have been many encouraging new findings in recent years, such as the proliferation of memory T, T helper 1(Th1), Th17, and Th22 cells in the peripheral blood of patients with CP/CPPS, IL-1, IL-6, IFN-γ, TNF-α, and immunoglobulins were elevated in the interleukin and semen of the tumor necrosis factor[1]. Prostate antigen-specific autoreactive T cells have been identified in patients with CP/CPPS[2]. These results suggest that some abnormalities in immune cells in the body may play a vital role in chronic prostatitis. Therefore, Understanding the potential role of immune cell abnormalities can contribute to a deeper comprehension of the pathogenesis of CP/CPPS and provide new targets for treating this disease.

The effect of immune cell abnormalities in CP/CPPS inflammation

Abnormal immune cells contribute to the promotion of inflammation.
In recent years, researchers have carried out a lot of clinical research and investigations on the epidemiology of chronic prostatitis and divided the type III chronic prostatitis (CP/CPPS) into two subtypes of prostatitis: Type IIIA, which is inflammatory CPPS, and Type IIIB, which is non-inflammatory CPPS. Type III is the most prevalent type of prostatitis, accounting for over 90% of cases[3]. The patients with Type IIIA CP all had local microcirculation disturbance of the prostate and were prone to pelvic pain and abnormal micturition. The leukocytes in the prostatic fluid were also slightly abnormal. Rivero VE *et al.* found that patients with CP/CPPS established an

inflammatory state without invasive infectious agents, suggesting that autoimmune processes may be involved[4]. After conducting a comprehensive review and comparing the inflammatory responses of autoimmune diseases and CP/CPPS, it may be more accurate to classify CP/CPPS as an autoimmune disease from biological immunology and the immune microenvironment perspective. As a result, immune cells and cytokines involved in the pathogenesis of CP/CPPS have become the focus of recent research.

Macrophages

Motrich RD et al. [5] collected peripheral blood and semen samples from patients with CP/CPPS and healthy controls. Inflammation in the male genital tract was indicated by high levels of IFN-γ, IL-17, IL-1β, and IL-8, as well as higher counts of leukocytes (mainly CD4 T lymphocyte and macrophages) in semen compared to controls. The study discovered that patients with CPPS displayed Th1 and Th17 immune responses specific to PAP (prostate acid phosphatase antigen). These immune responses were linked to chronic inflammation of the male genital tract and reduced semen quality. The evidence indicates that these immune responses may underlie the onset and progression of chronic pelvic pain and inflammation of the male genitalia. In their study, Liu Y et al. [6] discovered that macrophages and their associated cytokines play a crucial role in activating CP/CPPS. They observed dysfunction in T-regulatory and Th17 cells and aberrant regulation of Th1 and Th2 cells.
TNF-α is an inflammatory cytokine primarily produced by macrophages. Together with IL-8, it is susceptible to detecting serum and prostatic fluid in patients with CP. Additionally, the production of TNF-α in large quantities can promote the synthesis of prostaglandins and further facilitate the body's significant inflammatory response. TNF-α is an initial factor in the inflammatory response and can further stimulate the release of the pro-inflammatory cytokine IL-8 [7]. As a chemokine, IL-8 can bind to specific receptors and regulate the inflammatory process. According to the research of Yunhai Zhu *et al.* [8] on elderly patients with Type III CP and healthy people, the serum levels of IL-8 and TNF-α were measured in two groups. The results showed that the serum levels of TNF-α and IL-8 were significantly increased in elderly patients with type III CP; detecting these cytokines in serum helps evaluate the severity of type III CP. Linsday *et al.* [9] randomly divided type III prostatitis patients with sexual dysfunction into two groups for clinical experimental study. The study results confirm that residual urine and serum TNF-α and IL-8 levels in the treatment group decreased significantly after treatment. Therefore, Drug therapy reduces serum levels of TNF-α and IL-8 in patients with type III prostatitis, which may improve clinical symptoms by decreasing the expression of these cytokines.

DCs (epidermal cells)

According to recent research, abnormalities in the DC have been identified as a significant factor in inducing prostatitis. DCs, or epidermal cells, are a particular cell type in the immune system. In normal human prostate tissue, the number of DCs is small and only occasionally found in the interstitial space [10,11]. In the rat model of EAP (experimental autoimmune prostatitis), peritoneal DCs accounted for 1% of the total peritoneal cells. Correa SG *et al.* [12] demonstrated that injection of peritoneal DCs collected from the EAP model into normal rats, intravenously or intraperitoneally, induced an autoimmune response to the extract of the male accessory gland of rats. Peritoneal dendritic cells (DCs) are a significant contributor to the development of autoimmune prostatitis. YY Zhao *et al.* [13] speculated that DCs in the foreskin may recognize and present pathogens, activate T cells, and develop allergic inflammation and autoimmune responses that contribute to the pathogenesis of CP/CPPS.

T cell population

T lymphocytes primarily activate IFN-γ. This activation can promote the killing of pathogenic

microorganisms by macrophages and induce lymphokine-activated killer cell activity with IL-2. Additionally, it can encourage the expression of IL-2R in T lymphocytes [14]. In addition to macrophages, on this basis, Zhenyan Zhu *et al.* analyzed the effect of Shenling Baizhu San on the hemorheology index and the serum levels of TNF-α, IL-2, and IL-6 in patients with chronic prostatitis disease. The results showed that these biochemical indicators were significantly lower than those before treatment, and they can effectively relieve the symptoms, stabilize the hemorheology of the body, reduce the inflammatory reaction, and improve the clinical curative effect [15]. In addition, Yandong He *et al.* found that the expression of TNF-α in the prostate tissue of normal rats was significantly lower than that of CP/CPPS model rats[16]. These results suggest that TNF-α, IFN-γ, and IL-10 are involved in developing chronic prostatitis and directly affect the prognosis.

The role of abnormal immune cells in inhibiting inflammation

Following prostatitis, the initial inflammatory factors induce a series of inflammatory reactions. Some cells and cytokines express abnormally, causing the development of inflammation, while others participate in the alleviation and outcome of inflammation.

T cell population

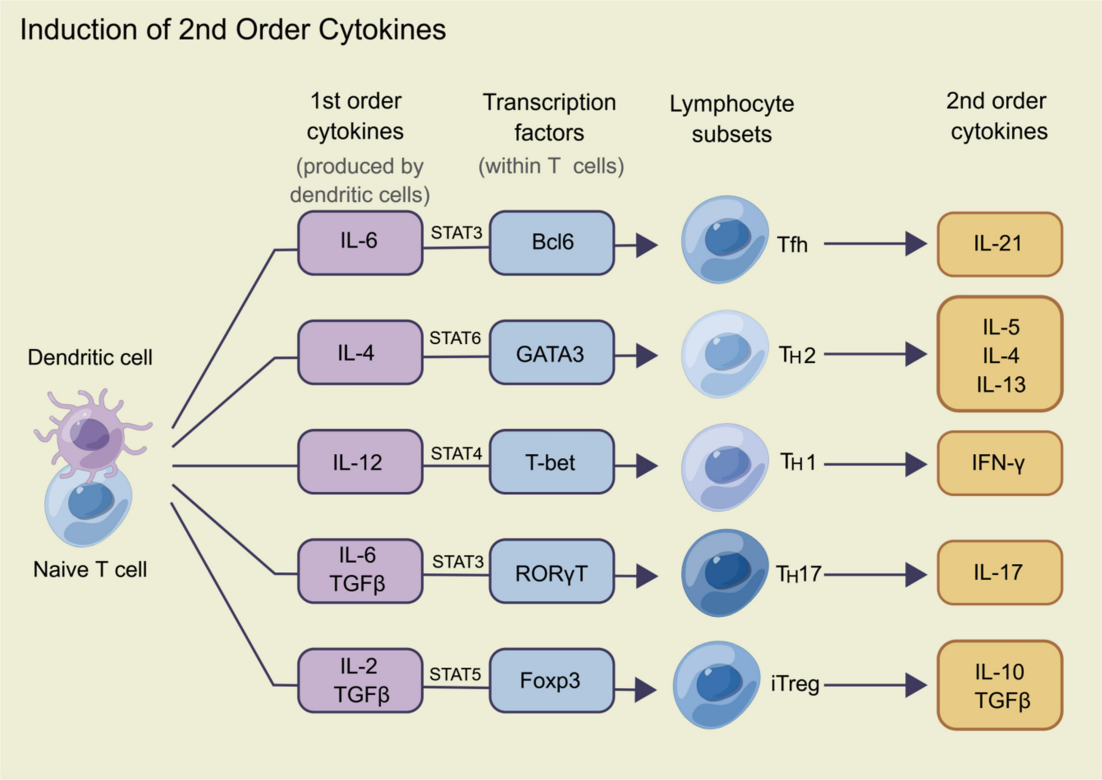
Treg cells, a subset of helper T cells, are responsible for inhibiting inflammatory processes and mediating negative regulation of immune inflammation [17]. Treg cells express the transcription factor Foxp3, which is critical for the stable expression of Foxp3. Treg cells entirely suppress different types of chronic inflammation and prevent their differentiation into inflammatory effector cells [18]. In addition, the percentage of Treg cells in the serum of patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) was markedly reduced [19]. The mRNA level of the Foxp3 gene was significantly decreased, the serum level of TNF-α was increased, and the serum level of TGF-β was decreased [20]. Chen J *et al.* [21] showed that Foxp3 promoter methylation levels were elevated, Foxp3 expression was reduced in the EAP model, and that injection of the DNA methylation inhibitor AZA into EAP mice alleviated prostate inflammation. Therefore, increasing the expression of Foxp3 by decreasing the methylation of Foxp3 promoter may be a potential therapeutic target of CP/CPPS. The findings confirm that Treg cells' loss of function and tolerance are significant factors in chronic prostatitis; this provides new ideas for improving and treating the condition.

NK cells (natural killer cells)

Natural killer cells were initially considered immune lymphocytes with cytolytic functions. Protecting the human body against viral infections and tumor invasions is crucial. Kodak JA *et al.* [22] showed that CD14+ monocytes respond to KLK3 and stimulate NK cells to secrete IFN-γ and that KLK3 will stimulate pbmcs(peripheral blood mononuclear cells) from patients' peripheral blood; it can induce the proliferation of NK cells and increase the level of IFN-γ. In normal rats, NK cells make up approximately 30% of the total lymphocyte count in the prostate, which was significantly higher than that in the mesenteric lymph nodes, bone marrow lymph nodes, blood, and spleen. Therefore, NK cells are likely to participate in the immune response to prostate-specific antigens and potentially regulate and inhibit the pathological process of prostate inflammation. However, the specific mechanism needs further study.

Numerous studies have shown that prostatitis is a complex inflammatory process and that many cells and inflammatory factors are involved in developing inflammation. We can focus on some potential cell or cytokine expression mechanisms to conduct in-depth research, open up new clinical treatment ideas, and maybe a breakthrough in the treatment of prostatitis.

Figure I: Induction of 2nd Order Cytokines



Study on the mechanism of pain induced by immune cell abnormalities in CP/CPPS

CP/CPPS is often associated with unexplained pain; abnormal cytokines such as IL-1β secreted by immune cells can increase the concentration of Cyclooxygenase II (Cox-2), increase the secretion of prostaglandin E2(PGE2), promote local inflammatory reaction, and induce or aggravate pain [23].

The effect of immune cell abnormalities in CP/CPPS pain

Mast cells

Mast cells play a pivotal role in the pathogenesis of chronic pelvic pain. As a multifunctional immune cell, the mast cell has become the main focus of CP/CPPS research. Upon activation, mast cells promptly release a diverse array of stored molecules, such as histamine, 5-hydroxytryptamine, tryptophan, thymosin, prostaglandin D2 (PGD2), and leukotriene B4, which elicit an early allergic response [24-26]. Mingxing Zheng *et al.* found an increase in the number and trypsin of mast cells in the prostatic fluid samples collected from patients with CPPS, indicating that the abnormal expression of mast cells is an essential link in the process of CPPS [27]. Z Song *et al.* [28] found that decreased and degranulated mast cells could reduce pelvic pain in CP rats. In the EAP mouse model, Rudick CN *et al.* [29] found a significant increase in nerve density in prostate tissue. Mast cells were comparably increased in the prostate tissue of immunized NOD and C57BL/6 mice and were found to be activated [30]. Miller LJ *et al.* [31] found increased NGF levels in the semen of CPPS patients, and Watanabe T *et al.* [32] found a direct correlation with the degree of pain. The level of NGF in the seminal plasma of patients with CPPS was increased and positively correlated with the severity of NGF pain.

Y He *et al.* [33] found that the dysfunction of CP rats could be alleviated by drug treatment, which down-regulated mast cell activation and TGF-β/Wnt/β-catenin pathway activity. These results

suggest that mast cells may play a vital role in the pathogenesis and development of CP/CPPS and further confirm the critical role of mast cells in pain in CP/CPPS. However, this inference is based partly on animal experimental evidence, and the specific role of mast cells in human CP/CPPS needs to be further studied.

T cell population

The differentiation and formation of Th17 and Treg cells are controlled by many cytokines [34], including IL-6, IL-21, IL-23, and TGF-β. In CP/CPPS, Th17 and Treg cells are essential inflammatory modulators. Th17 lymphocyte is a newly discovered subset of helper CD4 T cells, which may be involved in the pathogenesis of many autoimmune diseases and has attracted much attention in the prostatitis field. In the EAP mouse model, prostate and iliac lymph node tissues showed elevated levels of CD4+ and IL17+ cells. To eliminate the pelvic pain induced by the animal model, Prophylactic treatment and injection of IL-17 antibody 1 day before EAP induction and 1 day after pain assessment were sufficient. On day 10 after induction, administration of the same IL-17 antibody failed to prevent or improve chronic pelvic pain [35]. According to the results, IL-17 may have a significant role in inducing pelvic pain in EAP mice but not in maintaining it. CaMK4(human Ca2+/calmodulin-dependent protein kinase 4) activates Th17 cell differentiation via the Akt-mTOR signaling pathway. Inhibition of CaMK4 may be a potential therapeutic target for hyperactivation of Th17 cells in this disease [36]. Besides that, NOD mice infected with the CP1 strain of *E.coli* also induced chronic inflammatory response of Th1/Th17, resulting in inflammatory infiltration of the prostate and mediating chronic pelvic pain. It is suggested that IL-17 produced by Th17 cells may be a significant inducer of pelvic pain [37], but the mechanism of action needs further study.

CP/CPPS is a chronic pain syndrome characterized by anatomical dysfunction of pelvic floor muscles and pain perception dysfunction related to psychological and cognitive factors. Symptom relief typically occurs in the late stages of the disease. Studies have shown that inhibiting the expression of pain-promoting cells and cytokines is crucial for remission of CP/CPPS. Wanchun Wang divided patients with type IIIA chronic prostatitis into treatment and control groups at random. The study revealed that the treatment resulted in a reduction of TNF-α and IL-8 levels in both groups.

Furthermore, a positive correlation was found between the degree of pain and the expression of these cytokines. Patients' conditions improved significantly after inhibiting or reducing the abnormal expression of these cytokines. These findings suggest that measuring TNF-α and IL-8 levels may be valuable in assessing the condition of patients with Type IIIA CPPS and evaluating treatment effectiveness [38]. Jin Gan et al. discovered a noteworthy increase in the expression levels of the pro-inflammatory cytokine IL-6 and chemokine IL-8 in the semen of CP patients. The study found a correlation between IL-6 and IL-8 levels and NIH-CPSI scores, suggesting that decreased levels of IL-6 and IL-8 may alleviate pain symptoms [39]; this indicates that controlling the development of pain by modulating the levels of related inflammatory factors and indicators is a viable solution to achieve ultimate relief. Developing new drugs and early intervention of these cells and cytokines can be regarded as a potentially effective method to treat CP/CPPS.

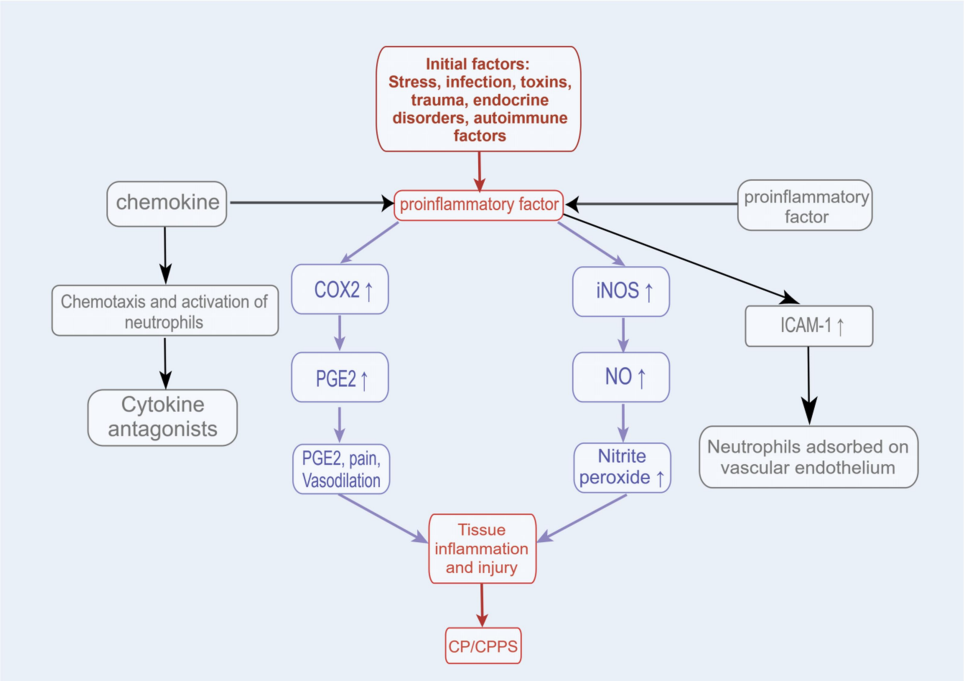
CP/CPPS gene genetics research

In recent years, research has suggested that genetic factors may be related to CP/CPPS and that the expression of many cells and cytokines involved in developing inflammation and pain is regulated by related genes. L Chen and J Chen analyzed the SNPs of IFN-γ, IFN-γ R1, AR, and CP/CPPS risk through data analysis and genetic models (single nucleotide polymorphism, SNP) and established a CP/CPPS risk prediction map [40]. The study discovered that the SNP RS2069718 in IFN-γ was associated with a higher risk of CP/CPPS, while RS10457655 in IFN-γ R1 was linked to an increased NIH-CPSI score. These findings could be used to construct predictive risk maps for CP/CPPS, and clinicians could more effectively identify patients with CP/CPPS by considering

age and genotype. Furthermore, Schneider *et al.* conducted a study on microRNAs isolated from exosomes in the blood and urine of patients with CPPS type III B and healthy men. They indicated that CP-derived urinary exosomes induce upregulation of prostate-cancer-related pro-inflammatory genes, such as CCR2 and TLR2, in THP-1 monocytes of the prostate [41].

Through the whole-exome association analysis of CP/CPPS and the metagenomic study of gut microbes, Yong Gao found that the HLA-DQB2 gene was associated with susceptibility to CP/CPPS, three indels, HLDRB5 and HLA-DRB9 genes were found to be associated with CPPS in the region sequencing study, so it can be concluded that CPPS is Genetic predisposition [42]. The study above discussed the influence of genetic factors on CP/CPPS and provided new clues for diagnosing and treatment of CP/CPPS. It suggested that individualized treatment should be carried out for CP/CPPS. Therefore, the study of CPPS by genetic epidemiology may help to determine the Genetic predisposition and genetic model of CPPS and make an essential supplement to the whole frame of disease mechanism.

Figure II: CP/CPPS Pathogenesis Map



CONCLUSION

Summary and prospect

CPPS is a urinary system disease that affects approximately 15% of men. It can cause a decline in quality of life and seriously damage the physical and mental health of patients, as well as impose a significant economic burden on their families. Although many therapeutic methods are available for CPPS, their effectiveness is not yet satisfactory. This article reviews the role of immune cells in the pathogenesis of CP/CPPS and aims to clarify the involvement of various immune cells in its development. Considerable progress has been made in the recent study of CP/CPPS. However, additional research is necessary to comprehend this condition's molecular mechanisms and clinical applications fully. To begin, we must identify the cause of the disease and determine which immune cells are responsible for the initial changes.

On the other hand, advanced detection technology should be utilized to classify the cells and cytokines involved in the occurrence and development of the disease; this will allow for the exploration of how to regulate their expression process, suppress abnormal expression, and search for suitable therapeutic targets. Additionally, changes in the immune system before and after treatment should be analyzed to identify suitable indices for predicting therapeutic effects. At the same time, the genetic study of CP/CPPS will lay a foundation for further diagnosis and effective treatment of CP/CPPS.

ABBREVIATIONS

CP/CPPS: Chronic Prostatitis/Chronic Pelvic Pain Syndrome
Th: T helper
IL: Interleukin
IFN: Interferon
TNF: Tumor Necrosid Factor
pbmc: peripheral blood mononuclear cell
PAP: Prostate Acid Phosphatase
Treg: T regulatory
EAP: Experimental Autoimmune Prostatitis
DC: Dendritic Cell
Foxp3: Forkhead box protein 3
TGF: Transforming Growth Factor
KLK3: Kallikrein-related peptidase 3
mRNA: messenger RNA
AZA: Azacitidine
NK: Natural Killer
Cox-2: Cyclooxygenase II
PGE2: Prostaglandin E2
NOD: Non-Obese Diabetic
NGF: nerve growth factor
CaMK4: Ca^{2+}/calmodulin-dependent protein Kinase 4
E.coli: Escherichia coli
CD4: Cluster of Differentiation 4
NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index
SNP: Single Nucleotide Polymorphisms
THP-1: Tohoku Hospital Pediatrics-1
CCR2: C-C Chemokine Receptor 2
TLR2: Toll-like Receptor 2

Figure I and Figure II were drawn using Figdraw (https://www.figdraw.com/).
The unique authorization codes are WPRIY8bd5e and UWWOW428f5.

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION
Xuan Y: Wrote the manuscript
Duan Y: Revised the manuscript
All authors contributed to the article and approved the submitted version.

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