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REVIEW

Chronic Prostatitis and Pelvic Pain Syndrome: Another Autoimmune Disease?

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Abstract

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), characterized by chronic pain in the perineum or lower abdomen regions, is a frequent disorder in men. Previous studies demonstrated that the immune mediators, including interleukin (IL)-1β, IL-6, interferon-γ, tumor necrosis factor-α, and immunoglobulins, are elevated in the expressed prostate secretions and seminal fluid of CP/CPPS men. The memory T, T helper 1 (Th1), Th17, and Th22 cells increase in the peripheral blood of CP/CPPS men. Additionally, prostate antigens specific-autoreactive T cells are identified in CP/CPPS patients. After generally reviewing and comparing the inflammatory responses in autoimmune diseases and CP/CPPS, we presumed that CP/CPPS is more likely to be defined as an autoimmune disease. Thus, a better understanding of autoimmune diseases would contribute to a deeper understanding of the CP/CPPS and provide new inspirations for the treatment of this disease.

Keywords Chronic prostatitis/chronic pelvic pain syndrome · Pathogenesis · Autoimmunity · Autoimmune diseases

Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a highly prevalent urological disorder with unclear etiology, with a prevalence ranging 8.4–25% (Habermacher et al. 2006; Zhang et al. 2019). Patients suffering CP/CPPS commonly complain about pain around the perineum, rectum, penis, testicles, and lower abdomen, leading to a decrease in patients' quality of life (QoL) (Zhang et al. 2020a). Although the consensus of the National Institutes of Health (NIH) defines the CP/CPPS as category III prostatitis without the evidence of urinary tract infection (Krieger et al. 1999), infection is still considered a causal factor that drives its pathogenesis (Hou et al. 2012; Murphy et al. 2019). Pathogens including uropathogens and *chlamydia* have been detected in the prostate secretions of CP/CPPS men (Abdelatif et al. 1991; Nickel et al. 2003a). Murphy et al. (2014) revealed the association between bacteria and CP/CPPS. They concluded that bacterial infection might play crucial roles in triggering the autoimmune activation, forming the prostatic inflammatory response, and driving CP/CPPS.

Autoimmune diseases will occur when the immune tolerance is disrupted. Subsequently, the immune system mistakenly attacks self-antigens, eliciting excessive activation of autoimmunity and causing organ and tissue lesions (Xiao et al. 2021). The autoimmune diseases, such as autoimmune thyroid disease, type 1 diabetes, systemic lupus erythematosus, and rheumatoid arthritis, have been systematically investigated. Genetic predisposition and environmental factors, such as infection, ultraviolet light, mental factors, smoking, and food ingredients, are identified as triggering factors to activate autoreactive T and B lymphocytes, resulting in tissue damage through autoantibodies and autoreactive cytotoxic T lymphocytes (Wang et al. 2015).

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In the past 2 decades, researchers proposed that infection, autoimmunity, defective urothelial integrity and function, and psychosocial status were the potential etiologies of CP/CPPS (Breser et al. 2017), and autoimmune etiology had been verified with an essential role in the pathogenesis of CP/CPPS (Lu et al. 2018). The experimental autoimmune prostatitis (EAP) model, which was established by autoimmunization of prostate antigens (PAgs), could simulate the autoimmune responses of CP/CPPS and had been widely used to investigate the immune alterations underlying CP/CPPS for more than 20 years (Donadio and Depiante-Depaoli 1997; Keetch et al. 1994). Several autoantigens have been identified to demonstrate the autoimmunity underlying CP/CPPS (Hou et al. 2009; Ponniah et al. 2000), and PAgs-specific lymphocytes were found in CP/CPPS patients (Motrich et al. 2005, 2020). Hence, exploring and unveiling the autoimmune responses in CP/CPPS could enlighten the diagnosis and treatment of CP/CPPS and improve patients' QoL.

In this paper, the etiology of autoimmune diseases was reviewed, and the similarities between autoimmune diseases and CP/CPPS were compared. Our findings might offer inspiration for the understanding of CP/CPPS and the treatment options for the patients.

Role of Pathogens in the Occurrence of CP/CPPS

Pathogens are considered a triggering factor of CP/CPPS, though there is insufficient evidence to confirm the association between infection and CP/CPPS. Bacterial species, including *Helicobacter pylori* (Karatas et al. 2010), *Chlamydia trachomatis* (Park et al. 2015), *Mycoplasma* and *Ureaplasma urealyticum* (Papeš et al. 2017), *Escherichia coli* (*E. coli*) (Rudick et al. 2011), *Burkholderia cenocepacia* (Nickel et al. 2015), nanobacteria (Zheng et al. 2014), and other Gram-positive species (Murphy et al. 2019), are identified to be associated with CP/CPPS. Antibiotics can reduce prostatitis-like symptoms mirrored by a decrease in NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) score (Franco et al. 2019). Furthermore, a bacterial DNA-encoding DNA sequence study revealed that the positive rate of bacteria in the prostate specimens from men with CP/CPPS is higher than that from men without prostatitis (Krieger et al. 2000). Rudick et al. (2011) isolated the CP1 strain of uropathogenic *E. coli* from CP/CPPS patients and then introduced it into mice, with the purpose of inducing the CP/CPPS model. However, chronic pelvic pain still existed in non-obese diabetic (NOD) mice even when this bacterium was cleared from the genitourinary tract. Meanwhile, this phenomenon could not be reproduced in C57BL/6 mice. Thus, infection is the initiation stimulus of CP/CPPS, and genetic susceptibility could be another factor. Similarly, Murphy et al. (2019) reported that Gram-positive bacteria accounted for the largest proportion in expressed prostatic secretion (EPS) flora of CP/CPPS men, and the three isolated strains from EPS, including *Enterococcus faecalis*, *Staphylococcus haemolyticus*, and *epidermidis*, could induce prostatitis-like symptoms in NOD mice rather than C57BL/6 mice. In clinical trials, CP/CPPS patients' responses to antibiotic treatment remain unsatisfactory (Magistro et al. 2016; Nickel et al. 2003b), though evidence suggests that bacteria promote the immune response in CP/CPPS. Therefore, treatments with a focus on reducing bacteria-induced inflammation would more warrant the relief of patients' symptoms.

Immunological Mechanisms Underlying CP/CPPS

Immunological Basis of CP/CPPS

The levels of cytokines and immune cells in the EPS, seminal plasma, urine, blood have been detected to reveal the immunological alterations in CP/CPPS. The levels of interleukin (IL)-1β, tumor necrosis factor (TNF)-α, immunoglobulin (Ig)A, and IgG to PAgs were elevated in the EPS, and the macrophages and T and B lymphocytes were observed in the urine and EPS of CP/CPPS men (Motrich et al. 2020; Nadler et al. 2000; Nickel et al. 2003a; Shortliffe and Wehner 1986). Hubert John and coworkers discovered that serum IL-6 and complement 3c (C3c) and C4 increased with the development of CP/CPPS, and ejaculate IL-6, IgA, and IgG levels in patients with CP/CPPS were higher than those in the healthy control group, and the seminal IL-6 levels decreased after antibiotic therapy (John et al. 2001, 2003; Stancik et al. 2008). They also revealed a phenomenon that T lymphocytes were mainly located within acini. In contrast, B lymphocytes were evenly distributed in the prostate stroma and gland, reflecting that increased cytokine and immunoglobulin levels might be secreted by activated T and B lymphocytes. They proposed that CP/CPPS was an autoimmune disease caused by autoimmune components. Additionally, IL-1β, TNF-α and IgA, IgM, C3, and fibrinogen were observed to deposit in the prostate of men with chronic prostatitis (Ablin et al. 1971; Doble et al. 1990; Xie et al. 2010). To further confirm these findings above, we analyzed these immune mediators in the prostate specimens of CP/CPPS patients. Immunofluorescence staining demonstrated that CD4 and interferon (IFN)-γ were deposited in the epithelial cells of the prostate gland in patients with benign prostate hyperplasia and suffering CP/CPPS (Supplemental Fig. 1A–B). This result was consistent with a previous study that a higher level of the IFN-γ was observed in seminal plasma of individuals with CP/CPPS than healthy

individuals (Miller et al. 2002). Besides, C3, collagen-I, collagen-III, IgA, IgM, IL-1β, and TNF-α were found deposited in the prostate of this CP/CPPS patient (Supplemental Fig. 1C). Hence, autoimmunity-driven prostatic inflammation possibly served as a vital factor in the pathogenesis of CP/CPPS.

Identification of Self-Antigens in Patients with CP/CPPS and EAP Models

Based on the autoimmune responses in CP/CPPS, researchers identified the autoantigens in the pathogenesis of CP/CPPS. For example, Hou et al. (2009) revealed that seminal vesicle secretory protein 2 and semenogelin were the aberrantly prostate-specific autoantigens in the autoimmune prostatitis model, and men with chronic prostatitis and autoantibodies were also identified in the serum. Besides, other autoantigens (including prostate and male accessory gland extracts, prostatic steroid-binding protein, prostatic spermine-binding protein (p25), prostatic acid phosphatase (PAP), and T2 peptide) have been demonstrated in animal models (Liu et al. 2021a). Prostate-specific antigen (PSA), PAP, MAD-PRO-34, and NY-CO-7 have also been observed in patients (Dunphy et al. 2004; Kouiavskaia et al. 2009; Motrich et al. 2005; Ponniah et al. 2000). The PAgs-specific autoreactive T cells and PAgs-specific IgG were found in CP/CPPS patients' blood (Dunphy et al. 2004; Kouiavskaia et al. 2009; Motrich et al. 2005; Pansadoro et al. 1996; Ponniah et al. 2000). Therefore, the loss of immune tolerance to PAgs elicited autoimmune responses leading to CP/CPPS.

Role of T Lymphocytes and Their Secreted Inflammatory Mediators in CP/CPPS

The critical roles of $CD4^+$T cells in the initiation and development of CP/CPPS have been demonstrated by an increasing body of evidence (Alexander et al. 1997; Breser et al. 2017). In response to bacterial invasion, the $CD4^+$T cells were activated and then differentiated into Th1, Th2, and Th17 subpopulations (Murphy et al. 2014), and the Th1 and Th17 cells promoted the progression of CP/CPPS (Breser et al. 2017).

The analysis of the immune profiling in the prostate of mice inoculated with bacteria isolated from patients with CP/CPPS suggested that $CD3^+CD8^+$, $CD3^+CD4^+$, and IFN-γ-secreting $CD4^+$ lymphocytes were infiltrated in the prostate, and total T cells, $CD3^+CD8^+$, and $CD3^+CD4^+$ lymphocytes increased in the lymph nodes draining the prostate (Murphy et al. 2019). Additionally, the elevated PSA was identified as a self-antigen recognized by IFN-γ-secreting $CD4^+$T cells in CP/CPPS men (Motrich et al. 2005; Pansadoro et al. 1996; Ponniah et al. 2000), and the proportion of autoreactive $CD4^+$T cells increased in patients' peripheral blood (Kouiavskaia et al. 2009). The genital tract inflammation and the reduced semen quality were correlated with PAgs-reactive Th1 and Th17 cells (Motrich et al. 2020). The regulatory T cells (Treg) were involved in maintaining immune tolerance, and the transcription factor of Foxp3 was a dominant characteristic of Treg cells (Murphy et al. 2014; Yang et al. 2015). The loss function of Treg cells was associated with the autoimmunity in CP/CPPS (Breser et al. 2016). Our previous studies indicated that the suppressive function of Treg cells was impaired with increased aberrant methylation of Foxp3 promoter, resulting in autoimmune responses and prostate tissue injury in EAP (Chen et al. 2019). Besides, the proportion of functional Treg cells decreased in EAP models, contributing to the development of CP/CPPS, while autophagy could restore its suppressive function (Liu et al. 2021b). We also investigated the proportion of T cell subpopulations in CP/CPPS men through the single-cell multi-omics analysis. The results suggested that memory T, Th1, Th17, and Th22 cells increased in the periphery of CP/CPPS men compared to the healthy control group (Zhang et al. 2020b). Based on the driver role of Th17 cells in CP/CPPS, we discovered that excessive activation of Th17 cells aggravated prostatitis-like symptoms, which was modulated by the Ca^{2+}-mediated CaMK4/Akt/mTOR-IL-17A signaling (Zhan et al. 2020). To sum up, aberration differentiation of lymphocytes, such as Th1, Treg, and Th17, in both the blood circulation system and local prostate might facilitate and intensify the CP/CPPS.

Therefore, the inflammatory signals can induce the differentiation of $CD4^+$T cells into T cell subsets. The immune tolerance was disrupted by the decrease in the number of Treg cells and the impaired function of Treg cells, making it unable to suppress the Th1- and Th17-driven immune responses in CP/CPPS (Fig. 1). The excessively activated autoreactive T and B cells promoted the autoimmune responses, causing prostatic inflammation and prostate injury.

Similarities Between Autoimmune Diseases and CP/CPPS in Immune Aberrations

In autoimmune diseases, gene-environment interactions disrupt the immune homeostasis, and naïve T cells are differentiated into pathogenic effector T cell subpopulations, including Th1, Th2, Th17, and follicular Th (Tfh) cells (Awasthi and Kumar 2019; Kuchroo et al. 2012). The declined frequency and function of Treg cells fail to counter Th1, Th2, and Th17-driven inflammatory responses, leading to the imbalance of Th1/Th2 and Th17/Treg in autoimmune diseases (Awasthi and Kumar 2019; Hill et al. 2007). As indicated above, the declined frequency and function of Tregs and increased frequency and function of

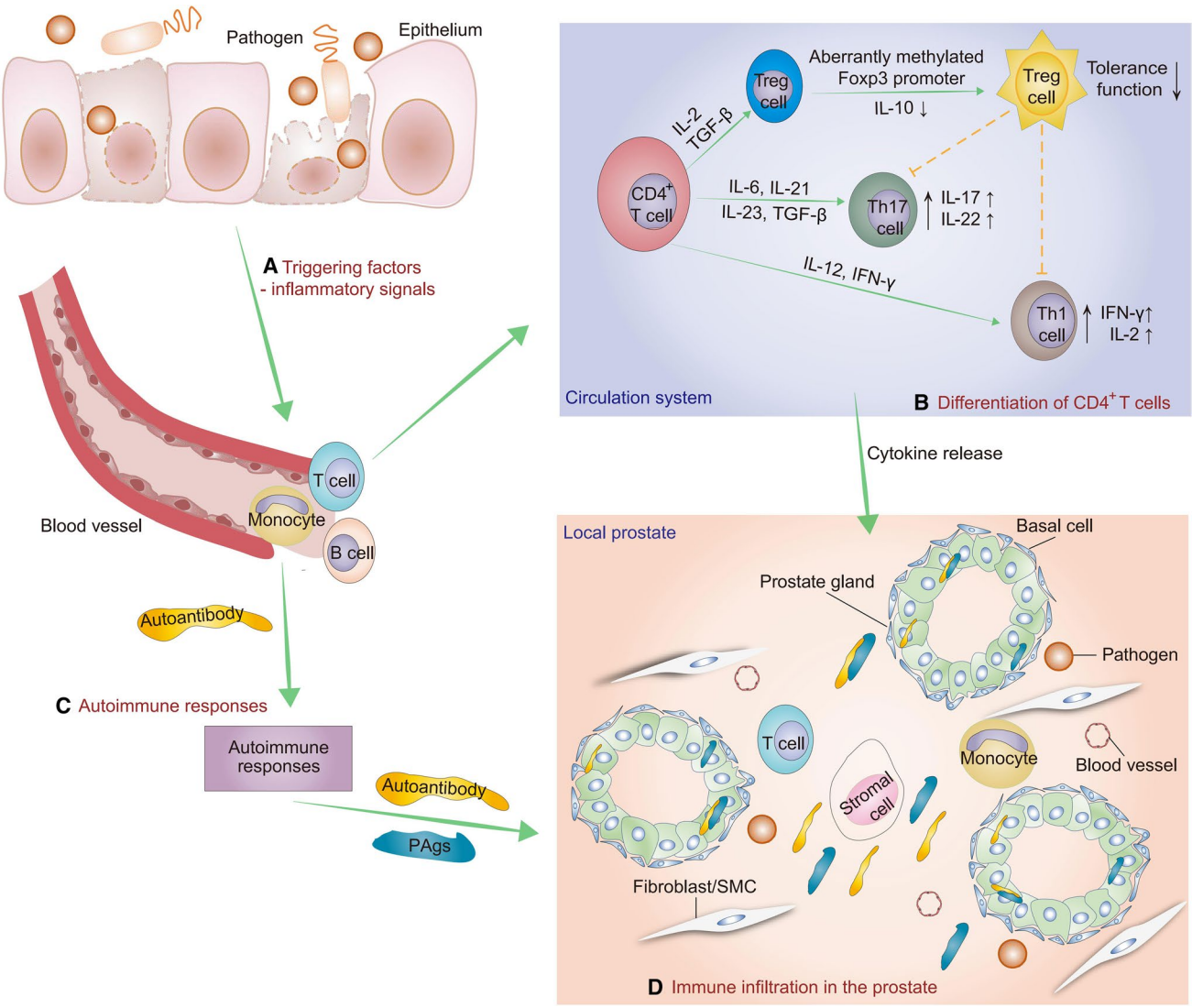

Fig. 1 Overview of the autoimmune responses in CP/CPPS. Putative autoimmune processes in the pathogenesis of CP/CPPS. **A** Triggering factors, including the invasion of pathogens, activated the immune system (Hou et al. 2012; Murphy et al. 2019); subsequently, T and B lymphocytes were stimulated by antigen process cells. **B** Activated $CD4^+$T cells aberrantly differentiated into subpopulations as Th1, Th17, and Treg cells (Murphy et al. 2014). The immune tolerance was disrupted by the decrease in the number of Treg cells and the impaired function of Treg cells, making it unable to suppress the Th1 and Th17-driven immune responses in CP/CPPS (Chen et al. 2019; Liu et al. 2021b; Zhan et al. 2020; Zhang et al. 2020b). **C** Humoral immunity played vital roles in the processes of immune responses. Invasion of pathogens disrupted the balance of the body's immune system, and abnormal B cells produced autoantibodies against self-antigens released into the blood (Ablin et al. 1971; Doble et al. 1990; Motrich et al. 2020). **D** The excessively activated autoimmune responses elicited prostatic inflammation and chronic pain (Motrich et al. 2020). *CP/CPPS* chronic prostatitis/chronic pelvic pain syndrome, *IFN-γ* interferon-γ, *IL-1β* interleukin-1β, *PAgs* prostate antigens, *SMC* smooth muscle cell, *TNF-α* tumor necrosis factor-α

Th1, Th2, and Th17 were well characterized in CP/CPPS cases (Chen et al. 2019; Murphy et al. 2014; Quick et al. 2013; Zhan et al. 2020). The IFN-γ-secreting Th1 cells and IL-17-secreting Th17 cells are related to the development of autoimmune diseases (Bettelli et al. 2004; Haase and Linker 2021; Vyas et al. 2019; Yasuda et al. 2019). In the humoral response, excessive activation of Tfh cells induces autoreactive B cells to produce autoantibodies, which recruits specific immune cells to target organs and causes tissue injury and clinical symptoms (Kuchroo et al. 2012; Ma et al. 2017). Moreover, "Th1-like" cells (also called Th17/Th1 cells) are differentiated from Th17 cells and can secrete both IL-17 and IFN-γ (Basdeo et al. 2017). The "Th1-like" cells are more pathogenic and could induce drug resistance to glucocorticoids in autoimmune disease (Ramesh et al. 2014). Therefore, the immune network plays a critical role in the pathogenesis of autoimmune disease and might serve as central therapeutic targets.

As illustrated by comprehensively reviewing the related literature, the immune responses in CP/CPPS and autoimmune disease share many similarities, which are summarized as follows. (1) CP/CPPS and autoimmune diseases are initiated by multifactorial etiologies, such as infection and mental status. (2) Autoimmune responses played critical roles in the pathogenesis of CP/CPPS and autoimmune disease. Moreover, the loss tolerance function of Treg cells and the aberrant activation of autoreactive T and B cells elicit the inflammatory responses, leading to tissue injury. (3) Th1- and Th17-driven autoimmunity have dominant roles in the autoimmune processes of these two conditions. (4) Therapeutic strategies aiming at relieving the inflammation infiltration are promising in the treatment of CP/CPPS and autoimmune diseases.

Inspiration from Autoimmune Disease in Treating CP/CPPS

CP/CPPS is a complex disease characterized by a multi-hit etiology. Pathogen infection and the loss of immune tolerance might cause autoimmune inflammatory damage to the prostate, leading to chronic pelvic pain. Therefore, the autoimmune processes might provide potential therapeutic targets for CP/CPPS patients. The current treatment approaches (such as α-blockers, 5-α reductase inhibitors, antibiotics, anti-inflammatories, phytotherapy, botulinum toxin A, allopurinol, and traditional Chinese medicine) have been widely investigated while CP/CPPS patients' responses to these treatment approaches remain unsatisfactory (Franco et al. 2019).

Targeting Aberrant Autoimmunity

The therapies targeting autoimmunity have been widely investigated in the treatment of autoimmune diseases. Initially, Treg cells present potentially therapeutic effects on autoimmune diseases. Treg cells have two subsets: natural Treg (nTreg) and induced (iTreg) cells. Among them, nTreg cells originate from the thymus, while iTreg cells are derived from conventional $CD4^+$T cells in the periphery (Ruszkowski et al. 2019). Since autoimmune diseases are partly attributed to the loss of tolerance function of Treg cells, adoptive transfer of Treg cells into the animal models or augmentation Treg function of animal models to restore immune tolerance seems promising in the treatment of autoimmune diseases (Esensten et al. 2018; Geem et al. 2015; Haribhai et al. 2016; Kumar et al. 2019). Furthermore, disease-modifying antirheumatic drugs (including methotrexate, sulphasalazine, leflunomide, gold salts, and hydroxychloroquine), corticosteroids, cytotoxic-immunosuppressants (cyclophosphamide, azathioprine, mycophenolate, and calcineurin inhibitors), nonsteroidal anti-inflammatory drugs, biologics, and small molecules (rituximab, belimumab) are widely employed in the treatment of autoimmune diseases to regulate the excessively activated autoimmune responses and relieve the autoimmune diseases (Fava and Petri 2019; Sparks 2019). Particularly, biotherapeutics targeting IL-1, TNF-α, IL-6, IL-23, IL-17, IL-4/13, IL-5, and CD20 have advanced substantially in recent years, and patients with immunologic and inflammatory diseases could benefit from these agents (Ghilardi et al. 2020).

Given the autoimmunity of CP/CPPS, we may acquire some inspiration from the treatment of autoimmune diseases. Several treatment agents for CP/CPPS could inhibit immune responses. For example, *Quercetin* and acupuncture have been demonstrated to exert anti-inflammatory activities and decrease the levels of cytokines such as IL-1β, IL-8, IL-10, and TNF-α in CP/CPPS men or animal models (Meng et al. 2018; Wazir et al. 2019). The monoclonal antibodies (mAbs) against nerve growth factor (NGF) and TNF-α are adopted to manage neurogenic inflammation and relieve the pain (Wazir et al. 2019). A randomized clinical trial suggested that tanezumab, a mAb of NGF, could improve the pain symptoms of patients with CP/CPPS (Nickel et al. 2012; Yeh et al. 2017). Quinolones, a kind of antibiotic often used to treat CP/CPPS, were discovered to promote IL-2 and colony-stimulating factor while inhibiting IL-1 and TNF-α synthesis (Dalhoff and Shalit 2003). Additionally, quinolones could modulate the immune responses by targeting the downstream effectors, including cyclic adenosine-3′,5′-monophosphate, phosphodiesterases, activator protein 1, nuclear factor (NF)-κB, NF/IL-6, and nuclear factor of activated T cells (Dalhoff and Shalit 2003). Hence, other than removing bacteria, some antibiotics can regulate the inflammatory responses. This could partly explain the effects of antibiotics on the treatment of CP/CPPS men without evidence of infection.

Application of Corticosteroids

In vertebrates, corticosteroids are secreted from the adrenal cortex, with anti-inflammatory and immunosuppressive effects (Stern et al. 2017). In CP/CPPS, corticosteroid therapy may significantly affect some patients by suppressing the autoimmune processes (Tomaskovic et al. 2009). Bates and Talbot (2000) applied short-course oral corticosteroids to four CP/CPPS men, and 75% of patients benefit from steroid therapy. Moreover, the rectal prednisolone administration for CP/CPPS concomitant with ulcerative colitis could relieve the pain (Talbot and Bates 2001). Therefore, it is necessary to conduct randomized clinical trials (RCTs) of corticosteroids in men with CP/CPPS (Magistro et al. 2016; Strauss and Dimitrakov 2010). Bates et al. (2007) performed the RCT involving 18 patients to investigate the effect of oral

corticosteroid on CP/CPPS, revealing that prostatitis-like symptoms were not improved after corticosteroid therapy, while the symptom of depression was improved. In another RCT involving 160 patients, prednisone and levofloxacin were simultaneously administered to patients with chronic nonbacterial prostatitis. The results demonstrated that QoL, pain symptoms, and voiding dysfunction were improved after the treatment leucocytes count was reduced in the EPS (Yang et al. 2009). The discrepancy between these two RCTs may result from the limited number of participants enrolled in the RCTs.

Genetic Analysis in Guiding Clinical Treatment

Additionally, genetic risk factors may have an essential role in affecting the therapeutic efficacy of CP/CPPS. Shoskes et al. (2002) determined that CP/CPPS men with low TNF-α and high IL-10 phenotypes tend to exert treatment failure regarding anti-inflammatory phytotherapy. Researchers proposed that genotype and phenotype could be applied to stratify CP/CPPS, so as to maximize the treatment effects (Dimitrakov and Guthrie 2009). To sum up, the identification of new therapeutic targets that intervene in the autoimmune responses in CP/CPPS might be effective in alleviating the disease.

Conclusions

In conclusion, the impaired function of Treg cells causes the aberrant differentiation of T cells, and the Th1/Th17-driven autoimmunity induces and aggravates prostatic inflammation and injury, leading to chronic pelvic pain. Given the crucial roles of autoimmunity in the initiation and progression of CP/CPPS, therapeutic strategies targeting the autoimmune responses are promising.

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Data Availability Not applicable.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

References

Abdelatif OM, Chandler FW, McGuire BS Jr (1991) Chlamydia trachomatis in chronic abacterial prostatitis: demonstration by colorimetric in situ hybridization. Hum Pathol 22:41–44. https://doi.org/10.1016/0046-8177(91)90059-x

Ablin RJ, Gonder MJ, Soanes WA (1971) Localization of immunoglobulins in human prostatic tissue. J Immunol 107:603–604

Alexander RB, Brady F, Ponniah S (1997) Autoimmune prostatitis: evidence of T cell reactivity with normal prostatic proteins. Urology 50:893–899. https://doi.org/10.1016/s0090-4295(97)00456-1

Awasthi A, Kumar H (2019) T cell subtypes and its therapeutic potential in autoimmune diseases and cancer. Int Rev Immunol 38:181–182. https://doi.org/10.1080/08830185.2019.1673472

Basdeo SA, Cluxton D, Sulaimani J et al (2017) Ex-Th17 (Nonclassical Th1) cells are functionally distinct from classical Th1 and Th17 cells and are not constrained by regulatory T cells. J Immunol 198:2249–2259. https://doi.org/10.4049/jimmunol.1600737

Bates S, Talbot M (2000) Short course oral prednisolone therapy in chronic abacterial prostatitis and prostatodynia: case reports of three responders and one non-responder. Sex Transm Infect 76:398–399. https://doi.org/10.1136/sti.76.5.398

Bates SM, Hill VA, Anderson JB et al (2007) A prospective, randomized, double-blind trial to evaluate the role of a short reducing course of oral corticosteroid therapy in the treatment of chronic prostatitis/chronic pelvic pain syndrome. BJU Int 99:355–359. https://doi.org/10.1111/j.1464-410X.2007.06667.x

Bettelli E, Sullivan B, Szabo SJ et al (2004) Loss of T-bet, but not STAT1, prevents the development of experimental autoimmune encephalomyelitis. J Exp Med 200:79–87. https://doi.org/10.1084/jem.20031819

Breser ML, Lino AC, Motrich RD et al (2016) Regulatory T cells control strain specific resistance to experimental autoimmune prostatitis. Sci Rep 6:33097. https://doi.org/10.1038/srep33097

Breser ML, Salazar FC, Rivero VE et al (2017) Immunological mechanisms underlying chronic pelvic pain and prostate inflammation in chronic pelvic pain syndrome. Front Immunol 8:898. https://doi.org/10.3389/fimmu.2017.00898

Chen J, Zhan C, Zhang L, Zhang L et al (2019) The hypermethylation of Foxp3 promoter impairs the function of Treg cells in EAP. Inflammation 42:1705–1718. https://doi.org/10.1007/s10753-019-01030-0

Dalhoff A, Shalit I (2003) Immunomodulatory effects of quinolones. Lancet Infect Dis 3:359–371. https://doi.org/10.1016/s1473-3099(03)00658-3

Dimitrakov J, Guthrie D (2009) Genetics and phenotyping of urological chronic pelvic pain syndrome. J Urol 181:1550–1557. https://doi.org/10.1016/j.juro.2008.11.119

Doble A, Walker MM, Harris JR et al (1990) Intraprostatic antibody deposition in chronic abacterial prostatitis. Br J Urol 65:598–605. https://doi.org/10.1111/j.1464-410x.1990.tb14827.x

Donadio AC, Depiante-Depaoli M (1997) Inflammatory cells and MHC class II antigens expression in prostate during time-course experimental autoimmune prostatitis development. Clin Immunol Immunopathol 85:158–165. https://doi.org/10.1006/clin.1997.4427

Dunphy EJ, Eickhoff JC, Muller CH et al (2004) Identification of antigen-specific IgG in sera from patients with chronic prostatitis. J Clin Immunol 24:492–502. https://doi.org/10.1023/B:JOCI.0000040920.96065.5a

Esensten JH, Muller YD, Bluestone JA et al (2018) Regulatory T-cell therapy for autoimmune and autoinflammatory diseases: the next frontier. J Allergy Clin Immunol 142:1710–1718. https://doi.org/10.1016/j.jaci.2018.10.015

Fava A, Petri M (2019) Systemic lupus erythematosus: diagnosis and clinical management. J Autoimmun 96:1–13. https://doi.org/10.1016/j.jaut.2018.11.001

Franco JV, Turk T, Jung JH et al (2019) Pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. Cochrane Database Syst Rev 10:Cd012552. https://doi.org/10.1002/14651858.CD012552.pub2

Geem D, Harusato A, Flannigan K et al (2015) Harnessing regulatory T cells for the treatment of inflammatory bowel disease. Inflamm Bowel Dis 21:1409–1418. https://doi.org/10.1097/mib.0000000000000343

Ghilardi N, Pappu R, Arron JR et al (2020) 30 Years of biotherapeutics development-what have we learned? Annu Rev Immunol 38:249–287. https://doi.org/10.1146/annurev-immunol-101619-031510

Haase S, Linker RA (2021) Inflammation in multiple sclerosis. Ther Adv Neurol Disord 14:17562864211007688. https://doi.org/10.1177/17562864211007687

Habermacher GM, Chason JT, Schaeffer AJ (2006) Prostatitis/chronic pelvic pain syndrome. Annu Rev Med 57:195–206. https://doi.org/10.1146/annurev.med.57.011205.135654

Haribhai D, Chatila TA, Williams CB (2016) Immunotherapy with iTreg and nTreg cells in a murine model of inflammatory bowel disease. Methods Mol Biol 1422:197–211. https://doi.org/10.1007/978-1-4939-3603-8_19

Hill JA, Benoist C, Mathis D (2007) Treg cells: guardians for life. Nat Immunol 8:124–125. https://doi.org/10.1038/ni0207-124

Hou Y, DeVoss J, Dao V et al (2009) An aberrant prostate antigen-specific immune response causes prostatitis in mice and is associated with chronic prostatitis in humans. J Clin Investig 119:2031–2041. https://doi.org/10.1172/jci38332

Hou DS, Long WM, Shen J et al (2012) Characterisation of the bacterial community in expressed prostatic secretions from patients with chronic prostatitis/chronic pelvic pain syndrome and infertile men: a preliminary investigation. Asian J Androl 14:566–573. https://doi.org/10.1038/aja.2012.30

John H, Barghorn A, Funke G et al (2001) Noninflammatory chronic pelvic pain syndrome: immunological study in blood, ejaculate and prostate tissue. Eur Urol 39:72–78. https://doi.org/10.1159/000052415

John H, Maake C, Barghorn A et al (2003) Immunological alterations in the ejaculate of chronic prostatitis patients: clues for autoimmunity. Andrologia 35:294–299. https://doi.org/10.1046/j.1439-0272.2003.00573.x

Karatas OF, Turkay C, Bayrak O et al (2010) Helicobacter pylori seroprevalence in patients with chronic prostatitis: a pilot study. Scand J Urol Nephrol 44:91–94. https://doi.org/10.3109/00365590903535981

Keetch DW, Humphrey P, Ratliff TL (1994) Development of a mouse model for nonbacterial prostatitis. J Urol 152:247–250. https://doi.org/10.1016/s0022-5347(17)32871-9

Kouiavskaia DV, Southwood S, Berard CA et al (2009) T-cell recognition of prostatic peptides in men with chronic prostatitis/chronic pelvic pain syndrome. J Urol 182:2483–2489. https://doi.org/10.1016/j.juro.2009.07.067

Krieger JN, Nyberg L Jr, Nickel JC (1999) NIH consensus definition and classification of prostatitis. JAMA 282:236–237. https://doi.org/10.1001/jama.282.3.236

Krieger JN, Riley DE, Vesella RL et al (2000) Bacterial dna sequences in prostate tissue from patients with prostate cancer and chronic prostatitis. J Urol 164:1221–1228. https://doi.org/10.1016/S0022-5347(05)67145-5

Kuchroo VK, Ohashi PS, Sartor RB et al (2012) Dysregulation of immune homeostasis in autoimmune diseases. Nat Med 18:42–47. https://doi.org/10.1038/nm.2621

Kumar P, Saini S, Khan S et al (2019) Restoring self-tolerance in autoimmune diseases by enhancing regulatory T-cells. Cell Immunol 339:41–49. https://doi.org/10.1016/j.cellimm.2018.09.008

Liu Y, Wazir J, Tang M et al (2021a) Experimental autoimmune prostatitis: different antigens induction and antigen-specific therapy. Int Urol Nephrol 53:607–618. https://doi.org/10.1007/s11255-020-02703-8

Liu Y, Zhang Y, Zhang M et al (2021b) Activated autophagy restored the impaired frequency and function of regulatory T cells in chronic prostatitis. Prostate 81:29–40. https://doi.org/10.1002/pros.24073

Lu JC, Shen JM, Hu XC et al (2018) Identification and preliminary study of immunogens involved in autoimmune prostatitis in human males. Prostate. https://doi.org/10.1002/pros.23684

Ma WT, Chang C, Gershwin ME et al (2017) Development of autoantibodies precedes clinical manifestations of autoimmune diseases: a comprehensive review. J Autoimmun 83:95–112. https://doi.org/10.1016/j.jaut.2017.07.003

Magistro G, Wagenlehner FM, Grabe M et al (2016) Contemporary management of chronic prostatitis/chronic pelvic pain syndrome. Eur Urol 69:286–297. https://doi.org/10.1016/j.eururo.2015.08.061

Meng LQ, Yang FY, Wang MS et al (2018) Quercetin protects against chronic prostatitis in rat model through NF-κB and MAPK signaling pathways. Prostate 78:790–800. https://doi.org/10.1002/pros.23536

Miller LJ, Fischer KA, Goralnick SJ et al (2002) Interleukin-10 levels in seminal plasma: implications for chronic prostatitis-chronic pelvic pain syndrome. J Urol 167(2 Pt 1):753–756

Motrich RD, Maccioni M, Molina R et al (2005) Presence of INF-gamma-secreting lymphocytes specific to prostate antigens in a group of chronic prostatitis patients. Clin Immunol 116:149–157. https://doi.org/10.1016/j.clim.2005.03.011

Motrich RD, Breser ML, Molina RI et al (2020) Patients with chronic prostatitis/chronic pelvic pain syndrome show T helper type 1 (Th1) and Th17 self-reactive immune responses specific to prostate and seminal antigens and diminished semen quality. BJU Int 126:379–387. https://doi.org/10.1111/bju.15117

Murphy SF, Schaeffer AJ, Thumbikat P (2014) Immune mediators of chronic pelvic pain syndrome. Nat Rev Urol 11:259–269. https://doi.org/10.1038/nrurol.2014.63

Murphy SF, Anker JF, Mazur DJ et al (2019) Role of Gram-positive bacteria in chronic pelvic pain syndrome (CPPS). Prostate 79:160–167. https://doi.org/10.1002/pros.23721

Nadler RB, Koch AE, Calhoun EA et al (2000) IL-1beta and TNF-alpha in prostatic secretions are indicators in the evaluation of men with chronic prostatitis. J Urol 164:214–218

Nickel JC, Alexander RB, Schaeffer AJ et al (2003a) Leukocytes and bacteria in men with chronic prostatitis/chronic pelvic pain syndrome compared to asymptomatic controls. J Urol 170:818–822. https://doi.org/10.1097/01.ju.0000082252.49374.e9

Nickel JC, Downey J, Clark J et al (2003b) Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multicenter trial. Urology 62:614–617. https://doi.org/10.1016/s0090-4295(03)00583-1

Nickel JC, Atkinson G, Krieger JN et al (2012) Preliminary assessment of safety and efficacy in proof-of-concept, randomized clinical trial of tanezumab for chronic prostatitis/chronic pelvic pain syndrome. Urology 80:1105–1110. https://doi.org/10.1016/j.urology.2012.07.035

Nickel JC, Stephens A, Landis JR et al (2015) Search for microorganisms in men with urologic chronic pelvic pain syndrome: a culture-independent analysis in the MAPP research network. J Urol 194:127–135. https://doi.org/10.1016/j.juro.2015.01.037

Pansadoro V, Emiliozzi P, Defidio L et al (1996) Prostate-specific antigen and prostatitis in men under fifty. Eur Urol 30:24–27. https://doi.org/10.1159/000474140

Papeš D, Pasini M, Jerončić A et al (2017) Detection of sexually transmitted pathogens in patients with chronic prostatitis/chronic pelvic pain: a prospective clinical study. Int J STD AIDS 28:613–615. https://doi.org/10.1177/0956462417691440

Park H, Sim SM, Lee G (2015) The presence of Chlamydia is associated with increased leukocyte counts and pain severity in men with chronic pelvic pain syndrome. Urology 85:574–579. https://doi.org/10.1016/j.urology.2014.11.008

Ponniah S, Arah I, Alexander RB (2000) PSA is a candidate self-antigen in autoimmune chronic prostatitis/chronic pelvic pain syndrome. Prostate 44:49–54. https://doi.org/10.1002/1097-0045(20000615)44:1%3c49::aid-pros7%3e3.0.co;2-7

Quick ML, Wong L, Mukherjee S et al (2013) Th1-Th17 cells contribute to the development of uropathogenic *Escherichia coli*-induced chronic pelvic pain. PLoS One 8:e60987. https://doi.org/10.1371/journal.pone.0060987

Ramesh R, Kozhaya L, McKevitt K et al (2014) Pro-inflammatory human Th17 cells selectively express P-glycoprotein and are refractory to glucocorticoids. J Exp Med 211:89–104. https://doi.org/10.1084/jem.20130301

Rudick CN, Berry RE, Johnson JR et al (2011) Uropathogenic *Escherichia coli* induces chronic pelvic pain. Infect Immun 79:628–635. https://doi.org/10.1128/iai.00910-10

Ruszkowski J, Lisowska KA, Pindel M et al (2019) T cells in IgA nephropathy: role in pathogenesis, clinical significance and potential therapeutic target. Clin Exp Nephrol 23:291–303. https://doi.org/10.1007/s10157-018-1665-0

Shortliffe LM, Wehner N (1986) The characterization of bacterial and nonbacterial prostatitis by prostatic immunoglobulins. Medicine 65:399–414. https://doi.org/10.1097/00005792-198611000-00005

Shoskes DA, Albakri Q, Thomas K et al (2002) Cytokine polymorphisms in men with chronic prostatitis/chronic pelvic pain syndrome: association with diagnosis and treatment response. J Urol 168:331–335

Sparks JA (2019) Rheumatoid arthritis. Ann Intern Med 170:itc1–itc16. https://doi.org/10.7326/aitc201901010

Stancik I, Plas E, Juza J et al (2008) Effect of antibiotic therapy on interleukin-6 in fresh semen and postmasturbation urine samples of patients with chronic prostatitis/chronic pelvic pain syndrome. Urology 72:336–339. https://doi.org/10.1016/j.urology.2008.04.005

Stern A, Skalsky K, Avni T et al (2017) Corticosteroids for pneumonia. Cochrane Database Syst Rev 12:Cd007720. https://doi.org/10.1002/14651858.CD007720.pub3

Strauss AC, Dimitrakov JD (2010) New treatments for chronic prostatitis/chronic pelvic pain syndrome. Nat Rev Urol 7:127–135. https://doi.org/10.1038/nrurol.2010.4

Talbot M, Bates S (2001) Variability of the symptoms of chronic abacterial prostatitis/chronic pelvic pain syndrome during intermittent therapy with rectal prednisolone foam for ulcerative colitis. Int J STD AIDS 12:752–753. https://doi.org/10.1258/0956462011924137

Tomaskovic I, Ruzic B, Trnski D et al (2009) Chronic prostatitis/chronic pelvic pain syndrome in males may be an autoimmune disease, potentially responsive to corticosteroid therapy. Med Hypotheses 72:261–262. https://doi.org/10.1016/j.mehy.2008.10.020

Vyas SP, Hansda AK, Goswami R (2019) Rheumatoid arthritis: 'melting pot' of T helper subsets. Int Rev Immunol 38:212–231. https://doi.org/10.1080/08830185.2019.1621865

Wang L, Wang FS, Gershwin ME (2015) Human autoimmune diseases: a comprehensive update. J Intern Med 278:369–395. https://doi.org/10.1111/joim.12395

Wazir J, Ullah R, Li S et al (2019) Efficacy of acupuncture in the treatment of chronic prostatitis-chronic pelvic pain syndrome: a review of the literature. Int Urol Nephrol 51:2093–2106. https://doi.org/10.1007/s11255-019-02267-2

Xiao ZX, Miller JS, Zheng SG (2021) An updated advance of autoantibodies in autoimmune diseases. Autoimmun Rev 20:102743. https://doi.org/10.1016/j.autrev.2020.102743

Xie H, Chen HD, Huang HC et al (2010) Bacterial 16S rRNA genes and expression of IL-1β, TNF-α and IgA in prostate tissues. Zhonghua Yi Xue Za Zhi 90:1970–1973

Yang MG, Zhao XK, Wu ZP et al (2009) Corticoid combined with an antibiotic for chronic nonbacterial prostatitis. Zhonghua Nan Ke Xue 15:237–240

Yang S, Fujikado N, Kolodin D et al (2015) Immune tolerance. Regulatory T cells generated early in life play a distinct role in maintaining self-tolerance. Science 348:589–594. https://doi.org/10.1126/science.aaa7017

Yasuda K, Takeuchi Y, Hirota K (2019) The pathogenicity of Th17 cells in autoimmune diseases. Semin Immunopathol 41:283–297. https://doi.org/10.1007/s00281-019-00733-8

Yeh JF, Akinci A, Al Shaker M et al (2017) Monoclonal antibodies for chronic pain: a practical review of mechanisms and clinical applications. Mol Pain 13:1744806917740233. https://doi.org/10.1177/1744806917740233

Zhan CS, Chen J, Chen J et al (2020) CaMK4-dependent phosphorylation of Akt/mTOR underlies Th17 excessive activation in experimental autoimmune prostatitis. FASEB J 34:14006–14023. https://doi.org/10.1096/fj.201902910RRR

Zhang J, Zhang X, Cai Z et al (2019) The lifetime risk and prognosis of chronic prostatitis/chronic pelvic pain syndrome in the middle-aged chinese males. Am J Mens Health 13:1557988319865380. https://doi.org/10.1177/1557988319865380

Zhang J, Liang C, Shang X et al (2020a) Chronic prostatitis/chronic pelvic pain syndrome: a disease or symptom? Current perspectives on diagnosis, treatment, and prognosis. Am J Mens Health 14:1557988320903200. https://doi.org/10.1177/1557988320903200

Zhang M, Liu Y, Chen J et al (2020b) Single-cell multi-omics analysis presents the landscape of peripheral blood T-cell subsets in human chronic prostatitis/chronic pelvic pain syndrome. J Cell Mol Med 24:14099–14109. https://doi.org/10.1111/jcmm.16021

Zheng J, Tang J, Yin S et al (2014) Comparison of polymerase chain reaction and immunologic methods for the detection of nanobacterial infection in type-III prostatitis. Urology 84:731.e739–713. https://doi.org/10.1016/j.urology.2014.05.038

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