Review Article
Trends in experimental autoimmune prostatitis: insights into pathogenesis, therapeutic strategies, and redefinition

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Abstract: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPSS) is a debilitating condition characterized by prostate inflammation, pain and urinary symptoms. The immune system's response to self-antigens is a contributing factor to CP/CPSS. In this review, we examine the use of experimental autoimmune prostatitis (EAP) in rodents to model salient features of autoimmune mediated CP/CPSS. By exploring etiological factors, immunological mechanisms, and emerging therapeutic strategies, our aim is to enhance our understanding of CP/CPSS pathogenesis and promote the development of strategies to test innovative interventions using the EAP pre-clinical model.

Keywords: CP/CPPS, experimental autoimmune prostatitis, AHR, ITE, inflammation, inflammasome, therapeutic strategies, autoimmunity, urology, translational animal models

Introduction

Prostatitis, or inflammation of the prostate gland, is a common urological condition in men. Prostatitis is responsible for nearly 2 million physician visits per year and $84 million in associated health care expenses [1]. Prostatitis is classified as type I (acute bacterial prostatitis); type II (chronic bacterial prostatitis), type III (chronic prostatitis/chronic pelvic pain syndrome, CP/CPPS), or type IV (asymptomatic inflammatory prostatitis) [2].

CP/CPPS, the most common prostatitis form, is characterized by persistent pelvic and perineal discomfort, and may include difficult and/or painful urination and ejaculatory pain [3-5]. The medical expenses for CP/CPPS are comparable to that of peripheral neuropathy, back pain, fibromyalgia, and rheumatoid arthritis [5]. Medical expenses associated with CP/CPSS increases with symptom severity [1]. Many men experiencing CP/CPPS also incur additional costs through work absenteeism and reduced productivity. Although antibiotics, alpha adre-

noreceptor antagonists, biofeedback and dietary modifications are sometimes prescribed for CP/CPPS, no therapies are particularly effective.

The onset, progression, severity and duration of CP/CPPS are influenced by an array of factors [1-3, 5, 6], and new research is needed to understand disease etiology and identify effective therapies. CP/CPPS is more common in middle-aged and older men than in younger men, and men over age 50 are at the highest risk [7]. A variety of potential CP/CPSS mechanisms have been examined, including infection, autoimmunity, compromised urothelial integrity and function, as well as psychosocial factors [3].

Autoimmune diseases are characterized by immune system activation against self-antigens, resulting in tissue damage and dysfunction [8]. While CP/CPPS was previously thought to be a non-inflammatory disorder, recent studies have revealed evidence of autoimmune dysregulation in this condition [3, 4, 9]. Abundance

Table 1. Summary of immunological mechanisms in EAP

Contributing factor to EAP	Description	Reference
Autoantigens and T Cell Response	Self-antigens from the prostate gland are perceived as foreign, triggering an immune response. Autoantigens, including prostate-specific antigens such as prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), are presented to T cells by antigen-presenting cells (APCs) and activate and expand CD4$^+$ T cells, to drive an immune response.	[10, 15, 74-76]
Inflammatory Mediators and Cytokines	Activation of autoantigen-specific T cells leads to production of pro-inflammatory cytokines, such as interleukin-17 (IL-17), interferon (IFN)-gamma (-γ), and tumor necrosis factor (TNF)-alpha (-α). These cytokines facilitate recruitment of neutrophils, macrophages, and dendritic cells into the prostate gland. Additionally, cytokines promote tissue inflammation, amplify immune responses, and contribute to the development of chronic inflammation.	[10, 18, 27, 71, 74]
Autoantibody Production	B cell activation in response to autoantigens stimulates autoantibody production, including anti-prostate antibodies. Autoantibodies may contribute to tissue damage and inflammation by forming immune complexes, activating complement cascades, and engaging Fc receptors on immune cells.	[20, 23, 30, 77-79]

of autoantibodies against prostatic proteins is elevated in sera from many CP/CPSS patients [10]. T cells from patients with CP/CPPS exhibited increased reactivity to prostatic antigens [4, 11]. Like most autoimmune diseases, more than one autoantigen is implicated [8].

One method for studying mechanisms and efficacy of pre-clinical treatment strategies for autoimmune mediated CP/CPSS is the rodent model of experimental autoimmune prostatitis (EAP). EAP has been induced in rodents to test efficacy of potential therapeutics including anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, immunomodulatory agents (such as cyclosporine A and mycophenolate mofetil) [12, 13], and herbal remedies and natural compounds [14].

EAP is initiated by immunizing rodents with prostate antigens and adjuvants [3, 10, 15]. The EAP phenotype in rodents resembles that of human CP/CPPS, and can include pro-inflammatory cytokine production, leukocyte infiltration, T-cell activation, chronic inflammation, fibrosis, and glandular atrophy [4, 9]. Factors that contribute to inflammation in rodents with EAP are summarized in **Table 1**. EAP in rodents is a progressive and chronic condition. Histological inflammation appears 5-10 days post-immunization and the timing depends on the species/strain of the host animal and the immunization strategy [4, 9, 15, 16]. Physiological phenotypes manifested in EAP rodents include pelvic pain, voiding dysfunction, and sexual dysfunction [3, 12, 15]. Pelvic pain appears 5 days post immunization and persists for more than 30 days as a chronic condition [15]. Histological inflammation is cor-

related with pain in rodents with EAP and both intensify over time [4, 15, 17, 18].

Experimental models of EAP

Two general approaches are used to induce chronic prostatitis in rodents: 1. Immunize rodents with extracts from all male rodent accessory sex glands, extracts specifically from rodent prostate gland, or natural or synthetic proteins selectively expressed by the rodent prostate to drive autoimmunity against the prostate gland. 2. Adoptively transfer activated immune cells such as T cells, trained against antigens in the prostate, into mice expressing those antigens in the prostate [9, 19, 20].

Immunization protocols for inducing EAP differ among research groups and these differences can influence the penetrance, onset, and severity of prostate inflammation. The most notable difference in EAP protocols is the rodent strain and species from which prostate antigens are collected and the strain and species into which antigens are introduced, and these include rats (Sprague Dawley (SD), Wistar, Copenhagen, Lewis) and mice (C57BL/6, and non-obese diabetic (NOD)) (summarized in **Table 2**) [20-22].

Some researchers drive EAP using pooled male accessory gland extracts (MAG) including seminal vesicles, prostate (anterior, dorsolateral, and ventral lobes), bulbourethral glands, ampullary glands, urethral glands, and preputial glands [19, 23-25].

The most widely used method to drive EAP in rodents is to immunize with prostate extracts (PAgs) pooled from the dorsolateral, anterior, and ventral prostate lobes of non-syngeneic

Table 2. Immunogens used to induce EAP in mice

Antigen	Mouse Strain	Age (wks)	Immunization Schedule	Antigen Dose per Immunization	Success Rate* (%)	Reference
PE	AJ	6-8	30 days: 1 × D0	375 mg	100	[26]
PE	C57BL/6J	6-8	30 days: 1 × D0	250 mg	100	[26]
SVS2	C57BL/6J	25	42 days: 3 × D0, D14, D28	200 mg	71.4	[20]
T2	C57BL/6J	6-8	35 days: 3 × D0, D14, D28	9 mg	100	[80]
PE	NOD	6	21 days: 2 × D0, D15	1 mg	100	[30]
PSBP	NOD	6	21 days: 2 × D0, D15	30 mg	80	[30]
MAG\	NOD(H2^{g7})	6	10 days: 1 × D0	1 mg	100	[24]
PE	SJL/J	6-8	30 days: 1 × D0	1 mg	100	[26]
p25	SWXJ(H-2$^{q.s}$)	8	63 days: 1 × D0	200 mg	100	[17]
MAG\	NOD(H2^{g7})	6	21 days: 2 × D0, D15	1 mg	37.5	[24]

\MAG antigen derived from rat. *Percentage of animals that develop histological inflammation.

rodents [4, 9, 16, 26]. PAg-specific lymphocytes have been identified in CP/CPPS patients [18, 27]. Intravenous PAg immunization induces CTL response and subsequent autoimmune prostatitis which is confined to the prostate [9]. Immunogenic peptides derived from PAP stimulate CD4+ T lymphocytes [3, 9, 17, 27]. The use of PAgs to induce EAP is specifically suited to study the adverse impact of prostatitis on fertility and mental health [12, 28] (**Figure 1**).

Other researchers drive EAP using isolated prostatic proteins from non-syngeneic hosts. Many autoantigens induce histological inflammation of the rodent prostate; however, only p25- and T2 also drive pelvic pain and urinary voiding dysfunction [9, 17, 20]. p25, a protein selectively expressed in prostate and which functions as a major mouse prostatic secretory glycoprotein, has been used to induce EAP with a phenotype that mimics the clinical presentation in humans and includes histological prostatitis, pelvic pain, and changes in voiding behavior associated with CP/CPPS [9, 17]. Rats immunized with p25 peptide exhibit urinary dysfunction, increased relative prostate weights, and heightened proinflammatory cytokines, all subsequently ameliorated by p25-specific CD4+ T cells provoking a Th1 response [17]. Remarkably, the bladder remains unaffected upon histological examination, suggesting prostate-specific pathology.

Synthetic prostatic steroid-binding proteins (PSBP) have been used to induce EAP and promote cellular- and humoral-specific autoimmune responses [29, 30]. PSBP, a tetrameric protein composed of two distinct subunits, showcases a unique arrangement - the first subunit harbors Cl and C3 polypeptides, while the second subunit harbors C2 and C3 polypeptides [29]. The transcript encoding the PSBP-C1 peptide is selectively expressed in ventral prostate and not dorsal prostate, bladder or kidney [31]. Leveraging this insight, peptides corresponding to the PSBP C1 subunit were synthesized and used to immunize mice. PSBP C1 peptides initiate cellular and humoral autoimmune responses. PSBP C1 peptide initiates substantial T and B cell responses in NOD mice, coinciding with significant lymphomononuclear cell infiltration of the prostate [9, 29, 30]. Notably, histopathological changes are observed by day 8 post-immunization, including the appearance of CD4+ T cells, and ablation of CD4+ T-cells confers resistance of PSBP C1 induced prostatitis [30, 32]. The focal point of inflammation from PSBP C1 induced prostate inflammation is in the ventral lobe, aligning with ventral prostate selective expression of PSBP. Noteworthy is the dominance of mast cells among inflammatory cells, accompanied by lymphocytes, monocytes/macrophages, histiocytes, and neutrophils contributing to epithelial atrophy [32]. Abundance of systemic inflammatory mediators IFN-γ and IL-12 is elevated in mice with PSBP induced EAP while abundance of IL-10 is reduced. PSBP's tetrameric nature and histopathological differences from human CP/CPPS have led to the adoption of immunogenic PSBP peptides. Limitations of PSBP as a driver of EAP include peptide cost and inconsistency of antigen presentation [4].
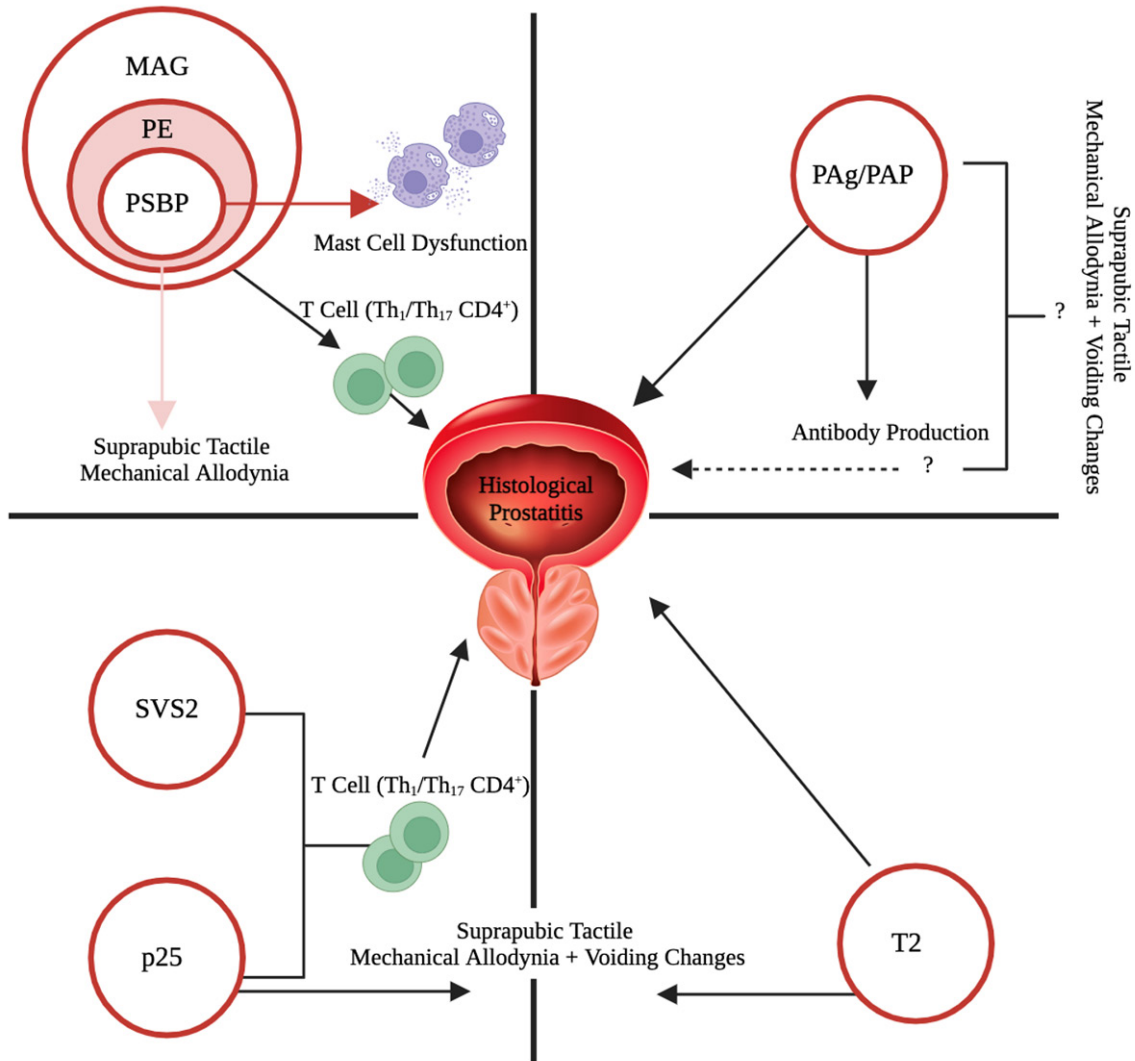
Figure 1. Differential EAP induction and disease-specific symptom mimicry: antigenic variability and targeted therapies (Adopted and revised from references [4, 9, 21]).

SVS2 and semenogelin are CP/CPPS autoantigens in mice and humans, respectively [20]. SVS2 and semenogelin derive from the seminal vesicle and not the prostate [9], and their function is to regulate seminal fluid viscosity [20]. SVS2 is implicated in spontaneous prostatitis. SVS2 expression is dependent on the autoimmune regulator (*Aire*) gene [20]. Genetic deletion of *Aire* results in multi-organ autoimmune reactivity in the eye, salivary glands, ovaries, stomach, and prostate [20, 33-35]. SVS2 reactive antibodies were detected in sera of *Aire* null mice. Wild-type mice immunized with SVS2 and *Aire*-deficient mice develop EAP [9, 20].

Despite the usefulness of the EAP model, there are some limitations that should be consid-

ered. One limitation is that the induction of EAP is highly dependent on the antigen used for immunization, and each antigen may lead to unique pathological and physiological EAP phenotypes (**Table 2**) [3, 9, 12]. Another limitation of the EAP model is that it does not fully reflect the complexity of human CP/CPPS, which involves multiple factors, such as infection, stress, and neuropathic pain [4, 9].

Haverkamp and colleagues used a unique, immunization-free approach to drive prostate inflammation in the POET-3 mouse. They collected splenocytes from Thy1.1+OT-I mice, which harbor a transgenic T cell receptor that recognizes ovalbumin. They applied ovalbumin to the splenocytes *in vitro*, and the resulting

Table 3. UPOINT CP/CPPS diagnosis and treatment therapies with UPOINT system description

UPOINT Domain	Clinical Presentation	Treatment
Urinary	LUT Syndrome	Alpha Blockers 5-Alpha-reductase inhibitors (5-ARIs)
Psychological	Depression Stress	5-serotonin and norepinephrine reuptake inhibitor
Organ-Specific	Targeted palpations exacerbate symptoms	Pollen Extract Eviprostat
Infection	Recurrent UTIs Bacterial localization	Antibiotics Acupuncture Pregabalin Botulinum Toxin-A
Sexual Dysfunction	Erectile Dysfunction	Phosphodiesterase inhibitors
Tenderness	Fibromyalgia Tenderness Spasm of perineum	Prostatic massage Transrectal radiofrequency Hyperthermia Low-intensity shockwave therapy (LiST)

*Adopted and revised from references [6, 7].

MHC class I-restricted, ovalbumin-specific, CD8+ T cells were transferred into mice expressing the ovalbumin transgene in prostate luminal epithelial cells (POET-3 and POET-3/*Luc/Pten*-/+ mice) to induce prostatitis in the anterior, dorsolateral, and anterior prostate regions [36]. POET-3 mice demonstrate robust recruitment of CD4+, CD8+ T-cells, and CD4+FOXP3+ T-regulatory cells, elevated cytokine/chemokine expression, and sustained prostate epithelial proliferation [22, 36].

Fundamental challenges for translational urological research are the identification and appropriate use of animals to model salient features of human disease. There is significant debate over whether animal can accurately replicate human disease [37]. Some argue, and with support from the literature, that animal models are not always predictive of human outcomes and may lead to false conclusions [38]. A major problem with animal models in benign urologic research is that the models and endpoints are not standardized (for example, see the variable methods for immunization of EAP mice in **Table 1**). There is a great need for strategy homogeny within the field to improve reproducibility and comparability between studies [9, 12, 17, 39]. Also, addressing the differences between animal and human physiology regarding disease presentation is needed to develop and achieve clinically relevant endpoints.

While whole animal models of prostatitis capture the complex interplay between prostate tissues and the immune system, alternative methods can be used to study select aspects of prostatitis:

1. *In vitro* cell culture: Primary prostate epithelial cells are stimulated with human recombinant tryptase-P/TPSB2 and co-cultured with leukocytes to examine paracrine signaling mechanisms involved in prostate inflammation. Cell based models provide a controlled environment for studying cell-cell interactions and molecular mechanisms [40].

2. *Ex vivo* tissue explants: Human or rodent prostates are harvested and maintained in culture to study the effects of immunological stimuli or therapeutic agents [41].

3. Human tissues: Prostatic tissues from patients with CP/CPPS are analyzed to identify histological features of the disease and biomarkers of disease severity [18].

4. Computational modeling: Baker's research uses computational models to predict regulatory mechanisms of CD4+ T cell functions and examine intersections between immunity and metabolism [42]. Lorenzo and colleagues modeled prostate cancer growth, an approach that could be applied to prostate hyperplastic responses to inflammation [43].

Current therapies for CP/CPSS

In urological research, managing CP/CPPS presents a substantial challenge. The UPOINTS system (**Table 3**) provides a nuanced approach, considering urinary, psychosocial, organ-specific, infection, neurologic, tenderness, and sexu-

al dysfunction factors [6, 7]. A major obstacle arises from the absence of detectable bacteria in urine, discouraging inappropriate antimicrobial therapy in favor of judicious antibiotic use [6].

Addressing urinary symptoms, conventional alpha-blocker treatments have shown limited improvement in prostatitis symptoms, with notable risks of adverse events like dizziness and hypotension [44]. Similarly, 5-alpha-reductase inhibitors exhibit a modest trend toward symptom relief, especially in cases concurrent with benign prostatic hyperplasia [5-7].

Psychosocial factors significantly contribute to CP/CPPS, correlating with psychiatric symptoms like depression, affecting symptom severity and quality of life [39, 45]. Selective serotonin and norepinephrine reuptake inhibitors, such as duloxetine, effectively alleviate CP/CPPS-associated pain with favorable side effects [46].

Organ-specific symptom treatments like pollen extract (cernilton) and eviprostat offer relief without adverse effects [47]. In cases without bacterial prostatitis, the efficacy of antimicrobial therapy, especially combined with alpha-blockers, remains uncertain due to inconsistent outcomes [47].

Neurologic manifestations involve abdominal or pelvic pain, alleviated by treatments like acupuncture and low-intensity shockwave therapy, though long-term efficacy of low-intensity shockwave therapy remains inconclusive [14].

Painfulness in the perineum or pelvic floor requires specialized approaches such as prostatic massage (contraindicated in acute bacterial prostatitis) and transrectal radiofrequency hyperthermia showing promise in improving pain and quality of life [14].

Addressing sexual dysfunction, phosphodiesterase inhibitors like tadalafil effectively improve CP/CPPS symptoms, especially pain and polyuria [39, 48]. Traditional Chinese medicine combined with Western interventions, like alpha-blockers and phosphodiesterase inhibitors, offers a holistic approach [14, 49].

However, limitations exist in current studies due to variability in patient populations, study designs, and cultural contexts, necessitating further research to refine CP/CPPS therapeutic strategies. Recent trials challenge the efficacy of alfuzosin, an alpha-adrenergic blocker, highlighting the need for rigorous exploration of novel treatments to enhance the quality of life for CP/CPPS patients [50, 51].

Effective CP/CPPS therapies remain elusive, given the array of symptoms and multifaceted disease causes. The UPOINTS system guides treatment strategies based on symptoms and causes, employing medications like antibacterial agents, anti-inflammatory drugs, analgesics, and those for benign prostatic hyperplasia (**Table 3**). Tailored adjustments are necessary based on individual responses, often requiring a multimodal approach [4, 5, 7, 14, 46, 50]. Alpha adrenoreceptor antagonists, including tamsulosin and alfuzosin, show promise in alleviating CP/CPPS symptoms, although ongoing debate surrounds the efficacy of antibiotics and anti-inflammatory agents.

Emerging therapeutic targets for CP/CPSS

Researchers are increasingly channeling efforts into the exploration of targeted therapies, including immunomodulatory agents and innovative drug delivery systems, to identify more efficacious remedies for CP/CPPS [2, 52]. These endeavors harbor the potential to elevate the quality of life for individuals grappling with this enigmatic condition, offering promise for future CP/CPSS therapy.

Recognizing autoimmunity as a mechanism for CP/CPPS has implications for treatment and management approaches. While conventional anti-inflammatory drugs are typically employed for inflammatory disorders, autoimmune diseases necessitate immunomodulatory therapies that specifically target the underlying autoimmune dysregulation. Adopting this new perspective could potentially pave the way for the development of more targeted and efficacious treatments for CP/CPPS. One strategy for CP/CPSS researchers is to co-opt therapeutic targets already identified in extra-prostatic autoimmune diseases [6]. One example is the aryl hydrocarbon receptor (AHR), a transcription factor activated by a variety of endogenous and exogenous chemical and which functions as a potent immunosuppressor [53-57]. AHR regulated genes vary by cell type and context, but many participate in immune

function, inflammation, and xenobiotic metabolism [54, 55]. In the context of autoimmune disease, AHR activation has been shown to have anti-inflammatory effects by promoting the differentiation of regulatory T cells and inhibiting the differentiation of pro-inflammatory Th17 cells [58]. Genetic loss of AHR signaling exacerbates inflammation in a mouse model of colitis [53, 59, 60]. The AHR signaling pathway has been experimentally manipulated with a variety of agonists, antagonists, and dietary constituents and below we focus on AHR ligands used in a preclinical setting to treat autoimmune disorders, acknowledging their broader relevance beyond the confines of prostatic pathophysiology.

The AHR agonist 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) reduces colitis [53]. ITE also impedes differentiation of Th17 T cells [54, 61] and suppresses production of pro-inflammatory cytokines such as IL-17 and IFN-gamma [53, 55].

The AHR agonist 6-formylindolo(3,2-b) carbazole (FICZ) has been assessed for its potential in treating irritable bowel disease [56, 57]. FICZ activates the AHR pathway and the tristetraprolin pathway to reduce cytokine abundance and inflammation in mice treated with dextran sulfate sodium to drive colitis [55, 57, 59, 61, 62].

The naturally occurring AHR agonist 3,3'-diindolylmethane (DIM) has demonstrated therapeutic promise within the experimental autoimmune encephalomyelitis (EAE) model, a relevant representation of multiple sclerosis [63, 64]. Administration of DIM post-EAE induction reduces inflammation and curtails cellular infiltration in the central nervous system [63]. DIM functions by remodeling the miRNA profile (miR-200c, miR-146a, miR-16, miR-93, and miR-22) in brain CD4$^+$ T cells, influencing cell cycle regulation and promoting apoptosis-related pathways [63].

Indole-3-carbinol (I3C), a compound derived from plants, is an AHR agonist that has been shown to curtail colonic inflammation and rectify microbial dysbiosis in intestinal inflammatory disease [54, 57]. I3C induces proliferation of beneficial gram-positive bacteria that produce butyrate, a potent anti-inflammatory agent. I3C has been shown to increase abun-

dance of IL-22 and modulate gut microbiota to mitigate colitis [54].

Despite promising potential for treating autoimmune disease, the use of AHR modulation as a therapeutic strategy for lower urinary tract diseases is not without challenges. One major limitation is the potential for off-target effects, as AHR is known to regulate a broad range of physiological processes beyond the immune system and tissue repair. Additionally, the lack of specific AHR agonists or antagonists with high affinity and selectivity presents a major hurdle in developing effective AHR-targeted therapies. Nonetheless, the potential benefits of AHR modulation for the effective treatment of lower urinary tract diseases warrant further investigation.

Toll-like receptor 4 (TLR4) signaling, which plays a major role in the immune response to gram-negative bacteria [65-68], is also a potential target in CP/CPSS. TLR4 signaling is activated by pathogen-associated molecular patterns (PAMPs) such as bacterial lipopolysaccharide (LPS) [66, 67] and has been linked to hyperactive immune responses, sepsis, acute lung injury, and chronic inflammation [66-68]. Genetic ablation of microRNA-155 (miR-155) was recently shown to reduce TLR4 signaling [65]. MiR-155 deficient mice are resistant to EAP-mediated pelvic tactile hypersensitivity and exhibit diminished TLR4/nuclear factor-kappa B (NF-κB) responses to EAP [65]. In contrast, mice that overexpress miR-155 are hypersensitive to EAP-induced prostatic inflammation and oxidative stress [65, 69].

Cyclooxygenase-(COX)-1 and -2 have been implicated in autoimmune disease and COX-2-selective inhibitors such as celecoxib are effective anti-inflammatory agents [70]. A recent study showed that celecoxib reduces depressive behaviors and increases sexual drive and improves erectile function in mice with EAP [12]. Celecoxib also reduced prostate inflammation and serum IL-1β/TNF-α concentrations and increased serum serotonin in mice with EAP [12].

Tumor necrosis factor alpha (TNFα) plays a critical role in autoimmunity [44, 71-73]. Insight into the signaling cascades initiated by TNFα has paved the way for therapeutic breakthroughs, notably the advent of TNFα inhibitors

such as Etanercept and Infliximab, both of which have demonstrated efficacy across various autoimmune diseases [71]. A recent study revealed an elevated prevalence of BPH in patients with autoimmune disease [71]. The use of TNFα antagonists for autoimmune disease appeared to reduce the risk of BPH and was associated with many outcomes that would be considered positive in CP/CPSS patients, a reduction of prostate epithelial proliferation, prostatic macrophages, and suppression of NF-κB activation [71].

Conclusion

This review offers new insights into the mechanisms of CP/CPSS. We defined autoimmune prostatitis as a form of CP/CPPS characterized by an immune-mediated response against self-antigens within the prostate gland. This condition arises when the immune system, in a dysregulated state, recognizes proteins and antigens specific to the prostate as foreign, leading to an inflammatory response that includes T-cell activation, cytokine production, and the formation of autoantibodies. The consideration of autoimmunity as a mechanism of CP/CPSS shifts from traditional views that bacterial infections or non-specific inflammatory processes are the sole mediators of this disease and acknowledges the complexity of CP/CPPS, integrating the role of autoimmunity as a key driver of the disease process. We have described EAP models and research involving these models which has been instrumental in redefining some forms of CP/CPSS as having an autoimmune component, raising the possibility of targeted immunomodulatory therapies for treating CP/CPSS. We also described potential new therapeutic strategies, such as the use of ITE or other short-acting AHR agonists to drive immunosuppression. This is a significant step in considering and testing new therapies that can more precisely target the underlying causes of autoimmune prostatitis, ultimately improving outcomes for patients afflicted with autoimmune mediated CP/CPPS.

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Disclosure of conflict of interest

None.

Abbreviations

5-ARI, 5-Alpha-reductase inhibitor; A/J, Inbred Albino Mouse strain; ADME, Absorption, Distribution, Metabolism & Excretion; AHR, Aryl hydrocarbon receptor; AHRE, Aryl hydrocarbon response element; Aire, Autoimmune regulator (gene); ARNT, AHR nuclear translocator; bHLH, basic helix-loop-helix; BPH, Benign Prostatic Hyperplasia; CD, Cluster of differentiation; cLPL, Colon lamina propria lymphocytes; COX-, Cyclooxygenase; CP/CPPS, Chronic Prostatitis/ Chronic Pain Syndrome; CTL, Cytotoxic T lymphocyte; DC, Dendritic Cell; DIM, 3,3'-diindolylmethane; DNA, Deoxyribonucleic acid; DSS, Dextran sulphate sodium; EAE, Experimental autoimmune encephalomyelitis; EAP, Experimental Autoimmune Prostatitis; EAU, Experimental autoimmune uveitis; FICZ, 6-Formylindolo-(3,2-b)carbazole; HAH, Halogenated aromatic hydrocarbon; Hsp-, Heat Shock Protein; I3C, Indole-3-Carbinol; IAA, Indole acetic acid; IBD, Irritable bowel disease; IBS, Irritable bowel syndrome; IDO, 2,3-dioxygenase; IL-, Interleukin; ITE, 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester; Kyn, Kynurenine; LiST, Low-intensity shockwave therapy; LUT, Lower Urinary Tract; LUTD, Lower Urinary Tract Disease; MAG, Male Accessory Gland; MLN, Mesenteric lymph nodes; MoA, Mechanism of action; NOD, Non-obsese diabetic (Mouse strain); NSAID, Non-steroidal anti-inflammatory drugs; p25, Prostatic spermine-binding protein; PAH, Polycyclic aromatic hydrocarbon; PAP, Prostatic Acid Phosphate; PCa, Prostate Cancer; PE, Prostate Extract; PEC, Predicted environmental concentration; PG-, Prostaglandin; PSA, Prostate-specific antigen; PSBP, Prostatein or steroid binding protein; SD, Sprague Dawley (rat strain); SJL, Swiss Jim Lambert (mouse strain); SVS2, Seminal vesicle secretory protein 2; T2, Peptide; TCDD,

2,3,7,8-Tetrachlorodibenzodioxin; Th-, T-helper cell; Tr1, Type-1 regulatory T cells; T_{reg}, T-regulatory cell; TTP, Tristetraprolin.

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