Etiology of chronic prostatitis/chronic pelvic pain syndrome – How animal models guide understanding of the syndrome

Stephen F. Murphy[1]
Praveen Thumbikat[2]
[1]Department of Urology, Feinberg School of Medicine, Northwestern University, Chicago, Vereinigte Staaten
[2]Department of Urology, Chicago, Vereinigte Staaten

Abstract

There remains a limited understanding of the etiology of CPPS. Given the diffuse nature of the symptoms and the heterogeneous nature of the patient population this is not surprising. Of the information that exists it is possible that further subdividing the patient population based on certain inflammatory criteria might be useful in basic research on CPPS going forward. Our laboratory and others have begun to understand and regard CPPS as an underlying autoimmune defect that is exacerbated by damage to the prostate resulting in a chronic symptomology. Much of this robust information on the emergence of CPPS has come from research performed in murine models of the disease.

Human studies

Various studies have sought to determine an association between CPPS and immune activation using samples from multiple sources including, expressed prostatic secretion (EPS), seminal plasma, semen and urine. These have shown not only an increase in the number of infiltrating cells (activated T and B cells, granulocytes and macrophages) [1], [2] but also increased levels of the IL2 receptor [3], [4] and specific inflammatory cytokines including IL1b, IL6, IL8, IgA and TNFa [5], [6], [7], [8]. As yet investigators have failed to determine a specific prostate antigen responsible for driving the autoimmunity in patients but research has been successful in isolating Th1 T-cells specific to prostate specific antigen (PSA) [9] in the peripheral blood of CPPS patients in the absence of carcinogenesis [10]. Auto-reactive CD4 T-cells have also been identified that respond to the seminal plasma of patients [11]. Further investigation to narrow down specific antigens have revealed IgA antibodies against Ny-Co-7 and MAD-PRO-34, both prostate specific, in CPPS patients [12], [13]. Taken together this data suggests that in humans there is some evidence of auto-reactivity against the prostate, which could mediate CPPS. This is supported histologically with one study showing an increase in the number of CD8+ T-cells in the prostate of patients compared to controls [13], [14]. Studies from our laboratory using a high-throughput multiplex array for over 40 cytokines and chemokines has shown an increased level of IL7 expression in CPPS patients compared to controls, and demonstrated that increased levels of IL7 was also positively correlated with increases in patient reported symptoms [15]. These findings were corroborated in the experimental autoimmune prostatitis (EAP) murine model where we identified prostate specific increases in IL7 expression [15]. IL7 is a driver of T-cell differentiation and function [16], [17], [18] and as such these findings also point to an underlying immune defect in CPPS patients.

Experimental autoimmune prostatitis

The experimental autoimmune prostatitis model (EAP) is a xenogenic mouse model of CPPS that is induced by a sub-cutaneous injection of a prostate homogenate or specific prostate proteins and an adjuvant [19], [20]. The model was first investigated in Wistar rats and has since been adapted into alternative forms in mice [21]. Early studies seemed to suggest that development of prostatitis was dependent on the prostate steroid binding protein (PSBP) which is was a candidate for a specific antigenic driver of pain as when used alone could induce CPPS-symptoms [22], [23], [24]. Additional studies determined that other antigens within the prostate homogenate are also important. Depending on the adjuvant used there are multiple different inflammatory and adaptive immune responses that are mounted that account for associated symptoms. Our model of EAP uses a whole rat prostate homogenate and the Titermax adjuvant, which we have demonstrated results in increased number of

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Th17 cells in B6 and NOD animals [15], [20]. Other models using CFA (complete freuds adjuvant) as an adjuvant, drive a more Th1-type (Il12p40 specifically) [25], [26] response without the similar increase or necessity for Th17 cells, but have also been successful in driving development of chronic symptoms in mice [25]. This use of different adjuvants to result in similar phenotypes is of particular interest and suggest that it maybe a defect in the ability of patients to control T-cell activation (Th1 or Th17 responses) by T-regulatory cells that is the underlying problem in patients rather than an excess of activation. This is further exemplified by the propensity for development of prostatitis in aged NOD mice compared to their B6 or Balb/c counterparts [27]. The NOD mouse is used in diabetes research where T-cell immune activation against pancreatic B-islet cells has been demonstrated [28], [29]. In the study of CPPS, NOD mice consistently develop pain responses that are significantly higher than their B6 counterparts in EAP models while also being uniquely susceptible to the development of chronic tactile allodynia in the CP1-induced model, see below [30]. NOD mice have been shown to have genetic polymorphisms in two genes that regulate T-cell function, *IDD3* and *CTLA4* [31], both of which have specific roles in maturation and functioning of T-regulatory cells [32]. This suggests that loss of T-regulatory cell function in these mice may account for the development of spontaneous prostatitis and prime the prostate immune microenvironment to development of chronic symptoms when activated.

Using the EAP model our laboratory demonstrated that two chemokines previously demonstrated to be associated with CPPS in humans, chemokine C-C motif ligands 2 and 3 (CCL2 and CCL3) were increased in prostate tissues during disease progression [33]. CCL2, also known as MCP1 (monocyte chemotactic protein 1) and CCL3, also known as MIP1a (macrophage inflammation protein 1 alpha) have been associated with development of multiple autoimmune disorders including rheumatoid arthritis [34], [35], [36], [37], [38]. In CPPS patients both chemokines were increased in EPS samples compared to controls but only MIP1a was positively correlated with increased symptoms severity [39]. From the mouse model we demonstrated that CCL3 was increased only at later time-points (day 20) following EAP induction [33]. This suggests that in patients as well as in mice that increased expression of certain chemokines may be dependent on when during disease course samples are collected and analyzed. Such differences may account for continuing difficulty in identifying a robust biomarker for CPPS as the immune microenvironment may be constantly shifting and changing.

Tryptase/PAR2/Mast cells

One cell type in particular that has emerged as a potential major mediator of inflammation and development of centralized pain in CPPS, the mast cell. Data from both human and mouse studies have revealed a central role for these cells in maintenance of chronic symptoms [21], [40], [41], [42], [43], [44], [45], [46], [47]. Mast cells are hematopoietic in nature and circulate in an immature form only differentiating fully once tissue resident. Such developmental processes are not unique to this cell type but do suggest some tissue specific cellular phenotype. These cells function as one of primary immune mediators to pathogenic infection and have multiple additional roles including tissue remodeling. Degranulation of mast cells upon activation is triggered by a variety of signals including the cytokine milieu, hormonal changes, physical changes and specific damage/pathogen-associated molecular patterns (D/PAMPs) [46]. Degranulation results in release of numerous factors and damage response elements, such as serotonin, prostaglandins, histamine and tryptase. In human disease mast cells are associated with a variety of autoimmune disorders including RA [40], [45], [48], [49], [50], [51], where increased numbers of cells and associated tryptase has been shown at affected sites. Mast cells have been shown to interact directly with T-cells both pro-inflammatory, Th17 cells and T-regulatory cells via the OX40 ligand [48], [52].

EPS from CPPS patients compared to controls has also been shown to have an increased level of tryptase and an increased number of mast cells [53]. Tryptase activates the protease-activated receptor 2 (PAR2), a member of the G-protein coupled receptor (GCPR) family that has known functions in pain and inflammation. The tryptase: PAR2 axis has been shown to be important for viseral pain and immune responses in ulcerative colitis and Crohn's disease [54]. Our laboratory has demonstrated significant increases in the levels of tryptase and carboxypeptidase A (CPA3) another mast cell released factor in EPS samples from patients, indicating increased mast cell activity in CPPS [53]. Extending these findings into our murine EAP model we also demonstrated that PAR2 global knock-out mice are resistant to the development of pain upon EAP induction. Loss of PAR2 receptor expression appears to ablate MAPK/ERK signaling at the level of the dorsal root ganglion (DRG) associated with the prostate. We hypothesize that the mast cell might therefore mediate cross-talk between the immune response and the neurologic system in CPPS development [53]. Inhibition of PAR2 receptor activity therapeutically, using a blocking antibody, ameliorates tactile allodynia in mice and we are currently implementing the use of

mast cell stabilizers clinically as part of a small trial. Taken together these data suggest that immunological activation may enhance mast cell activity, which can serve to coordinate neurological interactions resulting in chronic pain [53].

Bacteria in CPPS

While there is mounting evidence for the role of the immune system in the etiology of CPPS it is by no means well defined. Underpinning this is the source of the initial prostate damage. Our studies and others are beginning to determine that certain bacteria may be our best hope to further understanding this syndrome. Although CPPS is distinguished from the other sub-categories of prostatitis by the absence of an associated bacterial infection, bacteria can readily be detected and isolated from both EPS and urine samples. Comparisons of the microbiome isolated from voided bladder (VB) samples between patients and control samples have been performed and have not, as yet, demonstrated significant shifts in the microbial ecology [55], [56]. Currently as part of the MAPP project, research is underway that examines differences in the intestinal microbiome of patients versus controls. While these studies are useful from a therapeutic standpoint there is still a need to resolve deeper information into the etiology of the syndrome. A more robust approach from an etiological standpoint might be a deeper longitudinal characterization of microbiome shifts within the urogenital tract of patients to identify bacterial species that are prostate localized that are associated with CPPS symptoms over time. To this end our laboratory has focused on examining prostate localized bacterial isolates from CPPS patients to determine the role of specific human microbes in driving disease.

CP-1 (chronic-pain 1) is a prostate localized *E. coli* strain that was isolated from the EPS of a CPPS patient with active disease [30]. Our laboratory has demonstrated that intra-urethral infection with this bacterial species can induce chronic tactile allodynia in NOD but not B6 mice. Immune responses to the bacterial infection skew towards a Th17 response and infiltration of leukocytes to the prostate and inflammation are sustained after bacterial clearance [57]. We further demonstrate in this study that this immune activation and subsequent development of symptoms is transferable by adoptive transfer of *ex vivo* expanded T-cells that are skewed towards a Th17 phenotype [57]. It is important to note that to date no specific role for Th17 cells has been identified from human cells and the current data is mainly correlative. The specificity of these data was further demonstrated by comparison with a cystitis associated pathogenic *E. coli* strain, NU14, which failed to mount similar responses and did not result in development of chronic pain. These strains are evolutionarily distinct CP1 belonging to UPEC group B1 while NU14 is a group B2 strain. Further analysis revealed that NU14 is equally capable of adhering to prostate epithelial cells but that CP1 is inherently more invasive [58]. These studies underlined the bacterial specificity that we hypothesize to be very important in development and initiation of CPPS in humans. Furthermore this evidence also supports the theory that initial damage, such as a bacterial infection in certain genetic contexts can mount immune responses that fail to be controlled adequately resulting in development of chronic symptoms. The ability of the microbial ecology of the prostate to influence the immune microenvironment was examined further through our investigation on the potential of a commensal non-pathogenic bacterial strain, isolated from the prostate of a healthy man to control immune activation and ameliorate pain. Using our EAP model we demonstrate that intra-urethral instillation with a gram-positive *Staphylococcus epidermidis* species designated NPI (non-pain inducing), could reverse EAP-associated IL17 expression and significantly reduce tactile allodynia responses [59]. NPI alone does not induce tactile allodynia in either B6 or NOD mice but is capable of colonizing prostate tissues in both animal backgrounds. More recently we are examining the effect of instillation of this bacteria in the context of an ongoing CP1 infection and are demonstrating that NPI colonization can prevent CP1-induced pain from developing. Taken together these findings demonstrate that specific bacteria from the prostate may have a role in initiation of CPPS in humans, that this can be maintained in the absence of an ongoing infection and most importantly that it can be reversed upon restoration of healthy immune: microbial interactions.

To further emphasize this point we are currently examining the potential of gram-positive bacterial species, isolated from the EPS of CPPS patients to induce pain in mice. In prostatitis diagnoses, including CPPS, gram-positive bacteria are usually deemed clinically insignificant and traditional uropathogens are thought to be gram-negative in nature. We have observed however that gram-positive species make up a large proportion of the bacterial content of the EPS and that when isolated from patient samples are capable of potentiating disease in a manner similar to CP1. Our initial studies suggest that intra-urethral instillation with three of these strains, *S. epidermidis*, *E. faecalis*, and *S. hemolyticus*, induces chronic tactile allodynia in NOD but not B6 animals. Furthermore characterization of the immune response of these animals to bacterial infection reveals that it is not mediated by Th17 cells but may involved NK-cell immune activation. These findings further support our hypothesis that it is loss of regulatory control of immune responses in these mice that result in CPPS-like symptom emergence

rather than a particular flavor of adaptive immune response. This mirrors the seemingly conflicting evidence from the different EAP murine models of CPPS, which have shown opposing inflammatory processes to be dispensable and/or necessary for inflammation and pain development.

Conclusion

We have presented here the current understanding of the etiology of CPPS from a microbial and immunological perspective. From studies using both patient samples and murine models we postulate that it is the inter-play between bacteria and the immune system that is the major initiator of the syndrome and symptoms are then maintained owing to a host genetic defect in regulation of the adaptive immune response. Large patient-focused studies on the ongoing immune response throughout symptom maintenance and also the urinary microbiome changes in patients are necessary to further delineate this and more importantly to uncover potential therapeutics.

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Corresponding authors: Praveen Thumbikat, Department of Urology Chicago, Vereinigte Staaten, E-mail: thumbikat@northwestern.edu

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