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Original Article

Immune reaction of chronic nonbacterial prostatitis/pelvic pain syndrome and progress of treatment

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Abstract: Chronic prostatitis (CP) is one common disease in males with persistent course and repeated recurrence. The incidence of chronic nonbacterial prostatitis with chronic pelvic pain syndrome (CAP/CPPS) consists of 2.5%~16% of total cases, with its mechanism largely unknown. Current studies have suggested CP as one chronic male-specific disease caused by multiple factors and steps. In current studies regarding its pathogenesis mechanism, novel clinical typing and disease evaluation, the involvement of immune function is emerging. Similar to auto-immune disease, the pathogenesis mechanism of CAP/CPPS is related with innate immunity. During the whole process of occurrence and progression, multiple cytokines are involved and are closely related with T cell immune response. In this review, we discuss the typing of CAP/CPPRS, its relationship with auto-immune responses through analyzing the correlation of CAP/CPPRS with Th1 and Th2 cells as well as the immune therapy of CAP/CPPS, in an attempt to explore novel approaches for treating CAP/CPPS.

Keywords: Chronic nonbacterial prostatitis/chronic pelvic pain syndrome, autoimmune, Th1/Th2 treatment

Introduction

Chronic prostatitis (CP) has one persistent disease course with repeated recurrence, whose patients had no satisfactory countermeasures so far. As the most common chronic disease in urinary surgery, the pathogenesis mechanism of CP is still unknown, thus causing the lack of systemic and uniformity of both diagnosis and treatment courses. Current surveys about the incidence of CP have been affected by various factors including ethical groups, life styles, diet habit and sampling method. Even the different diagnostic standards could lead to huge variations of incidence [1]. For those disease affecting life quality of the population, NIH enlisted CP, cardiac arrest, unstable angina, active Crohn disease. Chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CAP/CPPS) is known to be related with innate immunity as multiple cytokines are involved in the occurrence and progression of CAP/CPPS, thus making it as one auto-immune disease [2, 3]. In this review, we will focus on the typing of CAP/CPPRS, the relationship of CAP/CPPS with auto-immune responses through evaluating the correlation of CAP/CPPRS with Th1 and Th2 cells as well as the immune therapy of CAP/CPPS, in an attempt to explore novel approaches for treating CAP/CPPS.

CAP/CPPS typing

In clinical practice, prostatitis is one common disease in adult males. By classical typing method, prostatitis includes acute bacterial prostatitis (ABP), chronic bacterial prostatitis (CBP), chronic non-bacterial prostatitis (NBP) and prostatodynia (PD) [4]. Such method is strongly based on the sub-typing of bacterial pathogens, and has been used as the guideline for clinical diagnosis of CP. Among all sub-types of CP, ABP and CBP have been widely accepted and utilized by clinicians, leaving the definition of NBP and PD controversial as progression in CP related research and increasing experienc-

es. CAP/CPPS is one new subtype proposed by NIH in 1995, and includes both NBP and PD in the original 4-class system. CAP/CPPS occupies about 90%~95% of all CP cases, and can be further divided into inflammatory (IIIa) and non-inflammatory (IIIb) types [5].

CAP/CPPS and autoimmunity

The clinical symptoms of CAP/CPPS is versatile, including long-period, recurrent pelvic pains, and sometimes urinary dysuria and sexual malfunction, all of which usually last for more than 3 months, thus severely affecting life quality of patients. Previous study indicated that only 6%~30% of CP patients can be diagnosed with inflammation by urine examination [6, 7]. For a large amount of CP patients, although having no evidence for inflammation in urine, expressed prostatic secretin (EPS) assay reveal elevated leukocytes, lymphocytes and inflammation related cytokine levels [8]. After repeated exploring, researchers found that autoimmune reactions targeting urinary system might be involved in the CP symptoms. Increasing number of evidences showed the participation of autoimmune related factors in the occurrence and progression of CAP/CPPS patients, suggesting CAP/CPPS as one autoimmune disease [9]. The following will discuss Th cells and cytokines in the pathogenesis of CAP/CPPS.

Th cells in CAP/CPPS

Th cell, also named as helper T lymphocytes, plays a role in the secretion of multiple cytokines in body immune functions. Th1 cell can induce cell immunity by secreting IFN-γ, IL-2 and TNF-α, while Th2 cell mainly participates in humoral immunity via stimulating B cells to transform into antibody secreting cells. Th2 cells mainly participate in the secretion of IL family cytokines such as IL-4, IL-5, IL-6 and IL-10 [10]. Body can maintain normal immune homeostasis largely due to the active participation of various body immune related cells. Among those cells, T cell subpopulation is of critical importance as they can interact to be involved in the body's immune response to effectively eliminate exotic antigens while keeping normal organ/tissue intact. To further study cytokine network, comprehensive studies have been performed regarding Th1/Th2 cell subpopulation. Under normal physiological condition, there is a dynamic balance of Th1/Th2 cells. The interruption by different cytokines affects proliferation and differentiation of Th1/Th2 cells. In CAP/CPPS, autoimmune reaction and Th cell proliferation may all participate in the whole occurrence and progression process. In anatomical perspective, male urinary system is under immune dominance. After certain injury such as autoimmune dysregulation, CAP/CPPS may occur due to acute/chronic inflammation, acute bacterial prostatitis and major trauma [11]. Ponniah et al extracted peripheral CD4+ lymphocytes from CP/CPPS patients, and co-culture those cells with PSA and PAP, and found specific proliferative reaction in a response to PSA [12]. Previous study also found significantly elevated Th1 cell number and Th1/Th2 cell ratio in peripheral blood of CAP/CPPS patients type IIIa and IIIb, suggesting the important role of immune factors in disease occurrence and progression. The onset of CAP/CPPS is closely correlated with body's autoimmune response enhancement. Under such circumstance, Th1 reaction dominates inside body, leading to misbalance of Th1/Th2, named as "clonal drift" [13, 14].

Cytokines in CAP/CPPS

In regulating body immune functions, cytokines are mainly produced by active immune cells, including lymphocytes, monocytes, fibroblasts and endothelial cells, all of which have synergistic effects to regulate local and systemic immune reaction. The regulation of body protein expression level is mainly achieved via specific binding with protein related receptors for exerting important regulatory function [15]. Based on specific roles of cytokine in CAP/CPPS, they can be further divided into pro-inflammatory factors, anti-inflammatory cytokine and regulatory cytokines [16]. Among those, pro-inflammatory cytokines mainly consist of TNF-α and IFN-γ [17]. Previous study has detected levels of those pro-inflammatory cytokines in CAP/CPPS patients and found significantly elevated levels in patients. Moreover, type II and type IIIa CP patients had relatively higher TNF-α level, which was positively correlated with body while blood cell count. The assay of TNF-α and while blood cell count in EPS in type IIIb CP patients found no significant difference, suggesting the value of TNF-α in identifying the inflammatory or non-inflammatory nature of CP [18]. The level of IFN-γ in EPS

from CAP/CPPS patients also suggested IFN-γ as one important index to diagnosing CAP/CPPS by serum assay [19]. Among all three kinds of cytokines, anti-inflammatory cytokine is of critical importance including IL-6 and IL-1, both of which can suppress inflammation and inhibit the activity of pro-inflammatory cytokines [20] and thus can be used to evaluate the treatment efficiency of CAP/CPPS treatment. IL-6 can be produced from monocytes, activated T cells/B cells. After activation of T cells, IL-6 can produce lymphocyte factors in conjunction with fibroblast to accelerate the formation of related antibody by B cell precursors. Those antibodies can work with colony stimulating factor in synergistic manners to facilitate the proliferation and differentiation of primitive bone marrow cells, whose potency for killing cells was gradually enhanced [21, 22]. IL-6 can be used to evaluate the treatment efficiency of CAP/CPPS, as its level is somehow connected with the number of monocytes in host blood. IL-10 is also one potent cytokine to restrict the secretion of immune mediators by mononuclear macrophage. Specifically, it can reduce the release of IL-1 and TNF-α, and to reduce the reactivity of IL-1 cytokine to suppress antigen presentation function, thus impeding Th1 type immune response. IL-10 is mainly produced by Th2 helper cells [23]. IL-2 is another modulatory cytokine produced by activated CD4 + T cells, CD8 + T cells, and can modulate body immune response with wide spectrum of bioactivity. Inside blood and tissue samples of CAP/CPPS patients, Il-2 can maintain the balance of TNF-α and IL-10, to inhibit the occurrence and progression of CAP/CPPS [24].

Th1/Th2 cells and variation of CAP/CPPS

In another study about Th1/Th2 levels of CAP/CPPS patients found elevated Th1 cell count, Th1/Th2 ratio in CAP/CPPS patients, especially in type IIIa and IIIb patients [25]. Under the stimulation of pro-inflammatory cytokines such as IFN-γ and TNF-α, the function of Th1 cell sub-population in CAP/CPPS patients was significantly potentiated while Th2 subpopulation function was depressed, resulting in a Th1/Th2 drift. Such abnormality further enhanced the secretion of pro-inflammatory cytokines to aggravate the autoimmune injury in CAP/CPPS patients. Animal study indicated elevation of CD4 + T lymphocytes in prostate tissues of CAP rats [26]. Clinical study also revealed the major component of inflammatory cells as T lymphocytes from CAP IIIb patients' tissue samples. With disease progression and tissue inflammation advancement, no significant change of Th2 cell count can be detected in CAP III and IIIb patients, but with remarkably increase of Th1 cell count, resulting higher Th1/Th2 ratio [27, 28]. Inside our body, due to the exposure of local antigen of prostate, body immune response can be activated via the antigen presenting cells inside prostate, thus inducing focal infiltration of immune cells in CAP/CPPS patients. Further release of pro-inflammatory cytokines into peripheral blood can cause gradual exacerbation of organ/tissue damage [29]. Under the continuous effect of various pro-inflammatory cytokines, Th1/Th2 drift may occur, as Th1 cell is persistently dominant, thus further aggravating the injury caused by body immune reaction.

Treatment of CAP/CPPS

CAP/CPPS patients had complex clinical manifestation and unsatisfactory treatment efficacy using current approaches, mainly due to the lack of knowledge regarding its pathogenesis, occurrence and pathology mechanism. Current choice of medicine mainly consists of antibiotics, α-receptor blocker, 5α-reductase inhibitor, plant extracts, non-steroid anti-inflammatory pills and Chinese herbs. Immune therapy against CAP/CPPS still requires further explorations.

As the major counter-measure for CAP/CPPS, antibiotics are widely used, although less than 10% patients showed bacterial positive in culture of urinary secretes [30]. After 12-week of ofloxacin treatment, about 57% of CAP/CPPS patients had significant improvements.

The anti-inflammatory therapy can somehow relieve focal or systemic inflammatory response to inhibit autoimmune response, and to reduce the pain transduction of patient's central nervous system to reduce the body sensitivity for pains [31].

In selecting medicines for CAP/CPPS patients, α-receptor blocker is commonly used to relax smooth muscles of bladder neck and prostate, relieve spasm of pelvic muscles, improve urine flow rate, and decrease focal pains of pelvic

regions. Another study has found that α-receptor blocker can rescue pathological apoptosis of CAP/CPPS patients, thus reducing the blockage of prostate [32].

5α-reductase inhibitor is an alternative choice as it can block the action of male hormone, reduce prostate edema, decrease pressure inside prostate tissue, induce counter-flow of prostate-urine, and decrease the size of prostate, thus managing and relieving focal inflammation of prostate. It is favorable in elder patients, especially with prostate hyperplasia.

Natural plant extract can also be used to treat interstitial cystitis, and can also be used for treating CAP/CPPS. This can effectively alleviate clinical symptoms of CAP/CPPS patients, decrease the disease severity and lower the occurrence times [33], thus improving life quality of patients.

Non-steroid anti-inflammatory pills were also often used in CAP/CPPS patients [34]. It can rapidly relieve pelvic pains and uncomfortable, especially for those with perineal discomfort and urine incontinence.

Moreover, Chinese herbs have also been promoted in treating CAP/CPPS in clinics due to its functions of anti-dampness, activating blood and dissolving stasis, and invigorating the kidney, with relatively high safety and efficiency.

Future perspective

With the rapid advancement of molecular biology, molecular immunology and related techniques, there are now increasing numbers of treatment approaches for CPPS with continuous improvement and innovation, leading to higher treatment efficacy. Recent studies on Th1/Th2 cell function along with its clinical significance in autoimmune disease obtained rapid progress for illustrating pathological and physiological roles of Th1/Th2 cells, and strengthened the knowledge of cytokine network, thus providing evidences for diagnosis and treatment of Th1/Th2 cell-induced autoimmune disease. The interaction between those cells from the internal immune network of our body via secreting different kinds of cytokines, which had both synergistic and counteracting regulatory mechanisms for mediating immune response and immune homeostasis [35, 36]. For CAP/CPPS, the selective induction or modulation of body Th1/Th2 cell immune response can achieve the homeostasis of those cells, thus benefiting the prognosis of disease. Regarding the improvement of treatment approach, the assay of distribution of Th1/Th2 cells in CAP/CPPS patients can help to effectively adjust the balance of internal Th1/Th2 cells, transforming body immune response to Th2 type from Th1 type, which is one important approach to help treating CAP/CPPS. In one word, it is worth further studies to determine immune therapy plan targeting immune mechanism of CAP/CPPS.

Disclosure of conflict of interest

None.

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