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The role of prostatic inflammation biomarkers in the diagnosis of prostate diseases

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ABSTRACT

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are chronic conditions, which are hormone-dependent and epidemiologically associated with prostate inflammation. As a large number of studies have demonstrated, the stimulation of T-cells at the level of prostatic chronic inflammatory infiltrates is followed by stromal and epithelial cell proliferation. The aim of this review is to present the actual level of knowledge in the field of prostatic immune response and chronic inflammation, and to analyze the relationships between chronic inflammation and BPH/PCa. The most studied prostatic inflammation biomarkers detected in biological fluids are also presented, together with their potential roles in the diagnosis and prognosis of prostatic disease.

Introduction

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) represent general health problems at a global level, due to their high incidence in the increasing population of aging males. Both of them are chronic diseases with a long evolution, characterized by early precursor lesions and slow progression [1]. BPH debuts as micronodular hyperplasia of the transitional and central zones of the prostate, which progresses to macroscopic nodular enlargement, accompanied by clinical symptoms only in its late evolution phase. The histological prevalence of BPH gradually increases from around 50% in men aged over 50 years to 80% in men over 70 years. Similarly, PCa develops from early precancerous focal lesions, situated in the peripheral zone, at the dorsal and dorsolateral sides of the prostate [2].

Despite these morphological differences, the two diseases share at least two common features: (1) they are hormone (androgen) dependent, and (2) they are frequently associated with chronic inflammation, which was detected on most of the pathological samples from patients with BPH (after open prostatectomy, or transurethral resection of the prostate), and with PCa (after prostate biopsy, or radical prostatectomy) [3]. A logical question arising from these observations is whether a relationship exists between chronic inflammation and BPH or PCa [4].

The epidemiological studies have already demonstrated that chronic inflammation due to infection or chronic exposure to toxic environmental agents is linked with several forms of neoplasia, including hepatic, gastric, and colorectal cancer [4]. This relationship is supported by observations of uncontrolled cell proliferation due to the local microenvironment, rich in inflammation cytokines and growth factors released in chronic inflammation.

The aim of this review is to present the actual level of knowledge regarding the roles of chronic inflammation in the ontogenesis of BPH and PCa. The most studied prostatic inflammation biomarkers detected in biological fluids are also presented, together with their potential roles in the diagnosis and prognosis of prostatic disease.

The physiopathology of chronic prostatic inflammation

Due to the continuous exposure to external antigens (i.e. microbes, viruses), the prostate has its own defense system, which is acting to maintain the sterility of the urinary and reproductive tracts. We can even consider, at this point, that the prostate is an immunocompetent organ, as the lungs or the intestine [5].

Inside the normal prostate of a young adult male, we can find only low counts of T lymphocytes (mostly of the $CD8^+$ cytotoxic type), macrophages, and B lymphocytes, in the periglandular area [5,6]. There are also lymphoid aggregates in the fibro-muscular stroma, composed by B lymphocyte follicles, surrounded by T cells (mainly of the $CD4^+$ type) [7]. The role of the $CD8^+$ T cells is probably that of an immunological barrier, preventing an autoimmune reaction to sperm components, or to other prostatic antigens.

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The products of normal prostatic secretion are immunogenic due to their proteolytic activity. The destruction of intraglandular epithelium (triggered initially by the infectious factors) increases the exposure of conjunctive tissue to these proteolytic products [5,8]. Among the most frequent infectious agents, we should note: *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Treponema pallidum*, *Trichomonas vaginalis*, Gram-negative bacteria (especially *Escherichia Coli*), and various viruses, including the human papilloma virus, herpes simplex virus, and cytomegalovirus. Finally, the prostatic immune system is exposed to both infectious antigens and autoantigens.

Due to the destruction of the prostatic ducts integrity, prostate specific antigen (PSA) is released from the acini and ducts to the interstitial space, and finally into the blood stream. As a consequence, increased PSA quantities have been detected in the peripheral blood of patients with chronic prostatitis/chronic pelvic pain syndrome, BPH, and prostate cancer [9].

The inflammatory reaction cells release several types of mediators, including cytokines and growth factors (including CXCL5 and CXCL8), which modulate the localized or systemic immune response; moreover, these inflammation mediators act also as antigenic stimulators on the prostatic cells, influencing prostate epithelial and stromal cell growth and/or apoptosis [7,10]. Additionally, the epithelial cells in BPH are releasing inflammation mediators, contributing by themselves to the inflammatory reaction.

Chronic inflammation causes local hypoxia, which is followed by the release of reactive oxygen species (ROS), and nitric oxide. The oxidative stress triggers the release of arachidonic acid, which is converted by the cyclo-oxygenases into prostaglandins, with important roles in the regulation of cell proliferation [11]. Additionally, hypoxia triggers the release of vascular endothelial growth factors (VEGF), stimulating the neoangiogenesis and fibroblast differentiation, which are promoting factors for prostatic hyperplasia or neoplasia [12].

Urinary reflux into the prostatic ducts of the peripheral area of the prostate is a source of chronic inflammation, due to chemical irritation. Crystalized uric acid from the urine is mistakenly interpreted as a distress signal and triggers the expression of the caspase-1-activating NALP3 "inflammasome", a multiproteic complex inside the macrophages, which initiates the release of inflammatory cytokines, finally bringing an influx of additional inflammatory cells [13].

Toll-like-receptors (TLRs), which are present on the prostatic glandular cells, are activated by the bacterial antigens and induce the secretion of inflammatory mediators by the BPH prostatic cells [14]. TLRs are implicated in both the innate and adaptive immune response, recognizing important pathogen ligands, including Gram-negative bacterial elements [15]. Their mechanism of action includes the stimulation of mitogen-activated protein (MAP) kinase pathway [10]. Finally, TLRs will improve the recruitment of inflammatory cells, but will also influence the growth of the prostatic cells [7]. The up-regulation of the TLR genes in patients with large prostates (due to BPH) could be one of the links between the development of BPH and the chronic immune response in the prostate [16].

The estrogens are considered as pro-inflammatory hormones, inducing the production of interferon gamma in lymphocytes, stimulating the accumulation of $CD4^+$ T-cells, and increasing the secretion of interleukin 4 and transforming growth factor beta [17].

Obesity, which is commonly associated with chronic inflammation and high levels of inflammation cytokines in the blood stream (including leptin, tumor necrosis factor alpha, C reactive protein, and interleukin 6, 8 and 1β), may have also an impact on prostatic cell growth [18]. Moreover, high-fat diets are associated with increased secretion and activity of macrophages and mast cells in the prostate [4]. As a consequence, several studies are analyzing the potential benefits of weight loss (especially targeting the abdominal fat) and low fat diets on the improvement of low urinary tract symptoms associated with BPH or CP/CPPS [19].

All the above described mechanisms of intraprostatic epithelial injury, initiated by infection, are further reducing prostate's defense capacity, generating an immune reaction, which finally facilitates prostatic cell proliferation and the inhibition of apoptosis (Fig. 1).

Pathological modifications associated with chronic inflammation of the prostate

Corpora amylacea are observed near the epithelial lesions and the focal inflammatory infiltrates, and are thought to contribute to the degenerative processes inside the prostate, leading finally to BPH or PCa [20].

Another important feature is the presence of proliferative inflammatory atrophy (PIA), described by De Marzo et al. [21]. PIA consists of lesions of regenerative proliferation of the glandular epithelium, appearing as simple atrophy or post-atrophic hyperplasia, associated with inflammatory infiltrate, more frequently detected in the peripheral areas of the prostate. Two different layers of cell are described—inflammatory cells in the epithelium and stroma, along stromal atrophy and fibrosis. These lesions have been recognized as possible precursors for prostatic intraepithelial neoplasia (PIN), or even for prostate adenocarcinoma.

The initiation of the neoplastic process occurs usually within a small group of cells from the PIA lesion, which are more vulnerable to genomic damage due by oxidative stress and hypoxia, caused by the down-regulation of the tumor suppressor genes [21,22]. As a confirmation, high-grade PIN (HGPIN) was observed nearby the PIA lesions, with morphological transitions from PIA to PIN detected inside the same acini or prostatic ducts [23]. Moreover, increased expression of proliferation markers, like Ki67, has been observed in the secretory cells from the PIA lesions, confirming their role in abnormal cell development [21].

The relationship between inflammation and chronic prostatitis

The pathogenesis of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is not yet fully understood, and there is no specific therapy, despite the large number of trials in this area; inflammation and autoimmune response have a clear role in the development of this condition [24]. It has been demonstrated that patients with CP/CPPS had higher levels of IL-1β, IL-6, TNF-α, and IL-8 in the seminal plasma [25]. Moreover, the levels of IL-1β and IL-6 were significantly more elevated in patients with type IIIa CPPS, than in those with type IIIb CPPS [24,26].

The relationship between inflammation and BPH

Most of the prostate pathological specimens obtained from patients with BPH contain inflammatory infiltrates, even in the absence of significant clinical symptoms or signs of infection. These infiltrates generally contain 70% T lymphocytes, 15% B lymphocytes, and 15% macrophages and mast cells [8]. A very important feature of this cell population is the preponderance of $CD4^+$ T-helper cells, which are much more frequent than in the normal prostate (up to 28 times higher) [8]. They stimulate directly the stromal and epithelial proliferation, increasing also the production of IL-15 in the stromal cells (Table 1). The inflammatory cell infiltration specific for BPH has been classified as glandular, periglandular, and stromal [6].

The macrophage infiltrate is stimulated by the down-regulation of the macrophage inhibitory cytokine 1 (MIC-1) gene, which is generally suppressed in the prostates of the patients with symptomatic BPH [27].

Epithelial cells in the prostate are also involved in antigen recognition, triggering in some cases an inflammatory reaction, which is starting very early during the adult life [5]. Chronic inflammation has as a consequence significant tissue damage, followed by slow wound healing and scarring, which is the initiator of BPH-specific nodules.

An increased activity of cyclo-oxygenase 2 (COX-2) under the influence of nitric oxide was observed in prostatic proliferative inflammatory lesions, being followed by the further release of pro-inflammatory