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Viewpoint

Prostatic Inflammation in Prostate Cancer: Protective Effect or Risk Factor?

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Abstract: The relationship between prostatic chronic inflammation (PCI) and prostate cancer (PCa) is unclear and controversial. Some authors reported that a history of chronic prostatitis may be correlated with PCa induction, while others associate chronic inflammation with less aggressive disease or consider inflammation as a possible protective factor against PCa. Four different types of prostatitis are known: bacterial acute prostatic inflammation, bacterial chronic prostatic inflammation, abacterial prostatitis/chronic pelvic pain syndrome, and asymptomatic prostatic chronic inflammation. Prostatic inflammation is underestimated during daily clinical practice, and its presence and degree often go unmentioned in the pathology report of prostate biopsies. The goal of this report is to further our understanding of how PCI influences the biology of PCa. We investigated the main pathogenetic mechanisms responsible for prostatic inflammation, including the cellular response and inflammatory mediators to describe how inflammation modifies the prostatic environment and can lead to benign or malignant prostatic diseases. We found that prostatic inflammation might have a pivotal role in the pathogenesis of prostatic diseases. Details about PCI in all prostate biopsy reports should be mandatory. This will help us better understand the prostatic microenvironment pathways involved in PCa biology, and it will allow the development of specific risk stratification and a patient-tailored therapeutic approach to prostatic diseases.

Keywords: prostatic neoplasm; prostate biopsy; prostatic inflammation

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1. Introduction

Chronic inflammation has been suspected of playing a major role in the pathogenesis of several neoplasms. However, in the pathogenesis of prostate cancer (PCa), its role is unclear and controversial.

The National Institutes of Health (NIH) has classified prostatitis into four categories [1].

- Type I (bacterial acute prostatic inflammation): microscopic appearance is characterized by groups of neutrophils within glandular acini and throughout the stroma, intra-ductal desquamated cellular debris, stromal edema, and hyperemia.
- Type II (bacterial chronic prostatic inflammation): presence of lympho-plasma cellular infiltrate in a peri-acinar distribution and sometimes a few lymphocytes between the epithelial acinar cells.

- Type III (chronic abacterial prostatitis/chronic pelvic pain syndrome): distinguished by dilated ducts and acini filled with neutrophils, histocytes, and desquamated epithelial cells. Additionally, granulomas secondary to inflammation may be present due to ruptured and dilated ducts or acini. In such cases, further granulomatosis subclassification by the pathologist should be reported as either infectious or non-specific granulomatous prostatitis, post-biopsy resection granulomatitis, or systemic granulomatous prostatitis. Among these, the most common are non-specific granulomatous prostatitis and post-biopsy granulomatitis. These conditions may also mimic PCa in digital rectal examination, prostate ultrasound, increased PSA levels, and histologic appearance [2].
- Type IV (asymptomatic prostatic chronic inflammation): detected after biopsy in patients who have no history and symptoms of prostatic diseases. Clinical presentation includes increased levels of PSA and/or an abnormal digital rectal examination [1].

Prostatitis Types I to III and prostatitis-like symptoms can seriously impact men's health and quality of life and represent a common cause of medical consultations, accounting for around 8% of urologist visits. Still, the real prostatitis prevalence remains uncertain [3,4].

Prostatitis might result from different mechanisms. Frequently, it is caused by specific Gram-positive or -negative bacterial subspecies according to prostatitis type, but uropathogenic organisms can be detected in fewer than 10% of symptomatic men, and they remain hidden in most cases [5]. If not properly treated, 10% of the acute bacterial prostatitis will transition to chronic bacterial prostatitis/chronic pelvic pain syndrome [6]. The prostatic reflux of contaminated urine through prostatic ducts can prompt and perpetuate acute and chronic prostatitis when bladder outlet obstruction (BOO) secondary to benign prostatic hyperplasia (BPH) is present. Additionally, sexually transmitted pathogens can be involved in prostatitis pathogenesis due to their ability to retrogradely reach the prostate [5]. Moreover, transrectal biopsy or urethral instrumentation are frequent etiologies of prostate infection due to a direct introduction of bacteria while performing the maneuvers [5]. Uncommonly the source of the infection originates in distant organs and microorganisms reach the prostate gland through hematogenous seeding [5]. Animal model studies report how sex hormone levels can alter the regulation of prostate inflammation. Different estrogen and androgen concentrations are related to different kinds of inflammatory response, each with its specific interleukin expression within the prostatic microenvironment [7]. It is also known that dietary variations such as fatty acid composition result in different metabolic phenotypes and impact prostate size, epithelial volume, inflammation, and gene expression [8,9].

The presence of prostatic inflammation is underestimated during daily clinical practice. Too often, details about inflammation are not mentioned in the pathological report, despite international guidelines that recommend specifying the presence or absence of inflammation and if present whether it is active or granulomatous inflammation [10].

Various authors have reported that a personal history of chronic prostatitis, as well as a history of sexually transmitted disease, may be causally related to PCa induction. Cheng et al. found STDs were not associated with overall PCa risk. A sub analysis showed Latinos reporting any STDs had a greater risk of disease than those with no STDs. Interestingly, foreign-born Latinos displayed a larger risk associated with STDs [11]. Gurel et al. demonstrated that the presence of chronic prostatic inflammation is associated with a 30% increase in the risk of PCa [12]. Recently, Sanguedolce et al. demonstrated that low-grade prostatic inflammation classified according to the Irani system [13], was associated with adverse pathology, (ISUP III and/or extra-prostatic disease) in patients with pre-operative ISUP I or II undergoing radical prostatectomy [14]. PCa induction appears to be influenced by a combination of factors associated with the prostatic tissue milieu or micro-environment. Here, inflammatory cells and mediators, such as chemokines, interleukins (IL), and cytokines, correlate with either favorable or unfavorable conditions for cancer development and progression [15].

On the other hand, a lower risk of PCa development has been reported in the context of prostatic inflammation [16]. Porcaro et al., in patients undergoing baseline random biopsies, found that prostatic chronic inflammation lowered the risk of a high PCa tumor burden, and was also associated with less aggressive PCa biology [17,18].

2. Prostatic Immunology and Intra-Cellular Pathways

It is known that the prostate is an immunocompetent organ that harbors many immune cell types [19,20]. These components can be activated by different inflammatory triggers and produce different mediators, activating intra-prostatic pathways that can be involved in the pathogenesis of all major prostate diseases [21].

Prostatic microenvironment alterations that occur when PCI is present, and other systemic conditions and external factors such as androgen hormone levels, age-related changes, and metabolic syndromes could influence prostatic immune cells to modify the cellular infiltrate and their cytokine secretions [21].

Different stimuli activate different inflammation-related pathways, resulting in several pathological modifications such as proliferative inflammatory atrophy, PCa, or BPH. Each of these might be related to various interleukins and cytokines, but even the same soluble mediator can have different effects, conditioned by the presence of immune cell populations, their membrane antigens, and the signaling that arises from their binding. For instance, benign prostatic enlargement has been associated with high levels of IL-2, IL-4, IL-13, IL-17, IL-23, TGF-β, and FGF-2 produced by lymphocytes subtypes TH1 and TH17, as well as macrophages and infiltrating dendritic cells. On the contrary, other pathological conditions may elicit secretion of IL-6-8-10 or TGF-α which contributes to cellular proliferation and PCa induction [22].

Immune responses against the tumors are dependent on the subset of T cells recruited to the tumor site, which is determined by the chemokines' and cytokines' local and systemic gradient. The presence of CD3+ tumor-infiltrating lymphocytes was significantly associated with shortened PSA recurrence-free survival in PCa patients [22]. Furthermore, the number of CD3+ cells in tumor areas and stromal areas was significantly higher in metastatic than in non-metastatic PCa [22]. High expression of epithelial CD4+ T_{regs} in normal prostatic tissue was associated with a four-fold increased risk of PCa in comparison with low expression of epithelial CD4+ T_{regs} [23]. Additionally, a greater number of epithelial CD4+ T_{regs} in normal prostatic tissue was positively associated with a higher Gleason score and pT-stage. An explanation for this association may relate to the high expressions of CD25 and FOXP3 that are found in this population of T cells, both being able to actively suppress antitumor immune response [22]. Also, tumor-associated macrophages (TAM) play a role in cancer progression. Increased density of TAM was correlated with increased Gleason score and conferred a poor prognosis. Together these findings strengthen the likelihood that in PCa patients, specific subtypes of immune cells, such as tumor-associated macrophages and CD3+ T cells, are associated with an unfavorable prognosis [22].

In this complex scenario, interleukins and cytokines may play a main role. IL-6 has been related to cancer initiation and progression. IL-6 and its receptor are released by cancer cells, and IL-6 circulating levels are elevated in patients with metastatic disease and hormone-refractory disease [22]. Chemokines like CCR5, CXCR3, and CXCR4 on the $CD4^+$ Th1 surface and cytokines like IL-2 are accountable for the attraction of immune system elements. An increase in inflammatory cell infiltrates leads to a higher PCa risk and poorer survival outcomes [22].

Chronic inflammation and ties to the immune system are involved in prostate carcinogenesis. In the prostatic microenvironment, chronic inflammation leads to oxidative stress via the generation of reactive oxygen species (ROS) and reactive nitrogen species released by immune cells as a consequence of chronic inflammation. Consequently, this results in DNA breaks and recruitment of epigenetic machinery which in turn favors DNA methylation, transcriptional silencing of genes, and gene fusion [22]. Oxidative stress might also underlie the relationship between fat intake and prostate cancer. Indeed, polyunsaturated

fatty acids were found to be related to an increased risk of a high-grade Gleason score of 8–10. Specifically, omega-6 fatty acids involve the metabolism of linoleic acid that is metabolized into arachidonic acid, which is a precursor of proinflammatory factors such as eicosanoids, prostaglandin E2, and leukotriene B4 [22].

3. The Protective Role of Inflammation in PCa Development

Immunosurveillance is a primary function of the human immune system, and the inflammatory response can prevent carcinogenesis by recognizing and eliminating tumor-specific antigens. Penetration of CD8+ T cells, or cytotoxic T lymphocytes, within the PCa microenvironmental niche confers a better prognosis. This is correlated to the expression of CCR5 on the CD8+ surface, where activation recruits cells having antitumor activity [15]. Cells expressing CD8 antigen have also been linked to BPH. In the condition of low androgen levels, CD8+ T cells infiltrate glandular epithelium and cause cell proliferation [24]. There is growing evidence that chronic inflammation is a main factor in BPH and lower urinary tract symptoms (LUTS). Data from the Medical Therapy of Prostate Symptoms (MTOPS) trial suggested that around 40% of baseline biopsy specimens had chronic inflammatory infiltrates. These patients showed higher PSA levels and larger prostate volumes suggesting a cause–effect relationship between chronic inflammation and BPH/LUTS [25]. A summary of the different cytokines and interleukins linked to PCa can be find by the reader in Table 1.

Table 1. Summary of cell types, cytokines, and interleukins involved in the prostate microenvironment during PCI and their link with PCa.

	Immune Cells	Cytokines and Interleukins	Receptors
Pro-Cancer	• T cells Th1 • T cells Th17 • Tumor-associated macrophages • tumor-infiltrating T cells CD3+ • T_{regs} CD4+	• IL-2 • IL-4 • IL-6 • IL-13 • IL-17	• CD25
Anti-Cancer	• Natural Killer cells • CD8+ T cells	• CCL5	• CCR5 • CD56

A meta-analysis on this subject was conducted by Vasavada et al., including 25 studies and a total of 20,585 patients, of which 6641 had prostate cancer. The presence of any type of inflammation (acute and chronic) was significantly associated with a lower PCa risk. When subanalysis by inflammation type was performed, acute inflammation in four studies and chronic inflammation in 15 were each associated with a lower prostate cancer risk [16].

Recently, Moreira et al. found a protective role of inflammation against PCa, based on data coming from the REDUCE trial. They showed how men with baseline PCI had significantly fewer high-grade tumors compared to those without PCI in a cohort of 889 men aged 50 to 75 years who had baseline prostate biopsies negative for PCa, but who, on 2-year follow-up biopsy, demonstrated PCa. The authors concluded that chronic inflammation in a negative biopsy was associated with lower prostate cancer grade among men detected with PCa in a 2-year follow-up biopsy [26].

An interesting pilot study by Barkin et al. analyzed natural killer (NK) cell activity (NKA) and used its measurement as a surrogate of PCa detection risk. Detection of lower NKA levels in whole blood samples was more likely correlated with a positive result at prostate biopsy. They were also able to propose an NKA cut-off value of 200 pg/mL, below which the relative risk of PCa was 2.76 (OR 13.33) [27]. Likewise, Gannon et al. examined the immune cell infiltration during androgen deprivation therapy for PCa. Higher counts of CD56+ NK cells were strongly related to less disease progression and protection from

biochemical recurrence in patients undergoing androgen deprivation therapy [28]. These findings are consistent with a possible protective role for NK cells in patients with PCa. They also confirm the influence of sex hormone status in inflammatory response modulation as shown in animal model studies [7,29].

4. Future Perspectives

New findings of the relationship between prostatic inflammation and PCa present the possibility of targeting these specific pathways with immunotherapy. An understanding of cancer cell–immune system interactions is needed to develop new effective immunotherapy. There has been great interest in programmed cell death protein (PCDP-1), specifically PD-1, and its ligand PD-ligand-1. T lymphocytes express PD-1 as part of an immunosuppressive mechanism, which favors cancer growth and progression [30]. Additionally, PCa vaccines that activate T-cell populations against tumor cells have been developed. Sipuleucel-T was the first vaccine approved by the FDA for men with asymptomatic or minimally symptomatic metastatic castration-resistant PCa [31].

Prostatic inflammation has a pivotal role in the pathogenesis of prostatic diseases. Its identification and molecular characterization are mandatory if we are to better understand the influence of inflammation on PCa biology and develop a specific risk stratification and patient-tailored therapeutic approach [31].

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