Collaborative Review – Prostatic Disease

The Controversial Relationship Between Benign Prostatic Hyperplasia and Prostate Cancer: The Role of Inflammation

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Abstract

Context: Prostate cancer (PCa) is the most common cancer in the adult male, and benign prostatic hyperplasia (BPH) represents the most frequent urologic diagnosis in elderly males. Recent data suggest that prostatic inflammation is involved in the pathogenesis and progression of both conditions.

Objective: This review aims to evaluate the available evidence on the role of prostatic inflammation as a possible common denominator of BPH and PCa and to discuss its possible clinical implication for the management, prevention, and treatment of both diseases.

Evidence acquisition: The National Library of Medicine Database was searched for the following Patient population, Intervention, Comparison, Outcome (PICO) terms: male, inflammation, benign prostatic hyperplasia, prostate cancer, diagnosis, progression, prognosis, treatment, and prevention. Basic and clinical studies published in the past 10 yr were reviewed. Additional references were obtained from the reference list of full-text manuscripts.

Evidence synthesis: The histologic signature of chronic inflammation is a common finding in benign and malignant prostate tissue. The inflammatory infiltrates are mainly represented by CD3+ T lymphocytes (70–80%, mostly CD4), CD19 or CD20 B lymphocytes (10–15%), and macrophages (15%). Bacterial infections, urine reflux, dietary factors, hormones, and autoimmune response have been considered to cause inflammation in the prostate. From a pathophysiologic standpoint, tissue damage associated with inflammatory response and subsequent chronic tissue healing may result in the development of BPH nodules and proliferative inflammatory atrophy (PIA). The loss of glutathione S-transferase P1 (GSTP1) may be responsible in patients with genetic predisposition for the transition of PIA into high-grade intraepithelial neoplasia (HGPIN) and PCa. Although there is growing evidence of the association among inflammatory response, BPH, and PCa, we can only surmise on the immunologic mechanisms involved, and further research is required to better understand the role of prostatic inflammation in the initiation of BPH and PCa. There is not yet proof that targeting prostate inflammation with a pharmacologic agent results in a lower incidence and progression or regression of either BPH or PCa.

Conclusions: Evidence in the peer-reviewed literature suggested that chronic prostatic inflammation may be involved in the development and progression of chronic prostatic disease, such as BPH and PCa, although there is still no evidence of a causal relation. Inflammation should be considered a new domain in basic and clinical research in patients with BPH and PCa.

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1. Introduction

Prostate cancer (PCa) and benign prostatic hyperplasia (BPH) are significant health concerns that may become increasingly prevalent in the coming years in relation to the gradual aging of the population [1–3]. PCa is the leading cause of nonskin cancer among men worldwide and, after lung cancer, is the second most common cause of death from cancer in men in the United States [4]. BPH represents the most common urologic disease among elderly males, affecting about one-quarter of men in their 50s, one-third in their 60s, and about half of octogenarian men [5,6].

BPH and PCa form in different areas of the prostate. The former is known to develop from the transitional zone (TZ) and central zone of the gland, while the latter develops from the peripheral zone (PZ). Only in about 20% of cases do the conditions coexist in the same zone [7]. BPH and PCa are considered chronic diseases, with early initiation and slow progression. BPH starts as a simple micronodular hyperplasia, evolving into a macroscopic nodular enlargement that gradually translates into a clinical entity. Similarly, PCa develops through early and late precancerous histologic modifications [3]. Furthermore, although there is no clear molecular and genetic relationship between BPH and PCa and they present two distinct pathogenetic pathways, epidemiologic studies suggest that because their incidence and prevalence rise with increased age, both conditions are hormone dependent and are associated with prostatic inflammation, which can represent a common denominator [1].

Neither BPH nor PCa is a single disease; rather, they express different features in terms of epithelial-to-stromal–ratio Gleason score or cancer volume. These aspects are often neglected in reference to prostate inflammation. We understand the difficulty in considering too many variables, but we are also concerned with the limitations of it.

Chronic inflammation secondary to infectious agents, to the exposure of other environmental factors, or to a combination of both is involved in the pathogenesis of about 20% of human cancers, including stomach, liver, and large intestine [8,9]. Epidemiologic, histopathologic, and molecular pathologic studies provide the emerging evidence of the possible role of prostatic inflammation as a crucial part of PCa pathogenesis and progression [10].

The molecular and cellular mechanisms involving stromal and epithelial components of the prostate leading to BPH remain unclear, notwithstanding a causative role of prostatic inflammation in the pathogenesis of BPH, which was first suggested in 1937 [11]. Today, although it is not yet defined when and why chronic inflammation occurs, it has been hypothesized that BPH is an immune-mediated inflammatory disease [5,12–15], and recent clinical trials have also suggested a relationship between prostatic inflammations and lower urinary tract symptoms (LUTS) related to BPH [16–18]. Epidemiologic evidence of a link between the use of anti-inflammatory agents and the risk of cancer led to novel therapeutic approaches that were proposed as a new frontier in the prevention and treatment of PCa [1,8]. In BPH patients, the relation between LUTS and inflammation is well known [2], as different prostatic conditions, including BPH, benefit from antibacterial and anti-inflammatory treatment.

We also acknowledge the lack of a standard definition of prostatic inflammation that probably exists only in the classification of chronic pelvic pain. The definition is clearly useful for clinical purposes but would be meaningless in research on prostate immunology. Inflammation is usually described in basic science papers in terms of cellular effectors and released mediators.

This is a nonsystematic review to evaluate the most recent evidence with respect to prostatic inflammation as a major pathway in the controversial relationship between BPH and PCa and discusses its potential clinical implications.

2. Evidence acquisition

The National Library of Medicine Database was searched for relevant articles published between January 2000 and October 2010 using the following Patient population, Intervention, Comparison, Outcome (PICO) terms: male, inflammation, benign prostatic hyperplasia, prostate cancer, diagnosis, prognosis, progression, treatment, and prevention. In addition, sources in the reference sections of the publications identified were added to the list. English-language text was not a specific parameter; however, only English-language publications were considered. Evidence was not limited to human data; data from animal studies were also included in the review. Each article title, abstract, and text were reviewed for their appropriateness and relevance. The initial list of selected papers was further enriched by individual suggestions from an expert panel of international opinion leaders on the topic who act as co-authors of the present review. The selection of references was by definition not all-inclusive, and selection bias was unavoidable.

3. Evidence synthesis

3.1. Prostatic inflammation

The presence of chronic histologic inflammation is a well-known finding in biopsy and surgical specimens of prostate tissue in patients with and without LUTS or prostatitis [6,19].

3.1.1. Interactions between immune cells and prostatic cells

Histologic inflammation was found in >78% of men enrolled in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial [16,17], demonstrating its ubiquitous nature in aging men, although its relation to histologic and clinical BPH is unclear [20]. Di Silverio et al [21], considering 3942 histologic examinations from BPH patients, described prostatic inflammation in 43% of cases; in these specimens, the most common type of inflammation was chronic (69%). The severity of the chronic inflammation was defined as mild in the 78% of cases, and it was associated with age and prostate volume. Irani et al [22] also proposed classifying
Prostatic inflammation on the basis of a hypothetical histologic grading related to the extension of inflammatory cells; furthermore, a histologic aggressiveness grading based on the effect that these inflammatory cells produces on prostate tissue has been described [22] (Table 1).

The prostate, like the intestine and the lung, is considered an immunocompetent organ and is populated by a small number of inflammatory cells (leukocytes) that increase with age, consisting of scattered stromal and intraepithelial T and B lymphocytes, macrophages, and mast cells [9]. In particular, Di Carlo et al [23] stated that, as in the normal prostate, the infiltrates around the peri-glandular area are mainly composed of T lymphocytes (70% CD8 cells), while lymphoid aggregates are located in the fibromuscular stroma. These aggregates, mainly (50%) consisting of B lymphocytes follicles surrounded by parafollicular T cells with CD4 cells, are two times more frequent than CD8 cells. In the adult prostate, a different inflammatory infiltrate pattern has been described in relation to the type and extension of inflammation. Several reports [5,12–15,24–26] evaluated the constituents of inflammatory infiltrates in BPH. Steiner et al [15] showed that the inflammatory infiltrates are mostly represented by CD3+ T lymphocytes (70–80%), CD19 or CD20 B lymphocytes (10–15%), and macrophages (15%). The phenotype of T cells also presented a reverse CD8-to-CD4 ratio—so much so that most T cells in the inflammatory areas expressed CD4. Robert et al [25] recently confirmed that in 282 patients with BPH, there was an inflammatory infiltrate constituted by T lymphocytes (CD3+ cells) in the 80% of cases associated with 52% of antigen-presenting cells, such as B lymphocytes (CD20+ cells), and 82% of macrophages (CD163+ cells).

Proliferative inflammatory atrophy (PIA), first described by De Marzo et al [27], designates discrete foci of proliferative glandular epithelium with the morphologic appearance of simple atrophy or postatrophic hyperplasia, which also occurs in association with inflammation. The key features of this lesion are the presence of two distinct cell layers, mononuclear and/or polymorphonuclear inflammatory cells in both the epithelial and stromal compartments, and stromal atrophy with variable amounts of fibrosis.

### 3.1.2. Origins of chronic prostatic inflammation

Although the presence of inflammatory infiltrates in human prostates is a well-described situation, its origin is still unclear—as is its causal relation to BPH—and different hypotheses have been proposed. Different pathogens are described, including bacterial infections, urine reflux with chemical inflammation, dietary factors, hormones, autoimmune response [9,28,29], and a combination of these factors.

Different viruses, such as the human papilloma virus, human herpes simplex virus type 2, and cytomegalovirus; several sexually transmitted organisms, such as Neisseria gonorrhoea, Chlamydia trachomatis, Treponema pallidum, and Trichomonas vaginalis; and Gram-negative pathogens, such as Escherichia coli have been identified in the prostate, and most of them could be responsible for the inflammatory response [9,13,29].

Another possible aetiologic agent for the development of prostatic inflammation is chemical irritation from urine reflux [3,9]. Crystalline uric acid has been considered a “danger signal” realised from dying cells, which is able to directly engage the caspase-1-activating NALP3 “inflammasome,” a multiprotein complex presented in leukocytes mostly in macrophages [30]. The consequence of this process is the production of inflammatory cytokines that can increase the influx of other inflammatory cells. The development of corpora amylacea in the prostate is considered another possible source of inflammation [3,9,31]. Corpora amylacea have been considered possible contributors to prostate inflammation, prostate infection, and prostate carcinogenesis, as they are frequently observed adjacent to the damaged epithelium and focal inflammatory infiltrates [32]. Another possible mechanism of prostatic inflammation referred to the role of the autoimmune response. Prostate injury secondary to the above-mentioned aetiologies can damage prostate epithelial cells, with a consequent release of immunogenic antigens and a breakdown in the prostate immune system. It has been proposed that some determinants of normal prostatic proteins, which are not expressed until after puberty, are not physiologically tolerated by the immune system. So far, when released, these antigens can determine an autoimmune response [6,9].

The interaction between gonadal sex hormones and the immune system is another well-known feature and may be the key to combine the “permissive” nature of androgens and oestrogens and the activation of lymphocytes essential for immune responses in prostate tissue. Oestrogens are commonly considered proinflammatory hormones and may be involved in the susceptibility to inflammation by influencing interferon γ (IFN-γ) production in lymphocytes [33]. Oestrogen also enhances the accumulation of Th1 CD4+ T cells in response to antigen and, probably more importantly, stimulates Th2 anti-inflammatory cytokine production (interleukin [IL]-4, transforming growth factor-β [TGF-β]), which is mostly seen in advanced BPH nodules. Another bridge between the immune and hormonal systems is the fact that IL-4 and IL-13, which are overexpressed in BPH nodules, are known to upregulate the production of 3β-hydroxydehydrogenase/isomerase type 1 (3β-HSD) by prostate epithelial cells, and 3β-HSD catalyses an essential step in the formation of active androgens [34]. Dietary factors such as high-fat-containing diets are also associated in animal

<table>
<thead>
<tr>
<th>Table 1 – Histologic grading and aggressiveness of prostatic inflammation (adapted from Sciarra et al [3])</th>
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<tbody>
<tr>
<td><strong>Histologic grading:</strong></td>
</tr>
<tr>
<td>0: No inflammation</td>
</tr>
<tr>
<td>1: Scattered inflammatory cell infiltrate without nodules</td>
</tr>
<tr>
<td>2: No confluent lymphoid nodules</td>
</tr>
<tr>
<td>3: Large inflammatory areas with confluence</td>
</tr>
<tr>
<td><strong>Histologic aggressiveness:</strong></td>
</tr>
<tr>
<td>0: No contact between inflammatory cells and glandular epithelium</td>
</tr>
<tr>
<td>1: Contact between inflammation and epithelium</td>
</tr>
<tr>
<td>2: Intestinal infiltrate with glandular disruption</td>
</tr>
<tr>
<td>3: Glandular disruption on &gt;25%</td>
</tr>
</tbody>
</table>

models with an increase in mast cells and macrophage prostatic distribution and activity [9,35,36].

Finally, as proposed by De Marzo et al [9], all of these mechanisms of chronic epithelial injury may be responsible for a decreased barrier function and facilitate the growth of infectious agents, with a chain reaction that further sustains and stimulates the inflammatory response and increases the prostatic inflammatory infiltrates. Whether or not inflammation has a cause-and-effect relationship with BPH and PCa remains unknown.

3.2. Association between benign prostatic hyperplasia and prostatic inflammation

BPH is a histologic condition defined by a hyperplastic growth of both epithelial (glandular) and stromal components in the prostate. Although epithelial cells are considered under the influence of androgens, mechanisms leading to the proliferation of stromal cells (smooth fibres cells and fibroblast) are less clear. Equally obscure is the interaction between the stromal and glandular components [37,38].

3.2.1. Clinical evidence

Although the pathogenesis of BPH is not yet completely understood, in the past few years, the role of chronic inflammation is emerging as an important factor in BPH development and progression [2]. BPH is frequently associated with chronic inflammatory infiltrates mainly composed of T and B lymphoid cells and macrophages [39]. Data from the Medical Therapy of Prostate Symptoms (MTOPS) trial suggested that about 40% of baseline biopsy specimens had chronic inflammatory infiltrates—in particular, in men with higher prostate-specific antigen (PSA) values and larger prostate volumes [18]. Furthermore, patients with chronic prostatic inflammatory infiltrates were at a higher risk of BPH progression and acute urinary retention when compared with patients without inflammatory infiltrates at baseline [18], thus suggesting that inflammation contributes to the development and progression of BPH. Among patients with small prostate volumes, only those with inflammation suffer retention episodes [18].

The REDUCE trial [16,17] confirmed these data. In this study, the degree of inflammation was scored as none, mild, moderate, or marked in 8824 patients who underwent prostatic biopsy. Only 22.6% of patients presented with no chronic inflammation on biopsy. Prostatic inflammation was also associated with higher prostatic volume (46.5 ml vs 43.4 ml; \( p < 0.0001 \)) and higher International Prostate Symptom Score (IPSS) results (8.8 vs 8.2; \( p < 0.0001 \)). Data on prostate inflammation in these studies are based on biopsy samples that somehow reflect the condition of the whole gland, although the possibility of a sampling error should be considered.

In a cohort study of 282 patients with and without BPH, Robert et al [25] observed chronic prostatic inflammation in 79%, 48%, and 20% of severe, intermediate, and no BPH patients, respectively. A significant association among the degree of prostatic inflammation, prostate volume, and urinary symptoms was also confirmed; mean prostate volume was 62 ml with low-grade inflammation and 77 ml in high-grade inflammation (\( p = 0.002 \)). Similarly, the mean IPSS score was 12 and 21 in low-grade and high-grade inflammation (\( p = 0.02 \)), respectively. It is sometimes difficult to separate statistical from clinical significance, but in this case, we think that a consensus can be reached about the fact that the difference between moderate and severe IPSS values is clinically relevant. What remains to be proven is the causative effect of inflammation on LUTS and whether treatment of low- and high-grade inflammation leads to symptom improvement.

3.2.2. Benign prostatic hyperplasia and inflammatory cells

Prostatic inflammation observed in BPH may cause cytokine release from inflammatory cells and a condition of relative hypoxia resulting from the increasing oxygen demand of proliferating cells that may end up in tissue injury [2]. Cytokines ad growth factors released from inflammatory cells may not just interact with immune effectors but also with stromal and epithelial cells of the prostate [6]. Also, BPH epithelial cells have been shown to release inflammatory mediators [6].

Kramer et al [12] first investigated the effect of lymphocyte-derived growth factors on prostatic stromal cell growth. They confirmed that BPH tissue contains infiltrates of T lymphocytes, B lymphocytes, and macrophages that are chronically activated and responsible for the release of cytokines—mostly IL-2, IFN-\( \gamma \), and TGF-\( \beta \)—that may support fibromuscular growth in BPH. Furthermore, an upregulation of different proinflammatory cytokines has been reported in BPH tissue—particularly IL-15 in stromal cells, IL-17 in infiltrating T cells, IFN-\( \gamma \) in basal and stromal cells, and IL-8 in epithelial cells [2].

Once initiated, this process determines chemotaxis of T cells attracted by increased production of proinflammatory cytokines such as IL-6, IL-8, and IL-5 [13,40]. When the density of T cells reaches a certain threshold, surrounding cells become targets and are killed, leaving behind vacant spaces that are replaced by fibromuscular nodules with a specific pattern of a Th0/Th3 type of immune response [13,15,20]. Dendritic cells, professional antigen-presenting cells, also play a crucial role in inducing, sustaining, and regulating T cell responses; so far, their activity contributes to the maintenance and progression of immune inflammation infiltrates in the aging prostate [5,41].

3.2.3. Benign prostatic hyperplasia and proinflammatory cytokines

Proinflammatory cytokines released by adjacent inflammatory cells may also induce cyclooxygenase-2 (COX-2) expression in the epithelial cells in BPH, which is associated with an increased proliferative rate [13,42]. Furthermore, even though BPH had no consistent overexpression of COX-2, as in PIA, the overexpression of IL-17 has been shown, and this may in turn upregulate COX-2 expression [13]. In BPH, IL-17 is overexpressed in 79% of patients and primarily produced by activated T cells as well as some epithelial and smooth muscle cells [13]. There is also evidence that growth and survival of T cells producing IL-17 require additional factors, such as IL-23. IL-23 is a heterodimeric
protein produced by the p40 subunit of IL-12 and another specific subunit, termed IL-23/p19. The functional IL-23 heterodimer is produced by activated dendritic cells, monocytes, and macrophages; through the IL-17/IL-23 pathway, it is involved in promoting the inflammation response [43–45]. IL-23 receptor expression has also been observed in BPH epithelial and endothelial cells [5].

Penna et al [28] recently showed in BPH tissue samples that human stromal prostate cells can act as antigen-presenting cells, activating alloantigen-specific CD4+ T cells to produce IFN-γ and IL-17. It appears that prostate stromal cells may induce and maintain an autoimmune response. In BPH stromal cells, IFN-γ and IL-17 induce production of IL-8 and IL-6. IL-6, a potent autocrine growth factor, and IL-8, a paracrine inducer of fibroblast growth factor 2 (FGF-2), are key growth factors for epithelial and stromal prostate cells. These results are consistent with a possible link between the autoimmune response—T cell–mediated—induced by stromal prostate cells and prostate hyperproliferation.

The possible role of TGF-β has also been extensively evaluated [5,46,47]. TGF-β, an inflammatory cytokine, has been shown to regulate stromal proliferation and differentiation in BPH, and it is a key factor for androgen control of prostatic growth. Recently, Descazeaud et al [46] investigated the TGF-β receptor II protein (TGFBRII) expression in 231 BPH patients using large-scale tissue microarray analysis. They observed a significant association between TGFBRII stromal staining and prostatic volume; BPH inflammation was also associated with TGFBRII staining. Stromal and glandular TGFBRII expression was more evident in cases with CD4 T lymphocyte infiltrate within the prostate gland.

Another source of inflammatory mediators is local hypoxia, which induces low levels of reactive oxygen species (ROS), which in turn can promote neovascularisation and fibroblast-to-myofibroblast transdifferentiation. In particular, an increased secretion of vascular endothelial growth factors such as FGF-7, TGF-β, FGF-2, and IL-8 is observed under hypoxic condition in vitro [2,42]. As a response to hypoxia, prostatic stromal cells upregulate the secretion of several growth factors that can determine prostatic growth.

Although there is no evidence of a causal relationship, the hypothesis that prostatic inflammation may play an important role in BPH development and progression is intriguing. T cell activity in inflammatory infiltrates may result in stimulation of stromal and epithelial cell proliferation that is sustained by autoimmune mechanism. Tissue damage and the subsequent chronic process of repetitive wound healing induced by inflammation end up in the development of BPH nodules.

### 3.3. Association between prostate cancer and prostatic inflammation

Chronic inflammation has frequently been associated in human and animals models with carcinogenesis, and it is considered a potential risk factor for malignancies in many organs, such as the liver, colon, bladder, lung, and pancreas [48]. Inflammation may play a role in carcinogenesis by causing cellular and genomic damage; promoting cellular turnover; and creating a tissue microenvironment inducing cell replication, angiogenesis, and tissue repair [43]. Chronic inflammation is associated with a milieu rich in proinflammatory cytokines, inflammatory mediators, and growth factors that may determine an uncontrolled proliferative response, with rapidly dividing cells more likely to undergo mutation, as observed in cancer [43,49]. The high prevalence of chronic inflammation infiltrates in pathologic samples of the prostate from radical prostatectomy (RP) specimens, prostate biopsy, and transurethral resection of the prostate has also suggested a possible link between chronic inflammation and PCs. This hypothesis is further supported by common molecular pathways observed in both processes. However, it is still controversial—although likely—that BPH and PCs may be influenced by the same population of inflammatory infiltrates. Furthermore, there are only limited data that observe differences in leukocyte/lymphocyte cell subpopulations in the PZs and TZs of the prostate. This opens new questions as to whether the same noxae attract T cells in both zones and which components predispose malignant or benign growth or, alternatively, whether there are zone-dependent differences in leukocyte/lymphocyte subtypes and what the determining trigger drawing the boundaries is.

#### 3.3.1. Prostate cancer carcinogenesis and inflammation

Several PCs susceptibility genes, such as RNASEL, MSR1, and MCI, which are located in regions linked to familiar PCs, or TLR4, MCI, PON1, BRCA2, CHEK2, and OGG are involved in PCs carcinogenesis. Most of these genes encode proteins with critical functions in the host in response to infection, inflammation, and oxidative stress; their mutation may reduce the possibility of preventing carcinogenesis through this pathway [50]. RNASEL encodes a latent endoribonuclease component of an INF-inducible RNA degradation pathway activated upon viral infection, and it is involved in viral defence [51,52]. MSR1 encodes subunits of a homotrimeric macrophage scavenger receptor capable of binding bacterial lipopolysaccharides and lipoteichoic acid as well as oxidised serum lipoproteins [52,53] and regulates the macrophage response to several Gram-negative bacterial infections. MCI is a member of the TGF-β superfamily and is involved in the inflammation pathway by regulating macrophage activity [9]. The lipopolysaccharide receptor Toll-like 4 (TLR4) plays a central role in the innate immune response to Gram-negative bacterial infections and to molecules produced by cell and DNA damage. Recognition of their ligands determines a cascade of events associated with the activation of the IL-1R receptor followed by the activation of the master inflammatory transcriptional regulator factor NF-KB and proinflammatory genes [43].

PIA, typically associated with prostatic inflammation, is considered a possible precursor of high-grade prostatic intraepithelial neoplasia (HGPIN) and PCs [27,50]. PIA lesions tend to occur in the periphery of the prostate and arise as a consequence of prostate epithelial cells' regenerative proliferation as a response to an injury caused by infection, cell trauma resulting from oxidant damage.
hypoxia, and autoimmunity [50]. PIA lesions are often observed adjacent to HGPIN or early cancer, and there is an identifiable genetic pathway between PIA, HGPIN, and cancer, with progressively frequent TP53 mutations as well as gains in centrometric DNA sequences of chromosome 8 and glutathione S-transferase P1 (GSTP1) CpG island hypermethylation [9,49,54]. Epithelial cells in PIA also show different molecular signs of stress, such as high levels of GSTP1, GSTA1, and COX-2 [50].

GSTP1 encodes a glutathione S-transferase, an antioxidant enzyme, that is involved in the detoxification of carcinogens and inflammatory oxidants in prostate cells. GSTP1, generally considered a signal of cellular stress, is overexpressed in PIA and increases in chronic prostatic inflammation [9]. GSTP1 inactivation, mostly by hypermethylation, is associated with HGPIN and PCa and may increase prostate cells’ susceptibility to additional genome damage caused by inflammatory oxidant or nutritional carcinogens, with a consequent selective growth advantage [55].

3.3.2. Eicosanoids, oestrogens, and inflammation

There is also emerging evidence of the important role of COX-2, a proinflammatory enzyme involved in the conversion of arachidonic acid to prostaglandin, in PCa carcinogenesis. COX-2 is upregulated in several human cancers, such as breast, lung, colon, rectal, and pancreatic cancers; COX-2 is an early-response gene induced by a variety of cytokines, such as IL-1, tumour necrosis factor α (TNF-α), NF-KB, and hormones, and it is also involved in the invasiveness, antiapoptosis, and angiogenesis of cancer [54,56–58]. Prostatic inflammation generates free radicals, such as nitric oxide and various species of ROS. Macrophages and leukocyte infiltration provide a further source of free radicals that can determine precancerous transformation through oxidative DNA damage, gene changes, apoptosis, protein structure and function alterations, and post-translational modifications, including those involved in DNA repair [31,59]. Normally, these highly reactive oxygen species are removed by the superoxide dismutase enzyme system. A consequence of these oxidative stress reactions is the production of arachidonic acid from membranes that will be converted by COX-2 to prostaglandin, which are involved in the regulation of cell proliferation. COX-2 reaction is also associated with ROS production and genomic damage [31,59]. COX-2 has been considered a promoter of proliferation in PCa, as its expression correlates with tumour progression [42,60]. Moreover, COX-2 can upregulate B-cell leukaemia/lymphoma 2 expression, with an associated decrease in apoptosis in the prostate tissue [61].

The relationship between the expression and function of different interleukins and growth factors involved in prostatic inflammatory processes are summarised in Table 2. Most of these molecules are also considered potentially to contribute to PCa initiation and progression [8].

The logic of a carcinogenic action of oestrogens in the prostate, based on several epidemiologic and experimental data, is also well known. Most countries throughout the world with high PCa rates also exhibit high breast cancer rates and vice versa [62]; African Americans have both higher oestrogens levels and higher PCa risks than American Caucasians [63]. Furthermore, the disruption of genes encoding oestrogen receptors in mice affects prostate epithelial cell proliferation [64], and a number of rodent models show a fairly consistent relationship among oestrogens, inflammation, and prostate carcinogenesis [59,65,66].

3.4. Inflammation as a possible link between benign prostatic hyperplasia and prostate cancer

BPH and PCa are the most common benign and malignant tumours, respectively, of elderly men; in approximately 20% of cases, they may coexist in the same prostate zone [33]. They should be considered chronic diseases that require a long time for initiation and progression. BPH needs a long period for its evolution from a simple micronodular hyperplasia to a macroscopic volume enlargement, and then to clinical expression [3]. Similarly, PCa evolves during a long period through the development of early and later precancerous modifications, and then (eventually) to a clinically significant PCa. Although the pathogenesis of BPH and PCa is not yet fully understood and several mechanisms seem to be involved in the development and progression of both diseases, there is growing evidence for the possible role of chronic prostatic inflammation in the development and progression of both conditions.

Chronic prostatic inflammation, a common condition in human prostates, can be initiated by several known and unknown stimuli that would determine proinflammatory status in the prostatic microenvironment. Prostate inflammation can be the expression of a localised condition (example given by sexual transmitted diseases) or as part of a chronic and systemic disease, such obesity and metabolic syndrome. Obesity is, for example, associated with low-grade chronic inflammation and a metabolic syndrome with high circulating levels of inflammation-related markers (leptin, IL-6, TNF) that may affect tumour growth [67]. Different groups are investigating the possibility of improving LUTS following reduction of abdominal obesity, but these data are too preliminary to be commented any further, and there is no evidence as to whether weight reduction improves inflammation.

Inflammatory infiltrates mostly composed of leukocytes are responsible for the secretion of cytokines, which are involved in the paracrine and autocrine regulation of stromal and epithelial cell growth (Table 2). As in the context of chronic inflammation and proinflammation cytokine expression, the activity of IL-6, IL-8, IL-15, and IL-17 has been considered to influence the development of both diseases [33,68], although further confirmatory studies are needed. Beyond the permissive role of sexual hormones, the pathophysiology of BPH and PCa remains basically unknown. Although age remains the most important risk factor for the development of both conditions, several other parameters have been considered to play a role (eg, inflammatory mediators, hormones, dietary factors, inflammatory genes, and oxidative stress), and there is no consensus as to which is the primary one.

Table 2 – Cytokine overview in benign prostatic hyperplasia and prostate cancer (adapted from Kramer et al [5])

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Expression pattern</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>IL-1α production of senescent prostate epithelial cells</td>
<td>Stimulation of the production of epithelial growth-promoting FGF-7 in fibroblastic stromal cells</td>
</tr>
<tr>
<td>IL-2</td>
<td>De novo IL-2 mRNA expression in BPH</td>
<td>Stimulation of the growth of stromal cell clones</td>
</tr>
<tr>
<td></td>
<td>T cells a major source of IL-2 mRNA</td>
<td></td>
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<tr>
<td></td>
<td>Small amounts created by epithelial cells</td>
<td></td>
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<tr>
<td></td>
<td>IL-2R α/β/γ expression on BPH T cells and epithelial and stromal cells</td>
<td></td>
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<tr>
<td>IL-4</td>
<td>De novo IL-4 mRNA expression in BPH</td>
<td>Inhibition of the proliferation of BPH stromal cell lines and slow-growing stroma cell clones (smooth muscle cells)</td>
</tr>
<tr>
<td></td>
<td>T cells a major source of IL-4 mRNA</td>
<td>Stimulation of growth of rapid-growing BPH stromal cell clones (fibroblasts)</td>
</tr>
<tr>
<td></td>
<td>Small amounts are created by epithelial cells</td>
<td>Enhanced proliferation of BPH T cells</td>
</tr>
<tr>
<td></td>
<td>IL-4R expression on BPH epithelial and stromal cells</td>
<td>Induction of 3β-hydroxysteroid dehydrogenase/isoermase type 1 in normal prostate epithelial cells</td>
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<tr>
<td>IL-6</td>
<td>BPH: IL-6 protein and mRNA expression in BPH stromal cell lines</td>
<td>Probably paracrine and autocrine epithelial cell growth regulatory loop</td>
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<td>Expression of IL-6 protein in epithelial cells, in culture supernatant of prostatic stromal cells, and IL-6R expression on stromal and epithelial cells</td>
<td>Growth factor for PCa cells</td>
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<td></td>
<td>PCA: IL-6 protein concentrations are increased (18 fold) in localised PCa</td>
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<td>IL-6R correlates with in vivo PCA proliferation assessed by Ki67 immunohistochemistry</td>
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<tr>
<td>IL-8</td>
<td>BPH: IL-8 production by cultured prostatic epithelial cells; senescent prostate epithelial cells produce IL-8 in vitro</td>
<td>Paracrine induction of FGF-2 in stromal cells</td>
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<td>IL-8 production by epithelial and stromal cells in situ</td>
<td>Potent growth factor for prostatic stromal and epithelial cells</td>
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<td>PCA: IL-8 production by PCA cells in vivo</td>
<td>Autocrine growth factor for prostatic epithelial cells</td>
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<td></td>
<td>IL-8 mRNA up-regulated (five-fold) in peripheral lymphocytes of PCA patients</td>
<td>Recruitment of inflammatory cells</td>
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<tr>
<td>IL-13</td>
<td>IL-13 expression by BPH T cells</td>
<td>Induction of 3β-hydroxysteroid dehydrogenase/isoermase type 1 gene transcription in benign and malignant mammary epithelial cells</td>
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<td>IL-13Rα chain expression by BPH epithelial and stromal cells</td>
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<tr>
<td>IL-15</td>
<td>Strong IL-15 protein expression by smooth muscle and fibroblastic stromal cells</td>
<td>Growth factor for BPH memory T cells</td>
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<td>De novo expression of IL-15 by BPH epithelial cells</td>
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<tr>
<td>IL-17</td>
<td>Increased IL-17 mRNA expression in BPH specimens (79%), produced by activated T cells</td>
<td>Strong induction of IL-6 and IL-8 production by prostate epithelial and stromal cells</td>
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<td>Ubiquitous expression of IL-17R</td>
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<tr>
<td>IL-18</td>
<td>PCA: Produced by macrophages</td>
<td>Antitumour immunity mediated</td>
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<td></td>
<td>Belongs to the IL-1 super-family</td>
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<td>IL-18 induces IFN-γ secretion</td>
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<td>IL-23</td>
<td>IL-23 reactivity in BPH smooth muscle cells</td>
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<td></td>
<td>IL-23R expression by BPH epithelial and endothelial cells</td>
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<tr>
<td>IFN-γ</td>
<td>IFN-γR expression by BPH T cells</td>
<td>Induction of the proliferation of BPH stromal cell lines</td>
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<td>TGF-α PCA: TGF-α is regulated by the proteolytic activity of stromal metalloproteinas, which liberate it from membranes of somatic cells</td>
<td>Stimulation of the growth of BPH epithelial cells</td>
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<td>Produced by tumour-associated macrophages</td>
<td>Tumour-promoting behaviour</td>
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<td>TGF-β expression in BPH stromal cells</td>
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<td>Produced also by BPH T cells</td>
<td>Induction of stromal cell growth by induction of differentiation</td>
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<td>Stimulation of the collagen synthesis of BPH stromal cells</td>
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<td>Induction of transdifferentiation of prostatic fibroblasts into myofibroblasts</td>
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<td>Growth factor for prostatic stromal and epithelial cells</td>
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</table>

IL = interleukin; FGF = fibroblast growth factor; BPH = benign prostatic hyperplasia; PCa = prostate cancer; INF = interferon; mRNA = messenger RNA.
So far, we can hypothesise that chronic prostatic inflammation could be considered one of the possible conditions associated with BPH, PCa, or both. However, what we know is probably only the tip of a large iceberg, and further research on inflammatory responses within the prostate is needed to improve our knowledge on the mechanisms involved in the interaction among inflammatory infiltrates, prostatic stroma, and prostatic epithelium. We also need to clarify whether chronic prostatic inflammation could be considered the starting point for the development of benign and malignant proliferative disease of the prostate. With this in mind, we need to improve our capability to diagnose, define the type of, and quantify asymptomatic prostatic inflammation. Research into the relationship among BPH, PCa, and inflammation may benefit from improving clinical imaging for the diagnosis of individual conditions and from a better histologic characterisation of the spatial distribution of inflammatory infiltrates, BPH nodules, and neoplastic and preneoplastic lesions (Fig. 1).

Fig. 1 – The distribution of inflammation, benign prostatic hyperplasia, proliferative inflammatory atrophy (PIA), high-grade intraepithelial neoplasia (HGPIN), and prostate cancer (PCa) in the human prostate: (A) a single slice of a prostate from a radical prostatectomy specimen, (B) a microscopic image (haematoxylin and eosin). (C) In a low-magnification microscopic image of the region indicated in (B) and a higher-magnification image of the different lesions observed, inflammation is shown by the red line and arrow, PIA by the white line and arrow, HGPIN by the green line and arrow, and PCa by the black line and arrow).

BPH = benign prostatic hyperplasia; PCa = prostate cancer; HGPIN = high-grade intraepithelial neoplasia; PIA = proliferative inflammatory atrophy.
3.5. Prostatic inflammation as a target for prevention and treatment

Patients with chronic prostatic inflammation could be considered at risk for BPH development and progression and—if associated with PIA and having a genetic predisposition—a higher risk for PCa. So far, prostatic inflammation has been considered a possible target for BPH and PCa prevention, and treatment and different anti-inflammatory agents have been tested in vitro and in vivo for the management of both conditions [8,10,39,61,69].

3.5.1. Phytotherapy and vitamin D receptor agonists

Phyotherapy is considered a promising therapeutic approach for chronic prostatic inflammation. Vela Navarrete et al [69] evaluated the effect of *Serenoa repens* on prostatic inflammation. They confirmed the diffuse inflammatory infiltration associated with BPH and observed a more significant reduction in the number of B lymphocytes (−36%) and inflammatory modulators such as TNF-α (628.6 ± 635.6 pg/mg vs 146.9 ± 87.3 pg/mg; −76%; *p* = 0.012) and IL-1β (38.5 ± 18.3 pg/mg vs 18.1 ± 9.9 pg/mg; −36%; *p* = 0.004) after 3 months of treatment. The downregulation of leukotriene B4 was also considered a possible effect of *S. repens* treatment in BPH cell cultures. So far, the beneficial effects observed in some patients with BPH treated with *S. repens* can be related to its anti-inflammatory action, together with its proapoptotic effect on the prostatic epithelium and stroma observed in vitro and the ability to inhibit 5α-reductase (5-AR) isoenzymes [6,69–73].

Vitamin D receptor agonist has been recently investigated as a possible option for the management of LUTS related to BPH. BXL 628, a potent vitamin D receptor agonist, was evaluated in in vitro BPH cell cultures and in an in vivo experimental model of autoimmune prostatitis, and it was able to inhibit prostatic growth and control prostatic inflammation by reducing intraprostatic cell infiltrates (CD4+, CD8+, macrophages, B cells) and decreasing IFN-γ and IL-17 secretion [6,39]. However, its possible role in BPH management is still to be defined.

3.5.2. Nonsteroidal anti-inflammatory drug and immunotherapy

The association of chronic inflammation with oxidative stress and free radical production, mostly mediated by the COX gene pathway, is at the basis of the possible chemopreventive effect of aspirin, a nonsteroidal anti-inflammatory drug (NSAID) that reduces inflammation by inhibiting COXs [8,61]. Although aspirin and the nonaspirin NSAIDs inhibit both COX isoforms—COX-1 and COX-2—new drugs, such as celecoxib, rofecoxib, and etoricoxib, selectively block COX-2, providing an anti-inflammatory activity and reducing some of the adverse effects associated with COX-1 blockade, such as gastrointestinal bleeding [8].

Several epidemiologic studies have evaluated the association between the use of NSAIDs and the risk of PCa. They found that an overall reduction of 55–66% [6,53], long treatment duration, and regular use of these drugs (at least 30 pills per months for 5 yr) [74] are associated with a further reduction in risk. The possibility of preventing and treating PCa with COX-2 inhibitors has also been suggested and investigated, but unfortunately, four clinical trials testing COX-2 inhibitors in the prevention and treatment of PCa have been stopped early for the possible relationships between chronic administration of these drugs and cardiovascular side-effects [8]. Actually, available data mostly refer to small pilot studies.

Pruthi et al [75] investigated celecoxib in the prevention of biochemical failure in patients with PCa treated with RP or external-beam radiation therapy. They observed in 8 of the 12 patients enrolled a significant attenuation in PSA increase after treatment. Di Silverio et al [76] evaluated the possibility of increasing the effectiveness of the off-phase of intermittent androgen-deprivation therapy (ADT) by adding a COX-2 inhibitor. Patients treated with etoricoxib 60 mg daily during the off-phase of intermittent ADT experienced a longer off-phase time and a lower PSA increase during the off-phases of each cycle compared to patients who received no additional COX-2 inhibitor treatment.

In a single-centre, non–placebo-controlled study, Di Silverio et al [61] studied the effect of combination therapy with 5-AR inhibitor (5-ARI) and a COX-2 inhibitor. 5-ARIs are known to block the conversion of testosterone into the dihydrotestosterone that results in apoptosis of prostate epithelial cells and a decrease in prostate size [16,17]. Combination therapy was associated with a significant increase in the apoptotic index compared to patients treated with finasteride alone. In addition, the combination therapy was more effective in improving urinary symptoms after a 4-wk treatment, whereas at week 24, the difference between the two treatments was no longer significant. Although these studies suggested a possible role for COX-2 inhibitors for the management of chronic prostatic diseases, the use of NSAIDs for their prevention and treatment remains experimental until larger cohort studies and clinical trials confirm data obtained from small series and epidemiologic experiences.

Cancer immunotherapy is a rapidly evolving treatment option in several human cancers. Most human cancer, such as prostatic carcinoma, develops in immunologically intact hosts; the interaction between tumour cells and the host immune system is considered important in tumour progression [10]. The evidence that inflammation is associated with PCa development as well as progression implies that a PCa immune system might be contributing to disease progression [10]. A better knowledge of T cell population as well as prostatic immune response could probably be used to improve PCa disease immunotherapy strategies [77].

As in rheumatoid arthritis, a prototype of inflammatory disease, targeting TNF-α proved effective in managing the disease and understanding the function and the regulation of inflammatory pathways in chronic prostatic disease, and it may help to further investigate, in large clinical trials, new targets and develop new therapeutic approaches with the aim of reducing or influencing prostatic inflammation response [13]. The possibility of treating prostatic inflammation leads to further questions as to the importance of investigating and developing new biomarkers or new
imaging modalities to diagnose inflammation beyond prostate biopsy, stratifying patients, and following the evolution after treatment. In past years, preliminary data suggested that the seminal level of IL-8 may be considered a valuable marker for detecting BPH inflammation [78]. The possibility of differentiating the inflammatory infiltrates from HGPIN or PCa by magnetic resonance imaging has also recently been investigated [79]. However, notwithstanding these reports, the question on what is the gold standard marker for prostatic inflammation continues to be debated, and answers are eagerly awaited.

4. Conclusions

Although we do not completely understand the pathways of chronic prostatic inflammation, the evidence summarised in this review suggests the important role of inflammatory infiltrates and their mediators in the development of chronic prostatic diseases such as BPH and PCa. Prostatic inflammation should not be considered only as an occasional histologic finding in prostate specimens but as a possible link between prostatitis, BPH, and PCa. Chronic prostatic inflammation may result from the immunologic response of different pathogen noxae that induce tissue damage and subsequent chronic processes of repetitive wound healing, and it may have a role in BPH growth and progression as well as in the prostate's vulnerability to developing cancer. Understanding the prostatic inflammation pathways is an important area in basic and clinical research in BPH and PCa and may help to identify new therapeutic targets and strategies for reducing the risk of benign and malignant tumours of the prostate. The combination of BPH and PCa represents a leading social and clinical burden in an aging population. A reduction in the incidence and progression of such conditions may have formidable economic consequences for national health services.

Author contributions: Cosimo De Nunzio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: De Nunzio.

Analysis and interpretation of data: De Nunzio.

Drafting of the manuscript: De Nunzio.

Critical revision of the manuscript for important intellectual content: De Nunzio, Kramer, Marberger, Montironi, Nelson, Schröder, Sciarrà, Tubaro.

Statistical analysis: De Nunzio.

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Supervision: Kramer, Marberger, Montironi, Nelson, Schröder, Sciarrà, Tubaro.

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