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Complex Mechanisms in Prostatic Inflammatory Response

Bob Djavan[a,*], *Elisabeth Eckersberger*[a], *Geovanni Espinosa*[a], *Gero Kramer*[b], *Alessandra Handisurya*[b], *Chung Lee*[c], *Michael Marberger*[b], *Herbert Lepor*[a], *Georg E. Steiner*[b]

[a] *Department of Urology, New York University, New York, NY, USA*
[b] *Department of Urology, University of Vienna, Vienna, Austria*
[c] *Department of Urology, Northwestern University, Chicago, IL, USA*

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Abstract

Context: The immunology of the prostate has developed into a new field of research in urology. The leukocyte population increases are not yet fully understood, but it has been demonstrated that most resected prostate tissue shows signs of inflammatory response.

Objective: This article reviews recent findings and discusses the complex mechanisms involved in the prostatic inflammatory response and the immunologic functions of the prostate, and the roles the prostatic inflammatory response in the cause of prostate disease such as benign prostatic hyperplasia (BPH).

Evidence acquisition: We performed a search of the medical literature with PubMed, using keywords such as *prostate cancer, inflammation of the prostate, leukocytes, estrogen*, and *cytokine* and genetic expression of inflammation. Articles and data were reviewed as to their relevance, and inclusion and exclusion criteria were determined prospectively.

Evidence synthesis: Evidence showing that inflammation of the prostate plays a role in prostate cancer (PCa) is mounting. Different types of inflammation exist and are distinguished according to the distribution and location of leukocytes and the histology of the surrounding tissue. Most resected prostate tissue shows signs of inflammatory response, and a relationship between T-cell infiltration and stromal proliferation can be found. Evidence for the importance of estrogen and proinflammatory cytokine interleukin (IL; IL-6, IL-8, IL-15, IL-17) also can be found. Early stages of investigation of the immunologic function of the prostate show that both prostatic epithelial and stromal cells express members of the toll-like receptor family and are therefore capable of recognizing foreign incoming antigens.

Conclusions: Although this area of study is new, the immunology and inflammatory responses of the prostate are seen as important components of further study of prostate diseases such as PCa and BPH. Data supporting the role of immunology and activated leukocytes in malignant cells are also an important finding and can possibly lead to new knowledge about malignant cells.

* Corresponding author.
E-mail address: Bob.Djavan@nyumc.org (B. Djavan).

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1. Introduction

Neglected and often underestimated in its significance, the immunology of the prostate has developed into a new field of research in urology, with the research of lymphokines gaining particular importance. Although research is still at an early stage, we know that both prostatic epithelial and stromal cells express members of the toll-like receptor (TLR) family and are therefore capable of recognizing foreign incoming antigens. The functional consequences of antigen binding of prostatic cells via TLRs are largely undefined, but preliminary data suggest that both cell types respond with increased production of proinflammatory cytokines. Another point of interest is the alteration associated with the frequently occurring chronic inflammation process accompanying both atrophic and benign hyperplastic changes. In this review, we summarize recent data and discuss the complex regulatory interaction between cells of the prostate and leukocytes.

2. Evidence acquisition

Data were acquired by a search of the medical literature with PubMed, using keywords such as *prostate cancer, inflammation of the prostate, leukocytes, estrogen*, and *cytokine* and genetic expression of inflammation. Articles and data were reviewed as to their relevance, and inclusion and exclusion criteria were determined prospectively. Because this field is relatively new and unstudied, evidence was not limited to humans data; data from animal studies (mice, rats and dogs) were included in the review to give the most up-to-date picture of the evidence.

3. Evidence synthesis

3.1. Leukocytes

The prostate is populated by small numbers of αβ T cells, B lymphocytes, macrophages, and mast cells [1,2]. T lymphocytes populate the prostate as early as the 12th week of gestation, reaching a peak between weeks 21 and 30 [3]. Although the number of leukocytes declines during weeks 31–40 of gestation, the normal prostate still harbors 7.3 ± 3.3 $CD3^+$ T lymphocytes per square millimeter, two-thirds of which are $CD8^+$ T cells. In the normal prostate, the T lymphocytes are evenly distributed throughout the interstitium and between the epithelial cells [1]. The number of T lymphocytes generally increases with age. In specimens taken from 50-yr-old patients, for example, up to 55 T lymphocytes per square millimeter have been counted without the presence of clustering or pathologic histologic alteration.

3.2. Inflammation

Although leukocytic increases are not yet fully understood, it is accepted that most resected prostate tissue shows signs of inflammatory reactions. Different types of inflammation exist and must be distinguished according to distribution and location of leukocytes and histology of surrounding tissue. The first type, formerly designated as *postinflammatory atrophy* [4], *chronic prostatitis* [5], and *lymphocytic prostatitis* [6], was recently termed *proliferative inflammatory atrophy* (PIA) [7]. PIA is characterized by discrete foci of proliferative glandular epithelium with the morphologic appearance of simple atrophy or postatrophic hyperplasia occurring in association with inflammation. The key features of PIA are the presence of two distinct cell layers of epithelial cells, mononuclear and/or polymorphonuclear inflammatory cells (80–85% of which are $CD3^+$ T cells) in both the epithelial and the stromal compartments, and stromal atrophy with variable amounts of fibrosis [8] (Fig. 1).

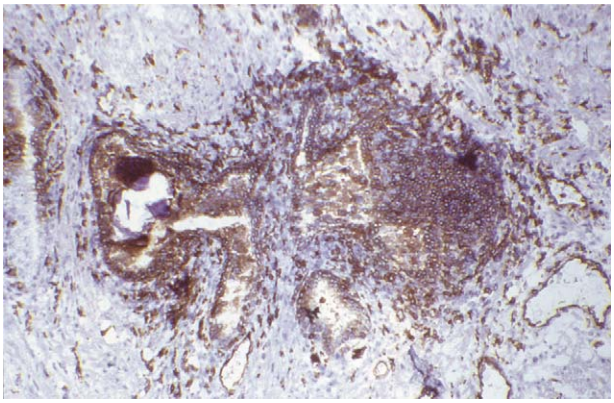

Fig. 1 – Proliferative inflammatory atrophy; immunohistochemistry using anti-CD3. Reproduced with permission of MedReviews®, LLC. Steiner GE, Djavan B, Kramer G, et al. The picture of the prostatic lymphokine network is becoming increasingly complex. Rev Urol 2002;4:171–7. Reviews in Urology is a copyrighted publication of MedReviews®, LLC. All rights reserved [8].

A second type of inflammation occurs with benign prostatic hyperplasia (BPH). Kohnen and Drach reported that 98% of 162 analyzed BPH specimens had an inflammatory infiltrate [9]. It has been shown that BPH specimens are often infiltrated by leukocytes and that the majority of infiltrating T lymphocytes are $CD4^+$ memory T lymphocytes [1,2,7,8,10,11]. Bierhoff and colleagues [12] described a "scattered" type of inflammation in BPH, characterized by significantly increased diffuse infiltrates of T lymphocytes in fibroblastic, fibromuscular, and smooth-muscular stromal nodules but decreased infiltration of mesenchymal nodules compared to the surrounding stroma (Fig. 2). The authors concluded that lymphocyte infiltrates of the stromal nodules must be strictly separated from inflammatory changes frequently accompanying BPH. Functional testing of BPH-tissue-infiltrating T cells showed that they display the functional features of activated T lymphocytes [3], although it is unclear whether this BPH-associated immunoreaction is triggered by foreign antigens, autoantigens, or both.

The incidence of chronic inflammatory prostatic diseases of noninfectious origin is shown to be eight times higher than that of bacterial prostatitis [13]. Taguchi et al first used the term *autoimmune prostatitis* in 1985 [14], after showing that the prostate became infiltrated following neonatal thymectomy. Zisman and colleagues [15] later

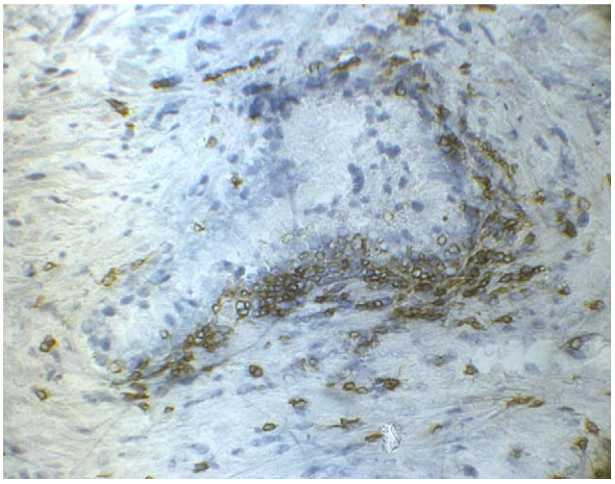

Fig. 2 – "Scattered" type of inflammation; immunohistochemistry using anti-CD3. Reproduced with permission of MedReviews®, LLC. Steiner GE, Djavan B, Kramer G, et al. The picture of the prostatic lymphokine network is becoming increasingly complex. Rev Urol 2002;4:171–7. Reviews in Urology is a copyrighted publication of MedReviews®, LLC. All rights reserved [8].

Table 1 – Overview

Proliferate role
Leukocytes (PIA) [7]
Involved in BPH
T lymphocytes ($CD4^+$ memory T) [1,2,8–11]
Lack of polyclonal B-cell activation [16,17]
IL-2 [25]
IL-4 (ratio to IL-2, 10:13) [25–27]
IL-7 [24]
IL-8 [37]
IL-15 [32]
IL-17 [44,45]
IFN-γ mRNA [26,27]
Estrogen (by way of increasing activity of IFN-γ) [31]
3β-HSD (by way of the formation of estrogens) [46]
Involved in prostate cancer
IL-6 [22,32]
IL-8 [37]
Proinflammatory cytokines [47]
Synergic T regulatory cells (by way of downregulating cytokines) [47]
Gene mutations: E265X and M1I [49]

3β-HSD = 3β-hydroxydehydrogenase/isomerase type 1; BPH = benign prostatic hyperplasia; IFN = interferon; IL = interleukin; mRNA = messenger RNA; PIA = proliferative inflammatory atrophy.

detected anti–prostate-specific antigen (PSA) antibodies in the sera of BPH patients and concluded that BPH may represent an organ-limited autoimmune condition without polyclonal B-cell activation. Animal models for the induction of autoimmune- or antigen-independent prostatitis have now been established [16,17], suggesting that some determinants of normal prostatic proteins are not tolerated by the immune system.

Normal human prostatic proteins such as PSA and prostate-specific membrane antigen have recently been used successfully as vaccines (Fig. 3) [18–20]. Functional experiments in mice [15], dogs [21], rats [22], and humans [23] suggest that prostatic inflammation is at least partly under hormonal influence and may be caused by a decrease in androgens and a simultaneous increase in estrogens. Additional evidence exists that in rats, genetic background and age are also associated with the susceptibility to lymphoid infiltration of the prostate [24]. It is speculated that growth factors released by these infiltrating leukocytes might alter growth of neighboring stromal cells and thus contribute to prostatic hyperplasia [2,13].

Kramer and colleagues demonstrated a direct relationship between T-cell infiltration, lymphokines, and stromal hyperproliferation in BPH [25]. In contrast to normal prostate tissues, benign hyperplastic tissues contained considerable amounts of interleukin (IL) 2 and IL-4 messenger RNA (mRNA) (ratio of 10:13). Screening for the major source of lymphokine production revealed that T-cell lines generated from the tissue expressed high amounts of interferon (IFN) γ, IL-2, and IL-4 mRNA and also small amounts of fibroblast growth factor (FGF) 2 mRNA, regardless of their CD4-to-CD8 ratio (Table 1).

Expression of IFN-γ, IL-2, and IL-4 mRNA in benign hyperplastic tissues suggests that the disease is associated with both classical types of T-cell responses, the type 1 and type 2 immune responses [26,27]. Type 1 T lymphocytes are

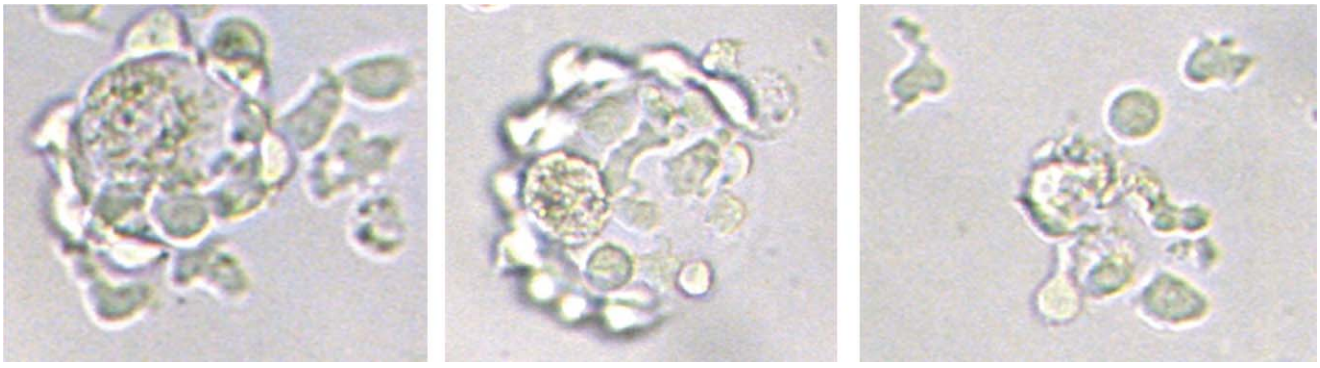

Fig. 3 – Kinetics of epithelial cell killing by prostatic T lymphocytes. Parallel time-lapse microscopy of autologous epithelial cell killing by prostatic T lymphocytes derived from a prostatic specimen with benign prostatic hyperplasia. Reproduced with permission of MedReviews®, LLC. Steiner GE, Djavan B, Kramer G, et al. The picture of the prostatic lymphokine network is becoming increasingly complex. Rev Urol 2002;4:171–7. Reviews in Urology is a copyrighted publication of MedReviews®, LLC. All rights reserved [8].

sources of IFN-γ, IL-2, and IL-10 and are involved in cell-mediated inflammatory reactions. Type 2 T lymphocytes are negative for IFN-γ and positive for IL-4, IL-5, and IL-13 and are found in association with strong antibody and allergic responses [28,29]. Most benign hyperplastic tissues and all polyclonal, long-term-cultured tissue-derived T-cell lines revealed no such dichotomy and exhibited Southern blot bands when probed for IFN-γ, IL-2, and IL-4. Preliminary results using intracellular cytokine detection confirmed these findings and revealed substantial numbers of IFN-γ^+ and IL-2^+ prostatic T lymphocytes that coexpress Th2 cytokines (IL-4 and IL-13). One explanation is that IFN-γ influences differentiation and that the combination of transforming growth factor (TGF) β1 and IFN-γ keeps $CD4^+$ T cells in a proliferating, IL-2-secreting state of T helper cell subtype 0 [30] with a memory phenotype similar to that described for BPH T cells.

In a recent study [23], marked differences were shown between normal stromal cells and prostatic stromal cells from BPH. Normal prostatic stromal cell lines were a functionally heterogeneous population that did not respond to IL-2, IL-7, and IFN-γ but revealed a significant dose-dependent inhibition of the proliferation by IL-4. In contrast, the majority of polyclonal BPH prostatic stromal cell lines responded to IL-2, IL-7, and IFN-γ with increased proliferation, which remained relatively high even after inhibition by IL-4.

3.3. Proinflammatory cytokine expression

A number of theories explain the causes of leukocytic inflammation. The effect of hormones on the regulation of proinflammatory genes has been addressed by several studies.

3.4. Estrogen

Evidence suggests that estrogen plays an important role in susceptibility to inflammation and regulation of IFN-γ production [31]. Estradiol (E2) was shown to increase activity or mRNA expression of IFN-γ promoter in lymphocytes. Treatment of rats with E2 resulted in upregulation of proinflammatory transcripts of macrophage inflammatory protein (MIP) 2, inducible nitric oxide synthase, IL-6, IL-1γ, and tumor necrosis factor (TNF) γ in the prostate after as little as 4 d, well before cellular inflammation occurs. Histologic signs of inflammation became evident only after 2–4 wk of E2 exposure (capsule implantation of solid E2).

Inflammatory cells were predominantly T lymphocytes and were consistently detected first in prostatic interstitium and then in the acini [31]. Among the various upregulated proinflammatory transcripts, the most dramatic results were shown for C-X-C chemokine and MIP-2, followed by IL-6. Only a small increase (1.5–3 times) was detected in IL-1β and TNF-α. In addition, modest upregulation of IL-4, IL-5, and IL-10 transcripts was shown in E2-treated animals, but there was no change in IL-2, IL-12, or cyclo-oxygenase (COX) 2 expression [24].

3.5. Interleukin 6

In the context of chronic inflammation and proinflammatory cytokine expression, IL-6 is one of the major physiologic mediators of acute phase reaction. It is a pleiotropic cytokine influencing antigen-specific immune responses and inflammatory reactions as well as hematopoiesis, bone metabolism, and neural development. Recognized sources of IL-6 include fibroblasts, activated macrophages or monocytes, activated T and B cells, endothelial cells, stromal cells, and a variety of cancer cells. IL-6 is secreted by both normal and neoplastic prostatic epithelial cells and can act as a growth factor for normal prostatic epithelial cells as well as for prostate cancer (PCa) cells [32,33].

Commonly used PCa lines (PC3, DU145, LNCaP) express high-affinity receptors for IL-6, and PC3 and DU145 cell lines secrete IL-6 [34,35]. Consequently, an autocrine growth factor loop has been suggested [36]. Furthermore, IL-6 protein concentrations are increased (approximately 18-fold) in localized PCa when compared to normal prostate tissue. Increased expression of IL-6 receptor is correlated with increased proliferation in vivo as assessed by Ki67 immunohistochemistry.

3.6. Interleukin 8

Another cytokine with proinflammatory properties is IL-8, often induced along with IL-6 in response to stimuli in vitro, including chemical and microbial stimuli and selected cytokines. IL-8 has chemotactic properties, attracting neutrophils and mononuclear cells into sites of inflammation. It is a primary inflammatory cytokine, secreted by monocytes, mitogen-stimulated T lymphocytes, neutrophils, eosinophils, fibroblasts, synovial cells, endothelial cells, mesothelial cells, epithelial cells, and keratinocytes.

Ferrer and colleagues reported production of IL-8 by several prostatic cell lines in vitro as well as by prostatic cancer cells in vivo [37]. Epithelial cells in normal prostate and BPH specimens were negative for IL-8. Another interesting finding is that IL-8 mRNA expression was upregulated as much as 5-fold in peripheral blood lymphocytes of patients with carcinoma of the prostate [38]. IL-8 produced by prostatic epithelial cells can act as a paracrine inducer of FGF-2 (a potent growth factor for prostatic stromal cells) production by prostatic stromal cells in vitro [39].

Enzyme-linked immunosorbent assays performed on normal and benign hyperplastic tissues have revealed substantial quantities of IL-8 in the normal prostate and elevated levels in the hyperplastic prostate. Grabstein et al concluded stromal proliferation might be controlled, at least in part, by IL-8 secreted by prostatic epithelial cells [40]. Although the data regarding IL-8 production by normal and/or BPH epithelial cells are conflicting, these studies have shown that large quantities of IL-8 can be expressed intraprostatically. Additional studies have shown that IL-8 in diseased prostate tissue can be ascribed to stromal as well as epithelial cells, with a functional role in recreating leucocytes expressing CXCR1 and CXCR2 IL-8 receptors [41].

3.7. Interleukin 15

IL-15 was first identified in the supernatant of kidney epithelial cells by its ability to replace IL-2 [42]. In contrast to IL-2, which is mainly produced by activated T cells, IL-15 is expressed constitutively in a wide variety of tissues and cell types but not in normal resting or activated T lymphocytes. IL-15 plays an important role in the homeostasis of lymphocytes and acts as a potent chemoattractant, inducing locomotion and migration of human T lymphocytes [31] and contributing to protective immune responses against microbial pathogens.

Handisurya and colleagues demonstrated that in the normal prostate, IL-15 was strongly expressed by smooth-muscle cells, weakly expressed by endothelial cells, and very weakly expressed (often only irregularly or not at all) by epithelial cells [43]. However, in BPH specimens, increased IL-15 expression was frequently found in luminal secretory epithelial cells. Because IL-15 is a potent stimulator of BPH-T lymphocyte proliferation, Wilkinson and Liew suggested that prostatic IL-15 might play an important role in lymphocytic infiltration and the maintenance of chronic inflammation in BPH tissue [42]. Theoretically, these lymphocytes generate inflammatory conditions characterized by increased IFN-γ production. Handisurya and colleagues also showed that elevated IFN-γ will augment IL-15 production by prostatic cells, which might result in increased chemoattractant activity and in the recruitment of more T lymphocytes by facilitating transendothelial migration into perivascular tissues [43].

3.8. Interleukin 17

Steiner et al recently identified another very potent player in the prostate: IL-17, a T-lymphocyte-derived proinflammatory cytokine [44]. It is expressed primarily by activated prostatic T lymphocytes and augments the production of other members of the proinflammatory cytokine family, which is why it is called the *local fine tuner* of immune response. In Steiner and colleagues' study, IL-17 had enormous capacities in stimulating IL-6, IL-8, and IL-1α and β protein and mRNA production multifold and was more powerful than, for example, lipopolysaccharide or the protein kinase activator phorbol myristate acetate. Although expression of IL-17 mRNA in human prostate is frequent, it is not produced by healthy prostatic cells or only in very small quantities, but levels are highly increased in diseased prostatic tissue. The vast majority of prostatic IL-17 is T-cell derived, and it has been shown that only activated BPH T-lymphocytes produce and secrete IL-17 [45].

3.9. The network

It is established that TGF-β inhibits growth, whereas FGF-2 stimulates growth. Less well known is that substantial amounts of both growth-regulating cytokines are produced by T lymphocytes [24]. An additional pathway by which T cells can influence the balance between cells and growth factors is via the natural antagonist of TGF-β: IFN-γ. TGF-β1 mRNA synthesis by prostatic stromal cells is stimulated by IFN-γ, whereas the uptake of TGF-β1 by prostatic stromal cells is inhibited. As previously discussed, IFN-γ simultaneously stimulates production of IL-15, thereby augmenting the influx of further T cells. These T cells are activated by an unknown antigen, and they respond by producing lymphokines such as IL-4 and IL-13. Both lymphokines have been shown to induce the production of 3β-hydroxydehydrogenase/isomerase type 1 (3β-HSD) by prostatic epithelial cells. Three-β-HSD is known to catalyze an essential step in the formation of active androgens and estrogens from dehydroepiandrosterone [46].

3.10. Prostate cancer

Chronic inflammation has frequently been associated with cancerogenesis in human and animal models. Proinflammatory cytokines were significantly linked with cancer and increasing age in the mouse model; however, prostate and bowel tissues lacked evidence of inflammatory cell infiltrates other than mast cells. Recent findings by Poutahidis et al [47] suggest that lymphocytes protect against cancer and that protection from PCa resides in anti-inflammatory $CD4^+CD25^+$ T regulatory (Treg) cells that downregulate inflammatory cytokines. The authors found that supplementation with syngeneic Treg cells collected from wild-type mice reduced the levels of IL-6 ($p < 0.05$) and IL-9 ($p < 0.001$) and lowered PCa risk ($p < 0.05$). Depletion of $CD25^+$ cells in 2-mo-old animals increased the expression of IL-6 ($p < 0.005$) within the prostate and increased the frequency of high-grade prostatic intraepithelial neoplasia ($p < 0.05$) and microinvasive prostatic carcinoma ($p < 0.05$) in dorsolateral prostate. Depletion of $CD25^+$ cells in young animals also increased the frequency of intestinal cancer in Min mice. Taken together, the authors showed that chronically elevated proinflammatory cytokines promoted carcinoma in Apc(Min/$^+$) mice. Treg lymphocytes downregulated inflammation-associated carcinogenic processes and contributed to immune and epithelial homeostasis.

Ravenna et al's global survey approach showed an upregulation in PCa samples of all of the studied genes, with the exception of estrogen receptor β [48]. The authors found that a laser-capture microdissection approach highlighted overexpression of proinflammatory molecules in each tumor sample examined, and they observed nuclear translocation of nuclear factor-kB subunit p65 in tumor tissues. Ravenna et al concluded that these data support the evidence that molecules typical of the innate immune system, similar to that of activated leukocytes, are produced by prostate epithelial cells and that their expression is upregulated in malignant cells.

3.11. Prostate cancer regenesis and inflammatory genes

According to De Marzo et al [49], few reliable genetic risk factors have been identified in correlation with inflammation. Indeed, allelic variants of genes involved in innate and acquired immunity play a vital role in determining inherited PCa, and allelic variants of the genes involved

in inflammatory pathways are candidates for genetic determinants of PCa risk. Inactive mutations (E265X and M1I) in ribonuclease L segregate with PCa in two cancer families: E265X with one of European descent and M1I of African descent. Recurring, inactivating mutations in macrophage scavenger receptor 1 were additionally revealed in a number of PCa families.

4. Conclusions

As a new area of study, the immunology and inflammatory responses of the prostate are important components of further study of prostate diseases such as PCa and BPH. Additional data supporting the role of immunology and activated leukocytes in malignant cells are also important and can possibly lead to new knowledge about malignant cells. The roles of estrogen and proinflammatory cytokine IL (IL-6, IL-8, IL-15, IL-17) also warrant further study, hopefully leading to deeper knowledge about their influence on prostate cell development. The current data and study findings provide a promising start in this new field and can be seen as a solid base for the further study.

Conflicts of Interest

The authors have nothing to disclose.

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