Role of Inflammation in Benign Prostatic Hyperplasia

Bilal Chughtai, MD, Richard Lee, MD, Alexis Te, MD, Steven Kaplan, MD

Department of Urology, Weill Cornell Medical College, New York, NY

Inflammation of the prostate may represent a mechanism for hyperplastic changes to occur in the prostate. There are a variety of growth factors and cytokines that may lead to a proinflammatory process within the prostate. There are several proposed mechanisms that lead to both the intrinsic and extrinsic basis of inflammation. Prostatic inflammation may represent an important factor in influencing prostatic growth and progression of symptoms. This article reviews the recent literature on inflammation leading to chronic prostatic diseases, such as benign prostatic hyperplasia.
[Rev Urol. *2011;13(3):147-150 doi: 10.3909/riu0535*]

Key words: Benign prostatic hyperplasia • Prostatic cytokines • Vitamin D • Inflammation • Prostatitis

Benign prostatic hyperplasia (BPH) affects aging men and represents the most common urologic disease among elderly men.[1] BPH is a growth of both epithelial and stromal cells from both the transition zone and periurethral areas.[2] BPH is a histologic diagnosis requiring tissue and the incidence is over 70% at age 60 years and over 90% at age 70 years. The histologic diagnosis of BPH may not necessarily lead to clinical symptoms. Lower urinary tract symptoms (LUTS) are classified as obstructive (hesitancy, weak stream, straining, and prolonged voiding), irritative (frequency, urgency, nocturia, urge incontinence, and voiding small volumes), or postmicturition (post void dribble, incomplete emptying). Most patients present with a combination of obstructive, irritative, and postmicturition symptoms. To date, there are multiple theories on the cellular and molecular processes underlying the pathogenesis of BPH leading to a symptomatic disease. It is well known that androgens play a key role, but there are other pathways that may influence BPH and the associated voiding symptoms.

Prostatic inflammation may represent an important factor in influencing prostatic growth and progression of symptoms. A variety of growth factors and cytokines have been implicated in the inflammatory process. This article reviews the current literature on causes of prostatic inflammation.

Etiology of BPH Inflammation

Infection/Prostatitis

There are no clear triggering events leading to BPH; one plausible hypothesis is one of an infective etiology. Several studies have demonstrated the presence of heterogeneous bacterial and viral strains in BPH specimens. Strains of bacteria and virus may lead to a production of proinflammatory cytokines and chemokines by BPH stromal cells, which may lead to prostatic growth.[3-5] Bacterial and noninfectious chronic prostatitis could be considered the pathogenetic background of hyperproliferative cellular pathways, possibly as a consequence of autoimmune responses against self-antigens released following tissue injury. Among self-antigen candidates, prostate-specific antigen (PSA) has also been shown to activate CD4+ T cells from patients with granulomatous prostatitis.[6] PSA antigenicity may be related to the completion of prostate development at puberty, to the impairment of cellular tolerance processes by age, or by hormonal changes in aging men.

Prostate-specific antigen antigenicity may be related to the completion of prostate development at puberty, to the impairment of cellular tolerance processes by age, or by hormonal changes in aging men.

There are several studies demonstrating that interleukins (ILs), which are proinflammatory, may lead to the progression of BPH. In in vitro assays, CD4+ T cells activated by BPH stromal cells markedly upregulate secretion of IL-12 and IL-23. McDowell and associates showed inflammatory cells can be attracted to the prostate tissue microenvironment and can selectively promote the proliferation of prostate epithelial cells.[7] Further studies have confirmed IL-17 leads to more proinflammatory cytokines, such as IL-6 and IL-8. Steiner and associates demonstrated that healthy prostates do not express IL-17, whereas prostates with inflammation and BPH do express this interleukin.[8] Wang and associates also found cyclooxygenase 2 (COX-2) in prostates with significant inflammation.[9] These findings are consistent with differential roles for the inflammatory infiltrate in the etiologies of benign proliferative disease in the prostate.

In a study of human prostate epithelial cells with stromal fibroblasts gene array, polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and proliferation assays were performed. The aging prostate stroma is characterized by the upregulation of several genes that encode secreted inflammatory mediators such as chemokines (CXCL1, CXCL2, CXCL5, CXCL6, CXCL12) and ILs (IL-11, IL-33).[6] Inflammatory mediators were found to be secreted by prostatic stroma and were sufficient to promote low-level increases in the proliferative rate of both epithelial and stromal fibroblast cell types. These processes may account for the low-level, but cumulative, proliferation of both epithelial and fibroblastic/myofibroblastic cell types that characterizes the aging-associated development of BPH.

Robert and colleagues profiled 282 patients who were treated with surgery for complicated and/or symptomatic BPH on tissue microarrays. The majority of patients had inflammatory cells infiltrating BPH tissues: 81% had T-lymphocyte markers, 52% had B-lymphocyte markers, and 82% had macrophage markers. International Prostate Symptom Score (IPSS) and prostate volume were significantly higher in patients with high-grade prostatic inflammation.[6] Mishra and colleagues confirmed this in 374 patients who underwent transurethral resection of the prostate (TURP) for either LUTS or urinary retention. They found that 70% of men with urinary retention had pathologic evidence of acute and/or chronic inflammation versus 45% of those without LUTS.[3]

A multicenter, open pilot study of saw palmetto, which is widely used in the treatment of men with LUTS, studied the effects of the inflammatory markers potentially involved in BPH.[10] Patients were randomized to receive either saw palmetto, 160 mg, bid, for 3 months or to be followed for 3 weeks without any treatment before surgery. Twenty-nine patients ultimately underwent TURP or retropubic adenomectomy. Adenoma samples demonstrated tumor necrosis factor-α (TNF-α) and IL-1β were dramatically lower in the saw palmetto–treated group. Both biologic markers have been used as indicators of prostatic inflammation in cases of chronic prostatitis.[11]

In a subgroup analysis of 1197 patients in the Medical Therapies of Prostate Symptoms (MTOPS) study, men in the placebo arm with inflammation were significantly more likely to experience symptom worsening or acute urinary retention than those without inflammation (5.6% vs 0.0%;

$P = .003$). This was found in spite of a weak correlation at baseline between inflammation and clinical BPH.[2] This was confirmed in the subgroup analysis of 8224 men in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. The relative contribution of inflammation, age, and body mass index was examined with the use of linear regression analyses.[12] Statistically significant but relatively weak correlations were found between average and maximum chronic inflammation and IPSS variables (correlation coefficients, 0.057 and 0.036, respectively; $P < .001$ for total IPSS). Both age and average chronic inflammation were significant in the linear regression after adjustment for other covariates; for both variables, more severe inflammation was associated with higher IPSS scores. The study selected older men, and decreased enrollment of men with a greater degree of inflammation and LUTS may have limited the strength of this relationship.

Oxidative Stress

Both chronic and acute inflammation may lead to events that can cause proliferation within prostatic tissue through a variety of mechanisms, notably oxidative stress.[13] Both tissue damage and oxidative stress may lead to compensatory cellular proliferation with resulting hyperplastic growth. Prostatic inflammation can lead to the generation of free radicals. These include nitric oxide (NO) and various species of oxygen. Both macrophages and neutrophils provide a source of free radicals that can induce hyperplastic transformations through oxidative stress to tissue and DNA. A feature of these oxidative stress reactions is the production of arachidonic acid from membranes. This process is associated with the generation of new reactive oxygen radicals. These reactions may also lead to conversion by the COX enzymes to prostaglandins. This has been recognized as an important factor in the regulation of prostate cell proliferation.[14] Prostate tissue is typically sheltered by oxidative stress by free radical scavengers such as superoxide-dismutase and glutathione-*S*-transferase (GST)–P1.[13]

NO and COX activity may play an important role in determining the association between inflammation and prostate growth. Inflammatory cells that are present in the prostate, the inducible NO synthase (iNOS), are the principal factors activating reactive nitrogens that can damage cells. NOS expression in human prostate tissue has been characterized by increased immunostaining in the epithelial cells of cases with BPH when compared with normal tissue.[9] NO also enhances COX activity, the second factor. COX-2 activity has been detected in all inflammatory cells in the epithelium and interstitial spaces of human prostate tissue and it is increased in proliferative inflammatory lesions, generating proinflammatory prostaglandins. Di Silverio and colleagues showed that, in human BPH tissue, COX-2 inhibition can produce a significant increase in prostate cell apoptotic activity.[15]

In a prospective, randomized, double-blind, placebo-controlled study, a total of 80 men with BPH was randomized to receive either celecoxib, 100 mg or placebo for 1 month.[16] The researchers found the celecoxib group had a mean nocturnal frequency that decreased from 5.17 to 2.5 versus the control group, whose frequency decreased from 5.3 to 5.12. The mean IPSS decreased from 18.2 to 15.5 and the control group decreased from 18.4 to 18.

Vitamin D Pathway

Agonists of the vitamin D receptor (VDR) have been found to arrest BPH development.[17] VDR agonists wield anti-inflammatory and immunoregulatory properties. This is a potentially useful treatment of diseases characterized by chronic inflammation and cell proliferation. The prostate is a target organ of VDR agonists and represents an extrarenal synthesis site of 1,25-dihydroxyvitamin D3. VDR agonists have mostly been explored clinically for the treatment of prostate cancer.

Inflammatory cells that are present in the prostate, the inducible nitric oxide synthase (iNOS), are the principal factors activating reactive nitrogens that can damage cells.

Administration of elocalcitol, a vitamin D analog, was shown to inhibit intraprostatic cell infiltrate in a mouse model.[18] Mechanisms of action underlying the capacity of elocalcitol to inhibit human BPH cell growth and inflammatory response include IL-8, which is produced by BPH cells and induces their proliferation. This activates calcium-sensitizing pathways implicated in the regulation of the inflammatory response. Elocalcitol treatment significantly inhibits IL-8 production and cell proliferation. These effects are associated with decreased COX-2 expression and prostaglandin E2 (PGE2) production, providing a possible explanation for the antiproliferative and anti-inflammatory properties of elocalcitol in BPH cells.

In an ex vivo study of 3 patients who underwent a suprapubic prostatectomy for BPH, it was found that elocalcitol, a VDR agonist, significantly

inhibited IL-8 production by BPH cells stimulated with inflammatory cytokines, and IL-8-induced proliferation of BPH cells.[17] This study provided a mechanism for which VDR agonist may play a role in prostatic inflammation.

Conclusions

Inflammation may be considered the third component of BPH pathogenesis. This is in addition to androgen receptor signaling in tissue remodeling typical of the advanced stages of the disease. Prostatic stromal cells exert a critical role in the induction of inflammatory responses by activating CD4+ lymphocytes. Thus, BPH may be viewed as a form of asymptomatic inflammatory prostatitis, whose pathogenesis may be triggered by a multitude of factors and pathways. The release of prostatic self-antigens following tissue damage may sensitize the immune system and start autoimmune responses. Among proinflammatory cytokines and chemokines produced by the prostatic microenvironment, stromal-derived IL-8 may be considered a key link between chronic inflammation and stromal cell proliferation. In particular, the effect of these pathways may represent a common denominator for all 3 components of BPH: static, dynamic, and inflammatory. ■

References

1. McVary KT. BPH: epidemiology and comorbidities. *Am J Manag Care*. 2006;12(suppl 5):S122-S128.
2. Roehrborn CG. BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. *BJU Int*. 2008;101(suppl 3):17-21.
3. Mishra VC, Allen DJ, Nicolaou C, et al. Does intraprostatic inflammation have a role in the pathogenesis and progression of benign prostatic hyperplasia? *BJU Int*. 2007;100:327-331.
4. Nickel JC. Prostatic inflammation in benign prostatic hyperplasia - the third component? *Can J Urol*. 1994;1:1-4.
5. Nickel JC. Inflammation and benign prostatic hyperplasia. *Urol Clin North Am*. 2008;35:109-115 [vii.].
6. Robert G, Descazeaud A, Nicolaiew N, et al. Inflammation in benign prostatic hyperplasia: a 282 patients' immunohistochemical analysis. *Prostate*. 2009;69:1774-1780.
7. McDowell ME, Occhipinti S, Gardiner RA, et al. A review of prostate-specific antigen screening prevalence and risk perceptions for first-degree relatives of men with prostate cancer. *Eur J Cancer Care (Engl)*. 2009;18:545-555.
8. Steiner GE, Newman ME, Paikl D, et al. Expression and function of pro-inflammatory interleukin IL-17 and IL-17 receptor in normal, benign hyperplastic, and malignant prostate. *Prostate*. 2003;56:171-182.
9. Wang W, Bergh A, Damber JE. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2, and cell proliferation in the glandular epithelium. *Prostate*. 2004;61:60-72.
10. Vela Navarrete R, Garcia Cardoso JV, Barat A, et al. BPH and inflammation: pharmacological effects of Permixon on histological and molecular inflammatory markers. Results of a double blind pilot clinical assay. *Eur Urol*. 2003;44:549-555.
11. Nadler RB, Humphrey PA, Smith DS, et al. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. *J Urol*. 1995;154:407-413.
12. Nickel JC, Roehrborn CG, O'Leary MP, et al. Examination of the relationship between symptoms of prostatitis and histological inflammation: baseline data from the REDUCE chemoprevention trial. *J Urol*. 2007;178:896-900; discussion 900-901.
13. Naber KG, Weidner W. Chronic prostatitis-an infectious disease? *J Antimicrob Chemother*. 2000;46:157-161.
14. Sugar LM. Inflammation and prostate cancer. *Can J Urol*. 2006;13(suppl 1):46-47.
15. Di Silverio F, Gentile V, De Matteis A, et al. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. *Eur Urol*. 2003;43:164-175.
16. Falahatkar S, Mokhtari G, Pourreza F, et al. Celecoxib for treatment of nocturia caused by benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled study. *Urology*. 2008;72:813-816.
17. Penna G, Fibbi B, Amuchastegui S, et al. The vitamin D receptor agonist elocalcitol inhibits IL-8-dependent benign prostatic hyperplasia stromal cell proliferation and inflammatory response by targeting the RhoA/Rho kinase and NF-kappaB pathways. *Prostate*. 2009;69:480-493.
18. Penna G, Amuchastegui S, Cossetti C, et al. Treatment of experimental autoimmune prostatitis in nonobese diabetic mice by the vitamin D receptor agonist elocalcitol. *J Immunol*. 2006;177:8504-8511.

Main Points

- Benign prostatic hyperplasia (BPH) is a growth of both epithelial and stromal cells from both the transition zone and periurethral areas. There are no clear triggering events leading to BPH although several studies have demonstrated the presence of heterogeneous bacterial and viral strains in BPH specimens. Most patients present with a combination of obstructive, irritative, and postmicturition symptoms.
- Both chronic and acute inflammation may lead to events that can cause proliferation within prostatic tissue through a variety of mechanisms, notably oxidative stress. Both tissue damage and oxidative stress may lead to compensatory cellular proliferation with resulting hyperplastic growth.
- Agonists of the vitamin D receptor (VDR) have been found to arrest BPH development. This is a potentially useful treatment of diseases characterized by chronic inflammation and cell proliferation. The prostate is a target organ of VDR agonists and represents an extrarenal synthesis site of 1,25-dihydroxyvitamin D3.
- Stromal-derived interleukin-8 may be considered a key link between chronic inflammation and stromal cell proliferation. In particular, the effect of these pathways may represent a common denominator for all 3 components of BPH: static, dynamic, and inflammatory.