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Inflammation in the Pathophysiology of Benign Prostatic Hypertrophy

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Article info

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Abstract

Context: Benign prostatic hyperplasia (BPH) is classically understood to be a disturbance in prostate homeostasis, but the underlying questions of how and why this disturbance occurs have yet to be answered definitively. An increasing body of evidence points to inflammation as a central component of the pathogenic process of BPH.

Objective: To review recent evidence regarding the association between histologic prostatic inflammation and the development and progression of BPH.

Evidence acquisition: This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed.

Evidence synthesis: Evidence from a canine model of BPH and human prostate tissue has confirmed the presence of inflammation as a component of BPH. Pronounced inflammation was observed in dogs with hormonally induced prostatic hyperplasia. Longitudinal biopsy indicated that the cell-mediated and humoral immune response was preceded by hyperplasia. In surgically treated human BPH specimens, high-level inflammation was significantly associated with prostate enlargement and symptom evolution. Current opinion is that chronic inflammation and endocrine changes lead to disturbed homeostasis and tissue damage or, alternatively, that abnormal stem cell expansion and disturbed homeostasis lead to chronic inflammation and endocrine changes. Either way, a "vicious cycle" is initiated that leads to hyperplasia with fibrosis and changes in prostate tissue composition.

Conclusions: Increased insight into BPH pathogenesis indicates that restoring tissue endocrine metabolism and reducing chronic inflammation are prostate-specific targets for the treatment of BPH.

Patient summary: Increasing insight into benign prostatic hyperplasia (BPH) pathogenesis indicates that restoring tissue endocrine metabolism and reducing chronic inflammation are prostate-specific targets for treatment of BPH.

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1. Introduction

Benign prostatic hyperplasia (BPH) is the most common urologic disease in elderly men, with an estimated prevalence of >70% at age 60 yr and >90% at age 70 yr [1,2]. BPH is a histologic diagnosis characterised by hyperproliferation of stromal and glandular cells in the transition zone and periurethral areas of the prostate gland [2,3]. The condition is often expressed clinically in the form of lower urinary tract symptoms (LUTS) [3,4]. Although several theories have been proposed to explain the progressive hyperplastic processes underlying BPH, the exact pathogenesis is not yet fully understood. Over the past decade in particular, accumulating evidence has suggested that inflammation contributes to the development and progression of prostatic hyperplasia [5]. In this review, some earlier aetiological theories are revisited, and evidence for inflammation as a central component of BPH pathogenesis is examined.

2. Evidence acquisition

This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed. The article is complemented by relevant related literature identified on PubMed and by hand searches of key references.

3. Evidence synthesis

3.1. Classical understanding of benign prostatic hyperplasia aetiology

Over the years, the classical understanding of BPH aetiology has centred around three main theories: the dihydrotestosterone (DHT) hypothesis, the embryonic reawakening theory, and the stem cell theory. Although each theory is not without some merit, none has been able to define the aetiologic trigger events responsible for progressive prostatic enlargement.

In the early 1980s, the prevailing assumption was that BPH resulted from an increased concentration of DHT, the most powerful androgen driving differentiation and growth in the early adult male. Although this hypothesis was ultimately proved incorrect, as DHT concentrations in prostate tissue actually decrease with age, 5α-reductase inhibitors were developed to treat BPH and continue to be prescribed with some success. Lending further support against the DHT hypothesis was the knowledge that DHT drives differentiation, not proliferation, in the prostate gland of an adult male. A defining event in the aging prostate gland is the increased ratio between prostatic oestradiol and DHT [6], which results in imbalance or disbalance in endocrine homeostasis.

During ontogenesis, epithelial buds arising from the urogenital sinus penetrate the surrounding mesenchyme and branch into the ductal system to form the primordium of the transition zone. After birth, prostatic morphogenesis reverts to the embryonic state [7]. According to the embryonic reawakening theory, the embryonic potential to drive prostate morphogenesis is reawoken in adulthood. Although plausible, this theory simply redefines the question, as it fails to identify factors or mechanisms responsible for the reawakening.

The stem cell theory is arguably the most complex of the various hypotheses and is intertwined with embryonic reawakening. The morphogenic potential of the entire prostate epithelium is known to reside within a small fraction of adult stem cells [8]. In BPH, it is proposed that epithelial growth results from alterations in stem cell properties which give rise to a clonal expansion of cell populations that develop into exocrine basal and luminal cells and neuroendocrine epithelial cells [9]. Branching morphogenesis increases glandular structures, leading to prostatic enlargement. As with embryonic reawakening, however, this theory fails to identify the factors or mechanisms that underlie the "derailment" of stem cell expansion.

Although the classical model of BPH can be described in general terms as a disturbance in prostate homeostasis, the real question is why and how this disturbance occurs. The current understanding is that prostatic inflammation is either an initiating or a promoting event, but either way, the presence of inflammation explains many of the uncertainties in BPH models developed to date.

3.2. The role of inflammation in prostate abnormalities

Mahapokai and colleagues investigated the immune response in hormonally induced prostatic hyperplasia in the dog (the best-described model for human BPH identified to date) [10] and followed the process sequentially by biopsy [11]. Marked infiltration with immune effector cells was observed. The majority of inflammatory cells (>80%) in the mononuclear infiltrates were T lymphocytes. B lymphocytes were found mainly in areas with marked follicular formation and diffuse infiltration, and macrophages were found primarily in areas with atrophic and cystic changes with and without inflammation. Longitudinal biopsy indicated that the cell-mediated and humoral immune response was preceded by hyperplasia. In brief, hormonal disbalance as a primary event led to pronounced inflammation, and the processes appeared to work in concert. Regardless of whether inflammation was a cause, a consequence, or a crucial promoting factor in the prostatic enlargement and BPH progression observed in this model, it was a conspicuous component of the process.

Although human samples are typically more representative of a given disease than animal models, in the case of BPH, human specimens provide a single snapshot rather than longitudinal evaluation of the process over time. Notwithstanding this limitation, Robert and colleagues examined a large cohort of surgically treated BPH specimens to evaluate inflammation intensity and to investigate the relationship between inflammation and LUTS [12]. A total of 227 prostatectomy specimens were used to build a tissue microarray of four spots per patient. A control tissue microarray was constructed using normal prostatic tissue samples from 10 donors after death. The inflammation score was determined on the basis of six cytologic parameters

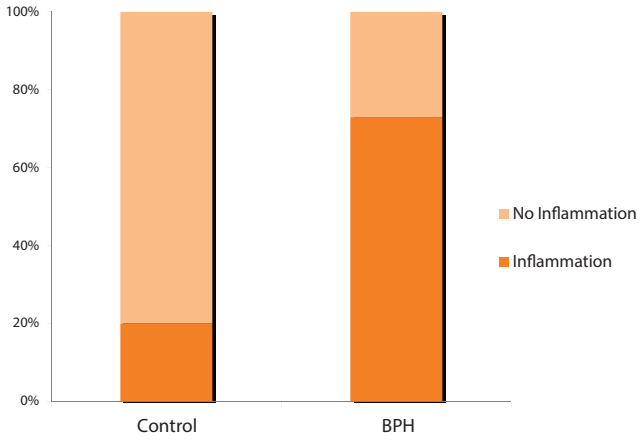

Fig. 1 – Incidence of prostatic inflammation in prostatectomy specimens from controls (donors after death) and patients with symptomatic benign prostatic hyperplasia [12]. BPH = benign prostatic hyperplasia.

(lymphocytes, macrophages, polynuclear leukocyte infiltrates, glandular atrophy, glandular destruction, and tissue fibrosis) and five immunohistochemistry markers: CD3 antibody for T lymphocytes, CD4 antibody for T4, CD8 antibody for T8, CD20 antibody for B lymphocytes, and CD163 antibody for macrophages. The median inflammation level was used to divide patients into two groups (high and low levels).

A significant increase in inflammatory processes was observed, with good correlation between cytology and immunohistochemistry (r = 0.772; p < 0.0001). Significant prostatic inflammation was recorded in 73% of surgically treated BPH specimens versus 20% of specimens from donors after death (Fig. 1). A high level of inflammation was associated significantly with greater prostate volume (104 vs 90 g; p = 0.002) and a higher mean International Prostate Symptom Score (21.2 vs 12.8; p = 0.02). No differences were observed between high- and low-level inflammation groups for age, prostate-specific antigen level, or uroflowmetry. The inflammatory infiltrate consisted of 37.4% macrophages, 37% T lymphocytes (two-thirds T8 and one-third T4), and 12.9% B lymphocytes. Although an inflammation diagnosis was considered feasible on biopsy cores using either cytologic or immunohistochemical techniques, for clinical purposes, the author identified the need for less invasive diagnostic methods such as biomarkers [13].

The presence of inflammation as a component of BPH has been confirmed in both a canine model and human prostate tissue. Clinical questions that arise are whether inflammation is a key factor in BPH progression and/or a potential actionable target for BPH therapy.

Known causes of inflammation include infectious agents, cell trauma due to oxidative stress, hypoxia, autoimmunity, and endocrine changes. Aging-related visceral fat accumulation may initiate or contribute to inflammation through the secretion of inflammatory adipokines [14]. In the case of BPH pathogenesis, the current hypothesis is that, whether cause or consequence, chronic inflammation is likely to be part of a domino effect (Fig. 2). Chronic inflammation and endocrine changes lead to disturbed homeostasis and tissue damage that, in turn, lead to compensatory cellular proliferation.

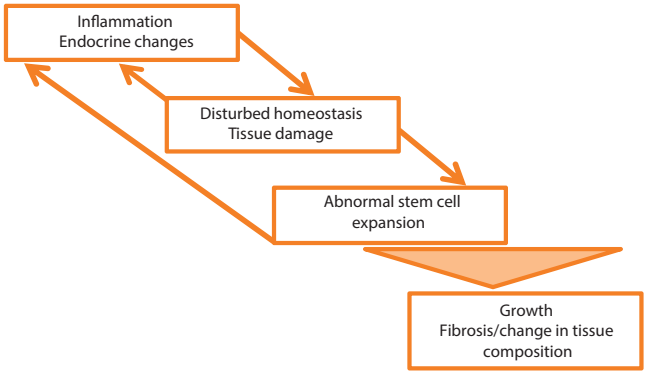

Fig. 2 – Proposed mechanism for the aetiology of benign prostatic hyperplasia. Inflammation is part of a "vicious cycle" of glandular changes that lead to alterations in prostate tissue volume and architecture.

Alternatively, it is possible that abnormal stem cell expansion and disturbed homeostasis lead to chronic inflammation and endocrine changes. Either way, a vicious cycle is initiated that leads to hyperplasia along with fibrosis and changes in tissue composition. Although the hypothesis requires confirmation, it already provides an interesting and testable model about the role of inflammation in the development and progression of BPH.

4. Conclusions

Current understanding of BPH aetiology suggests that gradual endocrine changes and chronic inflammation disturb prostate homeostasis, particularly the interaction between stroma and epithelium; the stroma harbours the infectious components. Glandular changes lead to alterations in tissue architecture and often volume. Consequently, restoring tissue endocrine metabolism and reducing chronic inflammation are prostate-specific targets for the treatment of BPH. As knowledge of the disease processes steadily improves, it is becoming increasingly clear that BPH is much more than an enlarged prostate.

Conflicts of Interest

The author has nothing to disclose.

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