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Role of interleukins, IGF and stem cells in BPH

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Abstract

The condition known as benign prostatic hyperplasia may be defined as a benign enlargement of the prostate gland resulting from a proliferation of both benign epithelial and stromal elements. It might also be defined clinically as a constellation of lower urinary tract symptoms (LUTSs) in aging men. The purpose of this review is to consider the ways in which inflammatory cytokines belonging to the interleukin family, members of the IGF family, and stem cells may contribute to the development and progression of BPH-LUTS. This might occur in three mechanisms: One, interleukin signaling, IGF signaling and stem cells may contribute to reactivation of developmental growth mechanisms in the adult prostate leading to tissue growth. Two, given that epidemiologic studies indicate an increased incidence of BPH-LUTS in association with obesity and diabetes, IGF signaling may provide the mechanistic basis for the effect of diabetes and obesity on prostate growth. Three, expression of interleukins in association with inflammation in the prostate may induce sensitization of afferent fibers innervating the prostate and result in increased sensitivity to pain and noxious sensations in the prostate and bladder and heightened sensitivity to bladder filling.

Keywords

Benign prostate hyperplasia; Interleukins; Insulin-like growth factor; Inflammation; Sensitization

1. Introduction

The condition known as benign prostatic hyperplasia may be defined as a benign enlargement of the prostate gland resulting from a proliferation of both benign epithelial and stromal elements. It might also be defined clinically as a constellation of lower urinary tract symptoms (LUTSs) in aging men. The purpose of this review is to consider the ways in which inflammatory cytokines belonging to the interleukin family, members of the insulin-like growth factor (IGF) family and stem cells may contribute to the development and progression of benign prostatic hyperplasia (BPH) and LUTS. This might occur by three mechanisms. One, interleukin signaling, IGF signaling and stem cells may contribute to reactivation of developmental growth mechanisms in the adult prostate leading to tissue growth. Two, given that epidemiologic studies indicate an increased incidence of BPH-LUTS in association with obesity and diabetes, IGF signaling may provide a mechanistic explanation for the effect of diabetes and obesity on prostate growth. Three, expression of

interleukins in association with inflammation in the prostate may induce sensitization of afferent fibers innervating the prostate and result in increased sensitivity to pain and noxious sensations in the prostate and bladder and heightened sensitivity to bladder filling.

The clinical manifestation of BPH is the presence LUTS such as urgency, frequency, weak stream, nocturia and incomplete emptying. These symptoms have been traditionally ascribed to bladder outlet obstruction as a result of benign enlargement of the prostate. However, the co-incidence of significant prostatic enlargement and LUTS is far from perfect. Many patients have considerable prostatic enlargement without symptoms and many patients have symptoms without prostatic enlargement (Bushman, 2009). Efforts to elucidate the role of inflammatory cytokines, growth factors like IGF and stem cells must accommodate the complex pathophysiology of LUTS in men.

The prostate gland is an encapsulated accessory sex gland that surrounds the bladder neck and proximal urethra. The exocrine gland is comprised of secretory ducts lined by pseudostratified columnar epithelial, basal and neuroendocrine cells surrounded by smooth muscle cells and fibroblasts enmeshed in a fibromuscular stroma. (Veltri and Rodriguez, 2007) The stromal to epithelial ratio is roughly 2:1 in the human prostate (Roy-Burman et al., 2004). Enlargement of the prostate in aging men involves hyperplasia of both ductal epithelium and stroma in the transition zone of the prostate as defined by McNeal (1990). The transition zone accounts for approximately 5% of total prostate volume and is located in the periurethral area of the gland. What drives proliferation within the transitional zone is currently unknown; however, McNeal noted that the proliferation closely resembled developmental differentiation and posited that epithelial hyperplasia may be the result of reactivation of embryonic pathways in the stroma. While many studies related to prostatic growth regulation and hyperplasia are performed in rodent models, it is important to recognize that the rodent prostate differs significantly from the human prostate in at least three important ways: (1) the rodent prostate is not encapsulated; (2) the rodent prostate is comprised of three anatomically distinct lobes – none of which correlates specifically to the transition zone; (3) the stromal to epithelial ratio in the rodent prostate is considerably lower (Roy-Burman et al., 2004).

It was originally believed that the clinical features of BPH were the results of prostatic enlargement and bladder outlet obstruction. However, the symptoms of BPH are only weakly correlated with prostate volume and the severity of obstruction does not correlate with specific symptoms or severity (Bosch et al., 1995; Nitti et al., 1994; Yalla et al., 1995).

More recently lower urinary tract symptoms have been more generally considered to result from derangement of normal bladder filling and emptying. Bladder filling is normally an isobaric process during which the bladder accommodates increasing volume without a rise in pressure through relaxation of the detrusor (smooth muscle of the bladder). Overactivity of either sensory fibers or motor dysfunction of the detrusor may produce premature urge to urinate – resulting in irritative symptoms of frequency and urgency. Emptying of the bladder is a function of both outlet resistance provided by the urethra and force of urine flow generated by the bladder smooth muscle contraction. Both increased outlet resistance and decreased detrusor contractility can impair emptying – resulting in symptoms of diminished stream and incomplete emptying (Bushman, 2009)

Inflammatory cytokines belonging to the interleukin family, members of the IGF family, and stem cells may contribute to the development and progression of BPH-LUTS by three mechanisms:

1. Interleukin signaling and stem cells may contribute to reactivation of developmental growth mechanisms in the adult prostate leading to tissue growth.

2. IGF signaling may provide a mechanistic explanation for the observed association of prostatic enlargement and LUTS with obesity and diabetes.
3. Expression of interleukins in association with inflammation in the prostate may induce sensitization of afferent fibers innervating the prostate and result in increased sensitivity to pain and noxious sensations in the prostate and bladder and heightened sensitivity to bladder filling.

2. Reactivation of embryonic growth pathways

Fetal prostate development involves panoply of signaling interactions between the epithelium and mesenchyme of the urogenital sinus occurring under the auspices of testosterone. McNeal postulated that the combined stromal and ductal hyperplasia in aging men resulted from a re-awakening of these mesenchymal–epithelial inductive interactions (see review by Cunha and Riche in this issue). A wide range of signaling factors expressed in the fetal prostate are expressed in the hyperplastic prostate – lending support to the concept that developmental growth pathways are reactivated in the adult prostate. What has been missing is identification of the inciting event or signaling that reawakens these signaling mechanisms. We will consider two: acute and chronic inflammation of the prostate and decreasing testosterone levels in the aging male.

2.1. Prostatic inflammation is extremely common

Inflammation diagnosed histologically by the presence of inflammatory cells infiltrating the prostatic stroma, epithelium and/or ductal lumen is extremely common in prostates of aging men (Delongchamps et al., 2008; Kohnen and Drach, 1979; Theyer et al., 1992; Steiner et al., 1994; Kramer and Marberger, 2006; Cotran et al., 1999). John McNeal (1968) reported an incidence of prostate inflammation in 44% of autopsy specimens and a similar prevalence of prostatic inflammation has been reported in many different studies. The causes of inflammation in the prostate remain a subject of debate. Potential causes include bacteria, viruses, environmental and dietary components, changes in systemic steroid concentrations (especially androgens and estrogens) auto-immune mechanisms, oxidative stress associated with androgen action, systemic inflammation associated with the metabolic syndrome and urinary reflux of noxious stimuli into the prostatic ducts (reviewed in DeMarzo, 2007). The immunologic features of inflammation associated with BPH, recently reviewed by Kramer et al. (2002), are characterized by an abundance of T-cells and expression of a variety of inflammatory cytokines, including interleukin-1 (Steiner et al., 2003). Prostatic inflammation involves both an inflammatory cell infiltrate and local tissue responses. Acute inflammation elicits the infiltration of neutrophils; chronic inflammation is mediated by T-cells. The leukocytes populating the interstitial spaces of the normal prostate are predominantly CD8+ T-cells, mast cells, macrophages and B lymphocytes (Steiner et al., 2002). The inflammatory infiltrate associated with BPH typically exhibits a nodular pattern with an increased preponderance of CD4+ T-cells and release of inflammatory cytokines including IFN- γ , IL-2, IL-4, IL-5 and IL-13 (Fibbi et al., 2010). Local tissue responses may be mediated in part by toll like receptors (TLRs) found on the prostatic epithelial cells (Penna et al., 2009). Activation of the TLR stimulates the release of local inflammatory mediators such as IL-1, IL-6, IL-8 and CXCL10 (Penna et al., 2009). These mediators recruit additional inflammatory cells as well as stimulating the inflammatory response in local tissue. Stromal cells may act as antigen presenting cells (APCs) to stimulate chronic inflammatory response through the production of IL-12 and IL-23 (Penna et al., 2009).

There is a clear association of BPH with inflammation. In a prospective study of autopsy specimens obtained from 93 men with histological evidence of BPH, chronic inflammation was found (primarily in the transitional zone) in 75% of prostates examined compared to 55% of prostates not affected by BPH (Delongchamps et al., 2008). Prostate biopsy of 8224

men enrolled in the REDUCE Trial revealed inflammation in 78% and chronic inflammation was more common than acute inflammation (78% versus 15%, respectively) (Nickel et al., 2008). Recent clinical trials examining the natural history of BPH/LUTS have revealed an unexpected correlation of prostatic inflammation with increased risk for worsening of LUTS, risk for urinary retention and need for surgery (Roehrborn, 2008).

Studies have revealed a general pattern of increased pro-inflammatory interleukin expression in human BPH. IL-1 is a pro-inflammatory cytokine released locally as part of the inflammatory response as well as being released by infiltrating leukocytes. Studies of human prostate tissue revealed increased IL-1 α in BPH as compared to normal prostate (Mechergui et al., 2009). IL-6 is an acute phase reactant, released by epithelial and stromal cells during acute inflammation. Epidemiologic studies have found an elevated level of circulating IL-6 in men with BPH under age 65 (Schenk et al., 2010), and studies of prostate tissue revealed increased levels of IL-6 in BPH as compared to normal prostate (Mechergui et al., 2009). IL-8 is a pro-inflammatory cytokine secreted by prostate epithelial cells that is involved in leukocyte chemotaxis. Elevated levels of IL-8 have been found in BPH tissue samples and to be the highest in men with BPH and chronic prostatitis (Liu et al., 2009). IL-15 is a pro-inflammatory cytokine involved in the recruitment of T lymphocytes. Expression of IL-15 has been found in both stroma and epithelium of human prostate tissue. Handisurya et al. (2001) found differential expression pattern of the IL-15 receptor in BPH and normal tissue. IL-17 is thought to be involved in local fine tuning of inflammatory signals. Steiner et al. (2002) showed minimal IL-17 mRNA expression in normal prostate but increased IL-17 mRNA and protein expression in 80% of BPH related T-cells and epithelial cells. IL-17 stimulation of BPH stromal cells resulted in release of IL-6 and IL-8. Recently genetic polymorphisms in the genes encoding IL-4 and the IL-1 receptor antagonist (IL-1R1a) were shown to be associated with the risk of BPH (Konwar et al., 2008).

2.2. Links between inflammation and hyperplasia

Inflammation could serve as the trigger for hyperplasia by producing a chronic state of wound repair and tissue regeneration. While prostatic inflammation has been shown to produce hyperplasia in animal models (Elkawaji et al., 2007; Jerde and Bushman, 2009) the mechanisms involved in this response have not been elucidated. It was recently shown that interleukin-1 signaling stimulates growth during development of the prostate and that the hyperplastic response to inflammation in the adult prostate involves a recapitulation of the growth-promoting role (Jerde and Bushman, 2009). IL-1 α and IL-1 β are not the only interleukins expressed in the developing prostate. IL-6, IL-8 and IL-12 are all expressed at robust levels in the developing prostate. Like IL-1 α and IL-1 β , they are down regulated in the adult but re-expressed in the prostate when inflammation is induced by bacterial inoculation. These observations suggest that interleukin signaling has an important growth-promoting role in prostate development and serves to reactivate developmental growth mechanisms as part of regenerative repair in response to injury and inflammation.

2.3. Links between stem cells and hyperplasia

Little has been done to elucidate a role for stem cells in the genesis of prostatic hyperplasia; however, the postulated “reactivation of embryonic inductive interactions” invites us to speculate a possible key role of stem cells. Recent work in our laboratory prompts us to suggest that decreasing androgen levels in the aging male may trigger proliferation of normally quiescent stem cells and instigate reactivation of developmental pathways important for progenitor cell expansion and ductal morphogenesis. Although prostate development is androgen-dependent, postnatal prostate growth is not a simple function of androgen levels. In fact, rapid growth of the mouse prostate during the first two weeks

postnatal occurs in a relatively low androgen environment and growth actually slows as the serum levels of androgen rise. We recently observed that castration of the adult mouse selectively induces proliferation of normally quiescent cells co-expressing stem cell markers CD44, CD117, CD133 and Sca-1 and migration of these cells into more distal locations in the prostatic ducts (Shi et al., 2009). This counterintuitive response of stem/progenitor cells to castration raises the intriguing possibility that age-associated decrease in serum androgen levels could spur activation of progenitor cell proliferation and reactivation of associated growth pathways.

3. Role of IGF signaling in the association of prostatic enlargement and LUTS with obesity and diabetes

3.1. IGF and prostatic growth

The role of IGF signaling in normal and cancerous prostatic growth is well established. The first demonstration of a growth-promoting role for IGF in the prostate was reported in tissue culture studies demonstrating *in vitro* growth of prostate epithelial cells in response to IGF (Cohen et al., 1991). This finding was confirmed in *in vivo* models showing that exogenous IGF promotes prostatic growth in rats (Toning et al., 1997). This was followed up by seminal studies by Ruan et al. (1999) demonstrating that IGF-I is required for prostate development. Two models of IGF over-expression further support potent growth-promoting effects of IGF in the prostate: Kaplan-Lefko et al. (2008) demonstrated that local enforced IGF expression induces hyperplasia in the prostate; and DiGiovanni et al. (2000) reported neoplastic transformation of prostate epithelium *in vivo* upon deregulated IGF synthesis. There are numerous anecdotal studies of IGF signaling anomalies that associate with prostate cancer in humans, including increased serum level of IGF-1 and IGF-2 peptides, local and systemic decreases in modulatory IGF binding protein (IGFBP) levels, and evidence that IGF itself is upregulated in prostate tumors (Monti et al., 2007). There is also *in vivo* evidence that cancer treatments including anti-androgens, Vitamin D analogs and castration are all associated with IGF suppression or upregulation of insulin-like growth factor binding protein expression resulting in suppression of IGF signaling (Huynh et al., 1998; Nickerson and Huynh, 1999; Nickerson et al., 1998). Taken in total, these cell culture, animal and human data demonstrate a significant role for IGF in prostate epithelial growth.

3.2. Evidence of IGF action in BPH/LUTS

Despite the growing literature of IGF and prostate cancer, little has been reported on a possible role for IGF in benign prostatic growth in BPH. Circulating IGF serum concentrations have been analyzed by several groups with conflicting results (Neuhauser et al., 2008; Sciarra et al., 2008; Stattin et al., 2001). In fact, the use of serum IGF concentration has been proposed as a method to distinguish BPH from cancer in men with elevated PSA, since prostate cancer is associated with higher circulating IGF than BPH (Trojan et al., 2006; Khosravi et al., 2001). However, reduced modulatory IGF binding protein levels do seem to be associated with BPH, and in particular, a high IGF1:IGFBP3 ratio is associated with increased BPH risk (Roberts et al., 2003). The reported data analyzing circulating serum IGF concentrations, however, ignore the role of locally induced IGF on growth, and a careful analysis of TURP specimens removed for BPH symptoms is warranted. In the developing prostate locally expressed IGF is indispensable for growth (Ruan et al., 1999), and is induced by local inflammatory mediators (Jerde and Bushman, 2009). Given the high prevalence of inflammation in BPH, a recapitulation of this interleukin-IGF signaling loop seems plausible. A preliminary analysis of BPH specimens has shown a very high IGF receptor activation in a small number of TURP specimens relative to non-diseased controls (Jerde et al., 2010), demonstrating the necessity for a more comprehensive analysis of local IGF signaling in hyperplastic human prostates.

3.3. Insulin-resistance, diabetes, BPH and IGF in men

Insulin-resistance is defined as a subnormal response to insulin despite normal or elevated insulin levels. It is the primary cause of type-2 diabetes in humans. Insulin-resistance/type-2 diabetes is associated with group of disorders such as obesity, dyslipidemia, hyperglycemia, hyperinsulinemia and hypertension-the so called “metabolic syndrome.” While there are dissenting opinions, the preponderance of the evidence supports the view that patients with insulin-resistance/type-2 diabetes are at higher risk of developing BPH and implicates diabetes-associated disorders in the pathogenesis of BPH (Kasturi et al., 2006). Further, epidemiological studies demonstrate insulin-resistance as an independent risk factor for BPH development (Hammarsten et al., 2009; Nandeesha, 2008).

During type-2 diabetes, β -cells secrete greater concentrations of insulin to counteract resistance of the insulin receptor in responsive tissues, thereby attempting to alleviate hyperglycemia. The resulting hyperinsulinemia has demonstrated growth-stimulating effects in numerous tissues (Laron, 2008). Vikram et al. (2010) have demonstrated augmented prostatic epithelial cell proliferation in insulin-resistant rats due to the growth-stimulating effect of insulin. In addition, mouse models of hypoinsulinemia cause significant prostate growth arrest (Ikeda et al., 2000; Vikram et al., 2008). Confirming a role for hyperinsulinemia in prostatic growth effects rather than diabetes in general, models of type 1 diabetes demonstrate no effect on prostatic growth (Yono et al., 2005; Yono et al., 2008).

It should be noted that patients with type-2 diabetes/insulin-resistance actually have lower circulating serum IGF levels than normal age-matched patients (Heald et al., 2006). Further, the presence and action of insulin receptor in the prostate of men with BPH is low or nonexistent (Cox et al., 2009). These disconnects might be explained by the pharmacological nature of the insulin and IGF receptors. The insulin receptor exhibits a high degree of homology with the IGF receptor (Ullrich et al., 1986), and these related ligands are well known to cross-activate their receptors (Frasca et al., 2008; Li et al., 2005). This suggests that insulin may cause prostatic growth during type-2 diabetes by activating the IGF receptor. Further, it is possible that local induction of IGF in co-morbid obese patients secondary to the increased inflammation in those patients may be pathogenic. This again underscores the need for a comprehensive analysis of BPH tissues to define the true mechanistic action of the insulin-IGF signaling pathways.

4. Inflammatory signaling and sensitization of prostatic afferents

Although chronic prostatic inflammation is generally considered to be asymptomatic, it is possible that inflammation contributes to development and progression of LUTS by producing visceral hypersensitivity, neuroinflammation and afferent sensitization (Geppetti et al., 2008; Comprat et al., 2006; Marchand et al., 1998; Nazif et al., 2007; Qin et al., 2005; Rudick et al., 2007; Ustinova et al., 2006, 2007). A number of studies have demonstrated increased density and sensitivity of afferent sensory C- and A δ -fibers in a variety of tissues subsequent to injury or inflammation, including the bladder, colon and lung (Dang et al., 2008; Hayashi et al., 2009; Tan et al., 2008; Traub et al., 2008). Afferent sensitization, a decreased threshold for activation of sensory afferents resulting in heightened sensitivity, is a common neurologic response to tissue inflammation and has been well documented in response to bladder and prostate inflammation (Brumovsky et al., 2009; Hayashi et al., 2009). Because afferent sensitization involves changes at the level of the pelvic ganglia and the sacral spinal cord, prostate inflammation can be expected to increase afferent sensitization of the bladder and may contribute to the development and progression of irritative bladder symptoms (frequency, nocturia, urgency). A variety of inflammatory mediators such as cytokines, chemokines, histamine, prostanoids, reactive oxygen species, growth factors, neuropeptides and neurotrophins may produce these effects.

Neuroinflammation is associated with release of several potent mediators of nociception and pain, including prostanoids, substance P and NGF. Substance P induces the expression of macrophage inhibitory factor, COX-2, and nerve growth factor (NGF), and induces the release of histamine, prostanoids and leukotrienes (Meyer-Siegler and Vera, 2004; Saban et al., 1997). NGF stimulates cell proliferation, further induces mast cell activation and potentiates the pain response (Persson et al., 1997; Nilsson et al., 1997; Tada et al., 1998; Steers et al., 1999).

Interleukins have been found to exert a potent influence on nervous system development, maintenance and activity. IL-1 β is essential for normal development and repair of the nervous system. Studies in a variety of species have demonstrated that IL-1 β stimulates expression of nerve growth factor (NGF) in glial cells, fibroblasts and mesangial cells (Juric and Carman-Krzan, 2000; Lui et al., 1988; Pshenichkin et al., 1994; Spranger et al., 1990). IL-1 β has been observed in the embryonic spinal cord as early as E12, and IL-1 β was subsequently observed in the developing dorsal root ganglia (de la Mano et al., 2007). Treatment of rats with anti-IL-1 β antibody suppressed cellular proliferation in the developing spinal cord and dorsal root ganglia (de la Mano et al., 2007) while IL-1 β treatment of the cultured superior cervical ganglia stimulated neurite outgrowth (Kannan et al., 1996). Recent studies in our laboratory have shown significantly decreased expression of the neurotrophic factor in IL-1R1 (–/–) mice both at baseline and in the inflamed prostate as compared to wild-type controls. Mice deficient in IL-6 signaling have been shown to exhibit delayed regeneration of sensory axons (Zhong et al., 1999). A number of studies have implicated IL-1 and IL-6 as important regulators of nociception (reviewed in Sommers and Kress, 2004). IL-6 deficient mice exhibit decreased peripheral sensitivity and a diminished hyperalgesic response to inflammation. (Xu et al., 1997; Zhong et al., 1999). Exogenous IL-1 has been shown to stimulate release of substance P and both IL-1 and IL-6 have been shown to increase sensitivity of afferent neurons (Ozaktay et al., 2006; Obreja et al., 2002; Oprée and Kress, 2000; Skoff et al., 2009; Vissers et al., 2005). These observations suggest that IL-1 and IL-6 activity associated with prostatic inflammation could increase sensitivity of afferent neurons innervating the prostate, urethra and bladder and contribute to development of LUTS by reducing the threshold for so-called irritative symptoms – frequency, urgency and nocturia.

5. Conclusion

Success in ameliorating the lower urinary tract symptoms associated with benign prostatic hyperplasia hinges on a complete understanding of their pathogenesis. Although these symptoms have historically been attributed to increased outlet resistance due to glandular enlargement with secondary effects on bladder function, accumulating evidence suggests increased outlet resistance is only one factor in the development of LUTS. Increasing attention is being paid to other mechanisms, especially the clear association of BPH with inflammation. As delineated in this review, inflammation-induced interleukin release may contribute to BPH/LUTS by inducing growth factor expression, reactivating canonical developmental growth pathways and producing glandular hyperplasia. These effects may be potentiated by impingement of the metabolic syndrome and diabetes on the mechanistic connection between inflammation and IGF/insulin signaling. In addition to direct growth effects, these signaling mechanisms may also sensitize afferent fibers and increase sensitivity to bladder filling (Fig. 1). These mechanisms provide new potential targets for preventive measures and therapeutic interventions.

Abbreviations

BPH	benign prostatic hyperplasia
LUTS	lower urinary tract symptom
IGF	insulin-like growth factor
APC	antigen presenting cell
IL-1R1a	IL 1-1 receptor antagonist
IGFBP	IGF binding protein
TURP	transurethral resection of prostate
NGF	nerve growth factor

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Fig. 1. Proposed mechanism for the interaction of inflammatory signalling, systemic insulin response, and the sensitization of afferent nerve fibers in BPH/LUTS.