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Developmental, Cellular and Molecular Biology of Benign Prostatic Hyperplasia

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The guest editors of this special issue in *Differentiation* are pleased to present this compendium of reviews, insights and future directions on the Developmental, Cellular and Molecular Biology of Benign Prostatic Hyperplasia (BPH). This issue summarizes the latest knowledge of the basic science in the pathogenesis of BPH. We thank all authors and peer reviewers who have contributed to this special edition.

The normal adult prostate is relatively growth quiescent. However, in disease states, the adult prostate continues to grow. BPH is a term used to describe benign growth of the adult prostate. Generally, BPH is observed histologically as new glandular or stromal growth. The term BPH is also used to describe a disease, which is commonly associated with lower urinary tract symptoms (LUTS). The incidence of BPH increases with each decade of life (beyond 40 years of age). In fact, BPH occurs in up to 90% of men who are ninety years of age or older (Berry et al., 1984). In the Western world, where life expectancy continues to rise, the incidence of BPH will almost certainly approach an incidence of 100% in aged men by the end of the century. The relationship of BPH to clinical symptoms and underlying molecular mechanisms are not completely understood. Elucidation of these associations will increase our understanding of BPH and enhance the ability to better treat or prevent this disease.

A recurring theme in this special edition and in BPH research in general, is the elucidation of historical processes associated with BPH pathogenesis (e.g. proliferation, inflammation, associated symptoms) by molecular mechanisms. In this regard, the use of gene expression arrays may identify potential signaling and genetic pathways associated with various forms of BPH (e.g. asymptomatic, symptomatic, cancer-associated) (Luo et al., 2002; Prakash et al., 2002). The ability to understand molecular events important in BPH development and maintenance will be crucial to better understand this disease. The field as a whole continues to progress from a molecular and cellular biological viewpoint, but more research is needed to discriminate between clinical and pathological types of BPH as well as associated conditions and symptoms.

The reviews embodied in this issue of *Differentiation* emphasize the diversity of BPH research. Cunha and Ricke present a historical role of stroma in the manifestation of BPH. The role of androgens and stroma are necessary in fetal and pubertal development of the prostate. In the adult prostate, the gland is generally growth quiescent unless genetic, physiologic, or environmental cues promote new growth. In fact, only during fetal development, puberty, inflammation and disease does the prostate proliferate and generate new prostatic tissue. John McNeal was the first to present the idea that BPH is a ‘reawakening’ in adulthood of developmental processes associated with prostatic organogenesis. In fact this concept is still a likely etiological process for BPH today.

Timms further explores the relationship between normal prostatic development subsequent to maturity and pathological prostatic enlargement that develops consequent to aging. He emphasizes that detailed prostatic microanatomy and ductal architecture during fetal and early post-natal development provide mechanistic insight into BPH growth in elderly men. Age, hormones and epithelial–mesenchymal interactions are all contributing factors to the pathogenesis of BPH. Control of the prostatic microenvironment in normal and abnormal growth is a multifactorial process. Susceptibility to the disease may include clinical co-morbid diseases, region-specific changes in cell–cell interactions and a variety of signaling pathways, and may include a novel role of the primary cilium as a regulator of signal transduction mechanisms. Recent work in animal models has shown that there are region-specific differences within the prostate that may be significant because of the dynamic and intricate interplay between the epithelium and mesenchyme. Because of the focal nature of BPH, a closer examination of normal morphogenetic patterns, which define the gland’s architecture, may facilitate a detailed understanding of the atypical growth patterns.

The manuscript by Mehta and Vezina is focused on the aryl hydrocarbon receptor (AHR), an orphan receptor, which is an evolutionarily conserved ligand-activated transcription factor that mediates toxic responses to dioxin-like environmental contaminants. The AHR functions during normal prostatic ductal formation during development and has been implicated in prostatic pathology. Inappropriate AHR activation has been associated with a decreased risk of symptomatic BPH in humans and has been shown to impair prostatic development and to disrupt endocrine signaling in rodents. One mechanism by which AHR signaling could provide therapeutic benefit for symptomatic BPH is by suppressing the prostatic immune response. AHR signaling has also been shown to exert anti-androgenic actions through indirect mechanisms and has been associated with decreased circulating estradiol levels. Thus, crosstalk between the activated AHR, estrogen receptor and androgen receptor pathways may promote prostatic pathobiology, including BPH development and progression.

The role(s) of steroid hormones in both normal prostatic development and abnormal prostatic enlargement is explored in the manuscript by Nicholson and Ricke. “Androgen blockade” by 5- α -reductase inhibitors, which inhibit conversion of testosterone into dihydrotestosterone, is a widely used component of standard care for men with LUTS attributed to an enlarged prostate. However, BPH is a multifactorial disease, and not all men respond well to currently available endocrine treatments, suggesting that factors other than androgens are involved. Testosterone, the primary circulating androgen in men, can also be metabolized via CYP19/aromatase into the potent estrogen, estradiol-17 β . In this regard, the prostate is also an estrogen target organ, and estrogens directly and indirectly affect growth and differentiation of prostate. The precise role of endogenous and exogenous estrogens in directly or indirectly regulating prostatic growth and differentiation in the context of BPH is an understudied area. Estrogens and selective estrogen receptor modulators (SERMs) have been shown to promote or inhibit prostatic proliferation and signify potential roles in BPH. Recent research has demonstrated that estrogen receptor signaling may be important in the

development and maintenance of BPH and LUTS; however, new models are needed to genetically dissect estrogen-regulated molecular mechanisms involved in BPH, and to identify estrogens and associated signaling pathways in BPH in order to target BPH with dietary and therapeutic SERMs.

The potential role(s) of chemokines and inflammatory cytokines in the pathogenesis and progression of BPH/LUTS are discussed in the manuscripts by Macoska and by Schauer and Rowley. Macoska emphasizes that chemokines, proteins that belong to a family of structurally related small, soluble, inflammatory mediators and growth factors, are actively secreted by cells within the prostatic microenvironment consequent to disruptions in normal tissue homeostasis due to the aging process or inflammation. The accumulation of senescent stromal fibroblasts, and, possibly, epithelial cells, may serve as sources of chemokine secretion in the aging and enlarged human prostate. Chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS) and histological inflammation may also potentially serve as rich sources of chemokine secretion in the prostate. Once bound to their cognate receptors, chemokines can stimulate powerful pro-proliferation signal transduction pathways and thus function as potent growth factors in the development and progression of Benign Prostatic Hyperplasia and lower urinary tract symptoms (BPH/LUTS). These functions have been amply demonstrated experimentally and particularly point to robust Mitogen Activated Protein Kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling, as well as global transcriptional responses, which mediate chemokine-stimulated cellular proliferative responses. A body of literature also suggests that chemokine-mediated angiogenesis may comprise a contributing factor to BPH/LUTS development and disease progression. Thus, the observed low-level secretion of multiple chemokines within the aging prostatic microenvironment may promote a concomitant low-level, but cumulative, over-proliferation of both epithelial and fibroblastic/myofibroblastic cell types that characterize the aging-associated development of increased prostatic volume and BPH. Though accumulated evidence is far from complete and suffers from some rather extensive gaps in knowledge, it argues favorably for the conclusion that chemokines can, and likely do, promote prostatic enlargement and the associated lower urinary tract symptoms, and justifies further investigations examining chemokines as potential therapeutic targets to delay or ablate BPH/LUTS initiation and progression.

In their manuscript, Schauer and Rowley discuss studies suggesting that BPH may arise from persistent and chronic inflammation, circulating hormonal level deregulation and aberrant wound repair processes. BPH has been etiologically characterized as a progressive, albeit discontinuous, hyperplasia of both the glandular epithelial and stromal cell compartments coordinately yielding an expansion of the prostate gland and clinical symptoms. Interestingly, the inflammatory and repair responses observed in BPH are also key components of general wound repair in post-natal tissues. These responses include altered expression of chemokines, cytokines, matrix remodeling factors, chronic inflammatory processes, altered immune surveillance and recognition as well as the formation of a prototypical 'reactive' stroma, which is similar to that observed across various fibroplasias and malignancies in a variety of tissues. Stromal tissue (both embryonic mesenchyme and adult reactive stromal myofibroblasts) has been shown to exert potent regulatory control over epithelial proliferation and differentiation as well as immunoresponsive modulation. Thus, the functional biology of a reactive stroma, within the context of an adult disease (BPH) typified by epithelial and stromal aberrant hyperplasia, is critical in understanding prostatic disease and beyond. The mechanisms that regulate reactive stromal biology in BPH represent targets of opportunity for new therapeutic approaches that may extend to other tissue contexts. Taken together, the studies described in the manuscripts by Macoska and by Schauer and Rowley describe several mechanisms

through which inflammation and an inflammatory prostatic microenvironment may contribute to the development and progression of BPH/LUTS.

Bushman et al. relates several studies focused on mechanisms through which inflammatory cytokines belonging to the interleukin family, members of the insulin growth factor (IGF) family and stem cells may contribute to the development and progression of BPH/LUTS. This might occur by three mechanisms. First, interleukin signaling, IGF signaling and/or stem cells may contribute to reactivation of developmental growth mechanisms in the adult prostate leading to tissue growth. Second, 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 prostatic growth. Third, 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 contribution of diabetes and insulin signaling to BPH/LUTS development and progression is further explored in the manuscript by Wang and Olumi. Diabetes significantly increases the risk of BPH/LUTS. The major endocrine aberration in connection with the metabolic syndrome is hyperinsulinemia. Insulin is an independent risk factor and a promoter of BPH. Insulin resistance may change the risk of BPH through several biological pathways. Previously work in the Olumi laboratory has shown that the expression of c-Jun in the fibroblastic stroma can promote secretion of IGF-I, which stimulates prostatic epithelial cell proliferation and activates specific target genes. Hyperinsulinemia stimulates the liver to produce more insulin-like growth factor (IGF), another mitogen and an anti-apoptotic agent, which binds insulin receptor/IGF-1 receptor and stimulates prostatic growth. The levels of IGFs and IGF binding proteins (IGFBPs) in prostatic tissue and in blood are associated with BPH risk, with the regulation of circulating androgen and growth hormone.

Diabetes and metabolic syndrome are also prominent in the manuscript by Jiang et al., which discusses the nature and origins of BPH within the context of type II diabetes, inflammation, and dyslipidemia. A number of drugs have been developed to treat insulin resistance including Metformin and the PPAR γ -agonists such as Thiazolidinediones (TZDs). Insulin and the functionally related insulin-like growth factors have sequence homology and can crosstalk through the same receptors. IGFs are associated with a series of IGF binding proteins, which can either present or sequester ligand. The similarities in function between insulin and the insulin-like growth factor/IGFBP axis has led to a series of investigations into IGF activity in obese, diabetic and BPH patients. Alterations in IGFBP levels, specifically reductions in IGFBP2, have been found in both BPH and obese patients. Increased levels of free serum IGF-1 have also been shown in obese patients, presumably due to changes in IGFBP levels. Epidemiologic links between BPH symptoms and elevated IGF-1 and decreased IGFBP3 have been reported in both Chinese and American patient cohorts. Based on these and other studies, Jiang et al. propose that PPAR γ signaling, which sits at the nexus of systemic metabolic disease and BPH/LUTS through its regulation of inflammation and insulin resistance, is a candidate for molecular manipulation in regard to BPH/LUTS. Therefore, the PPAR γ agonists, TZD-mediated regulation of insulin sensitivity, lipotoxicity and inflammation may improve prostatic health either directly in the prostate or indirectly by modulating systemic co-morbidities.

The association between BPH and another common aging-associated syndrome, cardiovascular disease (CVD), is explored in the manuscript by Freeman and Solomon. The prostate synthesizes and stores large amounts of cholesterol, and prostatic tissues may be

particularly sensitive to perturbations in cholesterol metabolism. Hypercholesterolemia, a major risk factor for CVD, is also a risk factor for BPH. Animal model and clinical trial findings suggest that agents that inhibit cholesterol absorption from the intestine, such as the class of compounds known as polyene macrolides, can reduce prostatic gland size and improve LUTS. Observational studies indicate that cholesterol-lowering drugs reduce the risk of aggressive prostate cancer, while prostate cancer cell growth and survival pathways depend in part on cholesterol-sensitive biochemical mechanisms. Taken together, these studies suggest that cholesterol metabolism plays a role in the incidence of benign prostatic disease and may provide novel therapeutic approaches to the prevention and treatment of BPH/LUTS.

Summary

BPH/LUTS is a relatively common disease, and one that will likely become more, rather than less, common as the United States population ages. It has been reported that enlarged prostates and associated LUTS in men over the age of 50 is the fifth most treated disease in the United States (Fenter TC et al., 2006). Paradoxically, BPH is vastly under represented from a research funding and scientific literature point of view. A review of the NIH RePORT Expenditures and Results and PubMed databases suggests that, although BPH/LUTS is much more frequently diagnosed and treated than prostate cancer, far fewer R01 grant awards and manuscripts are linked to BPH/LUTS than to prostate cancer.

There are multiple reasons for this disparity. One is that BPH/LUTS is a complex disease that develops and progresses through multiple mechanisms. As noted by many of the reviews presented in this special issue, this complexity does not lend itself well to developing relevant animal models that allow for genetic and pharmacologic manipulation. BPH is commonly assessed by proliferation, and animal models that demonstrate both new benign prostatic growth and lower urinary tract symptoms are rare. Furthermore, it has been difficult to model interactions between BPH and associated co-morbidities such as diabetes, metabolic syndrome and obesity. However, as demonstrated by several of the reviews presented in this special issue, new models and approaches that are better suited to dissect the molecular mechanisms associated with BPH are being developed that should facilitate our understanding and our ability to effectively treat this complex disease. It is hoped that this issue of *Differentiation* will heighten awareness of the opportunities available to make significant advances in understanding the development and progression of BPH/LUTS at the molecular and cellular level and through the use of novel and relevant animal models.

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