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Invited Review

The functional role of reactive stroma in benign prostatic hyperplasia ☆

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ABSTRACT

The human prostate gland is one of the only internal organs that continue to enlarge throughout adulthood. The specific mechanisms that regulate this growth, as well as the pathological changes leading to the phenotype observed in the disease benign prostatic hyperplasia (BPH), are essentially unknown. Recent studies and their associated findings have made clear that many complex alterations occur, involving 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 the 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 of a variety of tissue sites. Stromal tissue, both embryonic mesenchyme and adult reactive stroma myofibroblasts, has been shown to exert potent and functional 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 typified by epithelial and stromal aberrant hyperplasia, is critical to understand within the context of prostate disease and beyond. The mechanisms that regulate reactive stroma biology in BPH represent targets of opportunity for new therapeutic approaches that may extend to other tissue contexts. Accordingly, this review seeks to address the dissection of important factors, signaling pathways, genes, and other regulatory components that mediate the interplay between epithelium and stromal responses in BPH.

Contents

1. Benign prostatic hyperplasia and the reactive phenotype

The human prostate gland is composed of secretory epithelium arranged in glandular acini within a fibromuscular stroma composed primarily of smooth muscle. The stromal compartment

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also contains fibroblasts, vasculature, nerves and immune components. In an interactive manner, each of these epithelial and stromal components is likely involved in the genesis and evolution of benign prostatic hyperplasia (BPH). Understanding prostate gland development is helpful for interpreting some of the hyperplastic changes observed in BPH, since this disorder has been viewed historically as a type of re-established embryonic inductive process (McNeal, 1990, 1978).

Developmentally, prostate tissue forms via a highly conserved process termed branching morphogenesis, whereby epithelial buds from the urogenital sinus protrude into the adjacent mesenchyme, elongate and bifurcate into an arborized network of branches with terminal tips (Risbridger et al., 2005). These terminal tips eventually give rise to the epithelial duct system in a process similar to that observed within the renal or bronchiolar networks, collectively providing the final size and shape of the adult prostate (Risbridger et al., 2005). In humans the adult prostate gland encapsulates the initial 3 cm of the urethral tube descending from the bladder, linking the urethra and ejaculatory ducts at a diverticulum junction called the verumontanum. This structure is a vestigial remnant of the developmental layer that gives rise to the female uterus (Hunter and Davies, 1997).

This developmental process leads to the morphogenesis of a lobar structure into 4 distinct anatomical zones: peripheral, central, transitional and anterior (Fig. 1). The central zone contains the ejaculatory duct junctions, while the fibromuscular anterior zone lacks any glandular structures. The peripheral zone represents approximately 70% of the total prostatic volume, and is where the majority of prostate adenocarcinoma forms (McNeal, 1981). The transitional zone represents only 5% of prostatic volume; however, it is the exclusive zone where benign prostatic hyperplasia (BPH) occurs (McNeal, 1981) (Figs. 1 and 2). The prostate is enclosed within a thin, vascularized capsule external to a concentric smooth muscle layer that is continuous with the tissue layer surrounding the base of the bladder (Hunter and Davies, 1997) (Fig. 1).

Functionally, the adult prostate is an exocrine accessory reproductive gland that propels a complex proteolytic solution composed of acid phosphatase, citric acid, fibrinolysin, prostate specific antigen, and other enzymes and nutrients into the urethra during ejaculation (Hunter and Davies, 1997). The expelled prostatic secretions liquefy

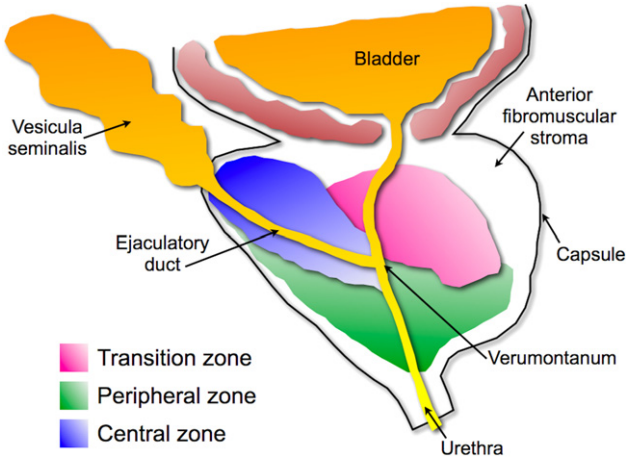

Fig. 1. *Schematic of the zonal anatomy of the human prostate.* As indicated, each zone houses distinct sections of the prostatic urethra. The central zone, where little if any disease develops, houses the ductal tube from the vesicular seminalis. The peripheral zone, the primary site of pre-cancerous and cancerous lesions, houses the descending penile urethra. The transition zone, the only site of benign prostatic hyperplasia, houses the transitional urethra composed of descending bladder and prostatic urethral sections. The verumontanum is the junction between the ejaculatory ducts and the prostatic urethra.

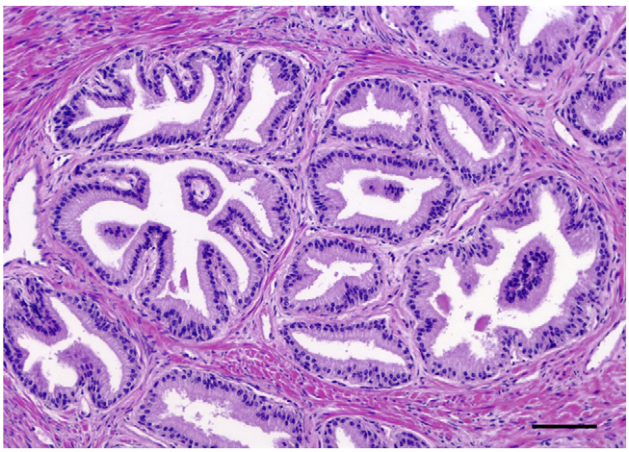

Fig. 2. *Histomorphology of nodular benign prostatic hyperplasia.* BPH is histologically defined as oblong hyperplastic tissue nodules, most often composed of epithelia and stroma. Pure stromal nodules, lacking any epithelial component, are rare but observed. Nodular growth proximal to the transitional zone urethral tube, constricting urine flow (see Fig. 1), accounts for the majority of BPH patient symptoms. H&E, magnification $\times 200$, scale bar $= 50\ \mu m$.

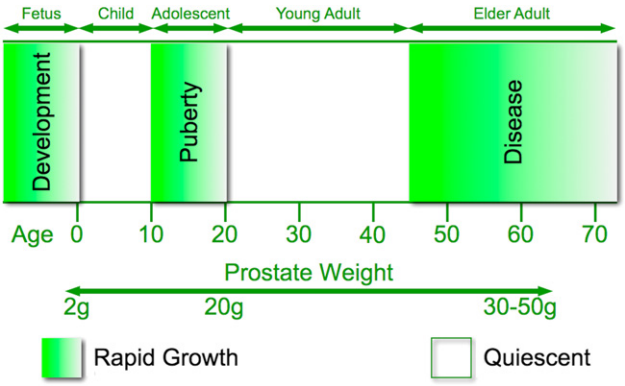

Fig. 3. *The human prostate continues to enlarge throughout life.* The human prostate passes through several phases of rapid growth and relative quiescence, but is the only male organ internal organ that continues to grow through all of adulthood. The various disease states reflect a resumption of rapid growth beyond normal control, including BPH. (Reproduced with kind permission from Springer Science+Business Media: Risbridger et al., 2005, Fig. 1, p. 174, ©Springer-Verlag.)

the ejected seminiferous solution in order to improve spermatozoan motility, as well as alkalinize the vaginal canal to promote increased viability (Hunter and Davies, 1997).

It is of interest that the human prostate gland is one of the only internal organs that continue to enlarge past development, past the androgenic surge at puberty and throughout adulthood (Fig. 3). The specific mechanisms that regulate this enlargement, as well as the pathological changes leading to the BPH phenotype, are essentially unknown. However, it is becoming clearer that many complex alterations occur that involve chronic inflammatory and wound repair processes. BPH is characterized by a progressive, but discontinuous, hyperplasia of both glandular epithelial and stromal cells leading to expansion of the prostate gland and clinical symptoms (McNeal, 1990; Price et al., 1990). BPH occurs as a definitive function of age specifically in the transition zone, while cancer foci occur primarily along the proximal peripheral zone. The biological distinction dictating this zonal specificity in prostate disease is as yet uncharacterized. Gene expression profiling of each zone within the prostate has revealed specific differences between the peripheral (cancer) and transitional zones (BPH) in gene products that modulate cell–cell stromal–epithelial interaction, which strongly suggests that