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EDITORIAL

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Prostate development and pathogenesis

The formation of the prostate and male sex accessory organs is driven by male sex hormones (androgens), and the study of prostatic development includes both developmental biology and endocrinology. The normal function of the prostate is to secrete components of seminal fluid. However, much interest in the prostate stems from the extraordinarily high incidence of benign prostatic hyperplasia (BPH) and prostatic cancer. BPH is one of the most common proliferative diseases in men. The incidence of BPH reaches 88% in men 80 years of age, and many men over 60 years seek surgical or drug therapy for BPH at an enormous economic cost (Walsh, 1984). Prostatic cancer is the most common cancer in men and the third leading cause of cancer-related deaths for North American males (Chiarodo, 1991; Jemal et al., 2006). The paradigm that developmental pathways and mechanisms frequently underlie disease holds true for the prostate, and there has been much comparison between prostatic developmental mechanisms and their expression and function in pathological conditions.

Many eminent anatomists have studied development of the prostate, as well as its anatomy over the centuries, and this is reviewed by Timms (this issue). Before 1950, studies of prostatic development mostly dealt with morphogenesis of the gland and were based solely on analysis of paraffin tissue sections. Studies of androgen deprivation in adulthood established the idea that the prostate is an androgen target organ whose growth, morphology, and function are dependent on the androgens produced by the testes. Alfred Jost and Dorothy Price, utilizing fetal castration and organ culture methods, established the idea that development of the prostate is dependent on the action of fetal testicular androgens (testosterone and its metabolites) (Jost, 1965; Price and Ortiz, 1965). Wilson et al. (1995) emphasized the importance of 5α-dihydrotestosterone, a particularly potent metabolite of testosterone, produced within the prostate by the enzyme 5α-reductase. 5α-dihydrotestosterone stimulates the development and growth of the prostate, but is not essential for prostatic bud formation (Mahendroo et al., 2001). Following the discovery of the androgen receptor (AR) and through the analysis of spontaneous mutations affecting the AR, it became evident that androgens required for prostatic development were acting through AR signaling (Wilson et al., 1995). These studies constitute the basic endocrinology of prostatic development. However, over a period of many years, it also became evident that the prostate is an estrogen-target organ. We now know that exogenous estrogens administrated developmentally elicited adverse effects manifested in adulthood (see McPherson et al., this issue).

Another important chapter in prostatic development began to emerge beginning in the early 1970s, with the concept from the Cunha laboratory that the development of the prostate was dependent on reciprocal interactions between the epithelium and the mesenchyme of the urogenital sinus (Cunha, 1970, 1972). This work extended the field of mesenchymal–epithelial interactions to an organ whose development was androgen dependent, placing this study at the interface between developmental biology and endocrinology. Realization that hormonal effects on the epithelium were mediated by paracrine mediators triggered by hormone action in mesenchymal/stromal cells lead naturally to the hypothesis that molecules such as growth factors might be the paracrine mediators of androgen action. The concept that the mesenchyme drives prostatic epithelial development has proven to be correct, and a variety of paracrine mediators involved in prostatic development have been identified (see Prins and Putz, this issue).

Returning to the pathogenesis of the prostate, the seminal work of Dr. John McNeal is an important milestone in prostatic biology. McNeal was an astute

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pathologist interested in BPH and prostatic cancer. He recognized that the neo-formation of ductal-acinar architecture in aging men during the pathogenesis of BPH resembled the process of prostatic development in the embryo. Accordingly, McNeal proposed the idea that the neo-formation of ductal-acinar architecture in the pathogenesis of BPH was due to the reactivation of embryonic inductivity in adult prostatic stroma. If this idea is true, then the BPH stroma must acquire (or have retained) embryonic-like inductivity, and adult prostatic epithelium must also acquire (or have retained) responsiveness to embryonic induction. For technical reasons, the ability of adult prostatic stroma to induce the neo-formation of branched ductal networks has not been established adequately and remains a challenging problem. Regarding responsiveness of the adult epithelium to embryonic induction, a series of studies from the Cunha lab have established the following: adult epithelial differentiation and function are dependent on continued stromal–epithelial interactions in which stromal cells maintain the epithelium in a growth-quiescent highly differentiated state (Cunha et al., 1985). Bringing fully differentiated growth-quiescent adult prostatic epithelium (or bladder epithelium) into contact with embryonic prostatic mesenchyme can completely reprogram adult epithelial differentiation, presumably due to transdifferentiation of adult epithelial cells or differentiation of adult multipotent stems cells resident in the epithelia of the adult urogenital tract (see review by Taylor and Risbridger, this issue).

Finally, studies from the Cunha lab established the idea that mesenchymal–epithelial interactions are reciprocal in nature. While the mesenchyme induces epithelial differentiation, the developing prostatic epithelium in turn induces mesenchymal differentiation. For organs of the urogenital system such as the prostate, this means that differentiation of the mesenchyme into smooth muscle is dependent on the paracrine action of the normal epithelium on the mesenchyme. From the studies pioneered by Simon Hayward, we have arrived at a unifying concept of normal development, adult homeostasis, and malignant progression.

The model involves the following events: the urogenital sinus mesenchyme induces the urogenital sinus epithelium to undergo prostatic ductal morphogenesis and differentiation. During prostatic epithelial differentiation, the epithelium signals the urogenital sinus mesenchyme to differentiate into smooth muscle cells that surround the epithelial ducts. Thus, differentiation of prostatic smooth muscle requires both androgens and an inductive signal from the epithelium. Once formed, the prostatic smooth muscle participates in reciprocal homeostatic interactions in which it maintains epithelial differentiation under the influence of androgens. In turn, the prostatic epithelium signals the maintenance of smooth muscle differentiation. Such reciprocal homeostatic interactions during adulthood maintain a highly differentiated state and growth quiescence in both cell types. The process of prostatic carcinogenesis, presumably initiated following genetic damage to the prostatic epithelium, is proposed to involve progressive disruption of these reciprocal homeostatic interactions, with the resultant de-differentiation of both the emerging prostatic carcinoma cells and the smooth muscle. As smooth muscle differentiation begins to drift, signaling from the prostatic smooth muscle to the epithelium becomes abnormal resulting in loss of control over epithelial differentiation and proliferation, thus establishing a vicious cycle of progressive de-differentiation of both the prostatic epithelium and the smooth muscle. The result is that the smooth muscle stroma de-differentiates into a fibroblastic stroma that induces epithelial proliferation thus promoting carcinogenic progression. In so doing, the stroma becomes an active player in carcinogenic progression (Hayward et al., 1996; Olumi et al., 1999). Recent studies using transgenic mice suggest that altered transforming growth factor (TGF)-β signaling within the stroma can lead to prostatic intraepithelial neoplasia (PIN), a precursor lesion for prostate cancer. This raises the possibility that altered stromal–epithelial interactions may precede or initiate the altered epithelial growth and histopathology leading to prostate cancer (Bhowmick et al., 2004).

By defining the biology of mesenchymal–epithelial interactions, hormone action, and role of growth factors and other morphogens in prostatic biology and pathogenesis, the conceptual and mechanistic framework has been established for modern studies that are beginning to uncover the molecular mechanisms of prostatic development, which is the subject of this compendium on prostatic development.

It has been established clearly that androgens and the AR are essential for the formation of the prostate, and that androgen signaling in mesenchymal cells leads to organ development by stromal–epithelial interactions and paracrine signaling between these compartments. This raises the question of which pathways and mechanisms mediate prostatic organogenesis and how the androgen axis may interact with, or regulate, these pathways and mechanisms. A similar question is how androgens and other endocrine hormones affect development and progression of prostatic disease. The issue of how steroid hormones control cellular growth, during development and disease, is of considerable importance and has been studied at the molecular level since the early 1980s. Because the AR functions as a transcription factor, it has been expected that exposure to androgens leads to changes in gene expression in mesenchymal cells that stimulate epithelial morphogenesis and cellular growth.

Two experimental approaches have been used to define which genes might mediate the effects of androgens and AR signaling; these are analysis of candidate molecules to see if their expression is androgen regulated and