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## Why Are Androgens Important For Prostate Development?

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Androgen steroid hormones, including testosterone and dihydrotestosterone, are produced by the male gonads and have substantial effects on almost every system of the male body including development of the sex-accessory glands, in particular, the prostate. During male sexual differentiation, androgens are necessary to properly pattern the embryonic prostate buds. Androgens are continuously important for adult prostate function and homeostasis. In the adult prostate, androgens are involved in regulation of inappropriate prostate growth during benign prostate hyperplasia and contribute to progression of prostate cancer. On the other hand, a number of studies indicate that androgen signaling is necessary to promote prostate induction and differentiation but is dispensable for glandular growth and branching. Thus, what is the role of androgens in development of the prostate? What are they important for and what not?

Androgens signal by activating the androgen receptor (AR), a member of the nuclear receptor family. The androgen-AR complex translocates to the nucleus and functions as a positive or negative transcriptional regulator for a multitude of cell cycle and differentiation factors. In male embryos, levels of androgens in the urogenital sinus mesenchyme are considerably higher then in females. Dihydrotestosterone has been found bound to the AR in the male urogenital mesenchyme indicating pathway activation [1-3]. The importance of androgens in prostate development is confirmed by reduction of prostate buds in feminized Tfm males that have a spontaneous AR mutation severely reducing its affinity to testosterone [4-6]. Allgeier et al. [6] showed that androgens regulate prostate bud specification and dorsal-ventral patterning. Exposure of wild type female, or Tfm male, embryos to dihydrotestosterone results in a masculine-like growth of prostate buds. Thus, at the early stage of prostate development androgens function to properly pattern male prostate buds. This androgen function is mediated by upregulation of the homeobox factor Nkx3.1 [6-8] and, possibly, by interaction with Foxa1/2 genes [9]. In addition, Vezina et al. [10] showed that dorso-ventral patterning of the prostate is regulated independent of androgens by the aryl hydrocarbon (dioxin) receptor pathway.

The three stages of prostate development include formation of epithelial prostate ductal buds, elongation and branching of prostate chords, and canalization and differentiation of the ducts into functional secretory units [11,12]. Genes and signaling pathways implicated in branching morphogenesis of the prostate are basically the same as those in the lungs and sex-independent glands, such as the lacrimal gland [13-20]. What makes morphogenesis of the male accessory glands unique is the fact that their induction and certain cell survival are dependent on androgens. Branching morphogenesis is a process of a repetitive induction and suppression of bud formation regulated by paracrine signaling between the gland epithelium and mesenchyme. Both steroid-independent and dependent bud induction and branching is positively regulated by the Fibroblast growth factor 10 (Fgf10) and inhibited by Bone morphogenetic proteins (Bmps) [12,16-20]. In the prostate, androgens are not involved in a direct regulation of either positive (Fgf10) or negative (Bmps) master regulators of branching morphogenesis [12,16,17,20]. This supports the notion that prostate branching is hormone-indifferent. Contrary to that, elongation of prostate buds, is dependent on mesenchymal androgen signaling which functions to upregulate expression of Sonic hedgehog levels in the prostate bud regions [21]. Unlike the lungs where growth factor receptors can drive budding and branching morphogenesis from an isolated lung epithelium in culture [22], initiation of prostate epithelium branching requires contact between the epithelium and mesenchyme [2,3,11]. It is of interest that during prostate induction and elongation, AR signaling specifically targets the mesenchymal prostate compartment [1,23]. Androgen-responsive epithelial-mesenchymal signaling pathways in the prostate include the Wnt, Insulin growth factor and Notch [24,25]. Bmps serve an important inhibitory function in prostate branching, in part, by restricting activity of the Notch receptor to prostate bud domains [12,16]. During development Notch signaling inhibits cell growth suppressor, Pten, and promotes proliferation of p63-positive basal epithelial progenitors [26]. Notch signaling is also necessary for prostate smooth muscle differentiation [26]. Activation of Notch signaling in prostate buds results in expression of transcriptional repressors Hey1, which is a co-factor of the AR and negatively regulates AR targets [27]. Thus, prostate bud formation and elongation likely involve a transient inhibition of AR-dependent epithelial differentiation. There is also an indication that androgens regulate sexually dimorphic expression of Wnt molecules in the prostate [24]. Wnt/βcatenin signaling can support prostate growth even in the absence of androgens [28,29]. However, canonical Wnt signaling is also known to inhibit branching [30]. Thus, the roles of different Wnts in prostate development and homeostasis require further investigation to discriminate between the canonical and non-canonical functions. An intriguing possibility is that androgens may not be necessary for prostate growth and branching once the bud is induced. Indeed, experiments by Donjacour and Cunha [31] in neonatal mice showed that prostatic ductal morphogenesis is sensitive to but does not require continuous androgen stimulation. Studies by Wu et al. concur that AR signaling promotes secretory differentiation but not growth or branching in the prostate [25].

An important androgen function is to promote prostate-specific differentiation of the luminal epithelium and expression of secretory proteins [11,25,32,33]. Androgen deprivation in adult males, due to surgical or chemical sterilization, or treatment with androgen antagonists, results in a dramatic increase in programmed cell death in the distal portions of the prostate and shrinkage of the gland to about 25% of its normal size [29,34-37]. The predominant increase in cell death in the distal luminal secretory epithelium can be considered

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to indicate a link between androgen-directed cell fate choice and lineage survival properties. However, this hypothesis has not gathered sufficient experimental support. Instead, analysis by Buttyan et al. [38] point that androgen deprivation causes a dramatic regression of the prostatic vascular system and that cell death in the prostate tissue is a result of a hypoxic response.

In summary, current understanding of prostate development indicates that although androgens are important for prostate induction and homeostasis, they are unlikely to be directly involved in executing prostate growth and branching programs. This does not preclude a possibility that androgen signaling ensures patterning and survival of particular prostate progenitor cells in the prostate epithelial buds and adjacent mesenchyme which then carry out the branching morphogenesis program by activating developmental mechanisms. Investigations into prostate development hold substantive translational value. A better understanding of prostate development not only promises to improve comprehension of how androgens pattern the male body plan, but may also shed light on the mechanisms of androgen function during inappropriate prostate overgrowth in benign prostatic hyperplasia and prostate cancer.

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