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Review

Androgens and mammalian male reproductive tract development ☆

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ABSTRACT

One of the main functions of androgen is in the sexually dimorphic development of the male reproductive tissues. During embryogenesis, androgen determines the morphogenesis of male specific organs, such as the epididymis, seminal vesicle, prostate and penis. Despite the critical function of androgens in masculinization, the downstream molecular mechanisms of androgen signaling are poorly understood. Tissue recombination experiments and tissue specific androgen receptor (AR) knockout mouse studies have revealed epithelial or mesenchymal specific androgen-AR signaling functions. These findings also indicate that epithelial–mesenchymal interactions are a key feature of AR specific activity, and paracrine growth factor action may mediate some of the effects of androgens. This review focuses on mouse models showing the interactions of androgen and growth factor pathways that promote the sexual differentiation of reproductive organs. Recent studies investigating context dependent AR target genes are also discussed. This article is part of a Special Issue entitled: Nuclear receptors in animal development.

1. Introduction

One of the most important functions of sex steroid receptors is in the sexually dimorphic development of the male and female reproductive tissues. The reproductive tissues arise from 'anlagen' or precursor structures which are identical in both male and female during early development. Subsequent male sexual differentiation of reproductive tract anlage starts after testicular differentiation and androgen production. Embryonic developmental programs control the formation of reproductive anlagen and these are not hormone-regulated, however subsequent growth and sex specific development are controlled by sex hormones. Several signaling cascades control reproductive organogenesis and this is a versatile system to study how hormones regulate organ growth and differentiation. Some molecular pathways have been identified in initial anlagen formation as well as later hormone driven development. These include fibroblast growth factor (FGF), hedgehog (HH), Wnt, transforming growth factor (TGF) signals and other "effector" genes. Androgen dependent signaling and downstream events are involved in not only developmental processes but also disease processes — such as hypospadias and prostate cancer.

2. Androgens regulate male reproductive tract masculinization

A characteristic feature of sexual reproduction is sexually dimorphic adult reproductive organs and these are formed during embryonic development and mature during post-natal puberty. In vertebrates, sex is defined by genetic determination of gonad type followed by the production of gonadal hormones that pattern the rest of the body into a male or a female phenotype and physiology. In mammals and other vertebrates, males are masculinized by androgens produced by the differentiated testes, which regulate reproductive tract patterning and other male characteristics.

In 1953, Alfred Jost castrated rabbit fetuses *in utero* before sexual differentiation of the genital tract and observed that they developed a feminine reproductive tract. Implantation of testosterone propionate crystals into the castrated fetuses led to male reproductive tract stabilization and differentiation [1]. It appeared that the testosterone may not be distributed through the bloodstream during early male reproductive development because male specific differentiation was rescued only in the side where testosterone crystals were placed [2,3]. Recently, circulating androgens have been also shown as important to induce Wolffian duct (WD) stabilization and subsequent formation of the epididymis, as well as the prostatic formation and masculinization of the genital tubercle (GT) and other male traits [4].

Androgen function is dependent on signaling through androgen receptor (AR), a member of the nuclear receptor superfamily [5–7]. Like other members of nuclear receptor superfamily, the AR structure

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is organized into functional domains, consisting of an N-terminal domain (NTD), a DNA binding domain (DBD), a C-terminal ligand binding domain (LBD), and a small hinge region between DBD and LBD. The DBD and LBD are highly conserved, whereas the NTD sequence varies among species which may underly different homeostatic control and signaling between species [8–10]. The NTD mediates the majority of AR transcriptional activity and is the most active co-regulator interaction surface. Spontaneous AR mutants with an androgen insensitivity phenotype have been known as *testicular feminized* (*Tfm*) in animals, and complete or partial androgen insensitivity in man (CAIS, PAIS) [11,12]. Various AR gene mutations have been identified in mouse, rat and man [13–15]. Rodent Tfm males lack a vas deferens, an epididymis and male accessory sex glands and are a valuable experimental model to investigate the mechanism of androgen receptor-mediated sex differentiation.

3. Differential AR signaling between epithelium and mesenchyme

The male reproductive tract develops principally from two embryonic anlagen: the WD and urogenital sinus (UGS) (Fig. 1). The WD, whose epithelium is mesodermal in origin, gives rise to the epididymis, ductus deferens, and seminal vesicle (SV). The UGS, whose epithelium is derived from the endoderm, gives rise to the bladder, prostate, bulbourethral glands, urethra, and periurethral glands. The epididymis functions in storing and preparing sperm for fertilization, including the resorption of fluid to concentrate sperm. The prostate and SV are male accessory sex glands that secrete proteins, zinc and sugars into seminal plasma and which provide a high proportion of the seminal fluid. Because of their secretory or resorptive functions, the epithelia within these organs are highly convoluted to provide a large surface area. The epididymis is a single epithelial tube that is highly coiled within the mesenchymal matrix. The prostate and SV are organs with branched or infolded epithelia surrounded by the mesenchyme. The development and patterning of these organs depend on androgen signaling, particularly, within the mesenchymal compartment.

At the beginning of the ambisexual stage of sex differentiation, AR expression is present in the mesenchyme of urogenital anlagen [16,17] and is absent from the epithelia. Despite the absence of AR in the epithelium, several androgen-dependent processes are observed in the epithelia during male reproductive tract development. For example, WD epithelia survive and avoid from cell death, SV and prostate epithelia bud or branch, and male mammary epithelial anlagen regresses. These observations suggest the paracrine interaction between mesenchyme (AR-positive) and epithelia (AR-negative) controls androgen dependent epithelial development.

The work of Cunha and colleagues using tissue recombination techniques has demonstrated that AR signaling in mesenchymal tissue is important for epithelial growth and morphogenesis (reviewed in [18–20]). For example, embryonic mesenchyme from the SV (AR-positive) induced cell proliferation and SV-like morphological differentiation of AR-negative ureter epithelium [21]. Conversely, Tfm mesenchyme that lacks AR did not induce epithelial morphogenesis, cell proliferation and cytodifferentiation despite the presence of wild type AR in the epithelia [18]. These experiments support the idea that mesenchymal androgen signaling plays a major role in epithelial cell proliferation and morphological differentiation during masculinization. These results led to the hypothesis that there are paracrine signaling

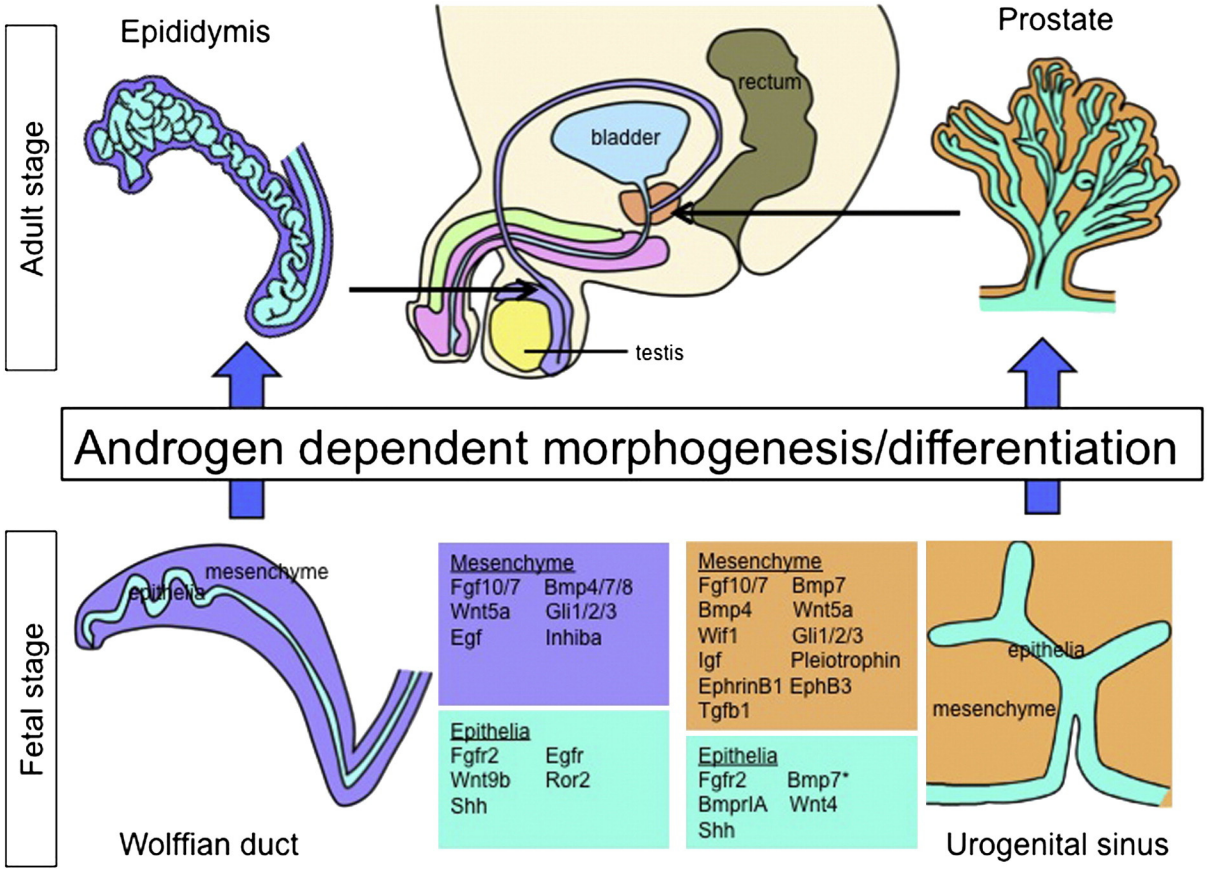

Fig. 1. A schematic diagram of male genital tract masculinization. WD epithelium is stabilized by androgen exposure, and the epididymis elongates and coils three-dimensional manner (left low and upper illustration). Prostate develops from the UGS. During sexual differentiation, solid buds from the urogenital sinus epithelium invade into the urogenital sinus mesenchyme where subsequent branching occurs (right low and upper illustration). Circulating or testis-derived androgens initiate these developmental processes through the mesenchymally expressed AR which regulates paracrine signaling to epithelia. Growth factor related genes which show tissue specific expression patterns are summarized in the scheme. *lobe-specific expression.

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