Endocrinology & Metabolic Syndrome
ISSN: 2161-1017

Grishina, Endocrinol Metab Synd 2012, 1:3
DOI: 10.4172/2161-1017.1000e109

Editorial Open Access

Hormonal and Cell Signaling Pathways in Genital Development

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Editorial

Sexual differentiation of the human body is under the control of sex specific substances produced by the differentiated gonads, testes in men and ovaries in women. This knowledge has been deduced already by the healers of ancient civilizations. The name for the masculinizing substance produced by testes, androgen, is derived from the Greek world for a man, Andros. Biochemically, androgen family of steroid hormones is composed of testosterone and testosterone derivatives metabolized in several tissues. Testosterone molecule was identified and isolated in the early 1930s by the Chicago University chemists Fred Koch and Lemuel McGee. Scientists were awarded Nobel Prize for this important discovery in 1939. Androgens contribute to differentiation of almost every system of the human body [1,2]. They are essential for induction of the masculine type morphogenesis and differentiation of the urogenital region, including the genital appendage and urogenital glands. Androgens also regulate the balance between the muscle and fat tissue mass. In turn, sexual differentiation and reproductive function of the female body is regulated by a group of steroid molecules named estrogens from the Greek world, Estrous, signifying the regular cycle of sexual excitability in females. Estrogens were first described by Charles Stockard and George Papaniclaou who reported a study of hormonal regulation of female physiology in guinea pigs [3]. In 1923, Edgar Allen and Adelbert Doisy isolated a potent estrogen, estradiol, from human ovaries [4].

A large body of physiological and biochemical evidence supports the inductive and directive sex hormone function in sexual differentiation. Androgens are expressed at high levels in the male during sexual development and in adult. Estrogens are expressed at high levels in females during reproductive system development and adult function. Androgens and estrogens can also reprogram sex specific body development when upregulated in or administered to opposite sex. Recent studies point that the scope of androgen and estrogen function is considerably broader then sexual specification and more universal than previously thought. First, androgens and estrogens are produced in both sexes. In addition to high level expression in the testes, androgens are produced by the adrenal glands, and metabolized in the male and female urogenital glands and genital tissues, and in the ovaries. Estrogen is produced at high levels in the ovaries, but it is also metabolized in both sexes in the liver and fat cells, and produced at low level by the male testes. Thus, sexual hormones are not sex exclusive. In fact, presence of androgens, estrogens and their respective receptors in both sexes presents the essential biochemical mechanism driving the binary choice in sexual differentiation. Secondly, both androgens and estrogens were found to carry non sexual functions in multiple organs and tissues. For instance, androgens and estrogens contribute to induction of specific secretory proteins in the mouse ocular glands [5]. Androgens have been suggested to promote differential predisposition to bladder cancer in men [6]. Thirdly, sexual hormones have been found to play important roles in development of the opposite sex organs. I will further review this interesting property. In this review, I will discuss the classic paradigms, and new concepts and molecular mechanisms, of the male and female hormone function on the example of sexual differentiation of the male genital appendage, the phallus.

The anabolic androgen, testosterone, is produced at high levels by the male testes and secreted into the bloodstream. Lower levels of testosterone are produced by the female ovaries and by the adrenal glands in both sexes. About 5% of circulating testosterone is converted to a three-fold more potent dihydrotestosterone by 5α-reductase metabolism in the male urogenital glands and genitalia [1]. In addition, dihydrotestosterone is metabolized from adenosterone in the liver in both males and females, and is absorbed and delivered by the vascular system [2]. Thus, the main factor in male sexual differentiation is that a potent androgen is localized to sites of its function in the male genitalia and exocrine glands. Androgens are necessary to induce the male specific shaping and growth of the phallus, including male specific remodeling and internalization of the urethra. Androgens are also essential for induction, differentiation and survival of the male sex-accessory exosecretory glands: the seminal vesicles and prostate, bulbourethral and preputial glands [7-12]. In males, estrogens are synthesized by Ledwig and germ cells in the testis by metabolism of testosterone via CYP19/aromatase that converts it into estradiol. Estrogens are also produced in the liver, adrenal glands and fat cells. Tissue-specificity of estrogen function is conferred by expression of estrogen receptors α and β. Interestingly, a potent estrogen, estradiol, was found to play several important functions in sexual differentiation of the male, in particular, at maturation of the sperm [13] and development of the prostate [9] and phallus [14]. Furthermore, developing male phallus also contains receptors for another female hormone, progesterone which role is not yet clears [15].

In the last 10 years, genetic and anatomic studies of human genital development have been complemented significantly by laboratory studies in mouse models. Development of genital appendage is considerably easier to study in mouse models that allow precise timing of embryonic stages and accessibility of embryos. Furthermore, recently engineered conditional mouse systems can be used to achieve time and tissue-specific manipulation of a target gene function, and a lineage specific tracing of cell fates and movement. By implementing these systems, several mouse development laboratories have significantly added to our understanding of genes and signals involved in patterning and morphogenesis of the genital region, and the hierarchy of interactions between hormonal and developmental signals [8,16-43]. Genital protrusion is initiated with formation of genital swellings at embryonic day 10 (E10) in the mouse of 19.2-5 days of gestation [22,23]. Notably, sexual differentiation of the genital tubercle is initiated only at E14. Thus the initial genital outgrowth and morphogenesis take place in sexually naive stages. This period, from E10 to E14, coincides with partitioning of the cloacal cavity into a topologically separate urethra and hindgut [23,24]. Distal outgrowth of the genital swelling mesenchyme occurs alongside extension of the ventral cloacal epithelium that at this stage forms a solid urethral plate

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Received July 19, 2012; **Accepted** July 23, 2012; **Published** July 26, 2012

Citation: Grishina IB (2012) Hormonal and Cell Signaling Pathways in Genital Development. Endocrinol Metab Synd 1:e109. doi:10.4172/2161-1017.1000e109

(Figure 1a) [22,23]. At this early stage, cloacal and genital tissues are already pre-patterned by the caudal homeobox genes Hox9 to Hox13 [25], the Sonic hedgehog (Shh) signaling molecule expressed in the endoderm [22,26,27], and Wnt [28,31,33] and Bone morphogenetic proteins (Bmp) in pericloacal mesenchyme [23,29]. The distal urethral epithelium is marked by expression of the Fibroblast growth factor 8 (Fgf8) similar to the apical ectoderm ridge during limb bud outgrowth [16,36]. Loss of the Fgf receptor 2 causes abnormal ventral positioning of the urethral opening in the male called hypospadias [32]. Intriguingly, Fgf8 appears to be dispensable for genital development indicating possible redundant roles genitally expressed factors, Fgf4, 8 and 10 [28,33].

Sexual differentiation of the genital appendage begins at E14 in the mouse and at 9 week of gestation in the human, and is induced by upregulation of testosterone production in the male [32-34]. The role of androgen signaling in genital development, and its downstream cellular and molecular mechanisms are still not completely understood. The current hypotheses postulate androgen roles in maintenance, survival and proliferation of genital progenitor cells and a directive function in sex specific differentiation. One obvious difficulty in these models is that a signal function both in cell fate maintenance and terminal differentiation can be seen as mutually exclusive. Genetic studies in mouse models indicate that androgens promote phallus differentiation by upregulating the levels of caudal homeobox proteins [25], and signaling by the canonical Wnt [17], Ephrin [44] and Fgf [32] pathways. In addition, Shh function is essential for male genital differentiation, and loss of signal results in a failure to internalize the urethra [27,62]. Shh activity has been suggested to promote proliferation of the periurethral mesenchymal cells [27]. Shh can also function to up regulate Wnt ligands (Figure 2) [30,33].

Androgen receptor signaling supports survival and proliferation of responsive tissues. This is consistent with a larger size of the male phallus compared to the female clitoris. However, besides the size, male and female genital structures differ substantially in the position and topology of the urethral duct. During sexual differentiation in the male, urethral plate extends to the distal tip of the genital appendage. In between E15 to birth, the central part of urethral plate becomes canalized forming a urethral duct while most of the ventral plate is displaced by mesenchyme [23,26,34-36] (Figure 1C,D). In contrast, in females, urethral opening is located axially and urethral plate epithelium is displaced to the ventral surface of the appendage. The process of male specific urethra differentiation is an intriguing topological problem. Hypothetically, the process of separation of the axial urethral duct form the perineal seam (Figure 2C, D) could be achieved by directed change in epithelial cell polarity similar to conversion-extension in Drosophila.

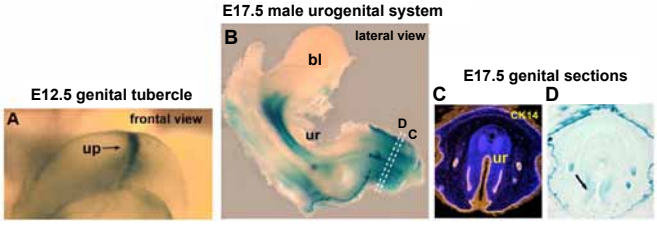

Figure 1: Genital development viewed in Bmp7-lacZ mouse model [29]. (A) Extending urethral plate (up) epithelium is marked by LacZ. (B) Lateral view of male urogenital system at E17.5, and genital sections (C, D). During sexual differentiation at E14.5-18.5 urethral cleft undergoes a progressive fusion starting from proximal (D) to distal (C) regions as the Bmp7-expressing mesenchyme (arrow in D) advances to the genital tip. Bl, bladder; ur, urethra; ck14, cytokeratin 14.

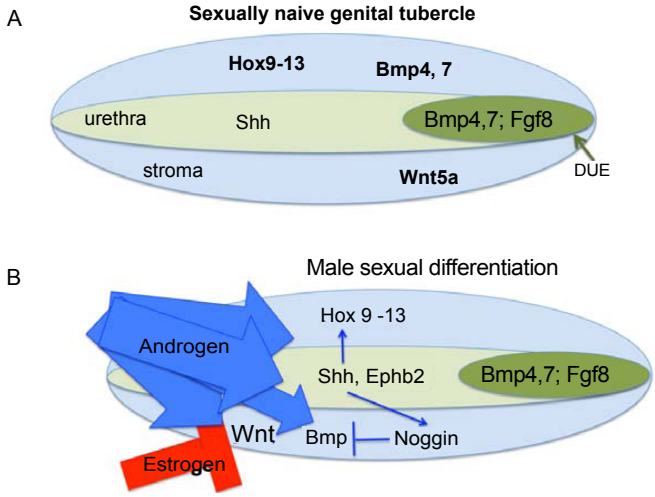

Figure 2: Model of hormonal and patterning signal interactions during sexual differentiation of the male genital appendage. DUE, distal urethral epithelium.

During mouse development such processes are regulated by the Wnt [45], Bmp [24] and Ephrin [44] polarizing signals. Downstream of these signals, c-Jun N-terminal and Rho kinases [24,44,45] regulate cell polarity by stabilizing actin skeleton and microtubule cell scaffold [37-38].

Androgen receptor is expressed both in the genital mesenchyme and epithelium. However, it is signaling in the mesenchyme that is essential for genital urethra internalization and remodeling [17]. Sexual differentiation of the genital urethra is mediated by dihydrotestosterone metabolized locally in the genital mesenchyme [46]. Several components of androgen signaling pathway have been genetically linked to proximo-distal defects in remodeling of the urethra, including the androgen receptor [47] and the 5-α-reductase type 2 that catalyzes dihydrotestosterone metabolism [48,49]. In the developing genital tubercle, several cell communication mechanisms are responsive to androgens, namely, the Fgf [32], Ephrin [44] and Wnt [17] pathways. Both Ephrin and Wnt signals can regulate cell adhesion and polarity. Fgfs are known proliferative factors and chemoattractants, that are essential for genital outgrowth [16]. Loss of the Fgf receptor 2 causes hypospadias in the male. Expression of the Fgf receptor 2 in genital explants can be disrupted by treatment with androgen antagonists [44] indicating dependence on androgen signal. Another important clue on the mechanisms of sexual differentiation came from the discovery that Wnt/β-catenin pathway is regulated differentially in the genital tubercle in male and female [17]. Specifically, female genital mesenchyme produces higher levels of the Wnt pathway inhibitors, Dkk2 and Sfrp1. Dkk2 levels are also increased in males deficient for androgen receptor or treated with an androgen receptor antagonist. Thus, canonical Wnt pathway functions in genital development as an important masculinizing factor downstream of androgen signal.

Very important advances in defining factors involved in urethral remodeling came from human genetics studies. Analysis of nonsense mutations in patients with penoscrotal hypospadias identified a Notch pathway transactivator, the Mastermind-Like Domain containing 1 (MAMLD1) gene [18,19]. MAMLD1 protein is transiently expressed in the developing Leydig cells. Gene knockdown results in a drastic reduction in testosterone production at a crucial point in genital development [19]. Thus, androgen deficiency was suggested as the most likely cause for MAMLD1-associated hypospadias. The situation,

however, can be more complex. MAMDL1 defects can be due, in part, to estradiol deficiency, as Sertoli cell differentiation is also disrupted in the mutant. Importantly, the MAMDL1/Notch pathway can play a role in cell fate and lineage choice in the urethral epithelium, and these functions have not been yet examined.

In addition to defects in androgen signaling, exposure to estrogenic compounds during pregnancy can also induce hypospadias in male fetuses in human and in rodents [39]. Estrogen receptors α and β are expressed in the developing male genital appendage [21] and mutations have been linked to hypospadias [39]. One of the suggested mechanisms of estrogen function in male urethral development involves regulation of the Activating Transcription Factor 3 (ATF3). Mutations in ATF3 have been linked to hypospadias [40-43]. ATF3 mediates the Transforming Growth Factor- β/Mitogen Activated Protein Kinase signaling that can feed into several pathways regulating cell survival, proliferation and polarity. Future ATF3 studies studies in the animal and explant models should unveil the cellular functions of ATF3 in urethral remodeling. Estrogens can also interfere with masculine differentiation by modulating the hypothalamic–pituitary–gonadal axis, by interfering with androgen receptor expression, or by suppressing testes differentiation [50,51].

In summary, recent studies show that male sexual differentiation is regulated by a balance of androgen and estrogen signals that modulate downstream epithelial-mesenchymal communications. Deregulation of the fetal endocrine environment is the major suspect for the unusually rapid raise in incidence of hypospadias in the United States since 1970s [52,53]. The most likely sources of endocrine disruptors are household chemicals, pesticides and herbicides commonly found in urban and suburban households [54]. Several of these endocrine disruptors have been shown experimentally to cause hypospadias and cryptorhidism in wild animals and rodent models [55-57]. Direct evidence to link endocrine disruptors to human genital malformations is still limited. That is due to experimental limitations of epidemiologic studies to access exposure effects at precise fetal developmental stages. Hormonal effects and their interactions with developmental factors are stage and cell lineage sensitive. For this reason, testing in animal models is certain to play a major part in defining the roles and effects of endocrine disruptors in embryonic development [59-61]. Further cellular biological studies in mouse models and genetic studies in human are most promising to bring a better understanding of male sexual differentiation and the etiology of genital malformations.

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