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Review

The regulation of spermatogenesis by androgens

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ABSTRACT

Testosterone is essential for maintaining spermatogenesis and male fertility. However, the molecular mechanisms by which testosterone acts have not begun to be revealed until recently. With the advances obtained from the use of transgenic mice lacking or overexpressing the androgen receptor, the cell specific targets of testosterone action as well as the genes and signaling pathways that are regulated by testosterone are being identified. In this review, the critical steps of spermatogenesis that are regulated by testosterone are discussed as well as the intracellular signaling pathways by which testosterone acts. We also review the functional information that has been obtained from the knock out of the androgen receptor from specific cell types in the testis and the genes found to be regulated after altering testosterone levels or androgen receptor expression.

Contents

Abbreviations: PTM, peritubular myoid cell; SSC, spermatogonia stem cell; DHT, dihydrotestosterone; BTB, blood testis barrier; AR, androgen receptor; SHBG, sex hormone binding globulin; ABP, androgen binding protein; FAK, focal adhesion kinase; ES, ectoplasmic specialization; ARE, androgen response element; EGFR, epidermal growth factor receptor; GDNF, glial derived neurotrophic factor; jsd, juvenile spermatogonial depletion mutant; TP, testosterone propionate; tfm, testicular feminization; GnRH, gonadotropin releasing hormone.

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1. Introduction

1.1. Spermatogenesis

Male fertility is dependent upon the successful perpetuation of spermatogenesis, the multi-step process of male germ cell expansion and development that occurs within the seminiferous tubules of the testes. Although other hormones facilitate the process of spermatogenesis, only the steroid hormone testosterone is essential to maintain spermatogenesis. Testosterone actions in the testis in relation to the regulation of spermatogenesis have been discussed in recent reviews [1–6]. Here, we summarize the spermatogenesis processes regulated by testosterone, cell specific actions of testosterone as well as the intracellular pathways and genes that are controlled by testosterone signaling in the testis.

Spermatogenesis occurs in the seminiferous tubules of the testis. The seminiferous tubules are composed of three major cell types: peritubular myoid (PTM) cells, Sertoli cells and germ cells. PTM cells surround the external wall of the tubule and contract to force sperm down the tubule. Sertoli cells relay external signals and provide factors required for the proliferation and differentiation of germ cells. PTM cells cooperate with Sertoli cells to produce the basement membrane of the seminiferous tubule and provide the niche for spermatogonial stem cells (SSCs) that produce the germ cells that will develop into sperm [7,8]. The cytoplasm of Sertoli cells extends from the basement membrane to the lumen of the tubule surrounding the developing germ cells. Leydig cells are present in the interstitial space between the tubules and produce testosterone, which diffuses into the seminiferous tubules, as well as blood vessels in the interstitial space (Fig. 1).

The division of SSCs along the basement membrane of the seminiferous tubule initiates the spermatogenesis process. The proliferation of SSCs results in either the production of two new stem cells to retain the stem cell pool or undifferentiated spermatogonia that are destined to develop into sperm. The undifferentiated spermatogonia undergo a series of mitotic divisions with incomplete cytokinesis to form chains of spermatogonia. Once the chains reach a length of 16 or 32 cells, they undergo differentiation en mass to become differentiated spermatogonia that are committed to becoming sperm. The differentiated spermatogonia undergo a series of divisions with a final mitosis resulting in the production of preleptotene spermatocytes that initiate the process of meiosis. At the conclusion of meiosis, haploid round spermatids are produced that undergo differentiation into elongated spermatids and then finally spermatozoa (Fig. 1).

Spermatogenesis is supported by somatic Sertoli cells that surround and nurture the developing germ cells. Sertoli cells contribute to the niche required to maintain the renewal of spermatogonial stem cells so that developing germ cells can be produced continuously. Sertoli cells also provide growth factors and nutrients for the developing germ cells. Specialized adhesion junctions are formed between adjacent Sertoli cells that in total form the blood testis barrier (BTB) near the basement membrane of the seminiferous tubules. The BTB divides the seminiferous tubule into basal and adluminal compartments. During the initial preleptotene stage of meiosis, spermatocytes "pass through" the BTB moving from the basement membrane to adluminal compartment. Once through the BTB, the germ cells continue to develop into spermatozoa in a defined, protected microenvironment. However, because the BTB denies germ cells in the adluminal compartment access to factors supplied by the circulatory system, the Sertoli cell must provide for the needs of the more mature germ cells [9,10].

1.2. Testosterone production and bioavailability

Testosterone is the major androgen in the testis that regulates spermatogenesis. Testosterone is produced by the Leydig cell in response to stimulation with luteinizing hormone (LH) and acts as a paracrine factor that diffuses into the seminiferous tubules. Androgen effects are mediated by the androgen receptor (AR, also denoted NR3C4), which is a 110 kD protein localized to the nucleus and cytoplasm. There are no functional receptors for androgen in germ cells [11–14]. Instead the testosterone that diffuses into Sertoli cells binds to the AR present in the cytoplasm and nucleus to initiate the functional responses required to support spermatogenesis. In the testis, testosterone also interacts with AR expressed in Leydig, PTM cells, arteriole smooth muscle and vascular endothelial cells.

Because of the localized production of testosterone from Leydig cells, testosterone levels in the testes of men and rodents are 25–125-fold higher than that present in serum [15–19]. The physiological importance of high testosterone levels in the testis is not fully understood. However, it has been established that sperm production decreases exponentially once testosterone levels in the testis fall below 70 mM [20]. The high levels of testosterone in the testis cannot be explained by a sequestration mechanism to "deactivate" the hormone because at least two thirds of testicular testosterone is free or weakly bound to albumen and is bioavailable. Only one third of testosterone is tightly bound by sex hormone binding globulin (SHBG) or androgen binding protein (ABP) [21,22]. Thus, the bioavailable testosterone in the testis greatly exceeds the kD for AR binding of approximately 1 mM [23].

2. AR expression

2.1. Developmental patterns of AR expression

In humans and rodents, AR is expressed in PTM cells at high levels from the fetal period throughout adulthood [24–27]. Adult Leydig cells also express AR at a constant level [28]. Sertoli cells do not express AR in fetal life [29]. In humans, AR is first detectable in the nuclei of a few Sertoli cells at the age of 5 months. Labeling is weak until 4 years of age and increases thereafter [24–27]. In monkeys, androgen binding activity of Sertoli cells cultured from infants is at least fourfold lower than that for cells cultured at puberty [30]. The lack of AR in the infant human and monkey likely explains the lack of Sertoli sensitivity to the testosterone that is present during the first few months after birth. In mice and rats, AR in the Sertoli cell is first expressed 3–5 days after birth after which AR levels increase up to 35 or 60 days of age [29,31–33]. Because testosterone

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