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Editorial

Role of Testosterone in Maintaining Polarity and Differentiated State of Sertoli Cells

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HIGHLIGHTS

- Testosterone causes the differentiation of immature Sertoli cells into mature cells.
- Testosterone is essential for maintaining the differentiated morphology of Sertoli cells and their function.
- In the absence of testosterone, Sertoli cells probably undergo the epithelial-mesenchymal transition (EMT) process and eventually, convert to immature cells.

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ABSTRACT

Differentiation and migration of spermatogonial stem cells (SSCs) from the basal to the adluminal compartment of the seminiferous tubules require a well-specialised scaffold created by a well-developed cytoskeleton in the large cytoplasm of the Sertoli cells. The connection between these scaffolds in two adjacent Sertoli cells and germ cells is provided by adherent junctions. The formation of such a regularly- fabricated scaffold and complex network of intercellular communication is disrupted in the absence of testosterone. In an androgen-free microenvironment, Sertoli cells probably undergo the epithelial-mesenchymal transition(EMT) process. The EMT in the Sertoli cells can be explained by the same mechanisms by which convert prostate cancer epithelial cells) positive for androgen receptor), treated with an androgen deprivation therapy (ADT), to mesenchymal cells. The potential of the plasticity and reprogramming of Sertoli cells could open a new window for basic and clinical studies, especially in assisted reproductive studies such as the approaches of the in vitro spermatogenesis or testicular tissue xenograft.

Keywords: Testosterone; Sertoli Cells; Sertoli Cell Maturation; Epithelial-Mesenchymal Transition; Androgen Deprivation

Editorial: The seminiferous tubules are the main site of sperm production in adult men. Indeed, in prepubertal boys, Sertoli and spermatogonial stem cells (SSCs) attach to a basement membrane in a spatial arrangement that forms a tubular structure. In addition, the outer space of the tubules is covered with peritubular myoid cells (PMC) by attaching to the basement membrane matrix, and the Leydig cells are located in the interstitial space of the tubules, which are the main source of testosterone production in the body (Figure 1) (1, 2). During puberty, the process of spermatogenesis begins with the production of the pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), whose receptors are located on Leydig and Sertoli cells, respectively(3). During this process, immature Sertoli cells differentiate into adult cells, which are characterized by long cytoplasmic appendages and the presence of tight junctions, as well as a specialized pattern of cytoskeletal arrangement in the area below the cytoplasmic membrane exposed to differentiating germ cells (Figure 1) (4). On

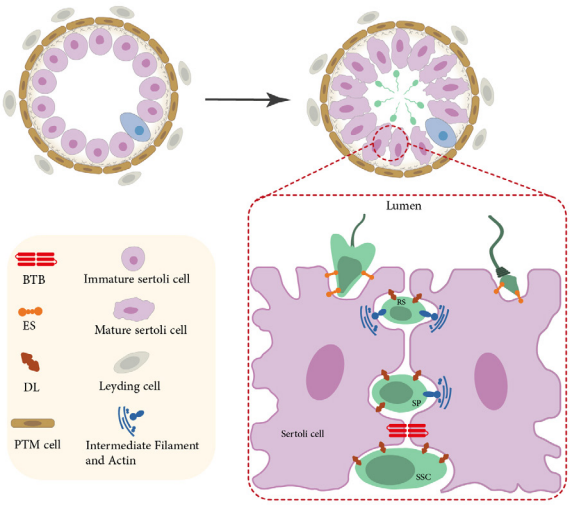

Figure 1. The morphology and biochemical differences in The immature and mature Sertoli cells. Immature Sertoli cells have an interstitial mesenchymal-epithelial morphology and are able to divide. At puberty, immature Sertoli cells undergo a reorganization in their cytoskeleton system to become elongated t cells and also form connections between themselves (tight junctions, forming BTB) and germ cells (desmosome- like junctions and specific structures named ectoplasmic specializations at the apical level). Furthermore, these specific junctions through connector proteins bind to the cytoskeletal system of SCs such as intermediate filaments and actin. In general, all these changes cause that Sertoli cells lose their proliferative capacity and switch to a differentiated and fixed status.

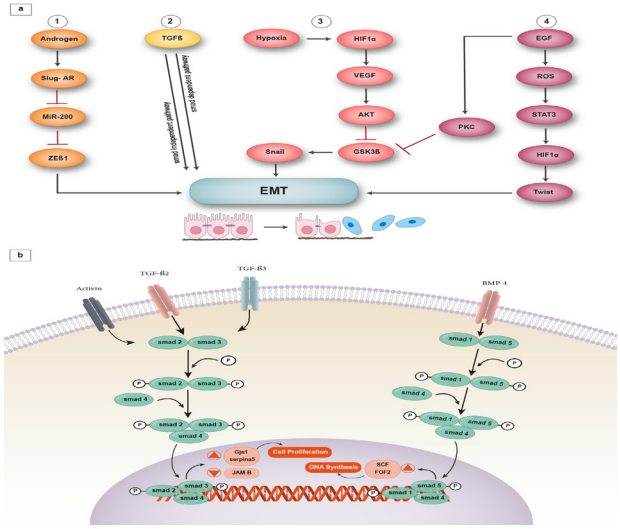

Figure 2. a) Schematic representation of signalling pathways governing EMT in prostate cancer. Transcription factors of the EMT (ZEB1, Snail, Twist) are regulated by androgen (1) TGF-β ligands (2), hypoxia (3) and mitogen factors such as EGF (4). ZEB1, a transcription factor, can induce EMT in androgen deprivation condition by creating a bidirectional negative feedback loop with androgen receptor. The activity of glycogen synthase kinase 3β (GSK3β) is inhibited by protein kinase C (PKC) and AKT pathway, resulting to a reduction in Snail ubiquitination and increase of its transcription. Schematic representation of the TGF-β/Smad signalling pathway and regulation of Sertoli cell proliferation(b). Members of TGF-β family (TGF-β2 and TGF-β3, Activin and BMP-4) with phosphorylating members of smad family can alter the expression of the target genes (, involving in DNA synthesis and SC proliferation. In addition, inhibition of the JAM-B expression by the activated TGF-β/Smad signalling pathway leads to disruption of BTB. TGIF (TG interacting factor motif), FGF-2 (fibroblast growth factor-2), SCF (stem cell factor) and Gjα1 (gap junction alpha-1).

the other hand, during puberty, SSCs undergo a process of differentiation and migration from the basement membrane to the lumen to generate mature spermatozoa (5, 6). The part of the cytoskeleton system of Sertoli cells that is in contact with the differentiating germ cells, forms a special arrangement that creates specific microenvironments (such as ectoplasmic specialization (ES) for germ cells, involved in the process of sperm cell release from the protective Sertoli cells (spermiation) (7, 8). In addition to the presence of such specific spaces in the cytoplasmic membrane of Sertoli cells, tight junctions formed between Sertoli cells separate SSCs and early spermatocytes cells from differentiating germ cells called the blood-testicular barrier (BTB) (6, 9). From the above, it can be inferred that such a developed and mature structure of Sertoli cells is critical to their function. Testosterone secreted by Leydig cells plays an important role in the development of spermatogenesis. The effect of testosterone is mediated through its receptor on Sertoli cells, Leydig, and PMCs, and interestingly, germ cells lack receptors for testosterone (3). Studies done to understand the role of testosterone in mice lacking the androgen receptor gene in Sertoli cells or in mice that have been castrated or treated by pharmacological agents inhibiting testosterone production or action showed that in the absence of testosterone or its receptor, the efficiency of the spermatogenesis process was dramatically reduced and the epithelium of seminiferous tubules showed abnormalities in BTB formation, spermiation and germ cell survival which eventually leads to infertility or abnormal sperm parameters reviewed in (10). These studies showed that in the absence of a testosterone receptor, Sertoli cells lack a large, well-developed cytoplasm, and the adherent junctions between Sertoli cells and Sertoli – germ cells were disrupted, which ultimately leads to meiotic block (11). In addition, the production of seminiferous fluid by Sertoli cells, which is necessary for the transport and feeding of the sperms, was drastically reduced (12). Studies show that there is a dual relationship between BTB formation and fluid production of seminiferous tubules with the progression of meiosis (13, 14). Therefore, these findings indicate that testosterone is essential for maintaining the differentiated morphology of Sertoli cells and their function. It has therefore been accepted that androgens directly induce maturation in Sertoli cells and modify their proliferation (reviewed in (15). In reviewing studies on understanding the mechanism of prostate cancer cell resistance to the standard treatment protocol, androgen deprivation reviewed in (16) and (17), we proposed that such a mechanism might better demonstrate the role

of testosterone in spermatogenesis. In prostate tissue, epithelial cells positive for androgen receptors attach to the basement membrane like the seminiferous tubules, forming a structure of tubular-alveolar gland (18). The proliferation and physiological activity of prostate epithelial cells depend on the androgen signalling pathway (19). To treat androgen-sensitive prostate cancer, an androgen deprivation-based treatment has been established that suppresses testosterone production. Some patients become resistant to this treatment protocol after 18 to 24 months of treatment, which is associated with a poor prognosis (20). In an attempt to find the mechanism of resistance to androgen deprivation therapy, studies have shown that prostate epithelial cells undergoing a process called epithelial-mesenchymal transition (EMT) lose their polarity and attachments to become mesenchymal cells that can migrate and attain stem cell-like properties and lack their androgen receptors. Interestingly, if these cells are re-exposed to testosterone, they can return to prostate epithelial cells and re-express androgen receptor (17). During the EMT process, prostate epithelial cells with reducing their adhesive proteins, such as E-cadherin lose their cellular connections to each other and the basement membrane, eventually leading to loss of basal-epical polarity of prostate epithelial cells. It should also be noted that androgen deprivation can cause EMT, even in normal prostate tissue. The EMT process in prostate epithelial cells is mediated by activating the family signaling pathways leading to expression of key transcription factors that proceed the EMT (Zeb1,Snail,Slug and Twist) (Figure 2a). Due to the fact that Sertoli cells are mesoepithelial cells and histologically have a structure similar to prostate tissue epithelial cells in terms of having androgen receptors and the formation of a tubular spatial structure, we could suggest that a EMT mechanism may explain changes in Sertoli cell structure following androgens deprivation and the role of testosterone can be attributed to maintaining the polarity and differentiated status of Sertoli cells. On the other hand, TGF-β family signaling pathways have been shown to control the proliferative and differentiated states of Sertoli cells, and also to support the migration of germ cells from the BTB by reducing the expression of junctional adhesion molecule (JAM) family reviewed in (21) (Figure 2b). Thus, testosterone can probably help maintain the polarity and differentiated state of Sertoli cells by regulating the TGF-β Family Signaling pathway.

Conclusions

Testosterone triggers the differentiation of immature Sertoli cells into mature cells and plays an essential role in maintaining their differentiated state. The absence of testosterone can cause the loss of polarity and their differentiated state, which probably occurs through the process of epithelial-mesenchymal transition.

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All authors contributed equally.

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Abbreviations

ADT	Androgen deprivation therapy
BTB	Blood-testicular barrier
EMT	Epithelial-mesenchymal transition
JAM	Junctional adhesion molecule
FBS	Fetal bovine serum
ES	Ectoplasmic specialization
PMC	Peritubular myoid cells

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