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# The Developmental Process of Spermatogenesis

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## Abstract

The multiplication and development of germ cells in the seminiferous tubules of the testiclesoccur through a complex series of cellular events that are controlled by multiple signals. It is composed of 6 stages in humans (Figure 1).

Spermatogonial stem cells are self-renewed via mitosis, meiosis and contribute to the formation of haploid spermatids from diploid spermatocytes. Through the process of spermiogenesis, spermatids undergo maturation and are transformed into functional spermatozoa which are released at spermiation after the breakage of intercellular bridges attaching the spermatids to Sertoli cells. Spermatogenesis is a continuous process requiring the contribution of numerous cell and regulatory factors. Its understanding is essential in order to advance research for treatment of male infertility. The different stages of spermatogenesis along with the main roles of Sertoli cell and BTB will be reviewed. Some emerging fields in research regarding the new classification was briefly examined for a better understanding of the complexity of the process.

## Introduction

Spermatogenesis is a process occurring in the Seminiferous Tubules (ST) of the testicles. The multiplication and development of germ cells occur through a complex series of cellular events that are controlled by multiple signals. While fourteen stages are found in rats, the seminiferous epithelial cycle is composed of 6 stages in humans [1]. Spermatogonial stem cells are self-renewed via mitosis, meiosis (I and II) and contribute to the formation of haploid spermatids from diploid spermatocytes. Through the process of spermiogenesis, spermatids undergo maturation and are transformed into functional spermatozoa which are released at spermiation after the breakage of intercellular bridges attaching the spermatids to Sertoli cells [2,3]. Intra-testicular and extra-testicular regulatory hormones involving the release of Follicle Stimulating Hormone (FSH) from pituitary and testosterone from leydig cells are the prime components of a well-organized spermatogenesis [4]. Sertoli cells control the milieu within the seminiferous tubules in order to facilitate the progression of germ cells to spermatozoa. Hense, spermatogenesis is regulated through the control of FSH on Sertoli cells and LH on Leydig cells.

### The seminiferous epithelium and hormonal regulation

The testis is composed of 400 to 600 ST, which is the functional unit of the test is where 300 million sperms per day are produced after puberty [5]. Sertoli cells have a significant role in supporting the growth of the gonadal cells and thus are known as the 'nurse' cells [6]. Leydig cells in return, under the influence of LH, supports the production of testosterone necessarily for the step by step process of spermatogenesis [7].

The Blood-Testis Barrier (BTB) is situated within the basement membrane of the ST, providing the microenvironment for the emergence of spermatids [8]. This barrier is well established at puberty, concomitantly with the onset of meiosis [9]. The basal and the ad-luminal compartments are the compartments found in the Seminiferous Epithelium (SE) which are separated by the BTB. The basal compartment includes undifferentiated spermatogonia (A and B) and preleptotene spermatocytes. The ad-luminal compartment is inhabited by the primary, secondary spermatocytes, haploid spermatids and spermatozoa. During the 6 stages of spermatogenesis, the junctions between Sertoli cells and reproductive cells are in a constant remodeling process to allow transportation through the SE. It is in the ad-luminal compartment that meiosis I and II, the formation up to the spermatozoa stage and spermiation take place [10].

### The different stages of the epithelial cycle

In humans, spermatogonia enter spermatogenesis every 16 days, divide in a continuous way through mitosis to produce different variety of cells. This is entitled "cycle of the seminiferous epithelium" [11]. The detail inspection of cross sections of tubules over the years uncovered 6 main stages of spermatogenesis or cellular associations[12].

## Cycle of the Seminiferous Epithelium

The epithelial cycle is composed of 6 different stages along the SE of the testis [13]. A stage refers to a specific segment of the SE over time [14]. The duration of spermatogenesis is around 64 days in which a type A spermatogonia is transformed into multiple haploid spermatozoa [15]. In this context, an epithelial cycle takes 16 days to be completed, yet it takes four cycles for a spermatogonia to become a spermatid along the section of a tubule (74 days).

### Spermatogonial proliferation and spermatocytes formation

Two types of spermatogonia (A and B) are present in the basal

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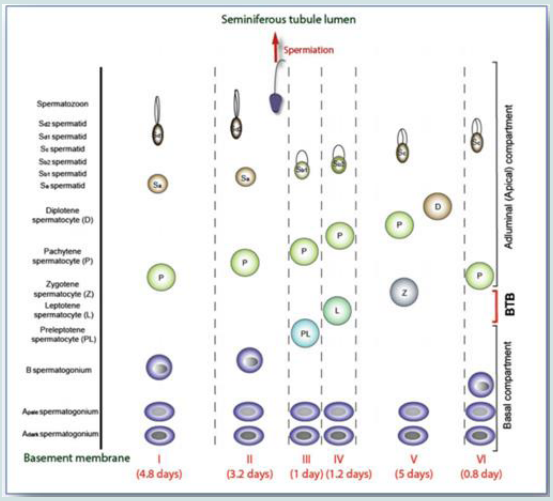


**Figure 1:** The six stages of the seminiferous epithelial cycle (I-VI) in the human testis (Picture copied from Chen et al. 2017).

compartment of the ST. Spermatogonia Ad (A dark type) and Ap (A pale type) represent type A spermatogonia. Spermatogonia Ap have a self-renewal property and thus are predominant while spermatogonia Ad are observed as the regenerative reserve of stem cells [12,16]. On the other hand, B type spermatogonia characterize the beginning of reproductive cell growth up to the spermatids stage. The multiplication of spermatogonia is synchronous through mitosis where the divided cells communicate via cytoplasmic bridges that dissolve at the spermatids stages [17].

The multiplication and differentiation of these cells is regulated by the tyrosine kinase receptor (cKIT) protein which is only manifested in spermatogonia, round spermatids and spermatozoa. Its ligand (cKIT ligand) is found at the level of Sertoli cells [18]. Retinoic acid is involved in the commencement of meiosis and the conversion of undifferentiated spermatogonia into type A spermatogonia [19].

Data in the literature is inconsistent about the stage of appearance of spermatogonia B. Clermont documented that that these cells were formed between stages VI and I, evident in stages I and II and divide into preleptotene spermatocytes in the late stage II [11]. After the ultimate spermatogonial division, cells undergo 2 stages of meiosis. A pair of spermatogonia Ap produces 8 preleptotene spermatocytes [20].

Stage III of the epithelial cycle represents the differentiation of spermatogonia B into preleptotene spermatocytes, which are shifted past the BTB while converting to leptotene spermatocytes. Thus, after the initiation of meiosis at puberty, spermatocytes are located in the SE at different stages: leptotene, zygotene, pachytene, and diplotene [21]. During meiosis I, diplotene spermatocytes are transformed into secondary spermatocytes (1N:2C) which are then transformed into two round spermatids (1N:1C) via meiosis II. To note that primary spermatocytes start their meiosis in the basal compartment of SE at the leptotene stage and reach the adluminal compartment through the BTB to proceed with further stages of division into secondary spermatocytes. Meiosis I involve DNA replication, condensation of chromosomes, pairing and crossing over of homologous chromosomes [17]. Lactate is the main energy source of spermatocytes which is metabolized by the Sertoli cells via glucose transporters (GLUT1). This mechanism is controlled by a close regulation between gonadotrophins, steroids and paracrine factors [22].

**Spermatids, spermiogenesis and spermiation**

Four haploid spermatids are the products of the two meiotic divisions of each spermatocyte.

Spermiogenesis is the process during which spermatids are transformed into spermatozoa. Different techniques of staining were used over the years to describe the formation of human spermatids [11]. Nuclear characteristics of spermatids were described by Holstein & Roosen by using glutaraldehyde fixation and toluidine blue stain. Subsequently, they were able to detect 6 main stages ($S_a$, $S_{b1}$, $S_{b2}$, $S_c$, $S_{d1}$, and $S_{d2}$) including morphological changes during which an acrosomic granule is produced in the Golgi apparatus and grows over the nucleus. Additional changes happen, including: acrosome formation, condensation of nuclear chromatin, detachment of the cytoplasm forming the residual body, which is subsequently digested by Sertoli cells via phagocytosis, and finally the formation of a mature spermatozoon [23]. Any disruption at the level of the acrosome formation, nucleus and/or flagellum maturation may lead to maturational arrest or hypospermatogenesis [24]. All these stages are still within the premises of the human testis.

Spermiation is the final process during which mature spermatozoa are delivered into the lumen of ST for their subsequent maturation in the epididymis. The delivery of matured spermatids is achieved via the Sertoli cells during which they separate from their connections and become spermatozoa [25]. Residual bodies including parts of the spermatids are digested into the Sertoli cells. The molecular mechanism is still poorly understood yet, it is dependent on FSH and testosterone [26].

**Spermatozoa**

The final product of spermatogenesis is the spermatozoa. The unique shape of spermatozoa permits its precise contact with the oocyte: nucleus is condensed, protected by an acrosome and attached to a flagellum to allow progressive motility. The motility is acquired during the transport in the epididymal ducts, depending on the normal development of axonemes, presence of mitochondria and implantation of flagellum at the nucleus [23]. To note that the highly condensed spermatozoa has a particular form of DNA packaging in the sperm nuclei where loops are packed as doughnuts, thus allowing the transfer of the genome in a compacted form to the zygote [27].

Generations of differentiated germ cells are illustrated from the basement membrane upward to the tubule lumen. Spermatogonia are established in stage V, present in all cellular associations. The preleptotene spermatocytes appear during stage III, are transported through the BTB, to undergo meiosis during the stage IV of the cycle. Newly formed spermatids are present in stage I with spherical nucleus. It is till the end of stage II that spermiation is noted.

Different methods were used to precisely characterize the morphology of germ cells within the SE. The present descriptions are based on initial studies done during the early 60s [11]. Although,

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these were innovative studies, they had flaws in describing the nuclear features of germ cells and the organization among the different stages. For a better understanding of the dynamics of spermatogenesis, it has been recently revisited by several investigators using high resolution light microscopy method on open testes biopsies from adult and elderly patients. They proposed new cellular associations in order to enable a more advanced and consistent source of reference [14]. The number of six stages originally proposed was maintained, yet the stages were better defined.

## Conclusion

Spermatogenesis is a continuous process requiring the contribution of numerous cell and regulatory factors. Its understanding is essential in order to advance research for treatment of male infertility. Numerous areas of the ST are occupied by different stages of spermatogenesis; hence several stages can be discerned in an isolated tubule section. The different stages of spermatogenesis along with the main roles of Sertoli cell and BTB were reviewed. Some emerging fields in research regarding the new classification was briefly examined for a better understanding of the complexity of the process.

## References

1. Cheng CY, Wong EW, Yan HH, Mruk DD (2010) Regulation of spermatogenesis in the microenvironment of the seminiferous epithelium: new insights and advances. Mol Cell Endocrinol 315: 49-56.
2. Yoshida S, Sukeno M, Nabeshima YI (2007) A vasculature-associated niche for undifferentiated spermatogonia in the mouse testis. Science 317: 1722-1726.
3. Neto FT, Bach PV, Najari BB, Li PS, Goldstein M (2016) Spermatogenesis in humans and its affecting factors. Semin Cell Dev Biol 59: 10-26.
4. Walker WH (2009) Molecular mechanisms of testosterone action in spermatogenesis. Steroids 74: 602-607.
5. Auharek SA, Avelar GF, Lara NM, Sharpe RM, Franca LR (2011) Sertoli cell numbers and spermatogenic efficiency are increased in inducible nitric oxide synthase mutant mice. Int J Androl 34: e621-e626.
6. Weber JE, Russell LD, Wong V, Peterson RN (1983) Three dimensional reconstruction of a rat stage V Sertoli cell: II. Morphometry of Sertoli–Sertoli and Sertoli–germ cell relationships. Am J Anat 167: 163-179.
7. Jarow JP, Chen H, Rosner TW, Trentacoste S, Zirkin BR (2001) Assessment of the androgen environment within the human testis: minimally invasive method to obtain intratesticular fluid. J Androl 22: 640-645.
8. Cheng YH, Wong EW, Cheng CY (2011) Cancer/Testis (CT) antigens, carcinogenesis and spermatogenesis. Spermatogenesis 1: 209-220.
9. Sharpe RM, McKinnell C, Kivlin C, Fisher JS (2003) Proliferation and functional maturation of Sertoli cells, and their relevance to disorders of testis function in adulthood. Reproduction 125: 769-784.
10. Chen H, Mruk D, Xiao X, Cheng CY (2017) Human spermatogenesis and its regulation. In Male Hypogonadism 49-72.
11. Clermont Y (1963) The cycle of the seminiferous epithelium in man. Am J Anat 112: 35-51.
12. Clermont Y (1972) Kinetics of spermatogenesis in mammals: seminiferous epithelium cycle and spermatogonial renewal. Physiol Rev 52: 198-236.
13. Xiao X, Mruk DD, Wong CK, Cheng CY (2014) Germ cell transport across the seminiferous epithelium during spermatogenesis. Physiology (Bethesda) 29: 286-298.
14. Nihi F, Gomes MLM, Carvalho FAR, Reis AB, Martello R, et al. (2017) Revisiting the human seminiferous epithelium cycle. Hum Reprod 32: 1170-1182.
15. Ehmcke J, Wistuba J, Schlatt S (2006) Spermatogonial stem cells: questions, models and perspectives. Hum Reprod Update 12: 275-282.
16. Ehmcke J, Schlatt S (2006) A revised model for spermatogonial expansion in man: lessons from non-human primates. Reproduction 132: 673-680.
17. Holstein AF, Schulze W, Davidoff M (2003) Understanding spermatogenesis is a prerequisite for treatment. Reprod Biol Endocrinol 1: 107.
18. Sandlow JI, FENG HL, Cohen MB, Sandra A (1996) Expression of c□KIT and its ligand, stem cell factor, in normal and subfertile human testicular tissue. J Androl 17: 403-408.
19. Hogarth CA, Griswold MD (2010) The key role of vitamin A in spermatogenesis. J Clin Invest 120: 956-962.
20. Rowley MJ, Heller CG (1971) Quantitation of the cells of the seminiferous epithelium of the human testis employing the Sertoli cell as a constant. Z Zellforsch Mikrosk Anat 115: 461-472.
21. Feng CW, Bowles J, Koopman P (2014) Control of mammalian germ cell entry into meiosis. Mol Cell Endocrinol 382: 488-497.
22. Dias TR, Alves MG, Silva BM, Oliveira PF (2014) Sperm glucose transport and metabolism in diabetic individuals. Mol Cell Endocrinol 396: 37-45.
23. Holstein AF, Roosen-Runge EC (1981) Atlas of human spermatogenesis. Grosse 1: 224.
24. Cheng CY, Mruk DD (2015) Biochemistry of Sertoli cell/germ cell junctions, germ cell transport, and spermiation in the seminiferous epithelium. Sertoli Cell Biol 333-383.
25. Russell LD, Griswold MD (1993) The sertoli cell cache river press. Clearwater, FL.
26. O'Donnell L, Nicholls PK, O'Bryan MK, McLachlan RI, Stanton PG (2011) Spermiation: the process of sperm release. Spermatogenesis 1: 14-35.
27. Ward WS (1993) Deoxyribonucleic acid loop domain tertiary structure in mammalian spermatozoa. Biology of reproduction 48: 1193-1201.