Chapter 9
What makes the process of spermatogenesis unique?

Stefan Schlatt and Swati Sharma

The generation of gametes is relevant for any higher species since recombination during meiosis is a crucial event establishing genetic diversity. The primary task of the gonad is homing of primordial germ cells, guidance of germ cells towards a species- and sex-dependent differentiation, adequate expansion of germline stem cells and meiosis and postmeiotic germ cell differentiation. The process of spermatogenesis is the unique male-specific track of germ cell development leading to the generation of sperm.

Unique somatic differentiation of the testis (red and orange box)

The initially indifferent gonadal anlage undergoes sex-specific gene expression during embryogenesis. The gene SRY on the Y-chromosome kicks on a cascade of gene expression leading to the appearance of a first testis specific cell type called Sertoli cells. These cells form dense aggregates engulfing primordial germ cells. The aggregates reorganize to develop into seminiferous cords which grow out longitudinally to form the seminiferous tubules making up 90% of the adult testicular mass. Newly formed cords terminate at the rete testis. Products are released to the outside via the initial segment (mesonephros derivative), efferent ducts and the epididymal and spermatic ducts. The seminiferous cords are lined by a basement membrane with the seminiferous epithelium populating the inside and peritubular cells colonizing the outside of the cords. The testis becomes a bicompartmental (and bifunctional) organ separated into a tubular (spermatogenesis) and an interstitial (steroidogenesis) compartment. Sertoli cells are the principle components of the seminiferous epithelium with tight basolateral contacts functioning as the blood-testis barrier. Leydig cells are testis-specific cells in the interstitium producing primarily androgens.

Initial male germ cell development (yellow boxes)

Primordial germ cells populate the indifferent embryonal gonad. In the male gonadal anlage, they are engulfed by Sertoli cells and are now considered gonocytes which remain mitotically quiescent. Later during development, gonocytes settle on the basement membrane between Sertoli cells to form a population of A-spermatogonia which function as reserve stem cells for the life-long generation of spermatozoa (Chapter 8).

Premeiotic spermatogonial expansion (red box)

The pool of A-spermatogonia consists of several subpopulations constituting a unique stem cell system. Features of the stem cell system differ between species. In general, stem spermatogonia rarely divide to give rise to cyclically proliferating A-spermatogonial populations. Individual A-spermatogonia are mobile cells migrating along the base of the seminiferous tubules. The dividing spermatogonia rarely complete mitosis and usually form interconnected cell clones. Depending on the species, few to several mitotic divisions culminate in spermatogonial clones of different size (primate: 32-64 cells, rodents: several hundred to thousand cells). Clones may eventually split into single cells or duplets to remain stem cells or as more extensive clones, as they enter the process of spermatogenic differentiation.

Meiosis (green box)

Meiosis is the most relevant process during spermatogenesis providing a track for haploidization with intense recombination of the genome (Chapter 10). The germ cell clones enter prophase of meiosis after a last S-phase prior to the preleptotene stage. The entry into meiotic prophase initiates a highly synchronized developmental program lasting for several weeks while cells pass through prophase of meiosis and subsequently undergo the two meiotic divisions. When entering meiosis germ cell clones disconnect from the basement membrane and become embedded between Sertoli cells. The blood testis barrier is reestablished basally before it opens apically keeping a tight blood testis barrier in the seminiferous epithelium.

Germline checkpoints assuring genomic integrity

The exquisite sensitivity of spermatogonia to toxins or radiation indicates unique checkpoint mechanisms. Even lowest doses of toxicant exposure or radiation impact and/or deplete all differentiating spermatogonia. Resting stem cells are less sensitive to damage and depletion. Depending on the intensity of exposure, they remain in the seminiferous epithelium. Restoration of spermatogenesis occurs via activation of the dormant stem cell populations. Repopulation from stem cells initiates either full, partial or no restoration of spermatogenesis. The exact target cell subpopulations and selective mechanisms for quality control checks in premeiotic germ cells remain to be established; however, the existence of rigorous selection among male germ cells is a unique feature of spermatogenesis.

Limits of clonal spermatogonial expansion (blue box)

Another unique feature of mammalian spermatogenesis is a peculiar cellular and histological organization. The seminiferous epithelium contains several layers of germ cells. Expanding A-spermatogonia form flattened interconnected clones along the basement membrane. All subsequent mitotic and meiotic divisions are highly synchronized enabling to define stages of the seminiferous epithelial cycle by morphological criteria visible in the synchronized cohorts of germ cells. Among other criteria, the acrosome development in round spermatids is a primary marker for definition of seminiferous epithelial stages. Species showing large germ cell clones due to extensive premeiotic expansion show a longitudinal arrangement of seminiferous epithelial stages (e.g. rodents) whereas species with small clones (e.g. primates) reveal mixed arrangements of seminiferous epithelial stages in individual tubular crossections.

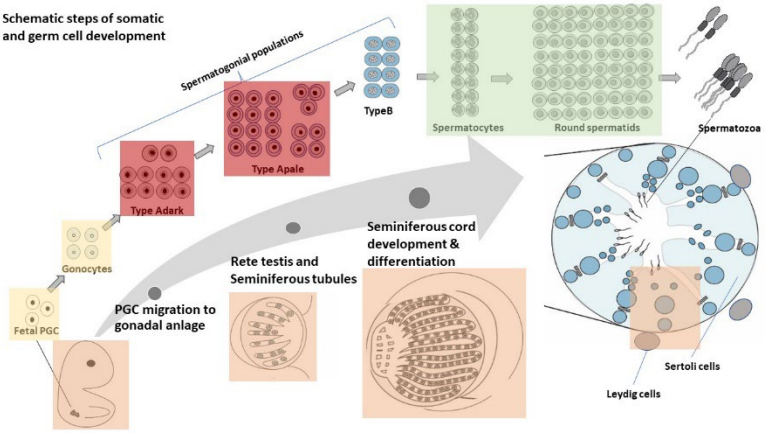

Figure 1. Schematic steps of somatic and germ cell development

Suggested reading

Clermont Y. Kinetics of spermatogenesis in mammals: seminiferous epithelium cycle and spermatogonial renewal. Physiol Rev. 1972;52(1):198-236.

Hermo L, Pelletier RM, Cyr DG, Smith CE. Surfing the wave, cycle, life history, and genes/proteins expressed by testicular germ cells. Part 1: background to spermatogenesis, spermatogonia, and spermatocytes. Microsc Res Tech. 2010;73(4):241-78.

McLachlan RI, Rajpert-De Meyts E, Hoei-Hansen CE, de Kretser DM, Skakkebaek NE. Histological evaluation of the human testis--approaches to optimizing the clinical value of the assessment: mini review. Hum Reprod. 2007;22(1):2-16.

Schlatt S, Ehmcke J. Regulation of spermatogenesis: an evolutionary biologist's perspective. Semin Cell Dev Biol. 2014;29:2-16.

Sharma S, Wistuba J, Pock T, Schlatt S, Neuhaus N. Spermatogonial stem cells: updates from specification to clinical relevance. Hum Reprod Update. 2019;25(3):275-97.