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1. Spermatozoa morphology and physiology: an introduction

Sperm cells (SPZ) are derived from spermatogenesis, a highly regulated developmental process starting from diploid precursors—spermatogonial stem cells—that undergo strictly orchestrated mitotic and meiotic divisions to form round spermatids. Extensive morphological and biochemical transformations in post-meiotic phase are required to differentiate round spermatids into highly specialized SPZ [1–3]. Thus, during spermiogenesis, the round spermatids transform into specialized and polarized cells that exhibit: at proximal end, the head containing an elongated and transcriptionally inactive nucleus which is apically surrounded by the Golgi-derived acrosome, and at the distal end, a tail surrounded at its proximal midpieces by mitochondrial sheet. A part from acrosome biogenesis, the spermiogenesis accounts for a radical chromatin remodeling that causes genome silencing [4] through histone replacement with transition proteins, firstly, and protamines later, to obtain a tightly packaged chromatin [5]. In parallel, a global reorganization of cytoplasmatic/cytoskeleton architecture drives elongation step with the development of a flagellum and the formation of cytoplasmic droplets which contain the excess cytoplasm.

In mammals, two post-testicular maturational events are required so that SPZ may reach their fertilization ability: the former occurring in the epididymis, the latter in female reproductive tract. The epididymis is a long convoluted tubule characterized by three main morphologically and functionally distinct regions (proximal caput, elongated corpus, and distal cauda) [6]. It represents the extracellular microenvironment in which a fine crosstalk between SPZ and epididymis epithelial cells takes place, generally through vesicles known as epididymosomes [7]. During their journey along the epididymis, SPZ remodel the lipid content of plasma membrane, especially cholesterol, receive a rich and complex repertoire of protein and non-coding RNAs (ncRNAs), especially microRNAs (miRNAs), long non-coding RNA
lncRNA), and tRNA fragments (tRFs) [8], and lastly they acquire progressive motility. After epididymal maturation, SPZ are still incapable to fertilize eggs; they have to spend some time in the female reproductive tract before they acquire this competence (fertilizing ability) through the capacitation process [9]. During this phase, SPZ undergo other important biochemical modifications in terms of steroid removal or protein modifications [10]; after that, they interact with cumulus-cell oocyte complex to penetrate the matrix of the cumulus oophorus [11]. Capacitated SPZ are subjected to acrosome reaction, a prerequisite event for sperm-egg fusion [12], then they penetrate the zona pellucida, to meet and fuse with the egg plasma membrane [13]. After this fusion, finely controlled by a large body of proteins, SPZ deliver to the oocyte their haploid genome. **Figure 1** summarizes the main features of spermatogenesis and SPZ maturation.

**2. The control of spermatogenesis and sperm quality**

Intricate neuronal circuitries, mainly governed by hypothalamic kisspeptin and gonadotropin releasing hormone (GnRH) reciprocal communications, centrally orchestrate reproduction [1] and lead to pituitary gonadotropin discharge and sex steroid biosynthesis in order to sustain spermatogenesis and sperm release. In addition to hormonal milieu, a complex network of intratesticular cell-to-cell communications regulates germ cell progression, coordinating mitosis, meiosis, differentiation, and maturation [2, 3]. Thus, SPZ morphological feature is critical to ensure proper physiological activity.
Spermatogenesis is highly sensitive to environmental stressors as energy availability, stress, life style, temperature, pollutants, heavy metals, or endocrine disruptor chemicals that act at several levels along the hypothalamus-pituitary-gonad axis [14–16]. In this respect, the activity of molecular chaperone/cochaperone, ubiquitination, but also DNA repair systems and antioxidants defenses ensures the physiological progression of spermatogenesis, avoids that damaged germ cells differentiate into SPZ, and deeply contributes to produce high-quality mature SPZ [17–19].

Conversely, impaired autocrine/paracrine/endocrine communication along the hypothalamus-pituitary-gonadal axis may impact spermatogenesis and have deleterious effects on male fertility due to: (1) spermatogenesis arrest and lack of SPZ, as in the case of hypogonadotropic hypogonadism; (2) defective production of gonadotropins/sex steroids with outcomes on spermatogenesis onset/progression and SPZ maturation; and (3) low sperm count and/or the production of defective spermatozoa with morphological abnormalities or impaired motility [20]. However, in 30–40% of male infertility cases, the etiology remains unknown and infertility is therefore idiopathic, being a multifactorial disorder in which molecular defects in spermatogenesis and sperm function occur [21].

3. Upcoming issue for paternal epigenetic inheritance

Once considered just a “carrier” for male haploid genome at fertilization, nowadays, the functional role of SPZ has been revised. In fact, a part haploid genome, SPZ, preserve some sperm-specific RNA components, absent in the oocyte, such as fragments of longer transcripts, able to control early embryogenesis [22–24]. Mature SPZ also contain a rich repertoire of ncRNAs, such as miRNAs, tRFs, lncRNAs, and PIWI-interacting RNAs (piRNAs). Their deregulation not only alters SPZ physiology but may affect SPZ contribution to a regular embryo development, through epigenetic dynamics [25], since there is a need to focus more attention on SPZ as carrier of transgenerational epigenetic inheritance.

The specific epigenetic signatures of SPZ include DNA methylation status, chromatin remodeling, and ncRNA pools. Unlike somatic cells, germ cells have hypomethylated DNA [26], and genome-wide hypermethylation of sperm DNA status is associated with pregnancy failure [27]. As reported in the previous paragraph, chromatin remodeling, made possible through histone replacement by protamines, is a key step of spermiogenesis and does not occur in oogenesis [5, 28]. Interestingly, a deregulated histone-protamine exchange induces DNA damage and male subfertility [29]. A small percentage of paternal genome retains histones and reveals a nucleosome organization, in not random distribution, thus affecting transcription factor accessibility to DNA at specific gene loci [30]. Furthermore, together with a well-known histone code, a protamine code has been suggested in SPZ [31]. Lastly, sperm RNA cargo plays an important role in SPZ epigenetic landscape. Several classes of RNAs have been identified in SPZ [32] and their possible contribution in the regulation of gene expression in embryo is currently under investigation. Surely these small RNAs take part in the sperm epigenetic transgenerational pattern of inheritance because they are vulnerable to paternal exposure to various
forms of stress and they are able to regulate developmental trajectories of the offspring. In fact, a high-fat diet (HFD) in male mice alters sperm miRNA content and, thus, glucose tolerance in both male and female offspring [33]. Similarly, sperm tRNA fragments injected from HFD males or from male mice with a protein restriction status to normal zygotes are vehicles of transgenerational transmission of metabolic disorders in the offspring [34, 35]. Therefore, DNA methylation, posttranslational histone modifications, chromatin remodeling, and ncRNA activity are plastic epigenetic mechanisms, modifiable in response to environmental and behavioral events and heritable from father to the offspring as an acquired mark [36]. This also means that paternal lifestyle or experiences, including physical activity, nutrition, and exposure to pollutants, can alter SPZ epigenome, with male infertility, embryo development failure, abnormal embryonic molecular makeup, and disease susceptibility of the offspring as a result [37].

4. Conclusions

The assessment of SPZ quality represents the main bioindicator of male fertility and the analysis of seminal plasma is a valid diagnostic instrument for male fertility, since it is enriched with molecules indicative of SPZ quality status. Furthermore, impressive advances have been made in conferring to SPZ a role in embryo development and in considering SPZ a carrier of “paternal experience” to the offspring. As a consequence, the combined assessments of SPZ quality and (epi)genetic study are necessary for the diagnosis and the development of personalized treatment for male infertility and to preserve embryo development and offspring health.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this chapter.

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