Chapter 1

Introductory Chapter: Spermatozoa - Facts and Perspectives

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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

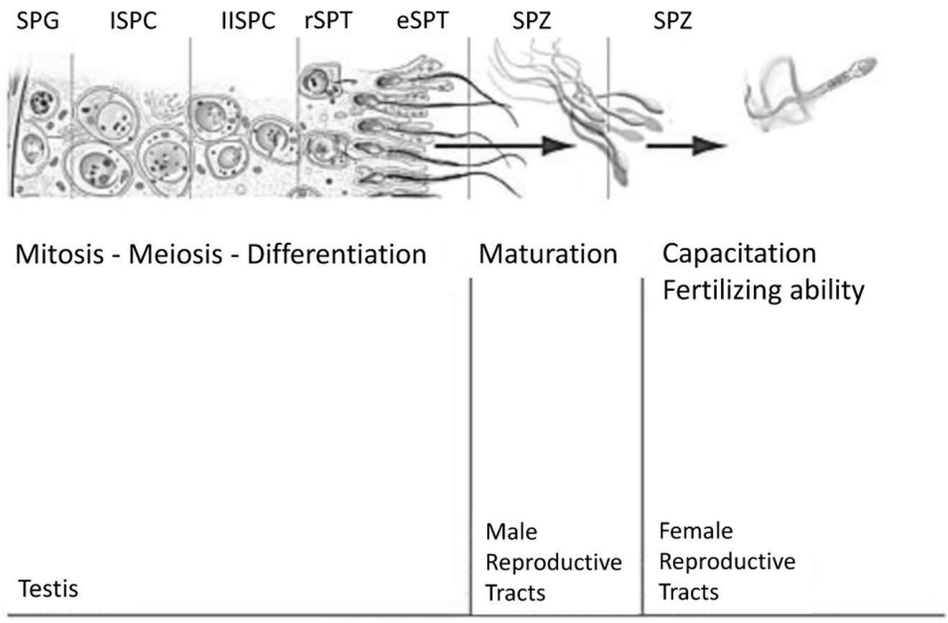

Figure 1. Schematic view of the main events characterizing spermatogenesis in testis, followed by spermatozoa (SPZ) maturation in male reproductive tracts and capacitation/fertilizing ability in female reproductive tracts. SPG: spermatogonia; ISPC: primary spermatocytes; IISPC: secondary spermatocytes; rSPT: round spermatids; eSPT: elongating spermatids; SPZ: spermatozoa.

(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 ovogenesis [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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References

[1] Pierantoni R, Cobellis G, Meccariello R, Fasano S. Evolutionary aspects of cellular communication in the vertebrate hypothalamo-hypophysio-gonadal axis. International Review of Cytology. 2002;**218**:69-141

[2] Cobellis G, Meccariello R, Pierantoni R, Fasano S. Intratesticular signals for progression of germ cell stages in vertebrates. General and Comparative Endocrinology. 2003; **134**:220-228

[3] Meccariello R, Chianese R, Chioccarelli T, Ciaramella V, Fasano S, Pierantoni R, Cobellis G. Intra-testicular signals regulate germ cell progression and production of qualitatively mature spermatozoa in vertebrates. Frontiers in Endocrinology (Lausanne). 2014;**5**:69

[4] Marcon L, Boissonneault G. Transient DNA strand breaks during mouse and human spermiogenesis: new insights in stage specificity and link to chromatin remodeling. Biology of Reproduction. 2004;**70**:910-918

[5] Miller D, Brinkworth M, Iles D. Paternal DNA packaging in spermatozoa: more than the sum of its parts? DNA, histones, protamines and epigenetics. Reproduction. 2010;**139**:287-301

[6] Cornwall GA. New insights into epididymal biology and function. Human Reproduction. 2009;**15**:213-227

[7] Sullivan R, Saez F. Epididymosomes, prostasomes, and liposomes: Their roles in mammalian male reproductive physiology. Reproduction. 2013;**146**:R21-R35

[8] Belleannée C, Calvo É, Caballero J, Sullivan R. Epididymosomes convey different repertoires of microRNAs throughout the bovine epididymis. Biology of Reproduction. 2013;**89**:30

[9] Chang MC. Fertilizing capacity of spermatozoa deposited into the fallopian tubes. Nature. 1951;**168**:697-698

[10] De Jonge C. Biological basis for human capacitation. Human Reproduction Update. 2005; **11**:205-214

[11] Sun F, Bahat A, Gakamsky A, Girsh E, Katz N, Giojalas LC, Tur-Kaspa I, Eisenbach M. Human sperm chemotaxis: both the oocyte and its surrounding cumulus cells secrete sperm chemoattractants. Human Reproduction. 2005;**20**:761-767

[12] Cross NL, Meizel S. Methods for evaluating the acrosomal status of mammalian sperm. Biology of Reproduction. 1989;**41**:635-641

[13] Ikawa M, Inoue N, Benham AM, Okabe M. Fertilization: a sperm's journey to and interaction with the oocyte. Journal of Clinical Investigation. 2010;**120**:984-994

[14] Chianese R, Cobellis G, Chioccarelli T, Ciaramella V, Migliaccio M, Fasano S, Pierantoni R, Meccariello R. Kisspeptins, Estrogens and male fertility. Current Medicinal Chemistry. 2016;**23**:4070-4091

[15] Chianese R, Troisi J, Richards S, Scafuro M, Fasano S, Guida M, Pierantoni R, Meccariello R. Bisphenol A in reproduction: Epigenetic effects. Current Medicinal Chemistry. 2018;**25**:748-770

[16] Chianese R, Coccurello R, Viggiano A, Scafuro M, Fiore M, Coppola G, Operto FF, Fasano S, Layé S, Pierantoni R, Meccariello R. Impact of dietary fats on brain functions. Current Neuropharmacology. Oct 17, 2017. DOI: 10.2174/1570159X15666171017102547

[17] Meccariello R, Chianese R, Ciaramella V, Fasano S, Pierantoni R. Molecular chaperones, cochaperones, and ubiquitination/deubiquitination system: Involvement in the production of high quality spermatozoa. Biomed Research International. 2014;**2014**:561426

[18] Sutovsky P, Moreno R, Ramalho-Santos J, Dominko T, Thompson WE, Schatten G. A putative, ubiquitin-dependent mechanism for the recognition and elimination of defective spermatozoa in the mammalian epididymis. Journal of Cell Science. 2001;**114**:1665-1675

[19] Hartl FU, Hayer-Hartl M. Molecular chaperones in the cytosol: from nascent chain to folded protein. Science. 2002;**295**:1852-1858

[20] Ray PF, Toure A, Metzler-Guillemain C, Mitchell MJ, Arnoult C, Coutton C. Genetic abnormalities leading to qualitative defects of sperm morphology or function. Clinical Genetics. 2017;**91**:217-232

[21] Bracke A, Peeters K, Punjabi U, Hoogewijs D, Dewilde S. A search for molecular mechanisms underlying male idiopathic infertility. Reproductive Biomedicine Online. 2018;**36**:327-339

[22] Miller D, Ostermeier GC. Towards a better understanding of RNA carriage by ejaculate spermatozoa. Human Reproduction Update. 2006;**12**:757-767

[23] Lalancette C, Miller D, Li Y, Krawetz SA. Paternal contributions: new functional insights for spermatozoal RNA. Journal of Cellular Biochemistry. 2008;**104**:1570-1579

[24] Sendler E, Johnson GD, Mao S, Goodrich RJ, Diamond MP, Hauser R, Krawetz SA. Stability, delivery and functions of human sperm RNAs at fertilization. Nucleic Acids Research. 2013;**41**:4104-4117

[25] Casas E, Vavouri T. Sperm epigenomics: Challenges and opportunities. Frontiers in Genetics. 2014;**5**:330

[26] Oakes CC, La Salle S, Smiraglia DJ, Robaire B, Trasler JM. A unique configuration of genome-wide DNA methylation patterns in the testis. Proceedings of the National Academy of Sciences USA. 2007;**104**:228-233

[27] Benchaib M, Braun V, Ressnikof D, Lornage J, Durand P, Niveleau A, Guérin JF. Influence of global sperm DNA methylation on IVF results. Human Reproduction. 2005;**20**:768-773

[28] Steger K, Klonisch T, Gavenis K, Drabent B, Doenecke D, Bergmann M. Expression of mRNA and protein of nucleoproteins during human spermiogenesis. Molecular of Human Reproduction. 1998;**4**:939-945

[29] Ni K, Spiess AN, Schuppe HC, Steger K. The impact of sperm protamine deficiency and sperm DNA damage on human male fertility: A systematic review and meta-analysis. Andrology. 2016;**4**:789-799

[30] Siklenka K, Erkek S, Godmann M, Lambrot R, McGraw S, Lafleur C, Cohen T, Xia J, Suderman M, Hallett M, Trasler J, Peters AH, Kimmins S. Disruption of histone methylation in developing sperm impairs offspring health transgenerationally. Science. 2015; **350**:aab2006

[31] Brunner AM, Nanni P, Mansuy IM. Epigenetic marking of sperm by post-translational modification of histones and protamines. Epigenetics & Chromatin. 2014;**7**:2

[32] Carrell DT, Aston KI, Oliva R, Emery BR, De Jonge CJ. The "omics" of human male infertility: integrating big data in a systems biology approach. Cell and Tissue Research. 2016;**363**:295-312

[33] Fullston T, Ohlsson Teague EM, Palmer NO, DeBlasio MJ, Mitchell M, Corbett M, Print CG, Owens JA, Lane M. Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content. FASEB Journal. 2013;**27**:4226-4243

[34] Chen Q, Yan M, Cao Z, Li X, Zhang Y, Shi J, Feng GH, Peng H, Zhang X, Zhang Y, J3 Q, Duan E, Zhai Q, Zhou Q. Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. Science. 2016;**351**:397-400

[35] Sharma U, Conine CC, Shea JM, Boskovic A, Derr AG, Bing XY, Belleannee C, Kucukural A, Serra RW, Sun F, Song L, Carone BR, Ricci EP, Li XZ, Fauquier L, Moore MJ, Sullivan R, Mello CC, Garber M, Rando OJ. Biogenesis and function of tRNA fragments during sperm maturation and fertilization in mammals. Science. 2016;**351**:391-396

[36] van Otterdijk SD, Michels KB. Transgenerational epigenetic inheritance in mammals: How good is the evidence? FASEB Journal. 2016;**30**:2457-2465

[37] Schagdarsurengin U, Steger K. Epigenetics in male reproduction: effect of paternal diet on sperm quality and offspring health. Nature Reviews Urology. 2016;**13**:584-595

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