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Sperm Cells, an Efficient Shuttle for the Intergenerational Epigenetic Memory

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Editorial

Fertility-the synergistic encounter and fusion of spermatozoa and oocyte-is a key feature for the perpetuation of the species.

Spermatogenesis is a highly orchestrated process allowing the differentiation of spermatogonial stem cells into mature sperm, through the succession of spermatogonia self-renewal, meiosis and post-meiotic maturation events. Infertility could result from the interruption of any of these processes due to the disturbance of endocrine, paracrine and autocrine communications along the Hypothalamus-Pituitary-Gonadal (HPG) axis. Actually, gonadal functions are also supported by an intricate intragonadal network of regulators that works in syntony with HPG axis [1-4]. Beyond testis, spermatozoa (SPZ), released from the germinal epithelium as functionally immature, travel along the epididymis-a long convoluted tubule connecting rete testis to the vas deferens, composed of three main anatomical regions (caput, corpus and caudal), with a considerable segment to segment variation. There, they encounter a novel extracellular milieu that modulates their biochemical composition and their functionality, thus allowing their maturation. Of great interest for reproductive biologists is to understand the way that epididymal epithelial cells-highly specialized cells in protein secretion-communicate to SPZ along their journey. In this respect, a central component of such a communication is epididymosomes. They are a population of 50-150 nm vesicles-heterogeneous in their lipid/protein composition and density-released through an apocrine secretory mechanism [5]. Intriguingly, these vesicles not only coordinate the activity of the different epididymal segments, but-thanks to their ability to form intimate associations with sperm membrane-they convey to SPZ a rich and complex protein and non-coding RNA (especially microRNA/miRNA and tRNA fragments) landscape [6].

Small non-coding single stranded miRNAs-endogenously produced by the cell, following several steps of maturation, directed by the nuclear Drosha and then by the cytosolic Dicer [7] are able to bind to target mRNA inhibiting their translation into proteins. MicroRNAs are a valid tool of intercellular communications, since the need to be disseminated into extracellular fluids to reach target cells. In their journey, miRNA may be associated to carriers such as lipoproteins, ribonucleoproteins or encapsulated in vesicles such as epididymosomes. Their role in reproduction is well-known, since the deletion of Dicer in Sertoli or germ cells impairs spermatogenesis, causing testicular degeneration and both meiotic and spermatogenic defects [8,9]. Additionally, by means of the conditional epithelial epididymal Dicer deletion approach a role of miRNA in influencing the specific segment-dependent gene expression pattern along the epididymis as well as sperm maturation has been suggested [10,11]. During their maturation, SPZ-that are transcriptionally quiescent cells, enable of de novo miRNA biogenesis-acquire a novel cohort of miRNA, predominantly conveyed by epididymosomes, according to a gradient of increasing complexity from caput to cauda of epididymis [12]. Nothing excludes that a miRNA cargo of non-epididymal origin may exist.

Recently, great attention has been focused on small RNA, other than miRNA. Deep sequencing analysis on RNA extracted from epididymis cauda SPZ of mice reveals that-in addition to well-known miRNA population-it exists a subset of small, 30-34 nt long, tRNA fragments, also termed tsRNAs or tRFs [13,14]. They derive from tRNAs after cleavage of their 5' ends". Testis and purified spermatocyte/spermatid populations show very low levels of tRFs, most of them with high methylation degree, suggesting that a robust tRNA cleavage takes place just in the epididymis.

Since these sperm epigenetic modulators, with a key role in epigenetic trans-generational patterns of inheritance, it is intriguing to understand how much sperm epigenome-that is deeply subjected to modifications during the post-testicular phase-is vulnerable to perturbation following paternal exposure to various forms of stress and how much it is able to alter the developmental trajectories of the offspring. Obesity and other associated health comorbidities are strong causes of sterility [15]. Diet-induced metabolic disorders may influence future generation's health independently of genetic inheritance. In this respect, sperm and its epigenetic changes are clearly implicated as potential mediators. Male mice subjected to a high-fat diet (HFD), besides to show altered testicular gene expression and sperm concentration/motility with an increased DNA damage, change their testis transcriptome and sperm miRNA content and impair glucose tolerance in both male and female offspring [16]. Despite the deregulated miRNA payload in father potentially alters the embryonic molecular makeup, its growth status, as well as the adult offspring phenotype, there is no evidence that the same miRNAs are also deregulated in male offspring sperm [17]. Together with miRNA, sperm tsRNAs exhibit changes in expression profiles, with several enzymatic modifications as m^5C and m^2G in case of HFD [13]. Interestingly, the injection of sperm tsRNAs from HFD males into normal zygotes generates metabolic disorders in the offspring with alteration in the gene expression of the main metabolic pathways [13]. Similarly to HFD, male mice with a protein restriction status trans-generationally transmit altered hepatic cholesterol biosynthesis to the offspring and have modified caudal sperm RNA repertoire, with increased abundance of glycine tsRNAs. From a functional point of view, glycine tsRNAs affect the expression of genes involved in embryo preimplantation [14].

Sperm epigenome is also very vulnerable to stress and cigarette smoke. Paternal experiences alter stress pathway regulation disturbing

the Hypothalamic-Pituitary-Adrenal (HPA) axis. Interestingly, the exposure of male mice to chronic stress before breeding changes global transcription pattern suggesting a deep epigenetic reprogramming [18]. In detail, sperm miRNA content robustly changes. As a consequence, offspring stress responsivity is deregulated [19]. Accordingly, cigarette smoking has been shown to alter sperm miRNA content with most of miRNAs involved in molecular pathways vital for healthy spermatozoa and normal embryo development [20].

In conclusion, recent efforts have been addressed to identify the contribution of sperm epigenome in embryo development and offspring health. In this respect, sperm miRNA and tRFs signature may be a potential candidate in the transmission of epigenetic characteristics from fathers to offspring, but most of all in conditioning metabolic and reproductive health or behavioural/neurological status of offspring. Such an item constitutes a new frontier of research in the biology of reproduction field with respect to intriguing regulatory mechanisms of embryo development and may also be a powerful diagnostic marker of male infertility.

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