The structure and role of mammalian sperm RNA: a review

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ABSTRACT: The main role of sperm is the delivery of the paternal genome into the oocyte during fertilisation. However, several lines of evidence have indicated that mammalian spermatozoa contribute more than just their DNA, namely, they also deliver a large range of RNA molecules. Microarray analysis has revealed a complex population of 3000 different kinds of messenger RNA that are delivered to oocytes by sperm and ejaculated spermatozoa are estimated to contain about 0.015 pg of total RNA. Some of the transcripts encode proteins crucial for early embryo development. Messenger RNAs from sperm also help to protect the paternal genes, which have an integral role soon after fertilisation. The molecular participation of the oocyte during fertilisation is well understood but the function of the sperm in this process remains unclear. During spermatogenesis the structure of the male haploid genome is permanently modified. Transition proteins (TNPs), protamines (PRMs) and histones (HILS-spermatid specific linker histone) play a unique role in spermatid chromatin compaction. In this review, the structure and role of sperm RNA as well as chromatin organisation during spermatogenesis are discussed.

Keywords: sperm; spermatozoal RNA; fertilisation

Contents

1. Introduction

Spermatogenesis is a cyclic process, in which diploid spermatogonia differentiate into mature haploid spermatozoa. Spermatogonia are differentiated to spermatocytes which undergo two meiotic divisions to generate round spermatids. During spermiogenesis the haploid round spermatids undergo an elongation phase and are differentiated into mature spermatozoa (Moldenhauer et al. 2003; Miller et al. 2005). Microarray analysis has revealed the presence of about 3000 different transcripts in ejaculated spermatozoa (Krawetz 2005; Martins and Krawetz 2005). Although the structure of sperm RNA is well described its role in spermatogenesis and male infertility remains un-

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clear. Several hypotheses have been advanced to try to explain the origin and physiological function of these transcripts. One hypothesis is that the RNA of spermatozoa is transcribed during spermatogenesis. However, at present there is no evidence to suggest transcriptional activity of spermatozoal RNA. In another theory it is proposed that the pool of spermatid RNA is the remainder of the untranslated material during spermatogenesis (Kramer and Krawetz 1997). This is supported by the fact that the same transcripts detected in sperm were also found in both testes. If this theory was proven by experimental data, spermatozoal transcripts would represent the historical entry of spermatogenesis.

The identified spermatozoal RNA encompasses the transcripts, which may be delivered to the ovum during fertilisation. The transcripts delivered to the ooplasm can play a crucial role in zygotic and early embryonic development (Wrzeska and Rejduch 2004; Ostermeier et al. 2004; Bukowska et al. 2011a; Kempisty et al. 2011). As mentioned before, the molecular contribution of the ovum during fertilisation is well known, whereas the role of sperm is still under discussion. It is a well-known theory that the paternal molecular contribution has a crucial role in early embryonic development and in determining the health of a child (Lalande 1996; Sutovsky and Schatten 2000; Kempisty et al. 2010). Therefore, many research groups have shown that mammalian spermatozoa play more important roles than just deliver their DNA into the ovum.

During spermatogenesis, the structure of the male haploid genome is permanently modified. Transition proteins (TNPs), protamines (PRMs) and histones seem to play a crucial role in this process. In particular, proteins such as HILS1 (spermatid specific linker histone), TNPs and PRMs plays an important role in spermatid chromatin compaction (Dadoune 2003; Meistrich et al. 2003). In haploid round spermatids histones are replaced by transition proteins. The second step of this process occurs in elongating spermatids and involves replacement of TNPs with protamines (PRMs). As a result of these changes chromatin becomes highly condensed and transcriptionally silent.

2. Chromatin structure in mammalian sperm

The identified spermatozoal RNAs encompass the transcripts of transition proteins (TNPs), protamines (PRMs) and spermatid-specific linker histone (HILS) (Roth and Allis 1992; Eddy 2002). Transition proteins and protamines are expressed during mammalian spermiogenesis. During chromatin remodelling in late spermatogenesis most somatic histones are replaced by DNA packaging proteins that are specific for germ cell lines (Caron et al. 2005). The mature spermatozoa have a high number of histone variants in comparison to the somatic cells and there exist differences between these germ cell-specific histones and those from somatic cells (Baarends and Grootegoed 2003; Churikov et al. 2004). For example, the synthesis of RNA is uncoupled from DNA replication. There are several types of histone variants; testis-specific histone H4, which can have differences in amino-acid sequence from the somatic H4 and H2A.X with different amino-acid sequence and structure. The transcript variants have a longer poly-A tails, which may increase transcript stability. The H3 transcript is specific for spermatogonia and later spermatids. H3.3A is a variant of histone H3 and is present in male germ cell development from spermatogonia to spermatids. In prophase I histone H3 is replaced by H3.3A and then H3.3B (Burfeind et al. 1994; Fernandez-Capetillo et al. 2004). There are little experimental data indicating the role of H3 histone and its transcript variants in the mechanism of transcription activation in spermatocytes. H2A and H2B transcript variants have a different structure in the N-terminal chain of the transcripts (Frank et al. 2003). TH2B is a testis-specific transcript variant of the H2B histone, which has differences in the structure of three phosphorylation sites (Ser 12, Thr 23 and Thr 34) (Green 2001; Monardes et al. 2005). As a result there are different combinatorial interactions between serine and threonine residues which could be a reason for the specific pattern of acetylation and methylation (Rousseaux et al. 2005). The Histone H1 family also has a several germ-cell specific variants. Differences in structure have been identified mostly in the C-termini and potentially determine their binding to chromatin. Two transcript variants of the histone H1 family, H1t and H1t2, exhibit high identity. The remodelling of sperm chromatin structure starts during the meiotic prophase. At that time histone-like somatic H1A and H1B are replaced by H1t transcript variants. Mutations in the gene coding H1t do not affect male fertility and, therefore, the role of H1t seems to be limited to the restructuring of chromatin. H1t2 transcript variants play an integral role in the establishment of cell polarity and high chromatin condensation during spermatogenesis (Martianov et al. 2005; Tanaka et al. 2005).

This histone variant is located under the nuclear membrane and basal acrosome of round spermatids. The position where the transcript is identified is the same for the initiation of chromatin compaction. It is thus suggested that H1t2 is a component of the chromatin organising centre in the head of spermatozoa.

Hils is a member of the linker histone family and is specific for late elongating spermatids (Yan et al. 2003; Iguchi et al. 2004). The cellular distribution in the nuclear matrix of Hils, transition proteins and protamines is almost the same, suggesting a role for this histone in the chromatin compaction process in maturing spermatids. Histone H1 has several Ser/Thr cyclin/CDK sites, which exert an important influence on cell mobility and which are absent in transcript variants such as H1t and H1t2. These results suggest a functional redundancy of these transcript variants. Yan et al. (2003) have shown that Hils exhibits several biochemical functions including the ability to bind reconstituted mononucleosomes and a role in the chromatin compaction process. Hils1 is expressed in late maturing spermatids that do not contain core histones in this stage. For this reason, it has been proposed that the mechanism of spermatid nuclear condensation is distinct from that specific for somatic linker histones. There is also a theory in which it is suggested that Hils plays a role in regulating gene transcription, DNA repair or other chromosome processes during spermiogenesis.

3. Transcriptional processes in male germ cells

Spermiogenesis is a complex process by which postmeiotic male germ cells differentiate into mature spermatozoa. This process involves structural and biochemical changes including nuclear chromatin condensation and acrosome formation (Ivell et al. 2004; Ronfani and Bianchi 2004). In male germ cells transcription is identified in post-meiotic spermatids. The process of sperm chromatin remodelling (regulation of protamine expression and chromatin compaction) includes several nuclear activation factors such as CREM, CREB, PAF-1, Y-box proteins p48/p52, nuclear factor 1, TLF, TFIID-TAF7 and TFIID-TAF7L. Transcription regulation in the sperm nucleus occurs in several steps; (i) methylation of specific DNA sequences, (ii) binding of trans-acting factors to TATA-box and CRE sequences in protamine promoters, and (iii) chromatin association in the nuclear matrix in the head of a sperm.

CREM is highly expressed in post-meiotic spermatids and is probably responsible for transcriptional activation of many haploid germ cell-specific genes included in the restructuring of the spermatozoan chromatin (Monaco et al. 2004; Hogarth et al. 2005; Kempisty et al. 2008). Inactivation of CREM results in the loss of postmeiotic cell-specific gene expression and leads to complete block of spermiogenesis. The late spermatids are completely absent at this stage and there is an increase in the number of apoptotic male germ cells. CREM-response transcription activation in somatic cells is dependent on CREM phosphorylation and subsequent CBP mobilisation. In male germ cells phosphorylation and histone acetyltranserase function is dependent on the specific co-activator ACT (activator of CREM in testis) (Don and Stelzer 2002). ACT is expressed in round spermatids, where it cooperates with CREM in regulating the transcription of various post-meiotic genes. Regulation of transcription plays an integral role in the early stages of spermatogenesis, when the spermatogonial cells are differentiated.

It has been postulated that cyclic AMP (cAMP) second messenger pathways play a crucial role in cellular growth and differentiation (De Cesare and Sassone-Corsi 2000; Don and Stelzer 2002). In addition, cAMP can be one of the important factors in determining spermatid mobility. All cAMP-responsive gene promoters have in common an 8-base enhancer termed the cAMP-response element (CRE), which contains a conserved core sequence, 5'-TGACG-3', first identified in the somatostatin gene by Montminy et al. (1986). Taylor et al. (1990) mapped CREB1 to 2q32.3-q34. The transcriptional activity of CREB requires phosphorylation of the protein on a serine residue at position 119. The CRE element (TGANNTCA) to which CREB binds is present in a number of T-cell specific genes, but the role of CREB in spermatid differentiation remains unclear (Tamai et al. 1997).

PAF-1 (protamine activating factor 1), activates PRM2 transcription in haploid cells by binding to a regulatory sequence located at position -64/-48. Yiu and Hecht (1997) postulated that any alteration in the gene sequence of these binding sites lead to inhibition of PRM2 transcription. There are a few transcription activating factors such as Tet-1 and nuclear factor 1, which bind to the PRM2 promoter-specific sequence and activate transcription of these genes (Tamura et al. 1992; Kempisty et al. 2006, 2007). So far, there are no regulatory

proteins identified, which by binding to these sequences lead to inhibition of transcription of the protamine genes.

The expression of HLA class II genes is regulated by cis-acting elements and transacting factors. The identified cis-acting elements include the Z-box, X-box, Y-box, octamer, and TATA box. The Y-box-binding protein (YB-1) is the most evolutionarily conserved nucleic-acid-binding protein (Torigoe et al. 2005). It is suggested that these proteins play an important role in several cellular processes including transcriptional regulation and DNA repair. Kohno et al. (2003) postulated that YB-1 plays a role in cell proliferation and differentiation. Although the presence of these proteins in spermatogenesis is well defined, their functions in the regulation of transcription initiation are yet to be elucidated. Yang et al. (2005) described the function of the Y-box family of DNA-/RNA-binding proteins as elements, which regulate transcription in the nucleus and which stabilise and store maternal and paternal mRNAs in the cytoplasm. Mutations of the genes encoding Y-box proteins lead to sterility in mice and to many disruptions in spermatogensis. In the testes of homozygotes levels of post-meiotic male germ cell mRNA were observed to be decreased while smaller reductions were seen in meiotic germ cell transcripts.

The structure of the TLF factor is well understood but its possible role in the process of transcription and function in human spermatogenesis are not yet understood. TLF is a member of the general transcription factor (GTFs) family, which includes TATA box-binding protein (TBP) important for the transcriptional initiation of eukaryotic genes (Kimmins et al. 2004). Both TBP and TLF factor were found to play a crucial role in embryonic development. Experiments using rat embryos as a model have shown that embryos without detectable TBP initiated gastrulation but died before it was completed. Mutation in the TLF-encoding gene resulted in the normal development of spermatogonia and spermatocytes but in a decreased number of round spermatids (Martianov et al. 2001). Although TLF is not required for embryonic development, it has been suggested that it plays an important role in transcriptional regulation of genes essential for spermiogenesis.

Transcription factor IID (TFIID) is a DNA-binding protein complex required for RNA polymerase II-mediated transcription of many genes in eukaryotic cells (Kleene 2005). TFIID is composed of the TATA-binding protein (TBP) and multiple TBP-associated factors (TAFs) including TAF1, TAF7 and TAF7L (Falender et al. 2005). The binding of TBP to the TATA-box results in transcriptional activation of PRM1/PRM2 promoters. Several lines of experimental data have revealed an important role for TAFs factors in transcriptional regulation. TAF7 has also been shown to play an important role in promoter recognition and to interact with specific transcriptional activators. Mutations in this subunit cause cell cycle arrest, which results in male infertility (Pointud et al. 2003). TAF7L is a testis- and germ-cell-specific protein with sequence similarity to somatic TAF7. The intracellular localisation of TAF7L is permanently changed from cytoplasmic in spermatogonia to nuclear in late pachytene spermatocytes and haploid round spermatids. The process of intracellular transport of TAF7L is connected with decreased expression of TAF7, which suggest that TAF7L replaces the TAF7 subunit in late spermatocytes. Experimental data have shown that TAFs are differentially expressed during all steps of male germ cell maturation (Hiller et al. 2001).

4. Process of sperm chromatin compaction

The maturation of spermatids into spermatozoa involves several important changes in chromatin structure and function. Chromatin structure in the sperm nucleus is similar to that in somatic cells. The organisation is based on looped domains attached at their bases to the nuclear matrix. The process of chromatin packaging into higher ordered structure in the eukaryotic genome is mediated by several molecular interactions, namely, DNA-DNA, DNA-histone and protein-protein interactions (Roux et al. 2004). Spermiogenesis is characterised by the expression of several nuclear proteins, which are connected with the process of chromatin condensation (Meistrich et al. 2003). The first step of chromatin condensation results in the appearance of haploid round spermatids and is characterised by the replacement of somatic histones with low molecular weight transition proteins (McLay and Clarke 2003). In this step the nucleus is elongated and chromatin appears as smooth fibres. In the next step of spermatid elongation transition proteins are replaced with protamines in the nuclear matrix. DNA in sperm chromatin is associated with 15% nucleohistones and 85% nucleoprotamines (Adham et al. 2001).

It has been postulated that the process of normal chromatin compaction in sperm has an important effect on early embryonic development and the production of viable offspring. Recent investigations have revealed an important role for the structure and function of transition proteins 1 and 2 (TNP1 and TNP2) on proper sperm chromatin condensation.

There are two types of transition proteins, transition protein 1 (TNP1) and transition protein 2 (TNP2) (Miller 2000; Kempisty et al. 2006). TNP1 is a spermatid-specific protein, which replace histones and then is itself replaced by protamines during the latter steps of spermatogenesis.

Luerssen et al. (1990) mapped human TNP1 to chromosome 2q35-q36. It was shown that mutation of the TNP1 gene leads to several abnormalities in sperm morphology, although testis weight and sperm production was normal. Mice lacking TNP1 exhibited a pronounced reduction in sperm mobility. Yu et al. (2000) postulated that TNP1 was not essential for histone displacement and that decreased levels of TNP1 might be partially compensated for by TNP2 and PRM2. The absence of TNP1 can lead to dysregulation of sperm protein replacement, which results in an abnormal pattern of chromatin compaction and reduced fertility.

The human TNP1 gene is located on a different chromosome than TNP2, PRM1 and PRM2 which have all been mapped to 16p13.3 (Viguie et al. 1990). The TNP2-PRM1-PRM2 chromosome locus spans 28.5 kb. The specific structure and chromosome localisation facilitates the concurrent expression of these genes. The structures of the PRM1 and PRM2 genes are highly conserved in the sperm of all mammalian species (Hernandez-Ochoa et al. 2005). The structural organisation of PRM1 and PRM2 genes implicates an important role for their transcriptional regulation. These loci are located in a large methylated domain that is flanked by a matrix attachment region (MAR). This region contains several alanine (Alu) elements, which are sites of potential methylation. The process of methylation leads to silence of gene expression while hypomethylation is responsible for chromatin binding to the nuclear matrix. In addition, the process of chromatin binding to the nuclear matrix is mediated by MAR sequences. Schmid et al. (2001) postulated that the MAR attachment process has an important role in the regulation of gene transcription but is independent of the state of methylation. The genes encoding protamines contain TATA-sequences, which play crucial roles in the initiation of transcription. The promoters of protamine genes contain cAMP response elements (CREs), which play an important role in regulating the transcription of these genes.

It has been reported that protamine expression and replacement has an important influence on normal spermatid differentiation during spermatogenesis. Therefore, any aberrations in PRM1 or PRM2 expression can lead to male infertility. Indeed, premature translation of PRM1 or PRM2 results in precocious nuclear chromatin compaction, which blocks the process of spermatid differentiation (Bunick et al. 1990; Oliva and Dixon 1990). Moreover, the sperm of infertile men exhibited an abnormal PRM1:PRM2 ratio. It was hypothesised that a normal PRM1 : PRM2 ratio was a more important factor for male fertility than the absolute concentrations of these two proteins. In conclusion, protamines are arginine-rich proteins that replace histones in the nuclear matrix in the head of sperm and play crucial roles in DNA condensation, DNA stabilisation and regulation of gene expression (Barone et al. 1994).

5. Role of sperm RNA

The molecular contribution of the ovum during fertilisation is well described but the role of sperm in this process remains unclear (Bukowska et al. 2011b). The role of spermatozoa lies first and foremost in their delivery of DNA to the oocyte. However, experimental data from several laboratories have shown that sperm contribute more than just their haploid genome. Miller et al. (2005) showed that human spermatozoa contain several molecules of mRNA, which could be defined as a specific genetic fingerprint of each step of spermatogenesis. To date about 3000 different transcripts comprising the paternal haploid genome have been described. All of these RNAs identified in spermatozoa had previously been detected in both testes. Although these transcripts were well described their role in male spermatogenesis remains unclear. Krawetz (2005) suggested that some of these mRNA, which were detected in the sperm nucleus were delivered into oocytes during fertilisation. Using the zona-free hamster egg/human sperm penetration assay Martins and Krawetz (2005) identified only protamine-2 (PRM2) and clusterin (CLU), which were consistently detected in spermatozoa and zygotes but not detected in unfertilised hamster oocytes. The role

of these transcripts is still discussed but they are implicated in fertilisation as well as zygotic and early embryonic development. It has been postulated that the paternal contribution plays an important role in several developmental processes and has a significant influence on the health of offspring. A better understanding of the roles of human sperm RNA may also hold the key to more successful somatic cell nuclear transfer as well as providing insights into the etiopathology of male infertility.

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