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Protein Acetylation and Spermatogenesis

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Abstract

Spermatogenesis refers to the developmental process of male germ cell formation from the spermatogonial stem cell to mature spermatozoa. The progression of male germ cells through the different phases of development, along with changes in cellular size and morphology, involves a coordinated change in their gene expression program at both the transcript and protein levels. It is well known that the stability, biological activity and cellular localization of proteins are regulated by post-translational modifications. In this review, we provide a brief update of current knowledge about the role of protein acetylation in mammalian spermatogenesis. Based on recent findings specific examples were cited to illustrate how these modifications are involved in controlling the different events that are important to the proper development of male germ cells.

Keywords: Spermatogenesis; Protein acetylation; Male germ cells

Spermatogenesis – A Complex Developmental Process in which Protein Post-Translational Modifications Play a Role

Spermatogenesis refers to the development of male germ cells from the spermatogonial stem cells to mature spermatozoa. The process can be divided into the mitotic, meiotic and postmeiotic (spermiogenic) phases. Spermatogonial stem cells, which are believed to be the 'A single' (As) spermatogonia, undergo self-renewal or expand mitotically to become 'A paired' (Apr), 'A aligned' (Aal), A1-4, intermediate and type B spermatogonia. Type B spermatogonia divide to become primary spermatocytes and enter a long meiotic prophase during which synapsis and recombination between homologous chromosomes occurs. Afterwards, two rounds of meiotic division take place to give rise to secondary spermatocytes, and subsequently round spermatids. The haploidic round spermatids undergo dramatic morphological changes, and transform into elongating and elongated spermatids, which are finally released into the seminiferous tubules as spermatozoa [1-5]. The complex nature of spermatogenesis is regulated and coordinated by induction of precise temporal expression of genes that are required for a particular phase of development [6-10]. It is evident that spermatogenic defects and male infertility occur when such temporal control is lost [11,12]. One of the unique features of spermatogenesis is the remarkable compaction of chromatin during the spermiogenic phase. The tight chromatin configuration leads to a cessation of gene transcription starting at the early elongating spermatid stage. To maintain the expression of gene products that are essential for completion of spermiogenesis, the mRNA transcripts of these genes are pre-synthesized and sequestered in specific cellular compartments until they are released for translation. As a result, the release and translational activation of these stored mRNA transcripts represents an additional modality for regulation of gene expression in male germ cells.

The execution of cellular activities and transmission of intracellular signals are often mediated by a transient addition or removal of specific chemical tags on proteins. Phosphorylation, acetylation, methylation, sumoylation and ubiquitination are the most common post-translational modifications involved in the regulation of different aspects of protein function, such as protein stability and turnover rate, protein-protein interaction, activation or deactivation of enzymatic activities, and cellular localization of proteins. In this article, we will discuss specific examples of the significance of the role of protein acetylation in spermatogenesis.

An overview of Protein Acetylation

Protein acetylation involves the catalytic transfer of an acetyl moiety from acetyl CoA to a free amino-group of the target protein. Two types of protein acetylation processes occur in eukaryotic cells. The first is lysine acetylation, in which the ε-amino group of a lysine residue on a polypeptide accepts the acetyl moiety. Lysine acetylation is a reversible, post-translational modification involving the addition or removal of acetyl moieties mediated by lysine acetyl transferases and deacetylases, respectively. Lysine acetylation was first identified in histone proteins [13]. Since then, an increasing number of non-histone proteins, including gene transcription-related factors, metabolic enzymes and other cellular regulators, have been reported to be ε-acetylated [14-16]. In somatic cells, acetylated core histone proteins are often identified in euchromatin and their presence at gene promoters is associated with active gene transcription [17,18]. For non-histone proteins, lysine acetylation can positively or negatively affect their biological functions [14,15].

The second type of protein acetylation is the transfer of the acetyl moiety from acetyl CoA to the α-amino group at the N-terminus of a polypeptide. The enzymes that catalyze the reaction are called N-terminal acetyltransferases (NATs). In contrast to lysine acetylation, protein N-terminal acetylation is irreversible and is a co-translational process that takes place during the synthesis of a polypeptide [19]. Six NAT complexes (namely NatA to NatF) have been identified in mammalian cells [20]. Among them, NatA is the most studied, and its potential role in spermatogenesis is discussed in the following section. It is estimated that up to 90% of mammalian proteins are α-acetylated at their N-termini [21]. Certain amino acid residues are found to be the preferred substrates for α-acetylation, but the specificity also varies with the specific NATs involved [22].

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Biological Significance of Protein Acetylation in Spermatogenesis

Facilitation of histone displacement in elongating spermatids

Since the early 1980s, studies of protein acetylation in mammalian spermatogenesis have focused on the acetylation of histones. During spermiogenesis nuclear histones are replaced by more basic transition proteins, and ultimately protamines to facilitate denser packaging of the paternal genome into the sperm head. It is estimated that approximately 85% of the histones are displaced from the chromatin [23]. In rats, histone H4 is found to be hyperacetylated in elongating spermatids just before eviction of histones [24-26]. The close timing of the two events suggests an involvement of histone H4 hyperacetylation in the histone displacement process, which is experimentally documented by inhibition of histone removal from chromatin in the absence of H4K16 acetylation [27]. Indeed, recent studies have pointed out that histone H4 hyperacetylation plays the pivotal role in initiation of histone displacement, and the functional link between histone H4 hyperacetylation and histone displacement resides in the testis-specific bromodomain protein Brdt. Brdt binds acetylated histone H4 through its bromodomains [28,29], and reorganizes acetylated chromatin in cell culture [28] and in round spermatid nuclei of the rat [30]. Specifically, the ablation of the first bromodomain of Brdt prevents histone displacement and genome compaction [31], and leads to sterility in male mice [32]. At the molecular level, Brdt interacts with Smarce1, a component of the ATP-dependent SWI/SNF family of chromatin remodeling complexes that function to destabilize histone-DNA interaction. In spermatid nuclei, the interaction between Smarce1 and Brdt is enhanced by histone H4 acetylation [30]. Meanwhile, Brdt can interact with itself [30,31]. Under conditions that promote histone acetylation, Brdt molecules interact in a head-to-tail manner, which identifies its directional alignment and probable "polymerization" on chromatin [31]. These observations suggest hyperacetylated histone H4 may serve as the signal to attract Brdt, which further recruits chromatin remodeling complexes to promote nucleosome disassembly, and ultimately facilitates the eviction of histones. Additional immunohistochemical analyses indicate core histones, besides histone H4, are hyperacetylated at specific stages of spermatogenesis, and the pattern of histone acetylation is similar between the mouse and human. In general, acetylation of core histones is observed in mitotic spermatogonia. The level of acetylation becomes reduced in pachytene spermatocytes and round spermatids (step 1-8), peaks in elongating spermatids (step 9-12), and is undetectable in elongated spermatids from step 13 onwards [33,34]. It remains unclear whether all hyperacetylated core histones are involved in the histone displacement process. Additionally, the enzymes responsible for histone hyperacetylation have not yet been fully characterized. The human CHROMO DOMAIN Y (CDY) and mouse Cdy-like (Cdyl) proteins have been suggested as the acetyl transferases that acetylate histone H4 preferentially [35]. The expression of Cdyl coincides temporally with histone H4 hyperacetylation pattern in elongating spermatids [35]. Interestingly, a reduction of histone deacetylase (Hdac1 and Hdac2) levels is also observed in elongating and condensing spermatids, and Cdyl binds the Hdacs and coenzyme A in a mutually exclusive manner [36]. These findings suggest that the acetylation level of histone H4 may be regulated by a dynamic balance between the acetyl transferase activity of Cdyl and the histone deacetylases it recruits.

Regulation of nucleo-cytoplasmic trafficking

The Dazap1/Prrp (Deleted in azoospermia associated 1/Proline-rich RNA binding protein) gene encodes a RNA-binding protein that is involved in RNA metabolic processes such as mRNA transport, splicing and translational stimulation [37-39]. Disruption of the Dazap1/Prrp gene leads to developmental and reproductive defects in mice [40]. Expression of Dazap1/Prrp is predominantly observed in the testis [41,42], in which its gene products display a dynamic expression pattern with respect to the stage of spermatogenesis. The cellular distribution of the Dazap1/Prrp protein is also dynamic: it is detected in both the nucleus and cytoplasm in late pachytene spermatocytes and round spermatids, but becomes exclusively cytoplasmic in elongated spermatids [43,44]. Shuttling of the Dazap1/Prrp protein between nucleus and cytoplasm is regulated by the acetylation of lysine residue 150 of the polypeptide. The acetylated Dazap1/Prrp proteins reside in the nuclei. In contrast, non-acetylated Prrp proteins accumulate in the cytoplasm, and are predominantly localized in the mitochondria [45]. It is postulated that retention of Dazap1/Prrp in the cytoplasm is mediated by the action of deacetylase or a blockade of acetylation, and may function to confine the protein to facilitate translation of its target transcripts in elongated spermatids. At present, the enzymes responsible for acetylation/deacetylation of Dazap1/Prrp remain unidentified.

Regulation of RNA processing and translation efficiency

Mvh (now known as Dead box polypeptide 4, Ddx4) encodes an evolutionarily conserved ATP dependent DEAD-box RNA helicase that is implicated in regulation of the translation of mRNAs. In adult mice, Mvh protein is detected exclusively in the testis, and is localized in the chromatid body, a cytoplasmic perinuclear structure that exists in pachytene spermatocytes and round spermatids [46]. The presence of mRNAs and components of the RNA-induced silencing complex (for example, Dicer, Argonaute 2 and 3, miRNAs) [47,48] suggest that the chromatoid body is the processing center for RNA storage and translational repression in male germ cells. The interaction between Mvh and Dicer [48], and RNA binding protein HuR [49] further supports the involvement of Mvh in translational regulation. Accordingly, the loss of Mvh function leads to defective differentiation of male germ cells at a stage before the appearance of chromatoid bodies [50].

In a recent study by Nagamori et al. [51], Mvh is shown to be preferentially acetylated in male germ cells during stage IV to VI of the seminiferous epithelial cycle. The acetylation of Mvh occurs during the period that the cytoplasmic histone acetyl transferase Hat1 and its cofactor p46 become enriched in the chromatoid body. Further biochemical analyses reveal that Hat1 directly acetylates Mvh at lysine residue 405 in the presence of p46, which, in turn, leads to a reduction in the RNA binding activity of Mvh. Specifically, acetylated Mvh displays weaker association with Eukaryotic initiation factor 4B (eIF4B) transcripts, which leads, at later stages (stage VII to IX), to an increase in eIF4B translation in male germ cells. The acetylation of Mvh by Hat1 may serve as a molecular control to determine the timing of translation of RNA transcripts that encode products essential to later stages of spermatogenesis. Further identification and functional validation of mRNA transcripts that become translationally active upon Mvh acetylation will prove the universality of this modification process in meiotic and post-meiotic male germ cells. It will be important to identify the signal that regulates the mobilization of Hat1 and p46 to chromatoid bodies, and determine whether the RNA-binding activities of other chromatid body RNA-binding proteins are modulated by acetylation.

Protein N-terminal Acetylation: The Unexplored Territory?

As previously mentioned, NatA is the most studied NAT. NatA is

comprised of the catalytic subunit Naa10p (also known as Ard1a), and the auxiliary subunit Naa15p (also known as Narg1, Nat1 or NATH) that docks the NatA complex to ribosomes. *Naa11* (also known as Ard1b) encodes an active retroposed version of the *Naa10* gene; and it is predominantly expressed in the mouse [52] and human [53] testis. Naa11p is functionally equivalent to Naa10p in reconstitution of NAT activity in the presence of Naa15p. Interestingly, *Naa10* and *Naa11* display opposite expression patterns during spermatogenesis. The level of *Naa10* is more abundant in pre-meiotic spermatogonia and becomes downregulated starting from meiosis. In contrast, *Naa11* expression is upregulated starting in meiosis. Nevertheless, the translation of Naa11p is delayed until the appearance of round spermatids [52]. It seems that the autosomal *Naa11* gene is induced to compensate for the loss of X-linked *Naa10* as the sex chromosomes become inactivated during male meiosis; this implies the functional importance of NatA activity in the completion of spermatogenesis. On the other hand, the Naa10p-associated NAT activity may be more important in mitotic spermatogonia, and the Naa11p-associated NAT activity is essential for post-meiotic male germ cells. In this sense, the function of Naa10p and Naa11p may have evolved to mediate cellular events related to proliferation and differentiation, respectively. This postulation is consistent with the differential expression of human NAA10p and NAA11p in the human promyelocytic NB4 cell line upon differentiation [54], and the involvement of NAA10p in promoting cancer cell proliferation. An important discovery is the identification of lysine acetyl transferase activity by Naa10p alone [55-58], which indicates that the catalytic subunit itself is enzymatically active, and displays altered substrate specificity with respect to NatA. At present there is insufficient amount of information to explain when and how Naa10p would function as a lysine acetyl transferase in place of NatA, or whether both enzymatic activities co-exist in the same cell. The high degree of sequence homology between Naa10p and Naa11p [52] suggests a similar possibility for Naa11p in male germ cells. A thorough comparison of the testicular proteome in the presence and absence of Naa10p and Naa11p activities is therefore crucial to the identification of their endogenous substrates, and the elucidation of their functional roles in male germ cell development.

Future Direction

As illustrated in the select examples, protein acetylation is involved in male germ cell development by (i) serving as a signal to trigger histone removal in elongating spermatids, (ii) inducing the release of stored mRNA transcripts for translation at the appropriate time, and (iii) controlling the cellular localization of target proteins. The protein acetylation process, thus, works in a similar fashion as protein phosphorylation in the transduction of cellular signals and mediation of different biochemical activities. The importance of histone hyperacetylation and its displacement identifies the indispensable role of acetyl group-reading proteins in the completion of spermatogenesis. These proteins in turn represent potential drug targets for male contraceptive development. One example is the thienodiazepine inhibitor (+)-JQ1, a small molecule that competes for bromodomain binding and thus blocks Brdt from recognizing acetylated histone H4. Treatment of mice with (+)-JQ1 achieves complete male sterility by reducing the production, and impairing the motility, of sperm. The contraceptive effect of (+)- JQ1 is totally reversible and the subjects show no adverse health effects [59]. These findings, in principle, suggest male infertility can be induced by chemicals that block the reading of histone acetylation marks in male germ cells. It will be important to examine if small molecules that block male germ cell-specific histone acetyl transferases may demonstrate contraceptive effects as well. Despite progress in unraveling the biological significance of protein acetylation, our current knowledge of the importance of this modification process in spermatogenesis is limited to lysine acetylation. The presence of the other Nat complexes in the testis, and the existence of testis-specific isoforms of their respective subunits have yet to be examined. Endogenous protein substrates of NatA in male germ cells remain to be identified. The availability of technologies for acetyl-proteome analysis [60], and in vivo gene silencing methodologies are expected to accelerate the identification of acetylated proteins from male germ cells and thus the elucidation of the functional role of NatA in spermatogenesis. Meanwhile, the association between the Ogden syndrome and genetic mutation of the *NAA10* coding region [61] highlights the significance of protein acetylation in human development. Would male infertility be associated with genetic mutations of the *NAA11* gene? Sequencing analysis of the *NAA11* gene between infertile and normal male subjects should be pursued to show if such a functional link exists.

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