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Advances in the relationship between protein acetylation and sperm DNA stability and sperm motility

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ABSTRACT. *Epigenetics is involved in regulating spermatogenesis and spermatogenesis. Acetylation of histone and non-histone plays a key role in the reconstruction of chromatin structure and sperm motility in spermatogenic cells. The binding protein (CBP) and P300 of cyclic adenosine monophosphate (cAMP) reaction element connexin (CREB) are two acetylase enzymes, which can acetylate core histone, and their acetylation can be inhibited by the acetylase inhibitor (INHAT). Testicle-specific Bromo domain (BRDT) proteins are conserved nucleoproteins that recognize acetylated and non-acetylated histones. In the early stage of spermatogenesis, BRDT regulates gene transcription; in the spermatogenesis stage, BRDT recognizes highly acetylated histones, which are then replaced by protamine to form dense chromatin. Deacetylation of non-histone alpha tubulin (alpha-Tubulin) decreases sperm motility, and acetylated alpha-tubulin (Ac-alpha-Tu) decreases significantly in oligoasthenospermia patients.*

Keywords: *Spermatogenesis; Histones; Heredity; Acetylation; Tubulin; Infertility, Male (male) sex*

0. Introduction

Epigenetic modification has strict temporal and spatial specificity, and plays an important role in spermatogenesis. Histone acetylation, methylation, phosphorylation and ubiquitination have become research hotspots. These modifications can affect spermatogenesis by altering the interaction between histone and DNA, histone and histone, altering chromatin structure, regulating transcription. DNA methylation in dense chromatin initiates paternal specific genetic imprinting during mitosis of primordial germ cells. During meiosis of spermatocyte, DNA

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phosphorylation promotes chromatin recombination and XY chromosome formation, and DNA ubiquitination, ubiquitination and H2AZ and H3.3 isomers incorporated into chromatin also participate in XY chromosome formation. DNA double-strand breakage, abnormal chromatin modification, changes in the expression of RNA and other non-coding RNA can lead to chromosome segregation during meiosis. This article reviews the relationship between protein acetylation and sperm DNA stability and sperm motility.

1. Histone Acetylation and DNA Stability

1.1 Sperm Formation and Histone Acetylation

During spermatogenesis, histone is highly acetylated and its chromatin is loose, which helps to convert histone to protamine. Five histones, H1, H3, H4, H2 A and H2B, have been identified. The genes encoding them have no introns and their transcription products have no ployA tails. Histones H3 and H4 are the most conserved. The core histones are H2A, H2B, H3 and H4 with relatively small molecular weight (11-15 ku). Paired histones form core histone octamer. About 147 BP of DNA coils surround core histones to form 1.75 superhelixes, thus forming the core structure of nucleosomes. As the basic unit of chromatin, nucleosomes are linked by proteins such as H1, which further fold into highly dense chromatin structure. Unlike somatic cells, germ cell DNA encapsulates different amounts of testis-specific histone H2A (TH2A), TH2B and TH3, and connective histone isomers H1t and HILS1. Acetylation of histone and histone isomers is essential for normal spermatogenesis, which can affect spermatogenesis and ensure stable transmission of genetic material by promoting gene transcription. Acetylation of non-histone also plays an important role in regulating spermatogenesis. For example, the deacetylation of alpha-tubulin decreases sperm motility, and the acetylation of alpha-tubulin (Ac-alpha-Tubulin) decreases significantly in oligoasthenospermia patients[1].

Histone acetylation refers to the introduction of hydrophobic acetyl groups into the amino-terminal lysine residues of histones. This increases the electrostatic attraction and steric hindrance between DNA and histone, weakens the interaction between DNA and histone, makes DNA easy to depolymerize, and makes chromatin

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relaxed, thus facilitating the transcription of genes by polymerase II (PolII). Histone deacetylation is related to gene silencing. During spermatogenesis, the core histones H2A and H2B, H3 and H4 of spermatogonia and pre-filamentous spermatocytes were highly acetylated; in extended spermatozoa, the acetylated core histones reappeared. Highly acetylated histones in spermatogonia and anterior spermatocyte promote gene transcription for meiosis. Apart from the common acetylation of several core histones, TH2B also has the same effect on amino terminal acetylation. Similar to core histones, acetylated TH2B was the most abundant (28.9%) in spermatogonia, but relatively low in spermatocytes (8.3%) and round spermatocytes (11.2%)[2].

1.2 Histone acetylase (HATs) and deacetylase (HDACs)

There are at least five types of HATs: CBP/p300 family, PCAF/GCN5 family, SRC/ACTR family, TAF II P250 family and MYST family. CBP/p300 can acetylate all four nucleosome core histones, and there are specific sites and multi-site acetylation modes on different histones. However, histone lysine residue acetylation is dynamically regulated by HATs and HDACs. Up to now, about 18 kinds of HDACs have been found, which can be divided into four categories: Class I includes HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10, which are homologous to yeast HDA1 and are phosphorylated-dependent and shuttle between cytoplasm and nucleus; Class II includes 7 kinds of SIRT1-7, which are homologous to yeast SIR2a; Class III includes HDAC1, HDAC2, HDAC3 and HDAC8, which are homologous to yeast transcription regulator RPD3 except HDAC3. Shuttle in the cytoplasm and nucleus, the rest in the nucleus; Category IV includes HDAC11[3].

HATs and HDACs coordinate to regulate spermatogenesis. Sperm DNA mitotic index (DFI) was positively correlated with HAT activity, while the proportion of normal sperm morphology was negatively correlated with acetylase index (HAT/HDAC activity ratio). Histone acetylation promotes the transcription of important genes during spermatogenesis. Testicular tissue-specific gene expression is regulated by various factors, such as promoter, enhancer and long-chain non-coding RNA (lncRNAs). A conserved non-coding sequence CNS1 can be used as a new enhancer of mouse testicular spermatocyte specific adhesion molecule 1 (Tcam1) gene. The transcription of lncRNA-Tcam1 is related to H3 acetylation. In

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spermatogonial cell line GC-1, acetylation of histone H3 in promoter region and dimethylation of H3 lysine at 4 sites can promote the transcription of Pou5f1 (POU domain class 5 transcription factor 1) and glial cell line derived neurotrophic factor family receptor alpha 1 (Gfr alpha 1) in spermatogonial cells, which are also subjected to HDACs and histone lysine. Effect of acid specific demethylase 1 (KDM1)[4].

Gfr alpha 1 was localized in type A spermatogonia, including As, Apair and Aligned spermatogonia, and co-localized with Pou5f1. Knockout of Gfr alpha 1 in testicular stem cells results in decreased cell proliferation, increased expression of Pou5f1 and other differentiation markers, and differentiation of stem cells into spermatogonia. Pou5f1, also known as Oct4, is highly expressed in spermatogonia. After knockout, the apoptosis of primordial germ cells increases, and its expression decreases with spermatogonial differentiation. Immunohistochemistry showed that H3K9ac was positive in human spermatogonia, spermatocytes, extended spermatocytes and ejaculated sperm. In normal male and infertile male sperm, H3K9ac binds to CRAT, G6PD, MCF2L promoters, SOX2, GAPDH, STK11IP, FLNA, PLXNA3, SH3GLB2, CTSD and other exons, and TH gene spacers. In infertile male sperm, H3K9ac binds only to CRAT, G6 promoters and SH3GLB2 promoters, and SH3GLB2 promoters. Sub [16]. H4K12ac is abundantly expressed at 2 kb before and after the transcription initiation site. The corresponding promoter expression gene of H4K12ac in mature spermatozoa is an important gene for spermatogenesis. The highest expression of PHF7 (testis-specific PHD finger protein-7) in mature spermatozoa suggests that H4K12ac may activate the expression of this gene. Exposure to benzopyrene (BaP) during neonatal period can long-term destroy testosterone production and spermatogenesis, possibly by reducing the acetylation level of steroid hormone synthesis fast regulator protein (STAR) promoter H3[5].

2. Acetylation of non-histone and sperm motility

2.1 Acetylation and deacetylation of Dazap1/Prrp, no. deleted in azoospermia associated 1/proline-rich RNA binding protein)

Acetylation of non-histone proteins regulates cytoplasmic transport. Dazap1/Prrp

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is mainly expressed in testis, and the encoded RNA connexin is involved in the metabolism of RNA. It is expressed in the cytoplasm and nucleus of pachytene spermatocyte and round spermatocyte, but only in the cytoplasm of extended spermatozoa. The shuttle of Dazap1/Prrp between cytoplasmic nuclei is regulated by the acetylation of lysine residues at 150 sites. Acetylated Dazap1/Prrp exists in the nucleus and deacetylated Prrp in the cytoplasm, especially in mitochondria. Acetylation of non-histone regulates RNA processing and translation efficiency[6].

2.2 Acetylation of Mvh

Mvh, also known as Ddx4 (Dead box polypeptide 4), encodes an evolutionarily conserved ATP-dependent DEAD box RNA helicase that regulates the transcription and translation of RNA. In the presence of p46, a cytoplasmic specific acetylase, Hat1, can directly acetylate 405 lysine residues of Mvh, resulting in a decrease in the RNA binding activity of Mvh. Furthermore, the interaction between acetylated Mvh and eIF4B (eukaryotic initiation factor 4B) was weakened, resulting in an increase in eIF4B translation at the late stage of spermatogenesis. Acetylation of non-histone proteins could affect the motility of mature sperm[7-10].

Histone acetylation is an important post-transcriptional modification in spermatogenesis. Influenced by acetylase such as CBP/p300, BRDT further regulates spermatogenesis by recognizing acetylated histones. Abnormal histone acetylation localization and expression are found in reproductive cells of infertile men and many factors participate in it. Acetylation of non-histone proteins (such as Dazap1/Prrp, Ddx4, especially Tubulin) regulates cytoplasmic transport and is associated with sperm motility.

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