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组蛋白及变体在染色质重塑中的功能：以水生动物精子发生为例*

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摘要 两性生殖中，精子作为携带父本信息的载体，是物种延续的关键因素。精子发生经历精原细胞、初级和次级精母细胞、圆形精子、成熟精子阶段。在圆形精子形成成熟精子过程中，染色质进行重塑，细胞形态发生剧烈变化，其中，组蛋白修饰和组蛋白变体在这些过程中发挥了重要作用：如甲基化主要与基因表达的激活或抑制有关；乙酰化激活转录活性并参与组蛋白沉积和 DNA 修复；磷酸化促进转录后修饰或参与 DNA 双链断裂修复；泛素化调节不同细胞途径中各式各样的蛋白质底物。组蛋白变体在调节染色体结构中发挥重要功能：如组蛋白 H1 变体在分化过程中具有抑制转录的作用；组蛋白 H2A 和 H2B 变体在精子染色质包装过程中发挥特有功能；H3.3 是 H3 最重要的变体，在细胞周期的各时期都有表达；组蛋白 H4 则是进化最慢的组蛋白之一，目前还没有发现其组蛋白变体。本文围绕组蛋白翻译后修饰，梳理了甲基化、乙酰化、磷酸化、泛素化等方面的最新进展和组蛋白变体在染色质重塑过程中的功能研究进展，随后针对各类组蛋白变体及其功能进行了总结，最后以半滑舌鳎(*Cynoglossus semilaevis*)为例简要介绍这些研究对水生动物精子发生的启示。

关键词 组蛋白；翻译后修饰；染色质重塑；精子发生

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1 组蛋白翻译后修饰及相关酶

1.1 组蛋白概述

组蛋白有 5 个主要家族：H1/H5、H2A、H2B、H3 和 H4 (Bhasin *et al*, 2006)，其基因不含内含子(Birnstiel *et al*, 1985; Liu *et al*, 1989)，是真核生物中最保守的蛋白质之一(Nelson *et al*, 2005)。组蛋白是组成真核生物染色体的基本结构蛋白，由两分子的 H2A、H2B、H3 和 H4 形成一个组蛋白八聚体，它们与 DNA 结合形成称为核小体的结构单元，这种核小体结构在真核生物基因组中，每 200 个碱基对就出现一次(Matsumura *et al*, 1970; Youngson, 1990)，是染色质的主要蛋白质成分，核小体之间再由 H1 组蛋白连接形成染色质。

表观遗传学可以被描述为不改变 DNA 序列的可遗传改变，与遗传变化(影响 DNA 突变介导的蛋白质结构)相比，表观遗传变化影响基因表达，从而影响

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细胞内蛋白质产物的数量。表观遗传变化是可逆的，并且与细胞所处环境的反应有关(Handy *et al*, 2011; Meyer *et al*, 2017; Maamar *et al*, 2018; Xavier *et al*, 2019; Allis *et al*, 2016)。动物细胞中表现出 3 组表观遗传变化：DNA 甲基化、组蛋白翻译后修饰和非编码 RNA (ncRNA)，本文将重点关注组蛋白修饰这一过程。

组蛋白修饰是通过在核心组蛋白的尾部存在的氨基酸(最常见的是赖氨酸)上添加一个官能团形成的(Peixoto *et al*, 2020)。组蛋白修饰的主要作用是通过染色质凝聚和解聚来控制基因表达(Zhang *et al*, 2001)，也可以为各种蛋白质提供结合部位(Patel *et al*, 2013)。在动物中已报道的组蛋白修饰有甲基化、乙酰化、磷酸化、泛素化、SUMO 化、ADP 核糖化和短链赖氨酸酰化等(Peixoto *et al*, 2020; Jha *et al*, 2017; Sabari *et al*, 2017)。

1.2 组蛋白甲基化

组蛋白甲基化是甲基转移到赖氨酸(K)的 ε-氨基或精氨酸(R)残基的 ω-胍基上的修饰，主要位于组蛋白 H3 或 H4 的 N 端。其中，赖氨酸残基能被单甲基化、二甲基化或三甲基化，而精氨酸残基只能被单甲基化或二甲基化(Chioccarelli *et al*, 2020)。甲基化不会改变组蛋白修饰的电荷势，主要与基因表达的激活或抑制有关(Zhang *et al*, 2001)。常见组蛋白甲基化修饰位点与功能见表 1 (Cell Signaling 网站)。组蛋白甲基转移酶(HMTs)是组蛋白甲基化的催化剂，负责赖氨酸甲基化的 HMT 称为组蛋白赖氨酸甲基转移酶(HKMT)，负责精氨酸残基甲基化的 HMT 称为精氨酸甲基转移酶(PRMT)(Godmann *et al*, 2007)。大多数赖氨酸甲基转移酶的催化结构域含有 SET 结构域(Marmorstein, 2003; Yang *et al*, 2018)。然而，存在一种独特的赖氨酸甲基转移酶 DOT1L(类似端粒沉默的干扰因子)，其缺乏固定的结构域，只催化核心组蛋白 H3 (H3K79me)赖氨酸 79 残基的甲基化(Yang *et al*, 2018)。HMT 将其底物甲基化到特定水平，同时氨基酸变化也可以改变甲基化活性。例如，粗糙脉孢菌(*Neurospora crassa*)组蛋白 H3K9 甲基转移酶突变

表 1 常见甲基化修饰位点和功能(Cell Signaling 网站)

Tab.1 Common methylation modification sites and functions (Cell Signaling website)

组蛋白 Histone	位点 Site	组蛋白修饰酶 Histone-modifying enzymes	功能 Function
H1	Lys26	组蛋白甲基转移酶 Ezh2 Histone methyltransferase Ezh2	转录沉默 Transcriptional silencing
H2A	Arg3	精氨酸甲基转移酶 PRMT1/6、PRMT5/7 Arginine methyltransferase PRMT1/6, PRMT5/7	转录激活 Transcriptional activation 转录抑制 Transcriptional repression
H3	Arg2	精氨酸甲基转移酶 PRMT5、PRMT6 Arginine methyltransferase PRMT5, PRMT6	转录抑制 Transcriptional repression
	Arg8	精氨酸甲基转移酶 PRMT5、PRMT2/6 Arginine methyltransferase PRMT5, PRMT2/6	转录激活 Transcriptional activation 转录抑制 Transcriptional repression
	Arg17	精氨酸甲基转移酶 CARM1 Arginine methyltransferase CARM1	转录激活 Transcriptional activation
	Arg26	精氨酸甲基转移酶 CARM1 Arginine methyltransferase CARM1	转录激活 Transcriptional activation
	Arg42	精氨酸甲基转移酶 CARM1 Arginine methyltransferase CARM1	转录激活 Transcriptional activation
	Lys4	H3K4 甲基转移酶 Set1(酿酒酵母) H3K4 methyltransferase Set1 (*Saccharomyces cerevisiae*)	允许常染色质(二甲基化) Permissive euchromatin (di-Me)
		H3K4 甲基转移酶 Set7/9(脊椎动物) H3K4 methyltransferase Set7/9 (vertebrates)	转录激活(三甲基化) Transcriptional activation (tri-Me)
		H3K4 甲基转移酶 MLL、ALL-1 H3K4 methyltransferase MLL, ALL-1	转录激活 Transcriptional activation
		组蛋白甲基转移酶 Ash1 Histone methyltransferase Ash1	转录激活 Transcriptional activation

续表 1

组蛋白 Histone	位点 Site	组蛋白修饰酶 Histone-modifying enzymes	功能 Function
H3	Lys9	组蛋白甲基转移酶 Suv39h Histone methyltransferase Suv39h E3 泛素连接酶 Clr4 E3 ubiquitin ligase Clr4	转录沉默(三甲基化) Transcriptional silencing (tri-Me)
		组蛋白赖氨酸甲基转移酶 G9a Histone lysine methyltransferase G9a	转录抑制 Transcriptional repression 基因印迹 Genomic imprinting
		组蛋白甲基转移酶 SETDB1 Histone methyltransferase SETDB1	转录抑制(三甲基化) Transcriptional repression (tri-Me)
		Dim-5(粗糙脉孢菌) Dim-5(*N. crassa*) Kryptonite(拟南芥) Kryptonite (*Arabidopsis thaliana*)	DNA 甲基化(三甲基化) DNA methylation (tri-Me)
		乙酰鞘氨醇酰胺水解酶 Ash1 N-acyl sphingosine amide hydrolase Ash1	转录激活 Transcriptional activation
	Lys27	组蛋白甲基转移酶 Ezh2 Histone methyltransferase Ezh2	转录沉默 Transcriptional silencing X 失活(三甲基化)X inactivation (tri-Me)
		组蛋白赖氨酸甲基转移酶 G9a Histone lysine methyltransferase G9a	转录沉默 Transcriptional silencing
	Lys36	组蛋白甲基转移酶 SET2 Histone methyltransferase SET2	转录激活(延伸) Transcriptional activation (elongation)
	Lys79	组蛋白赖氨酸甲基转移酶 Dot1 Histone lysine methyltransferase Dot1	常染色质 Euchromatin 转录激活(延伸) Transcriptional activation (elongation) 检查点反应 Checkpoint response
H4	Arg3	精氨酸甲基转移酶 PRMT1/6 Arginine methyltransferase PRMT1/6	转录激活 Transcriptional activation
		精氨酸甲基转移酶 PRMT5/7 Arginine methyltransferase PRMT1/6	转录抑制 Transcriptional repression
	Lys20	组蛋白甲基转移酶 PR-Set7 Histone methyltransferase PR-Set7	转录沉默 Transcriptional silencing
		组蛋白甲基转移酶 Suv4-20h Histone methyltransferase Suv4-20h	异染色质(三甲基化) Heterochromatin (tri-Me)
		N-乙酰鞘氨醇酰胺水解酶 Ash1(黑腹果蝇) N-acyl sphingosine amide hydrolase Ash1 (*D. melanogaster*)	转录激活 Transcriptional activation
		组蛋白甲基转移酶 SET9 Histone methyltransferase SET9	检查点反应 Checkpoint response

(F281Y)后，从三甲基酶转变为单甲基酶，在人类(*Homo sapiens*) DIM5 同源组蛋白 N-赖氨酸甲基转移酶 2 基因(G9a)突变后(F1205Y)，从去甲基酶转变为单甲基酶(Collins *et al*, 2005)。在斑马鱼(*Danio rerio*)中，prmt5 (精氨酸甲基转移酶 5)缺失后，将影响斑马鱼性腺细胞的正常迁移，最终导致性腺细胞凋亡。研究表明，prmt5 在脊椎动物性腺发育过程中扮演着十分重要的角色(Zhu *et al*, 2019)。研究人员系统地检测了组蛋白修饰 H3K4me3、H3K27ac、H3K27me3 和 H3K36me3 在斑马鱼精子、卵子、4 细胞时期、256 细胞时期和穹顶期胚胎基因组内的分布特性。结果表明，精子基因组增强子上的“去记忆化(dememorization)”在受精之前就已经开始发生(Wu *et al*, 2018)。组蛋白去甲基化是由组蛋白去甲基酶(HDMTs)执行的(Yang *et al*, 2018)。已报道的部分组蛋白甲基转移酶类和组蛋白去甲基酶类见表 2 (Godmann *et al*, 2007; Marmorstein *et al*, 2003; Yang *et al*, 2018; Collins *et al*, 2005; Zhai *et al*, 2017)。

表 2 组蛋白甲基转移酶类和组蛋白去甲基酶类

Tab.2 Histone methyltransferases and histone demethylases

组蛋白甲基转移酶类 Histone methyltransferases (HMTs)	组蛋白去甲基酶类 Histone demethylases (HDMTs)
赖氨酸 Lysine	赖氨酸 Lysine
包含 SET 结构域(组蛋白尾部) Contains the SET domain (histone tail)	KDM1/LSD1(赖氨酸特异性脱甲基酶 1) KDM1/LSD1 (lysine specific demethylase 1)
包含非 SET 结构域(组蛋白核心) Contains a non-SET domain (histone core)	JmjC (包含 Jumonji 域) JmjC (including Jumonji domain)
精氨酸 Arginine	精氨酸 Arginine
PRMT(蛋白质精氨酸甲基转移酶)家族 PRMT (protein arginine methyltransferase) family	PAD4/PADI4

1.3 组蛋白乙酰化

组蛋白乙酰化是发现最早的影响转录调控的组蛋白修饰之一，也是目前研究最多的。组蛋白乙酰化是在组蛋白乙酰转移酶(HATs)的作用下，在核心组蛋白(H2A、H2B、H3 和 H4) N-末端赖氨酸侧链的 ε-氨基上加入乙酰基。乙酰化中和了赖氨酸残基的正电荷电势，削弱了 DNA 和组蛋白之间的相互作用力，导致染色质松动并激活转录活性。此外，溴结构域蛋白与乙酰基残基结合并使染色质重塑，从而参与组蛋白沉积和 DNA 修复(Legube *et al*, 2003)。常见组蛋白乙酰化修饰位点和功能见表 3 (Cell Signaling 网站)。组蛋白乙酰转移酶 HAT 分为 A 型或 B 型。A 型酶位于细胞核中，含有溴结构域，能够结合已经嵌入染色质结构中的乙酰化组蛋白。B 型乙酰转移酶位于细胞质中，只能修饰新合成的组蛋白。因此，B 型酶主要乙酰化细胞质中新合成的组蛋白，并且更保守(Thiagarajan *et al*, 2016)。组蛋白脱乙酰酶(HDAC)负责组蛋白的去乙酰化过程，根据功能和序列相似性，HDAC 蛋白可分为四大类。Ⅰ类、ⅡA 类和ⅡB 类被视为“经典”HDAC，其活性可被曲古抑菌素 A(TSA)抑制，而Ⅲ类是 NAD^+依赖性蛋白家族，不受 TSA 影响。Ⅳ类仅与其他类存在序列相似性，被视为非典型类。与 HAT 相比，HDAC 的位点特异性较低，通常会相互产生大型复合物和额外的蛋白质(Milazzo *et al*, 2020)。研究表明，斑马鱼的生殖质聚集和 PGC 特化需要 Sinhcaf 介导的组蛋白去乙酰化的调控作用(Tao *et al*, 2022)。研究人员母源敲降斑马鱼 3 个关键组蛋白乙酰转移酶，这种敲降导致了胚胎乙酰化的降低并引起基因组激活的异常以及胚胎死亡(Zhang *et al*, 2018)。

1.4 组蛋白磷酸化

组蛋白磷酸化是氨基酸侧链的羟基加入磷酸基团，主要发生在组蛋白 N 端的丝氨酸、苏氨酸和酪氨酸上。磷酸化为组蛋白引入了额外的负电荷电势，改变了染色质的结构。磷酸基团的存在增加了转录因子和酶与 DNA 结合的能力，促进转录后修饰(PTMs)或参与 DNA 双链断裂(DSB)修复。所有组蛋白均可被磷酸化并且磷酸化位点多变，如在细胞分裂期间，H1 的 1~3 个丝氨酸可发生磷酸化，而在有丝分裂时期，H1 有 3~6 个丝氨酸或苏氨酸发生磷酸化，其他 4 个核心组蛋白的磷酸化可以发生在 N 末端区域的丝氨酸残基上(Chioccarelli *et al*, 2020)，常见组蛋白磷酸化修饰位点与功能见表 4 (Cell Signaling 网站)。鱼类研究揭示了组蛋白磷酸化与精子发生、精子成熟和受精过程密切相关。虹鳟(*Oncorhynchus mykiss*)转铁蛋白已从精浆中分离出来，并在所有检测到的丝氨酸、苏氨酸和酪氨酸残基处均被磷酸化。此外，不同的磷酸化谱可以触发不同的精子激活机制，这表明蛋白质磷酸化在各种鱼类中具有关键的调节作用。睾丸精子磷酸化的研究不仅有助于阐明性腺分化的生物学基础，而且为鉴定水产鱼类性别控制调节的生物标志物提供了新的视角。磷酸化作为经典的组蛋白修饰在精子发生中广为报道，磷酸蛋白质组学技术被用于确定雄性不育或生殖缺陷的潜在机制。如在半滑舌鳎(*Cynoglossus semilaevis*)中发现 RAN 结合蛋白(RanBP2)存在 4 个磷酸化位点，并作为中心分子与多个细胞周期蛋白(Cdc5l 和 Cdc40)相互作用(Li *et al*, 2023)。在中华绒螯蟹(*Eriocheir sinensis*)中发现 H4 组蛋白磷酸化与雄蟹的繁殖能力密切相关，可作为精子成熟度的表观遗传标记(Zhang *et al*, 2020)。

表 3　常见组蛋白乙酰化修饰位点和功能(Cell Signaling 网站)

Tab.3　Common histone acetylation modification sites and functions(Cell Signaling website)

组蛋白 Histone	位点 Site	组蛋白修饰酶 Histone-modifying enzymes	功能 Function
H2A	Lys4 (酿酒酵母) Lys4 (*S. cerevisiae*)	组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
	Lys 5 (哺乳动物) Lys 5 (mammals)	组蛋白赖氨酸乙酰转移酶 5 Tip60 Histone lysine acetyltransferase 5 Tip60 组蛋白乙酰转移酶 p300/CBP Histone acetyltransferase p300/CBP	转录激活 Transcriptional activation
	Lys7 (酿酒酵母) Lys7 (*S. cerevisiae*)	组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
H2B	Lys5	组蛋白乙酰转移酶 p300 Histone acyltransferase p300 组蛋白乙酰转移酶 ATF2 Histone acetyltransferase ATF2	转录激活 Transcriptional activation
	Lys11 (酿酒酵母) Lys11 (*S. cerevisiae*)	组蛋白乙酰转移酶 Gcn5 Histone acetyltransferase Gcn5	转录激活 Transcriptional activation
	Lys12 (哺乳动物) Lys12 (mammals)	组蛋白乙酰转移酶 p300/CBP Histone acetyltransferase p300/CBP 组蛋白乙酰转移酶 ATF2 Histone acetyltransferase ATF2	转录激活 Transcriptional activation
	Lys15 (哺乳动物) Lys15 (mammals)	组蛋白乙酰转移酶 p300/CBP Histone acetyltransferase p300/CBP 组蛋白乙酰转移酶 ATF2 Histone acetyltransferase ATF2	转录激活 Transcriptional activation
	Lys16 (酿酒酵母) Lys16 (*S. cerevisiae*)	组蛋白乙酰转移酶 Gcn5 Histone acetyltransferase Gcn5 组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
	Lys20	组蛋白乙酰转移酶 p300 Histone acyltransferase p300	转录激活 Transcriptional activation
H3	Lys4 (酿酒酵母) Lys4 (*S. cerevisiae*)	组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
	Lys9	组蛋白乙酰转移酶 Gcn5 Histone acetyltransferase Gcn5 类固醇受体辅助激活因子 SRC-1 Steroid receptor coactivator SRC-1	转录激活 Transcriptional activation
	Lys14	组蛋白乙酰转移酶 Gcn5 Histone acetyltransferase Gcn5 组蛋白乙酰转移酶 PCAF Histone acetyltransferase PCAF	转录激活 Transcriptional activation
		组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
		组蛋白赖氨酸乙酰转移酶 5 Tip60 Histone lysine acetyltransferase 5 Tip60	DNA 修复 DNA repair
		类固醇受体辅助激活因子 SRC-1 Steroid receptor coactivator SRC-1	转录激活 Transcriptional activation
		组蛋白乙酰转移酶延伸复合物催化亚基 ELP3 Histone acetyltransferase extension complex catalytic subunit ELP3	转录激活(延伸) Transcriptional activation (elongation)

续表 3

组蛋白 Histone	位点 Site	组蛋白修饰酶 Histone-modifying enzymes	功能 Function
H3	Lys14	hTFⅢC90	RNA 聚合酶Ⅲ转录 RNA polymeraseⅢ transcription
		TAF1	RNA 聚合酶Ⅱ转录 RNA polymeraseⅡ transcription
		组蛋白乙酰转移酶 Sas2 Histone acetyltransferase Sas2	常染色质 Euchromatin
		组蛋白乙酰转移酶 Sas3 Histone acetyltransferase Sas2	转录激活(延伸) Transcriptional activation (elongation)
		组蛋白乙酰转移酶 p300 Histone acyltransferase p300	转录激活 Transcriptional activation
	Lys18	组蛋白乙酰转移酶 Gcn5 Histone acetyltransferase Gcn5	转录激活 Transcriptional activation
			DNA 修复 DNA repair
		组蛋白乙酰转移酶 p300/CBP Histone acetyltransferase p300/CBP	DNA 复制 DNA replication
			转录激活 Transcriptional activation
	Lys23	组蛋白乙酰转移酶 Gcn5 Histone acetyltransferase Gcn5	转录激活 Transcriptional activation
			DNA 修复 DNA repair
		组蛋白乙酰转移酶 Sas3 Histone acetyltransferase Sas3	转录激活(延伸) Transcriptional activation (elongation)
		组蛋白乙酰转移酶 p300/CBP Histone acetyltransferase p300/CBP	转录激活 Transcriptional activation
	Lys27	组蛋白乙酰转移酶 p300/CBP Histone acetyltransferase p300/CBP	转录激活 Transcriptional activation
	Lys36	组蛋白乙酰转移酶 Gcn5 Histone acetyltransferase Gcn5	转录激活 Transcriptional activation
	Lys56 (酿酒酵母) Lys56 (*S. cerevisiae*)	Spt10	转录激活 Transcriptional activation
			DNA 修复 DNA repair
H4	Lys5	组蛋白乙酰转移酶 Hat1 Histone acetyltransferase Hat1	组蛋白沉积 Histone deposition
		组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
		组蛋白赖氨酸乙酰转移酶 5 Tip60 Histone lysine acetyltransferase 5 Tip60	DNA 修复 DNA repair
		组蛋白乙酰转移酶 ATF2 Histone acetyltransferase ATF2	转录激活 Transcriptional activation
		组蛋白乙酰转移酶 p300 Histone acyltransferase p300	转录激活 Transcriptional activation
	Lys8	组蛋白乙酰转移酶 Gcn5 Histone acetyltransferase Gcn5	转录激活 Transcriptional activation
		组蛋白乙酰转移酶 PCAF Histone acetyltransferase PCAF	

续表 3

组蛋白 Histone	位点 Site	组蛋白修饰酶 Histone-modifying enzymes	功能 Function
H4	Lys8	组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
		组蛋白赖氨酸乙酰转移酶 5 Tip60 Histone lysine acetyltransferase 5 Tip60	DNA 修复 DNA repair
		组蛋白乙酰转移酶 ATF2 Histone acetyltransferase ATF2	转录激活 Transcriptional activation
		组蛋白乙酰转移酶延伸复合物催化亚基 ELP3 Histone acetyltransferase extension complex catalytic subunit ELP3	转录激活(延伸) Transcriptional activation (elongation)
		组蛋白乙酰转移酶 p300 Histone acyltransferase p300	转录激活 Transcriptional activation
	Lys12	组蛋白乙酰转移酶 Hat1 Histone acetyltransferase Hat1	组蛋白沉积 Histone deposition 端粒沉默 Telomeric silencing
		组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
		组蛋白赖氨酸乙酰转移酶 5 Tip60 Histone lysine acetyltransferase 5 Tip60	DNA 修复 DNA repair
		组蛋白乙酰转移酶 p300 Histone acyltransferase p300	转录激活 Transcriptional activation
	Lys16	组蛋白乙酰转移酶 Gcn15 Histone acetyltransferase Gcn15	转录激活 Transcriptional activation
		MOF(黑腹果蝇) MOF(*D. melanogaster*)	转录激活 Transcriptional activation
		组蛋白乙酰转移酶 Esa1 Histone acetyltransferase Esa1	转录激活 Transcriptional activation
		组蛋白赖氨酸乙酰转移酶 5 Tip60 Histone lysine acetyltransferase 5 Tip60	DNA 修复 DNA repair
		组蛋白乙酰转移酶 ATF2 Histone acetyltransferase ATF2	转录激活 Transcriptional activation
		组蛋白乙酰转移酶 Sas2 Histone acetyltransferase Sas2	常染色质 Euchromatin
	Lys91 (酿酒酵母) Lys91 (*S.cerevisiae*)	组蛋白乙酰转移酶 Hat1/Hat2 Histone acetyltransferase Hat1/Hat2	染色质组装 Chromatin assembly

1.5　组蛋白泛素化

泛素是一种由 76 个氨基酸组成的小蛋白，组蛋白泛素化是指将泛素加入侧链赖氨酸残基的 ε-氨基上，常见泛素化修饰位点与功能见表 5 (Cell Signaling 网站)。泛素化过程是由 3 种酶共同作用的级联反应，包括泛素激活酶(E1)、泛素结合酶(E2)和泛素连接酶(E3) (Sun *et al*, 2021)，泛素化被去泛素化酶(DUBS)去除。有研究表明，泛素结合酶 E2 在克氏原螯虾(*Procambarus clarkii*)和大黄鱼(*Larimichthys crocea*)等物种的配子发生和性腺发育过程等方面都有重要的调控作用(韩坤煌等, 2017; 钱照君等, 2016)。研究发现，在半滑舌鳎中，*Ubc9* 基因作为一种 E2 结合酶基因，参与了胚胎发生和性别修饰(Hu *et al*, 2013)。中国对虾(*Penaeus chinensis*)在感染 WSSV 后通过泛素–蛋白酶体途径(ubiquitin-proteasome pathway, UPP)对某些特殊靶蛋白进行选择性降解，影响细胞的凋亡过程(李旭鹏等, 2018)。泛素羧基端水解酶 5 基因(UCHL5) 与脊尾白虾(*Exopalaemon carinicauda*)卵巢发育有密切关系(高威等, 2022)。泛素化包括单一泛素化和多泛素化。单一泛素化主要通过改变染色质结构或为其他蛋白质复合体提供相互作用来控制基因

的表达(Osley *et al*, 2006)，而多泛素化参与了广泛的过程，包括蛋白–蛋白相互作用、蛋白降解等。泛素化能够调节不同细胞途径中各式各样的蛋白质底物。泛素化在鱼类性别分化和精子发生中发挥着重要作用。鳗鱼(*Monopterus albus*)中泛素羧基末端水解酶 UCH-L1 (一种去泛素酶)在性腺转化和配子发生过程中高表达，并可能发挥重要的调节作用(Sun *et al*, 2008)；虹鳟中组蛋白泛素化严格调控精子发生过程中

表 4 常见组蛋白磷酸化修饰位点与功能(Cell Signaling 网站)

Tab.4 Common histone phosphorylation modification sites and functions(Cell Signaling website)

组蛋白 Histone	位点 Site	组蛋白修饰酶 Histone-modifying enzymes	功能 Function
H1	Ser27	未知 Unknown	转录激活 Transcriptional activation 染色质解缩 Chromatin decondensation
H2A	Ser1	MSK1	转录抑制 Transcriptional repression
H2A	Ser129 (酿酒酵母) Ser122 (*S. cerevisiae*)	Mec1, Tel1	DNA 修复 DNA repair
	Ser139 (哺乳动物 H2A.X) Ser139 (mammalian H2A.X)	ATR, ATM, DNA-PK	DNA 修复 DNA repair
	Thr119 (黑腹果蝇) Thr119 (*D. melanogaster*)	NHK1	有丝分裂 Mitosis
	Thr120 (哺乳动物) Thr120 (mammals)	Bub1 VprBP	有丝分裂 Mitosis 转录抑制 Transcriptional repression
	Thr142 (哺乳动物 H2A.X) Thr142 (mammalian H2A.X)	WSTF	细胞凋亡 Apoptosis DNA 修复 DNA repair
H2B	Ser10 (酿酒酵母) Ser10 (*S. cerevisiae*)	Ste20	细胞凋亡 Apoptosis
	Ser14 (脊椎动物) Ser14 (vertebrates)	Mst1	细胞凋亡 Apoptosis
	Ser33 (黑腹果蝇) Ser33 (*D. melanogaster*)	TAF1	转录激活 Transcriptional activation
	Ser36	AMPK	转录激活 Transcriptional activation
H3	Ser10	Aurora-B kinase	有丝分裂 Mitosis 减数分裂 Meiosis
		MSK1, MSK2	立早基因激活 Immediate-early gene activation
		IKK-α	转录激活 Transcriptional activation
		Snf1	转录激活 Transcriptional activation
	Ser28 (哺乳动物)	Aurora-B kinase	有丝分裂 Mitosis
	Ser28 (mammals)	MSK1, MSK2	立早基因激活 Immediate-early gene activation
	Thr3	Haspin/Gsg2	有丝分裂 Mitosis
	Thr11 (哺乳动物) Thr11 (mammals)	Dlk/Zip	有丝分裂 Mitosis
	Tyr41	JAK2	转录激活 Transcriptional activation
	Tyr45	PKCδ	细胞凋亡 Apoptosis
H4	Ser1	CK2	DNA 修复 DNA repair

鱼精蛋白的替代(Nickel *et al*, 1987)；在塞内加尔鳎鱼(*Solea senegalensis*)中发现了 400 多个与精子发生相关的基因，其中包括多个泛素化相关基因(Forne *et al*, 2011)；半滑舌鳎精子发生过程中，E3 泛素连接酶基因 *neurl3* 和 *Cs-rchy1* 在雄性性腺分化与精子发育中起着重要作用(Sun *et al*, 2021; Xu *et al*, 2016)。

表 5　常见泛素化修饰位点与功能(Cell Signaling 网站)

Tab.5　Common ubiquitin modification sites and functions (Cell Signaling website)

组蛋白 Histone	位点 Site	组蛋白修饰酶 Histone-modifying enzymes	功能 Function
H2A	Lys119 (哺乳动物) (mammals)	Ring2	精子发生 Spermatogenesis
H2B	Lys120 (哺乳动物) (mammals)	UbcH6	减数分裂 Meiosis
	Lys123 (酿酒酵母) (*S. cerevisiae*)	Rad6	转录激活 Transcriptional activation
			常染色质 Euchromatin

1.6　其他组蛋白修饰

除去以上提到的常见修饰，其他少见的修饰也存在于组蛋白尾部，如 SUMO 化(由类似泛素的小修饰物修饰)、巴豆化和丁酰化(S)等。然而，到目前为止，关于它们作用的文献资料很少(Cavalieri *et al*, 2021; Wang *et al*, 2019)，因此，本文只进行简要描述。已有研究表明，SUMO 化发生在丝氨酸残基上，其在缺陷的精子质基上也有发生。组蛋白巴豆化是调控精子质量(活力和形态)的标志，与染色质重构和结构性异染色质有关(Talamilo *et al*, 2021; Metzler-Guillemain *et al*, 2008; Kekalainen *et al*, 2022; Marchiani *et al*, 2014; Vigodner *et al*, 2020)。赖氨酸巴豆化(KCR)是组蛋白赖氨酸酰化修饰之一，巴豆化主要在组蛋白赖氨酸的ε-氨基中发挥关键作用。丁酰化与雄性生殖细胞减数分裂和减数分裂后细胞中活跃的基因转录有关(Dai *et al*, 2014)，同时发现，其在小鼠(*Mus musculus*)中与精子核蛋白交换和精子头部形成密切相关(Meyer-Ficca *et al*, 2011、2015)。

2　组蛋白在染色质重塑和精子发生中的功能

2.1　精子发生过程中染色质重塑的动态及调控

精子发生过程中存在独特的染色质重塑过程，超过 90%的核心组蛋白被精巢特异性组蛋白变体取代，然后是过渡蛋白(TPS)，最后是鱼精蛋白(PRM) (Balhorn *et al*, 1989; Russell *et al*, 1990)。富含赖氨酸和半胱氨酸残基的鱼精蛋白不同于核心组蛋白，它们可以将精子基因组包装成一种独特的环状染色质结构(Luger *et al*, 1997)。精子染色质形成含有约 50~100 kb DNA 的环状，导致染色质结构比基于核小体的染色质浓缩 5~10 倍(Balhorn *et al*, 1989; Poccia *et al*, 1986)。这种结构对于 DNA 进入比间期体细胞核小 7 倍的细胞核中是至关重要的，并保护父本的基因组免受物理和化学损害。较为特殊的一个物种为斑马鱼，其精子染色体不存在鱼精蛋白–组蛋白交换过程，早期胚胎发育过程中也没有广泛的 DNA 去甲基化过程(Zhang *et al*, 2018)。

大量研究表明，广泛存在的染色质重塑是精子发生的关键步骤(Balhorn *et al*, 1989; Russell *et al*, 1990; Royo *et al*, 2016; Yoshida *et al*, 2018)。但由于这一过程本身极其复杂，且目前尚无体外实验系统对其进行研究，组蛋白向鱼精蛋白转化的分子和调控机制尚需进一步阐明。此外，染色质重构体被认为是在精子发生过程中加速染色质广泛重塑所必需的，但它们在重塑过程中的作用尚不清楚(Yamaguchi *et al*, 2018)。

简而言之，鱼精蛋白取代组蛋白的过程需要(Ⅰ)组蛋白翻译后修饰(PTMs)促进基于组蛋白的染色质结构的打开，特别是组蛋白超乙酰化并掺入组蛋白变体；(Ⅱ)溴结构域蛋白与乙酰基残基结合并使染色质重塑；(Ⅲ)DNA 链断裂的形成和修复；以及(Ⅳ)鱼精蛋白的掺入(Rousseaux *et al*, 2008; Hud *et al*, 1993; Ward *et al*, 1991; Braun *et al*, 2001; Balhorn *et al*, 1977; Gatewood *et al*, 1990; Erkek *et al*, 2013; Ihara *et al*, 2014; Carone *et al*, 2014; Samans *et al*, 2014)。本文重点关注(Ⅰ)这一过程。

2.2　组蛋白变体取代核心组蛋白调控精子发生

组蛋白变体是指连接组蛋白 H1 和 H5 及其变体，以及核心组蛋白 H2A、H2B、H3 和 H4 的变体。相比之下，组蛋白变体更容易被甲基化、乙酰化、磷酸化、SUMO 化和泛素化修饰(Champroux *et al*, 2018; Boussouar *et al*, 2008)。组蛋白变体可以改变核小体和染色质结构调控基因转录。组蛋白变体不仅在 S 期表达，也在其他各个细胞周期表达，但其整体表达水平比较低。这些组蛋白变体具有独特的生物物理特性，一些可调节核小体结构，而另一些可与基因组的特定区域结合(Kamakaka *et al*, 2005)。组蛋白变体基因结构也不同于核心组蛋白基因的结构，它们含有内含子，通常合成 RNA 需要合成一个 polyA 尾巴(Old *et al*, 1984)。作为精子发生的重要调控手段，染色质重塑主要是通过整合精巢特异性组蛋白变体的翻译后修饰(PTMs)来发生的(Royo *et al*, 2016; Yoshida *et al*, 2018)。在特定的生殖细胞类型中检测到不同的

H1/H5、H2A、H2B 和 H3 组蛋白变体，或者精巢特异表达组蛋白变体(Greiner *et al*, 2004; Drabent *et al*, 1996; Yan *et al*, 2003)。然而，目前尚未检测到精巢特异的 H4 变体。本文主要关注 H1 及其变体，以及 H2A、H2B 和 H3 变体。

2.2.1 H1 及其变体　　在 5 类组蛋白中，组蛋白 H1 的多样性最大。在哺乳动物中，已鉴定出 11 种 H1 变体，包括 7 种体细胞 H1 变体(H1.0、H1.1、H1.2、H1.3、H1.4、H1.5 和 H1x)和 4 种生殖细胞特异性 H1 变体(H1T、H1T2、H1LS1 和 H1oo)。其中，H1T、H1T2 和 HILS1 是睾丸特异表达的 H1 变体。H1.1~H1.5 是体细胞中普遍表达的 H1 的主要类型，但它们的表达在不同的组织和细胞类型中受到严格调控。与体细胞 H1 相比，H1T 对 DNA 的结合亲和力较低，对染色质的浓缩程度较小(Pan *et al*, 2016)。组蛋白 H1T 仅存在于粗线期精母细胞和早期圆形精子细胞中，占大鼠(*Rattus norvegicus*) H1 总量的 55% (Lennox *et al*, 1984; Doenecke *et al*, 1997)。缺乏 H1.1 或 H1T 的小鼠具有生育能力，并显示出正常的精子发生。与 H1T 不同之处是，H1T2 高度富集了精氨酸残基和 S/TPXK/R 位点(Martianov *et al*, 2005)。H1T2 存在于早期精子细胞的细胞核中，在圆形和细长的精子细胞中具有特殊的极性定位，且与精子细胞核顶端的染色质有关。小鼠体内 H1T2 的缺失严重损害了染色质凝聚和圆形精子细胞的形态转化。这些结果表明，H1T2 是正常精子发生所必需的，并在染色质凝聚和确定细长精子细胞的细胞极性方面发挥关键作用。H1T2 已被发现与鱼精蛋白相互作用，它的消除导致鱼精蛋白含量的减少，这表明 H1T2 在组蛋白到鱼精蛋白的转变中起着功能作用。H1T2 和组蛋白甲基转移酶 Ezh2 相互作用并共存于圆形精子细胞的顶端，这可能表明在精子细胞伸长过程中，H1T2 通过调节组蛋白 H3K27 的甲基化调控染色质重塑从而发挥作用(Tanaka *et al*, 2005)。H1T2 和 HILS1 是关系最远、保守程度最低的 H1 变体。H1T2 和 HILS1 的表达仅限于精子细胞。HILS1 在早期和伸长的精子细胞中表达，其核定位在很大程度上与过渡蛋白和鱼精蛋白的定位重叠。HILS1 比 H1T2 具有更高的 DNA 结合亲和力，这可能是晚期精子细胞染色质凝聚增加的原因(Yan *et al*, 2003; Tanaka *et al*, 2005)。

2.2.2 H2A 和 H2B 变体　　H2A 和 H2B 的一些变体已经在结构和功能分析中进行了研究，与典型的核心组蛋白相比，它们的稳定性较差。在核小体中，精巢 H2A 和 H2B 变体在与体细胞核心组蛋白相互作用时将导致核小体的不稳定。组蛋白 H2A 及其变体的差异主要表现在 C 端尾部的序列差异和其长度(Costanzi *et al*, 1998)。已经在哺乳动物中发现了多种睾丸特异的 H2A 和 H2B 组蛋白变体，包括 TH2A、TH2B、H2AL1、H2AL2、H2AL3 和 H2A.B 等(Wolffe *et al*, 1997; Bucci *et al*, 1982)。H2AL2 在减数分裂后的伸长精子细胞中特异表达，此时，TPS 也开始积累，这表明其对精子基因组组装和雄性生育是必需的，同时，H2AL2 对于过渡蛋白在核小体上的装载和有效的 PRM 组装也起着关键作用(Govin *et al*, 2007; Barral *et al*, 2017)。H2A.B 在粗线期精母细胞到圆形精子细胞中都会被表达，且 H2A.B 参与组蛋白–鱼精蛋白替换是通过调节 H2AL2 和 TP1 染色质的掺入和解聚。H2A.B 在精子发生、转录起始、RNA 剪切等过程中具有重要功能。H2A.B 易形成开放的核小体结构，并破坏染色质结构，导致染色质松散。但这种开放的核小体极不稳定，难以获得高精度结构(Zhou *et al*, 2021; Soboleva *et al*, 2012)。TH2A 和 TH2B 是 2 种精巢特异的 H2 变体，这 2 个基因位置相邻，共享一个启动子，表明它们可能共同发挥作用(De Lucia *et al*, 1994)。TH2A 和 TH2B 可能具有调节染色质开放或总组蛋白水平的功能，以促进精子形成期间的组蛋白替代(Montellier *et al*, 2013)。通过生化实验，研究人员认为，TH2A 和 TH2B 可以形成结构不稳定的核小体(Wolffe *et al*, 1997)。TH2A 和 TH2B 基因敲除会导致精子发生过程中组蛋白替换缺陷(Li *et al*, 2005)。H2A.Z 是组蛋白 H2A 的变体，在基因转录、DNA 复制、基因组稳定性维持等过程中发挥重要作用。H2A.Z 通过精确定位于基因组的特定位点来改变染色质结构并实现其功能。SWR1 催化的 H2A.Z 替换反应可以将 H2A.Z 核小体精准地定位到正确的染色质区域，又称“核小体编辑”。研究发现，在酵母中 SWR1 的重要亚基 Swc2 具备特异识别并感知底物 H2A 核小体的能力，进而揭示了 SWR1 催化 H2A.Z 替换 H2A 的过程中维持反应单向性的分子机理(Dai *et al*, 2021)。

2.2.3 H3 变体　　H3 具有多个变体，如 H3.1、H3.2、H3.3、H3T、H3.X、H3.Y、CENP-A 和 H3.5 (Shinagawa *et al*, 2015; Padavattan *et al*, 2015)。H3.1 和 H3.2 复制组蛋白在 S 期高表达，H3.3 非复制性组蛋白在 S 期达不到峰值。H3.3 有助于形成开放的染色质构型，是染色质重组和组蛋白–鱼精蛋白替代所必需的(Yuen *et al*, 2014)。编码组蛋白 H3.3 的基因在整个细胞周期都持续表达，并能使组蛋白变体 H3.3 能以一种不依赖 DNA 复制的方式整合进入染色质，且组蛋白变体 H3.3 在转录、基因组稳定性和有丝分

裂等过程中发挥着重要作用(Bucci *et al*, 1982; Sullivan *et al*, 1994; Xu *et al*, 2014)。H3.3 的干扰会导致雄性不育(Ray-Gallet *et al*, 2011; Tagami *et al*, 2004; Ahmad *et al*, 2002; Goldberg *et al*, 2010)，其生殖细胞的染色质重组存在缺陷，正常的鱼精蛋白掺入也失败(Yan *et al*, 2003; Hodl *et al*, 2009)。H3T 可能在组蛋白与鱼精蛋白的替代过程中发挥着开启染色质的作用，含 H3T 的核小体具备更为开放的构象(Tachiwana *et al*, 2010)。H3.5 在人类睾丸中高度表达，与其他睾丸特异性组蛋白不同，H3.5 主要在未成熟生殖细胞中表达，而睾丸特异性组蛋白通常在减数分裂过程中组蛋白向鱼精蛋白转化过程中表达。H3.5 可能在 DNA 合成中发挥作用，但不参与细胞凋亡，其表达受促性腺激素调控，表明这种表观遗传调控在正常的精子发生过程中是重要的(Shiraishi *et al*, 2018)。体外研究揭示，H3.5 具备降低核心组蛋白 H4 疏水作用的能力(Padavattan *et al*, 2017; Huynh *et al*, 2016)。

因此，精巢特异的组蛋白变体可能具有核小体不稳定的共同特征。综上所述，体细胞核心组蛋白被具有开放结构的组蛋白变体取代并形成不稳定的核小体，为各种组蛋白修饰以及随后的染色质重塑和 DNA 重组奠定了基础，其修饰的异常也往往与其密切相关。

3　组蛋白修饰对水生动物精子发生的启示：以半滑舌鳎为例

水生动物尤其是许多鱼类中存在性别生长二态性，因此，在重要养殖鱼类中运用性别控制技术，培育单性苗种具有重要的经济意义。半滑舌鳎是东北亚地区的特色养殖鱼类，属于我国海水鱼体系的九大品种之一，作为雌雄生长差异最显著的鱼类之一，1 龄雌鱼体重可达雄鱼的 2~4 倍。半滑舌鳎具有独特的精子发生现象，其伪雄鱼(基因型为 ZW，但表型为雄鱼的个体)W 型精子缺失，只能产生 Z 型精子，而 Z 精子由于携带父本表观遗传信息，产生的后代更容易变为伪雄鱼。显著的雌雄生长差异、特定类型配子缺失使得半滑舌鳎成为研究鱼类精子发生，继而开发新型性控技术的理想模型。

我们前期在雄鱼和伪雄鱼精巢中筛选出一系列基因，在转录本上存在差异，但蛋白序列的差异极小。而通过比较精巢磷酸化和泛素化蛋白，发现多个蛋白存在磷酸化和泛素化差异。更有趣的是，雄鱼和伪雄鱼精巢中，存在差异磷酸化和泛素化的组蛋白分别有 9 个和 12 个，但这些蛋白在翻译水平却无差异。由于半滑舌鳎精巢特异组蛋白变体国内外研究较少，表 6 梳理了半滑舌鳎组蛋白及其变体(UniPort 网站)。半滑舌鳎独特的精子发生现象是否暗示在“基因-mRNA-蛋白”这个经典中心法则之外，还存在翻译后修饰等其他的调控机制，导致了伪雄鱼精子发生异常？半滑舌鳎的多个组蛋白都行使怎样的功能？这些问题都需要进一步的深入探索，以此为切入点，研究翻译后修饰在精子发生的调控机制，将有助于探明特定类型精子缺失的内在因素，将不仅拓展翻译后修饰对精子发生调控机制的认知，也可为养殖鱼类高雌苗种培育提供新的解决方案。

表 6　半滑舌鳎组蛋白及其变体(UniPort 网站)

Tab.6　Histone and its variants of Chinese tongue sole (UniPort website)

组蛋白 Histone	细胞组分 Cellular component	生物过程 Biological process	分子功能 Molecular function
H1.0-B	核小体 Nucleosome	核小体组装 Nucleosome assembly	DNA 结合 DNA binding
H1.1-like	核小体 Nucleosome	核小体组装 Nucleosome assembly	DNA 结合 DNA binding
H2A	核小体 Nucleosome	未知 Unknown	DNA 结合 DNA binding 蛋白质异源二聚化活性 Protein heterodimerization activity 染色质的结构成分 Structural constituent of chromatin
H2B	核小体 Nucleosome	未知 Unknown	DNA 结合 DNA binding 蛋白质异源二聚化活性 Protein heterodimerization activity 染色质的结构成分 Structural constituent of chromatin

续表 6

组蛋白 Histone	细胞组分 Cellular component	生物过程 Biological process	分子功能 Molecular function
H2A.1	核小体 Nucleosome	染色质组织 Chromatin tissue	DNA 结合 DNA binding 蛋白质异源二聚化活性 Protein heterodimerization activity 染色质的结构成分 Structural constituent of chromatin
H2A.2	核小体 Nucleosome	大脑发育 Brain development 染色质组织 Chromatin tissue	蛋白质异源二聚化活性 Protein heterodimerization activity 染色质的结构成分 Structural constituent of chromatin
H2.0-like homeobox	核 Nucleus	转录调控 Transcriptional regulation	DNA 结合转录因子活性 DNA binding transcription factor activity RNA 聚合酶Ⅱ特异性 RNA polymerase Ⅱ specificity
H3	核小体 Nucleosome	未知 Unknown	DNA 结合 DNA binding 蛋白质异源二聚化活性 Protein heterodimerization activity 染色质的结构成分 Structural constituent of chromatin
H3.2	核小体 Nucleosome	未知 Unknown	DNA 结合 DNA binding 蛋白质异源二聚化活性 Protein heterodimerization activity 染色质的结构成分 Structural constituent of chromatin
H3-like centromeric protein A	核小体 Nucleosome	未知 Unknown	DNA 结合 DNA binding 蛋白质异源二聚化活性 Protein heterodimerization activity 染色质的结构成分 Structural constituent of chromatin
H4	核小体 Nucleosome	未知 Unknown	DNA 结合 DNA binding 蛋白质异源二聚化活性 Protein heterodimerization activity 染色质的结构成分 Structural constituent of chromatin

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Function of Histones and Variants in Chromatin Remodeling: A Case Study of Spermatogenesis in Aquatic Animals

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Abstract Epigenetics refers to heritable changes that do not affect DNA sequences. Compared to genetic changes, epigenetic changes affect gene expression and protein products in cells, and these changes are reversible and dependent on the environment. There are three major types of epigenetic changes: DNA methylation, histone post-translational modifications (PTMs) increase the functional diversity of the proteome through the covalent addition of functional groups or proteins, proteolytic cleavage of regulatory subunits, or degradation of whole proteins), and non-coding Ribonucleic Acid.. This study focused on post-translational histone modifications.

There are five main histone types: H1/H5, H2A, H2B, H3, and H4. Genes encoding histones do not contain introns and are among the most conserved proteins in eukaryotes. Histones are basic structural proteins comprising eukaryotic chromosomes. Generally, two molecules, H2A, H2B, H3, and H4 form a histone octamer that combines with DNA to form a structural unit called a nucleosome. This nucleosome

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appears every 200 bp and is connected by H1 histones to form chromatin.

Histone modification refers to the addition of functional groups to histone tails, most commonly lysines. This process regulates gene expression by altering chromatin structure through condensation and depolymerization. Additionally, histone modification creates binding sites for various proteins. Histone modifications reported in animals include methylation, acetylation, phosphorylation, ubiquitination, SUMOylation (which is a small ubiquitin-related modifier involved in post-translational modification of proteins), ADP-ribosylation (which is a small ubiquitin-related modifier involved in post-translational modification of proteins), and short-chain lysine acylation.

Many studies have shown that chromatin remodeling is a key step in spermatogenesis, involving the transformation of histones to protamines. Briefly, protamine replacement requires (Ⅰ) histone PTMs to promote the opening of histone-based chromatin structures, especially histone hyperacetylation and incorporation into histone variants; (Ⅱ) binding of bromine domain proteins to acetyl residues and remodeling of chromatin; (Ⅲ) formation and repair of DNA strand breaks in chromatin remodeling; and (Ⅳ) incorporation of protamine. Herein, we focused on Process (Ⅰ).

In bisexual reproduction, sperm, as a paternal information carrier, is a key factor in a species continuation. Spermatogenesis includes various stages, including spermatogonia, primary and secondary spermatocytes, round sperms, and mature sperms. During round sperm transformation into mature sperm, chromatin remodeling occurs and cell morphology undergoes dramatic changes, in which histone PTMs and variants are essential. Histone PTMs patterns affect gene expression over a wide range, such as methylation, which is mainly related to gene expression activation or inhibition; acetylation, which activates transcriptional activity and participates in histone deposition and DNA repair; phosphorylation, which promotes post-transcriptional modification or participates in DNA double-strand break repair; and ubiquitin, which regulates various protein substrates in different cellular pathways. Histone variants have special functions in regulating chromosome structure. For example, histone H1 variants inhibit transcription during differentiation, histone H2A and H2B variants play a unique role in sperm chromatin packaging, H3.3 is the most important variant of H3, which is expressed in all stages of the cell cycle and participates in chromosome formation outside the S phase, Histone H4 is one of the slowest evolving proteins, and no histone variant has ever been found. Focusing on post-translational histone modifications, this study reviews the latest progress in methylation, acetylation, phosphorylation, and ubiquitination. Subsequently, the histone variants and their functions in chromatin remodeling are summarized. Finally, using *Cynoglossus semilaevis* as an example, this study briefly introduces the implications of these studies on spermatogenesis in aquatic animals. Elucidating the effect of PTMs on spermatogenesis will aid in exploring the regulatory mechanism of specific sperm (W-type) absence, which expands the fundamental theory of reproductive biology and provides novel solutions to monosex fry cultivation in aquaculture.

Key words　Histone; Post-translational modification; Chromatin remodeling; Spermatogenesis