组蛋白变异体及组蛋白修饰在哺乳动物配子和植入前胚胎发育中的研究进展

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摘要 组蛋白变异体置换及组蛋白翻译后修饰是重要的表观遗传调控方式, 在哺乳动物配子发生和植入前胚胎发育过程中起着重要作用。H2A.Z、H3.3和CENP-A等多种组蛋白变异体的沉积或移除可以改变核小体和染色质的局部状态, 影响基因表达, 从而参与调控配子和植入前胚胎发育。甲基化和乙酰化等组蛋白修饰在相应的酶的作用下建立或擦除, 进而促进或干扰转录调控因子的招募, 激活或抑制基因的表达。近年来, 随着单细胞或少量细胞表观遗传全基因组检测技术的迅速发展, 组蛋白在哺乳动物配子和植入前胚胎发育过程中发挥的关键作用被逐渐阐明。该文简要总结了组蛋白变异体置换及组蛋白修饰在哺乳动物配子发生及植入前胚胎发育中的研究进展, 并探讨了其生物学功能和表观遗传调控机制。

关键词 表观遗传; 组蛋白变异体; 组蛋白修饰; 配子; 植入前胚胎

Progress in Research on Histone Variants and Histone Modifications during Mammalian Gametogenesis and Preimplantation Embryonic Development

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Abstract Epigenetic regulation with specific emphasis on the modes of histone variants and post-translational modifications are involved in mammalian gametogenesis and preimplantation embryonic development. Deposition or replacement of various histone variants, such as H2A.Z, H3.3 and CENP-A, regulate gene expression by fine-tuning nucleosome or local chromatin structure. Writing, reading and erasing of histone modifications are mediated by distinct enzymes, and activate or inhibit gene expression by regulating recruitment of transcriptional regulators in chromatin. Recent years saw great progress in low-input or single-cell genome wide epigenomic profiling techniques, shedding more light on the role of histone variants and histone modifications during gametogenesis and embryogenesis. This review provides an overview of recent findings and discusses potential mechanisms that shape the current paradigms regarding the roles of histone variants and histone modifications during mammalian gameto-

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genesis and preimplantation embryonic development.

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核小体是染色质的基本结构单位, 由各2个分子的组蛋白H2A、H2B、H3、H4构成的八聚体和约146 bp的DNA缠绕而成。组蛋白H1与核小体间的DNA结合, 维持和稳定染色质高级结构[1]。除H4外的组蛋白均可被组蛋白变异体替换。H2A的变异体主要包括H2A.X、H2A.Z、H2A.Bbd、macroH2A等; H2B有两种睾丸特异性的变异体H2BFWT(histone H2B type WT)和TH2B(testis-specific histone H2B); H3的变异体主要包括H3.3、CENP-A(histone H3-like centromeric protein A)、H3.1T、H3.5、H3.X和H3.Y等[2](表1)。

组蛋白翻译后修饰是一种重要的表观遗传调控方式。组蛋白N-端残基如赖氨酸、精氨酸、丝氨酸等残基上能够发生不同的共价修饰, 改变染色质的开放程度, 调控基因转录[3]。组蛋白的甲基化、乙酰化、泛素化等翻译后修饰在时间和空间上特异性组成了组蛋白密码(histone code)[4]。这些“密码”在配子发生以及植入前胚胎发育过程中能够被特定蛋白质所识别, 调控染色质状态以及与转录因子的结合, 实现对基因的调节作用[5]。

高度折叠的染色质结构能够保护DNA免受损伤, 但又阻碍了DNA复制、修复以及基因转录等以DNA为模板的细胞过程。组蛋白变异体置换及组蛋白修饰能够调节染色质的局部结构和转录因子的结合, 确保DNA相关生物学过程的正常进行。近年来, 随着单细胞表观遗传分析方法和全基因组染色质分析技术的迅速发展, 精准捕捉组蛋白变异体以及组蛋白修饰的动态变化成为可能, 这为深入理解组蛋白的生物学功能及其表观遗传调控机制奠定了基础。本文总结了组蛋白变异体置换及组蛋白修饰在哺乳动物配子发生及植入前胚胎发育过程中的研究进展, 探讨了其生物学功能和分子机理。

1 组蛋白变异体置换对哺乳动物配子发生和植入前胚胎发育的调控

组蛋白变异体赋予了染色质独特的性质, 能够为核小体结合因子提供特定的结合位点, 或作为转录、复制、重组和修复的调节因子, 调节染色质可及性, 参与基因表达调控[6]。大多数的组蛋白变异体在体细胞中表达, 但是在哺乳动物发育过程中, 组蛋白变异体的表达具有独特的时空特异性[2]。H3.3、CENP-A、H2A.Z和H1FOO等多种组蛋白变异体在哺乳动物配子发生和植入前胚胎发育过程中动态沉积于染色体, 调控配子和胚胎发育以及细胞谱系分化等生物学过程[2,7](表1)。

1.1 H3.3

H3.3是组蛋白H3家族重要的变异体, 作为一种母源因子, 在卵母细胞和植入前胚胎发育过程中发挥至关重要的作用。组蛋白变异体H3.3由*H3f3a*和*H3f3b*两个基因编码, 并且H3.3与组蛋白H3.1/H3.2相比仅存在4~5个氨基酸的差异[2]。早期的研究显示, *H3f3a*和*H3f3b*同时缺失会导致胚胎在E6.5死亡[8]; *H3f3a*突变体雌性小鼠可育, 但雄性不育; *H3f3b*敲除导致生长缺陷, 甚至出生时死亡[9], 提示*H3f3b*对H3.3的功能有更大的贡献。卵母细胞特异性敲除研究表明, *H3f3a*和*H3f3b*的母源缺失会导致卵母细胞停滞在初级卵母细胞阶段, 不能发育为成熟的卵母细胞[9](表1)。成熟卵母细胞和受精卵中H3.3分布呈现“非经典模式(non-canonical pattern), 即H3.3在活性染色质处的富集受到抑制, 相对均匀地分布在整个基因组中; 而在2-细胞胚胎中, 非经典模式以复制依赖的方式迅速转换为经典模式, 即H3.3在转录起始位点(transcription start site, TSS)周围富集[10], 提示胚胎正常发育需要H3.3重新建立经典分布模式。组蛋白分子伴侣Hira介导H3.3沉积在转录活性基因的增强子区域, 使染色质结构松弛并招募转录结合蛋白和RNA pol II, 激活基因转录[11]。而Hira的母源性缺失导致严重的卵巢表型、增加染色质可及性, 并使DNA损伤积累, 表明Hira介导的组蛋白H3.3置换对染色质稳态维持以及转录调控和发育进程至关重要[12]。

精子发生过程中大部分组蛋白被鱼精蛋白取代, 这一转变促进了精子头部染色质高度凝缩, 使基因表达沉默, 保护父系基因组的DNA免受损伤和诱变干扰[13]。在受精之后, 鱼精蛋白被H3.3取代, 促进精子中的父系基因的正常表达[14]。在体细胞核移植(somatic cell nuclear transfer, SCNT)胚胎中, 供体细胞核中的H3.3被卵细胞质中的H3.3取代, 从而促进

核移植后基因组的重编程[15]。母源H3.3的缺失导致SCNT胚胎在2-或4-细胞阶段阻滞, 添加外源H3.3能够恢复胚胎的重编程能力[16-17]。此外, H3.3和其他组蛋白变异体还存在相互作用。研究发现, 组蛋白变异体H3.3和H2A.Z同时存在会增加核小体结构的不稳定性, 有助于转录因子与启动子和其他调节位点的结合, 从而促进基因的转录[18-19]。

1.2 CENP-A

着丝粒位点处存在一种特殊的组蛋白H3变异体, 在哺乳动物中被称为CenH3或CENP-A。CENP-A是着丝粒的表观遗传标记, 其调控机制对着丝粒的建立具有重要的生物学意义[20]。在细胞分裂过程中, 着丝粒核小体中的H3被CENP-A取代, 募集动粒牵拉染色体使其分离[20-21]。HJURP是CENP-A的分子伴侣, 对于CENP-A正确沉积在着丝粒染色质中起着核心作用。HJURP下调导致着丝粒处CENP-A大量减少, 新合成的CENP-A无法沉积, 最终导致有丝分裂中染色体分离缺陷[22]。有趣的是, CENP-A没有其他H3变异体那么保守, 可能正在快速进化[23]。

CENP-A是着丝粒的关键组分, 是维持基因组稳定所必需的组蛋白变异体。在哺乳动物中, 卵母细胞着丝粒CENP-A非常稳定, 可能是确保着丝粒从卵子到胚胎精准传递的基础[24]。CENP-A的敲低导致动粒的结构和功能改变, 导致卵母细胞的同源染色体分离异常[25]。CENP-A缺失的小鼠在E6.5天出现有丝分裂缺陷以及发育阻滞[26](表1)。此外, CENP-A的过表达导致其错误定位于染色体臂, 形成稳定的CENP-A-H3.3异型核小体。该异型核小体位于转录因子结合位点, 参与阻断转录抑制因子CTCF(CCCTC binding factor)的结合, 调控基因转录[27]。组蛋白分子伴侣DAXX缺失导致过表达的CENP-A无法定位在染色体臂上, 表明CENP-A在染色体臂上的异位插入依赖DAXX调控[27]。这些结果提示, CENP-A通过调控着丝粒的形成及其完整性, 在卵子和植入前胚胎发育过程中发挥重要的功能。

1.3 H2A.Z

在核心组蛋白中, 组蛋白H2A的变异体最多, 其中研究最广泛的是H2A.Z。H2A.Z是一种高度保守的组蛋白, 其染色质沉积由染色质重塑复合物SRCAP介导, 并且这一过程可逆[28]。H2A.Z存在于成熟卵母细胞中, 但在受精后完全消失, 直至囊胚期再次出现[29]。H2A.Z的异常掺入阻碍植入前胚胎发育进程[29], 而H2A.Z缺失则导致胚胎在植入前死亡[30]。这些结果提示, H2A.Z的动态变化对胚胎发育及细胞增殖分化至关重要(表1)。

H2A.Z在启动子和增强子上高度富集, 增加增强子的染色质可及性, 促进OCT4、MLL等转录因子的结合, 参与调控胚胎干细胞(embryonic stem

表1 哺乳动物主要的组蛋白变异体及其功能

Table 1 Main histone variants and functions of mammals

组蛋白变异体 Histone variants	分布 Tissue distribution	功能 Function	参考文献 References
H1 family			
H1FOO	Oocyte Specific	Oocyte maturation and sperm chromatin remodeling after fertilization	[31-32]
H2A family			
H2A.Z	Global	Chromatin remodelling and embryonic development, abscence of H2A.Z leads to embryonic lethality	[30,33]
H2A.Bbd	Testes and brain	Formation and maintenance of active chromatin structure	[34]
MacroH2A	Global	Represses transcription and participates in stable X chromosome inactivation	[35-36]
H2A.X	Global	DNA damage response and chromatin remodelling	[37]
H3 family			
H3.3	Global	Oocyte reprogramming and embryonic development, transcriptional activation	[9,17]
CENP-A	Global	Epigenetic markers of centromere, chromosome segregation	[25-26]
H3.X	Testes and brain	Not known	[38]
H3.Y	Testes and brain	Transcriptional activation	[38]
H2B family			
H2BFWT	Testes	Not known	[39]
TH2B	Testes	Histone-to-protamine transition	[40]

cell, ESC)的自我更新与分化[33]。mESC的MNase-X-ChIP-seq的结果显示, 含有组蛋白变异体H2A.Z的核小体比常规核小体“展开”程度更高, 并且参与转录调控和CTCF的结合[41]。这表明H2A.Z可能在建立复杂的基因表达模式所需的染色质结构中起着关键作用。H2A.Z可与染色质重塑因子Chd4相互作用, 防止Chd4蛋白被蛋白酶体降解, 维持mESC的自我更新能力[42]。此外, H2A.Z与PRC2(Polycomb repressive complex 2)以及Ring1B(Polycomb repressive complex 1, PRC1的组分之一)在发育沉默的基因处共定位[43], 提示H2A.Z可能与mESC中多梳抑制复合物介导的基因沉默有关。总之, 沉积在染色质上的H2A.Z与转录因子及染色质重塑因子发生相互作用, 调控基因表达, 参与植入前胚胎发育及分化过程。

1.4 H1FOO

组蛋白H1又被称为连接体组蛋白, 在小鼠中至少存在11种组蛋白H1变异体, 这些变异体在配子发生和胚胎发育过程中发生表达变化[44]。其中, H1FOO是一种卵母细胞特有的H1组蛋白变异体[31], 成熟的卵母细胞中积累了丰富的*H1FOO* mRNA, 有助于维持卵母细胞成熟状态[45]。H1FOO在合子中高度表达, 但在2-细胞阶段显著降低[32]。H1FOO C末端结构域含有比其他H1变异体更多的带负电荷的氨基酸, 因此其染色质结构凝聚能力比其他变异体更弱, 更容易形成松散的染色质[32]。敲低H1FOO导致合子原核中染色质结构更加紧密, DNA复制延迟, 并且雄原核外围区域中组蛋白H3变异体H3.1/3.2的沉积明显增加; 而H1FOO的过表达导致2-细胞阶段染色质结构松弛[32], 提示H1FOO的移除使合子至2-细胞阶段染色质结构变得紧密。此外, 已有研究显示, 在体细胞核转移胚胎中H1与H1FOO的置换十分活跃。在体细胞核移植后的几分钟内, 供体细胞来源的H1被H1FOO快速取代; 而在2-细胞至4-细胞阶段, H1FOO又被体细胞的H1取代[46]。这些结果提示, H1FOO通过调控染色质结构参与卵母细胞成熟以及植入前胚胎发育过程。

2 组蛋白修饰在哺乳动物配子向植入前胚胎转变中的传递和重编程

组蛋白修饰是指组蛋白N末端在相应酶的作用下发生甲基化、乙酰化、泛素化等翻译后修饰的过程。甲基、乙酰基等修饰基团能够影响核小体上DNA的缠绕状态, 改变染色质的可及性, 进而影响转录调控因子与染色质的相互作用[47]。随着微量ChIP-seq等一系列表观遗传测序技术的发展, 组蛋白修饰在生殖和胚胎发育等过程中发挥的重要作用逐渐被阐明。

2.1 组蛋白甲基化修饰

组蛋白甲基化是最早发现的组蛋白修饰之一, 多数发生在赖氨酸残基和精氨酸残基上。组蛋白不同位点发生赖氨酸甲基化修饰可调控基因转录。H3K4、H3K36甲基化被视为转录激活标记, 而H3K9、H3K27甲基化则通常被视为转录抑制标记[3](表2)。

同一种组蛋白修饰在雌雄配子以及植入前胚胎发育过程中呈现出不同的动态变化。精子中, H3K4me3维持经典的窄峰模式, 富集在以TSS为中心的富含CpG的区域; 受精卵中, 父本基因组基本检测不到H3K4me3信号, 表明其已被擦除; 而在成熟的卵母细胞中, H3K4me3富集在TSS远端CpG含量低的区域, 这种模式被称为“非经典H3K4me3(non-canonical H3K4me3, ncH3K4me3)”[48]。卵子中的ncH3K4me3可以传递给胚胎, 但合子基因组被激活(zygotic genome activation, ZGA)之后, ncH3K4me3逐渐消失, 经典H3K4me3逐渐建立[48]。H3K27me3是兼性异染色质的标志, 在哺乳动物发育相关基因的启动子处高度富集[49-50]。H3K27me3与H3K4me3十分类似, 同样在卵母细胞及植入前胚胎发育的过程中建立“非经典H3K27me3(non-canonical H3K27me3, ncH3K27me3)”; 不同的是, 2-细胞阶段H3K27me3水平显著降低, 尤其在发育相关基因中几乎被擦除, 在植入后胚胎中才重新建立[51-52]。与H3K27me3相比, H3K27me2广泛分布在受精卵整个基因组中, 雄原核中*de novo* H3K27me2水平较低, 但其可能是*de novo* H3K27me3的底物[49]。

组蛋白甲基化修饰可以通过调控转录因子的结合调控基因表达。在ESCs发育相关转录因子的基因区域内, 组蛋白H3K4me3和H3K27me3构成“二价结构域(bivalent domains)”[53]。H3K4me3和H3K-27me3两种修饰方式在基因表达调控中具有拮抗作用[54]。H3K4me3招募染色质重塑酶, 使染色质松弛, 促进转录; 而H3K27me3促进致密染色质结构的形成, 阻碍转录因子的结合, 抑制转录[54]。H3K4me3和H3K27me3的二价平衡促使胚胎发育相关基因保持

沉默, 但它们仍保留了当特定分化程序启动时能够被及时激活的潜能[54]。

哺乳动物中组蛋白甲基化水平由组蛋白甲基转移酶和组蛋白去甲基化酶动态调控。哺乳动物中六种H3K4甲基转移酶(SETD1A、SETD1B、MLL1–MLL4)的突变均导致胚胎致死[55]。Mll2(又称Kmt2b)是建立ncH3K4me3的主要甲基转移酶, *Mll2*的母源缺失导致雌性不育和卵巢早衰[56-57]。Mll3/4协同参与增强子区域H3K4me1的建立, 并调控父系基因组Minor ZGA。*Mll3/4*敲除导致胚胎在4-细胞至8-细胞阶段发育停滞[58], 提示父本H3K4me1对Minor ZGA和植入前胚胎发育至关重要。组蛋白去甲基化酶Kdm5b和Kdm5a主动去除ncH3K4me3结构域, *Kdm5b*和*Kdm5a*缺失导致胚胎在4-细胞到8-细胞的转变过程中出现发育延迟, 在囊胚阶段发生发育阻滞[59]。精原细胞中条件性敲除赖氨酸去甲基化酶*Kdm1a*, 导致H3K4me2和H3乙酰化水平上升, 精子发生异常, 精子数量显著减少, 最终导致雄性不育[60]。此外, 组蛋白甲基转移酶G9a通过其SET结构域介导组蛋白H3K9me2的建立[61]。G9a母源缺失的卵母细胞中H3K9me2富集减少, 异染色质组装受损, 出现染色体分离异常, 最终导致胚胎发育停滞[61]。Jmjd2c是含JmjC结构域的组蛋白去甲基化酶, *Jmjd2c*缺失导致胚胎多能性和细胞增殖相关基因表达显著下调, 孤雌激活的胚胎在囊胚期发生发育阻滞[62]。

组蛋白甲基化修饰影响异染色质蛋白质HP1在染色体上的定位。甲基转移酶催化H3K9完成甲基化修饰后, HP1才能识别并结合组蛋白H3, 使染色质结构更为致密[63]。在mESC中, HP1的富集程度影响组蛋白H3K36me3的富集, *HP1*敲除导致H3K36me3的富集程度下降, 基因表达被抑制, mESC更新速度变慢、分化进程受阻[64]。

2.2 组蛋白乙酰化修饰以及去乙酰化

组蛋白乙酰化是一种重要的表观遗传学修饰方式。在精子发生过程中, 组蛋白H4高度乙酰化出现在组蛋白与鱼精蛋白转换之前, 能够抑制组蛋白与DNA的结合, 促进组蛋白的移除以及鱼精蛋白的载入[65]。在卵母细胞和植入前胚胎中, 组蛋白乙酰化水平发生动态变化。在小鼠GV期卵母细胞中, 可检测到组蛋白H4赖氨酸5、8、12和16(H4K5ac, H4K8ac、H4K12ac和H4K16ac)以及组蛋白H3赖氨酸9、14(H3K9ac和H3K14ac)等位点发生乙酰化。随着生发泡破裂(GV breakdown, GVBD), 组蛋白逐步去乙酰化。其中, H4K5Ac和H4K16Ac在第一次减数分裂后期的卵母细胞中短暂地出现, 但在MII期卵母细胞中再次被去乙酰化[66]。受精后, H4K5ac、H4K8ac和H4K12ac在2-细胞胚胎的核外围富集, 从4-细胞阶段开始消失[67]。在组蛋白去乙酰化酶抑制剂曲古霉素A(trichostatin A, TSA)处理的胚胎中, ZGA的标记蛋白合成速率增加, 提示乙酰化修饰可能促进*ZGA*基因的表达[67]。H3K27ac被视为基因转录的标志, 位于基因的增强子区域[68], H3K27ac水平在受精卵第一次有丝分裂后显著降低[69]。H3K56ac在整个植入前胚胎发育过程中富集在转录调控区域[70]; H3K64ac广泛分布于成熟卵母细胞中, 在MI期间和合子PN2阶段短暂消失, 但在随后的胚胎发育过程中始终存在; H3K122ac则仅存在于生长阶段和成熟的卵母细胞中, 受精后至囊胚阶段几乎检测不到H3K122ac[70]。

在小鼠以外的哺乳动物卵母细胞成熟和发育过程中, 组蛋白乙酰化水平也发生动态变化。人卵母细胞中组蛋白乙酰化情况与小鼠基本相同[71]。H3K9ac和H4K12ac在绵羊的GV期及GVBD期的卵母细胞中能够被检测到, 在MI卵母细胞中消失, 在MII卵母细胞中再次出现[72]。猪生长期卵母细胞中可检测到H3K9ac、H3K14ac、H3K18ac, 随着卵母细胞成熟和染色质浓缩, 上述乙酰化修饰同样发生去乙酰化[73]。体外成熟的牛卵母细胞组蛋白H4乙酰化情况也与小鼠十分相似[74]。此外, 在体外受精(*in vitro* fertilization, IVF)的牛1-细胞和2-细胞胚胎出现高水平的H3K9ac和H3K18ac, 8-细胞期显著降低, 在随后的发育阶段逐渐恢复[75]。牛SCNT胚胎的H3K9、H3K18、H4K5和H4K8乙酰化水平显著高于体外受精胚胎, 但H3K9、H3K18乙酰化水平在8-细胞期降低, 在囊胚时期SCNT胚胎和IVF胚胎中乙酰化修饰及强度并无明显差异[75]。

组蛋白乙酰转移酶(histone acetyltransferases, HATs)和组蛋白去乙酰化酶(histone deacetylases, HDACs)分别催化乙酰基团的添加和去除, 参与调控卵母细胞和胚胎发育。乙酰基的添加能够中和赖氨酸残基上的正电荷, 降低组蛋白对染色质的亲和力, 使染色质结构开放, 促进转录因子结合及基因转录; 反之, 若去除乙酰基, 基因转录被抑制[76]。乙酰转移酶*KAT8*(lysine acetyltransferase 8)的母源缺失导致卵

泡和卵母细胞发育异常, 雌性不育[77]。此外, 组蛋白去乙酰化酶*HDAC1*缺失导致胚胎在E7.5发育异常, 并在E10.5死亡[78]。*HDAC2*的母源缺失导致MII期卵母细胞中H4K16ac水平升高, 并且出现纺锤体组装和染色体分离缺陷[79]。*HDAC3*缺失导致胚胎在E9.5死亡[80]。这些结果提示, HATs和HDACs在小鼠卵泡发育和雌性生殖中发挥重要作用。

组蛋白乙酰化是克隆胚胎基因表达以及胚胎全能性获得的关键调控事件[81]。组蛋白特定氨基酸残基(H3K9和H3K14)的乙酰化与转录活性密切相关。组蛋白去乙酰化酶抑制剂Scriptaid处理可促进SCNT胚胎的基因转录和蛋白表达, 提高SCNT胚胎的发育能力[82]。另一种组蛋白去乙酰化酶抑制剂TSA同样可以提高SCNT胚胎的发育能力。TSA处理胚胎后, 组蛋白乙酰化水平上升, 细胞核体积增大, 并且2-细胞阶段RNA合成水平显著增强[83]。总的来说, 组蛋白乙酰化可能参与受精后的染色质重塑, 调控植入前胚胎发育; 并且组蛋白乙酰化动态变化由HATs和HDACs调控, 这些酶的功能异常或缺失会导致严重的生殖细胞生成障碍甚至胚胎死亡。

2.3 组蛋白泛素化修饰

组蛋白泛素化通常是一个由泛素激活酶(E1)、泛素结合酶(E2)、泛素连接酶(E3)连续催化的过程。组蛋白H2A泛素化是由泛素羧基末端甘氨酸与H2A的赖氨酸之间形成异肽键催化而成, 单泛素化或多泛素化的组蛋白通过调控染色质的局部结构, 促进或抑制下游蛋白与染色质的结合, 参与多种细胞生物学过程[94]。

H2A是最早发现的可发生泛素化修饰的组蛋白, PRC1可介导H2A在赖氨酸残基上发生单泛素化[95]。值得注意的是, 体外的一项研究表明, H3K36特异性甲基转移酶ASH1L、HYPB、NSD1和NSD2都被ubH2A抑制, 推测Polycomb可能通过调控ubH2A来抑制H3K-36me2/3, 但这一推论还有待进一步验证[96]。ubH2A大量富集在不活跃的近着丝粒区、失活的X染色体和发育基因沉默的区域[95]。在DNA损伤反应中发现的一种E3泛素连接酶RNF8的缺失导致雄性小鼠睾丸中组蛋白泛素化水平降低, 鱼精蛋白减

表2 哺乳动物配子发生及植入前胚胎发育相关的组蛋白修饰及其功能

Table 2 Role of histone modifications in mammalian gametogenesis and early embryonic development

组蛋白修饰 Modification	示例 Examples	细胞 Cell	功能 Functions	保守性 Conservation	参考文献 References
Methylation	H3K4me2	Sperm	Transcriptional activation	Non-conservative	[84]
	H3K9me2	Oocyte, embryo	Gene silencing	Conservative	[85]
	H3K4me3	Sperm, oocyte, embryo	Transcriptional activation	Conservative	[3,48,86]
	H3K9me3	Oocyte, embryo	Gene silencing	Conservative	[87]
	H3K27me3	Oocyte, embryo	Transcription suppression	Conservative	[49,54]
	H3K36me3	Sperm, oocyte, embryo	Marker of transcribing gene bodies	Conservative	[88]
Acetylation	H3K9ac	Oocyte, embryo	Transcriptional activation	Conservative	[89]
	H3K27ac	Embryo	Transcriptional activation	Conservative	[68]
	H3K56ac	Oocyte, embryo	Transcriptional activation	Non-conservative	[70]
	H3K64ac	Oocyte, embryo	Transcriptional activation	Non-conservative	[70]
	H3K122ac	Oocyte	Enhancer function	Conservative	[70]
	H4K5ac	Oocyte, embryo	Zygotic genome activation	Conservative	[67]
	H4K8ac	Oocyte, embryo	Zygotic genome activation	Conservative	[67]
	H4K12ac	Oocyte, embryo	Zygotic genome activation	Conservative	[67]
Ubiquitination	H2AK119ub1	Embryo	Gene silencing	Non-conservative	[90]
	H4K91ub	Embryo	DNA protection	Conservative	[91]
Crotonylation	H4K77cr	ESC	Endoderm differentiation	Not known	[92]
	H4K91cr	ESC	Endoderm differentiation	Not known	
Citrullination	H3Cit2	Embryo	Transcriptional activation	Not known	[93]
	H4Cit3	Embryo	Transcriptional activation	Not known	

少, 无法产生成熟精子[97], 提示ubH2A参与调控精子发生过程。组蛋白H4K91泛素化可保护DNA免受损伤, 维持胚胎基因组的稳定[91]。PRC1介导的H2AK119ub1与H3K27me3类似, 在卵子中形成了非经典的H2AK119ub1域, 参与卵子中部分H3K27me3印记的建立[90]。H2AK119ub1缺失导致ZGA过程中发育基因过早激活, 胚胎发育发生阻滞[90]。ubH2A在卵母细胞和精子中与H3K27me3有大部分重叠, 但在植入前发育过程中大多数ubH2A结构域中不存在H3K27me3富集[98]。PRC1和ubH2A通过抑制谱系特异性基因的表达维持ESC的多能性。敲除组蛋白H2A去泛素化酶Usp16后, ubH2A介导的谱系特异性基因被抑制, ESC无法分化。因此, H2A去泛素化是ESC基因表达和分化的关键调节事件。总的来讲, ubH2A通过调控基因沉默参与精子发生及ZGA等过程, 并在ESC的多能性维持中发挥重要作用。

2.4 其他组蛋白修饰方式

随着研究的不断深入, 多种新的组蛋白修饰被发现。巴豆酰化(crotonylation)是一种与胚胎分化相关的组蛋白修饰方式。巴豆酰基由巴豆酰辅酶A提供, 巴豆酰辅酶A促进组蛋白巴豆酰化。巴豆酰辅酶A是线粒体或过氧化物酶体脂肪酸氧化以及赖氨酸、色氨酸代谢的中间产物。巴豆酰化在内胚层分化相关基因的启动子区域高度富集, 促使ESC向内胚层分化[92](表2)。组蛋白瓜氨酸化(citrullination)是另一种与植入前胚胎发育相关的新近发现的组蛋白修饰。组蛋白瓜氨酸化的水解过程将携带正电荷的精氨酸转化为瓜氨酸, 改变蛋白质携带的电荷, 从而改变蛋白质的结构、功能及分子间的相互作用[93]。肽酰基精氨酸脱亚氨酶(peptidylarginine deiminase, PADI)参与调控组蛋白瓜氨酸化, 抑制PADI1会导致组蛋白H4Cit3和H3Cit2、H3Cit8、H3Cit17水平降低, 转录活性降低, 使大多数胚胎在4-细胞阶段发生发育阻滞[93]。

3 结语与展望

组蛋白变异体置换与组蛋白修饰一直是表观遗传学研究的热点。组蛋白变异体通过特异的分子伴侣或染色质重塑因子沉积在染色质上, 改变局部的染色质状态, 调控基因的表达, 参与调控配子发生和植入前胚胎发育中的多种重要事件[2,7]。组蛋白修饰在胚胎发育过程中经历广泛的建立、擦除和重建, 精准调控发育进程[47,68]。近年来, 随着单细胞或少量细胞全基因组表观遗传分析技术的发展, 组蛋白变异体及组蛋白修饰的动态变化及其发生机制被逐渐阐明, 但许多组蛋白相关的表观遗传信息的生物学功能及其调控机制仍需进一步研究。是否存在更多新的组蛋白修饰和组蛋白变异体？组蛋白变异体置换的确切机制是什么？置换后染色质结构发生何种改变？如何影响基因表达？“组蛋白密码”如何协同作用？其具体机制是什么？对这些科学问题的深入研究将有助于加深对哺乳动物配子发生及植入前胚胎发育过程的理解, 并为生殖相关疾病的临床研究和治疗提供理论参考。

参考文献 (References)

[1] IZZO A, SCHNEIDER R. The role of linker histone H1 modifications in the regulation of gene expression and chromatin dynamics [J]. Biochim Biophys Acta, 2016, 1859(3): 486-95.

[2] BUSCHBECK M, HAKE S B. Variants of core histones and their roles in cell fate decisions, development and cancer [J]. Nat Rev Mol Cell Bio, 2017, 18(5): 299-314.

[3] BANNISTER A J, KOUZARIDES T. Regulation of chromatin by histone modifications [J]. Cell Res, 2011, 21(3): 381-95.

[4] MARGUERON R, TROJER P, REINBERG D. The key to development: interpreting the histone code [J]? Curr Opin Genet Dev, 2005, 15(2): 163-76.

[5] MORGAN M A J, SHILATIFARD A. Reevaluating the roles of histone-modifying enzymes and their associated chromatin modifications in transcriptional regulation [J]. Nat Genet, 2020, 52(12): 1271-81.

[6] KURUMIZAKA H, KUJIRAI T, TAKIZAWA Y. Contributions of histone variants in nucleosome structure and function [J]. J Mol Biol, 2021, 433(6): 166678.

[7] MARTIRE S, BANASZYNSKI L A. The roles of histone variants in fine-tuning chromatin organization and function [J]. Nat Rev Mol Cell Bio, 2020, 21(9): 522-41.

[8] JANG C W, SHIBATA Y, STARMER J, et al. Histone H3.3 maintains genome integrity during mammalian development [J]. Gene Dev, 2015, 29(13): 1377-92.

[9] TANG M C, JACOBS S A, MATTISKE D M, et al. Contribution of the two genes encoding histone variant h3.3 to viability and fertility in mice [J]. PLoS Genet, 2015, 11(2): e1004964.

[10] ISHIUCHI T, ABE S, INOUE K, et al. Reprogramming of the histone H3.3 landscape in the early mouse embryo [J]. Nat Struct Mol Biol, 2021, 28(1): 38-49.

[11] CHEN P, ZHAO J C, WANG Y, et al. H3.3 actively marks enhancers and primes gene transcription via opening higher-ordered chromatin [J]. Gene Dev, 2013, 27(19): 2109-24.

[12] NASHUN B, HILL P W, SMALLWOOD S A, et al. Continuous histone replacement by hira is essential for normal transcriptional regulation and de novo DNA methylation during mouse oogenesis [J]. Mol Cell, 2015, 60(4): 611-25.

[13] CHO C, WILLIS W D, GOULDING E H, et al. Haploinsuf-

ficiency of protamine-1 or -2 causes infertility in mice [J]. Nat Genet, 2001, 28(1): 82-6.

[14] KONG Q R, BANASZYNSKI L A, GENG F Q, et al. Histone variant H3.3-mediated chromatin remodeling is essential for paternal genome activation in mouse preimplantation embryos [J]. J Biol Chem, 2018, 293(10): 3829-38.

[15] NASHUN B, AKIYAMA T, SUZUKI M G, et al. Dramatic replacement of histone variants during genome remodeling in nuclear-transferred embryos [J]. Epigenetics, 2011, 6(12): 1489-97.

[16] WEN D C, BANASZYNSKI L A, ROSENWAKS Z, et al. H3.3 replacement facilitates epigenetic reprogramming of donor nuclei in somatic cell nuclear transfer embryos [J]. Nucleus, 2014, 5(5): 369-75.

[17] WEN D C, BANASZYNSKI L A, LIU Y, et al. Histone variant H3.3 is an essential maternal factor for oocyte reprogramming [J]. P Natl Acad Sci USA, 2014, 111(20): 7325-30.

[18] JIN C Y, ZANG C Z, WEI G, et al. H3.3/H2A.Z double variant-containing nucleosomes mark 'nucleosome-free regions' of active promoters and other regulatory regions [J]. Nat Genet, 2009, 41(8): 941-5.

[19] JIN C, FELSENFELD G. Nucleosome stability mediated by histone variants H3.3 and H2A.Z [J]. Genes Dev, 2007, 21(12): 1519-29.

[20] GAMBOGI C W, BLACK B E. The nucleosomes that mark centromere location on chromosomes old and new [J]. Essays Biochem, 2019, 63(1): 15-27.

[21] REGNIER V, VAGNARELLI P, FUKAGAWA T, et al. CENP-A is required for accurate chromosome segregation and sustained kinetochore association of BubR1 [J]. Mol Cell Biol, 2005, 25(10): 3967-81.

[22] DUNLEAVY E M, ROCHE D, TAGAMI H, et al. HJURP is a cell-cycle-dependent maintenance and deposition factor of CENP-A at centromeres [J]. Cell, 2009, 137(3): 485-97.

[23] MALIK H S, HENIKOFF S. Major evolutionary transitions in centromere complexity [J]. Cell, 2009, 138(6): 1067-82.

[24] SMOAK E M, STEIN P, SCHULTZ R M, et al. Long-term retention of CENP-A nucleosomes in mammalian oocytes underpins transgenerational inheritance of centromere identity [J]. Curr Biol, 2016, 26(8): 1110-6.

[25] LI L, QI S T, SUN Q Y, et al. CENP-A regulates chromosome segregation during the first meiosis of mouse oocytes [J]. J Huazhong U Sci-Med, 2017, 37(3): 313-8.

[26] HOWMAN E V, FOWLER K J, NEWSON A J, et al. Early disruption of centromeric chromatin organization in centromere protein A (Cenpa) null mice [J]. P Natl Acad Sci USA, 2000, 97(3): 1148-53.

[27] LACOSTE N, WOOLFE A, TACHIWANA H, et al. Mislocalization of the centromeric histone variant CenH3/CENP-A in human cells depends on the chaperone DAXX [J]. Mol Cell, 2014, 53(4): 631-44.

[28] WONG M M, COX L K, CHRIVIA J C. The chromatin remodeling protein, SRCAP, is critical for deposition of the histone variant H2A.Z at promoters [J]. J Biol Chem, 2007, 282(36): 26132-9.

[29] NASHUN B, YUKAWA M, LIU H, et al. Changes in the nuclear deposition of histone H2A variants during pre-implantation development in mice [J]. Development, 2010, 137(22): 3785-94.

[30] FAAST R, THONGLAIROAM V, SCHULZ T C, et al. Histone variant H2A.Z is required for early mammalian development [J]. Curr Biol, 2001, 11(15): 1183-7.

[31] FURUYA M, TANAKA M, TERANISHI T, et al. H1foo is indispensable for meiotic maturation of the mouse oocyte [J]. J Reprod Develop, 2007, 53(4): 895-902.

[32] FUNAYA S, OOGA M, SUZUKI M G, et al. Linker histone H1FOO regulates the chromatin structure in mouse zygotes [J]. Febs Lett, 2018, 592(14): 2414-24.

[33] HU G Q, CUI K R, NORTHRUP D, et al. H2A.Z facilitates access of active and repressive complexes to chromatin in embryonic stem cell self-renewal and differentiation [J]. Cell Stem Cell, 2013, 12(2): 180-92.

[34] SANSONI V, CASAS-DELUCCHI C S, RAJAN M, et al. The histone variant H2A.Bbd is enriched at sites of DNA synthesis [J]. Nucleic Acids Res, 2014, 42(10): 6405-20.

[35] NUSINOW D A, HERNANDEZ-MUNOZ I, FAZZIO T G, et al. Poly(ADP-ribose) polymerase 1 is inhibited by a histone H2A variant, MacroH2A, and contributes to silencing of the inactive X chromosome [J]. J Biol Chem, 2007, 282(17): 12851-9.

[36] SUN Z, BERNSTEIN E. Histone variant macroH2A: from chromatin deposition to molecular function [J]. Essays Biochem, 2019, 63(1): 59-74.

[37] PIQUET S, LE PARC F, BAI S K, et al. The histone chaperone FACT coordinates H2A.X-dependent signaling and repair of DNA damage [J]. Mol Cell, 2018, 72(5): 888-901.

[38] WIEDEMANN S M, MILDNER S N, BOENISCH C, et al. Identification and characterization of two novel primate-specific histone H3 variants, H3.X and H3.Y [J]. J Cell Biol, 2010, 190(5): 777-91.

[39] BOULARD M, GAUTIER T, MBELE G O, et al. The NH2 tail of the novel histone variant H2BFWT exhibits properties distinct from conventional H2B with respect to the assembly of mitotic chromosomes [J]. Mol Cell Biol, 2006, 26(4): 1518-26.

[40] MONTELLIER E, BOUSSOUAR F, ROUSSEAUX S, et al. Chromatin-to-nucleoprotamine transition is controlled by the histone H2B variant TH2B [J]. Gene Dev, 2013, 27(15): 1680-92.

[41] WEN Z Q, ZHANG L W, RUAN H H, et al. Histone variant H2A.Z regulates nucleosome unwrapping and CTCF binding in mouse ES cells [J]. Nucleic Acids Res, 2020, 48(11): 5939-52.

[42] ZHAO H, HAN Z, LIU X, et al. The chromatin remodeler Chd4 maintains embryonic stem cell identity by controlling pluripotency- and differentiation-associated genes [J]. J Biol Chem, 2017, 292(20): 8507-19.

[43] ILLINGWORTH R S, BOTTING C H, GRIMES G R, et al. PRC1 and PRC2 are not required for targeting of H2A.Z to developmental genes in embryonic stem cells [J]. PLoS One, 2012, 7(4): e34848.

[44] FALBO L, COSTANZO V. Epigenetic regulation of replication origin assembly: a role for histone H1 and chromatin remodeling factors [J]. Bioessays, 2021, 43(1): e2000181.

[45] DUAN J, ZHU L, DONG H, et al. Analysis of mRNA abundance for histone variants, histone- and DNA-modifiers in bovine *in vivo* and *in vitro* oocytes and embryos [J]. Sci Rep, 2019, 9(1): 1217.

[46] GAO S R, CHUNG Y G, PARSEGHIAN M H, et al. Rapid H1 linker histone transitions following fertilization or somatic cell nuclear transfer: evidence for a uniform developmental program in mice [J]. Dev Biol, 2004, 266(1): 62-75.
[47] XU R M, LI C, LIU X Y, et al. Insights into epigenetic patterns in mammalian early embryos [J]. Protein & Cell, 2021, 12(1): 7-28.
[48] ZHANG B, ZHENG H, HUANG B, et al. Allelic reprogramming of the histone modification H3K4me3 in early mammalian development [J]. Nature, 2016, 537(7621): 553-7.
[49] MENG T G, ZHOU Q, MA X S, et al. PRC2 and EHMT1 regulate H3K27me2 and H3K27me3 establishment across the zygote genome [J]. Nat Commun, 2020, 11(1): 6354.
[50] SEAH M K Y, MESSERSCHMIDT D M. From germline to soma: epigenetic dynamics in the mouse preimplantation embryo [J]. Curr Top Dev Biol, 2018, doi: 10.1016/bs.ctdb.2017.10.011.
[51] LIU X Y, WANG C F, LIU W Q, et al. Distinct features of H3K-4me3 and H3K27me3 chromatin domains in pre-implantation embryos [J]. Nature, 2016, 537(7621): 558-62.
[52] ZHENG H, HUANG B, ZHANG B J, et al. Resetting epigenetic memory by reprogramming of histone modifications in mammals [J]. Mol Cell, 2016, 63(6): 1066-79.
[53] VASTENHOUW N L, SCHIER A F. Bivalent histone modifications in early embryogenesis [J]. Curr Opin Cell Biol, 2012, 24(3): 374-86.
[54] BERNSTEIN B E, MIKKELSEN T S, XIE X, et al. A bivalent chromatin structure marks key developmental genes in embryonic stem cells [J]. Cell, 2006, 125(2): 315-26.
[55] ECKERSLEY-MASLIN M A, ALDA-CATALINAS C, REIK W. Dynamics of the epigenetic landscape during the maternal-to-zygotic transition [J]. Nat Rev Mol Cell Bio, 2018, 19(7): 436-50.
[56] ANDREU-VIEYRA C V, CHEN R H, AGNO J E, et al. MLL2 is required in oocytes for bulk histone 3 lysine 4 trimethylation and transcriptional silencing [J]. PLoS Biol, 2010, 8(8): e1000453.
[57] HANNA C W, TAUDT A, HUANG J H, et al. MLL2 conveys transcription-independent H3K4 trimethylation in oocytes [J]. Nat Struct Mol Biol, 2018, 25(1): 73-82.
[58] AOSHIMA K, INOUE E, SAWA H, et al. Paternal H3K4 methylation is required for minor zygotic gene activation and early mouse embryonic development [J]. Embo Rep, 2015, 16(7): 803-12.
[59] DAHL J A, JUNG I, AANES H, et al. Broad histone H3K4me3 domains in mouse oocytes modulate maternal-to-zygotic transition [J]. Nature, 2016, 537(7621): 548-52.
[60] LAMBROT R, LAFLEUR C, KIMMINS S. The histone demethylase KDM1A is essential for the maintenance and differentiation of spermatogonial stem cells and progenitors [J]. FASEB J, 2015, 29(11): 4402-16.
[61] YEUNG W K A, BRIND'AMOUR J, HATANO Y, et al. Histone H3K9 methyltransferase G9a in oocytes is essential for preimplantation development but dispensable for CG methylation protection [J]. Cell Rep, 2019, 27(1): 282-93.
[62] WANG J, ZHANG M, ZHANG Y, et al. The histone demethylase JMJD2C is stage-specifically expressed in preimplantation mouse embryos and is required for embryonic development [J]. Biol Reprod, 2010, 82(1): 105-11.
[63] MISKA E A, ZEGERMAN P, PARTRIDGE J C, et al. Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain [J]. Nature, 2001, 410(6824): 120-4.
[64] ZAIDAN N Z, SRIDHARAN R. HP1gamma regulates H3K36 methylation and pluripotency in embryonic stem cells [J]. Nucleic Acids Res, 2020, 48(22): 12660-74.
[65] ZAMUDIO N M, CHONG S Y, O'BRYAN M K. Epigenetic regulation in male germ cells [J]. Reproduction, 2008, 136(2): 131-46.
[66] 刘琳琳, 杜鸿斌, 孙梦莹, 等. 组蛋白修饰在卵母细胞发育中功能和调控机制的研究进展[J]. 生命科学(LIU L L, DU H B, SUN M Y, et al. Function and regulatory mechannism of histone modifications during oocyte development [J]. Chinese Bulletin of Life Sciences), 2021, 33(6): 709-17.
[67] WORRAD D M, TURNER B M, SCHULTZ R M. Temporally restricted spatial localization of acetylated isoforms of histone H4 and RNA polymerase II in the 2-cell mouse embryo [J]. Development, 1995, 121(9): 2949-59.
[68] XIA W K, XIE W. Rebooting the epigenomes during mammalian early embryogenesis [J]. Stem Cell Rep, 2020, 15(6): 1158-75.
[69] SANTENARD A, ZIEGLER-BIRLING C, KOCH M, et al. Heterochromatin formation in the mouse embryo requires critical residues of the histone variant H3.3 [J]. Nat Cell Biol, 2010, 12(9): 853-62.
[70] ZIEGLER-BIRLING C, DAUJAT S, SCHNEIDER R, et al. Dynamics of histone H3 acetylation in the nucleosome core during mouse pre-implantation development [J]. Epigenetics, 2016, 11(8): 553-62.
[71] VAN DEN BERG I M, ELEVELD C, VAN DER HOEVEN M, et al. Defective deacetylation of histone 4 K12 in human oocytes is associated with advanced maternal age and chromosome misalignment [J]. Hum Reprod, 2011, 26(5): 1181-90.
[72] TANG L S, WANG Q, XIONG B, et al. Dynamic changes in histone acetylation during sheep oocyte maturation [J]. J Reprod Dev, 2007, 53(3): 555-61.
[73] BUI H T, THUAN N V, KISHIGAMI S, et al. Regulation of chromatin and chromosome morphology by histone H3 modifications in pig oocytes [J]. Reproduction, 2007, 133(2): 371-82.
[74] MAALOUF W E, ALBERIO R, CAMPBELL K H. Differential acetylation of histone H4 lysine during development of in vitro fertilized, cloned and parthenogenetically activated bovine embryos [J]. Epigenetics, 2008, 3(4): 199-209.
[75] WU X, LI Y, XUE L A, et al. Multiple histone site epigenetic modifications in nuclear transfer and *in vitro* fertilized bovine embryos [J]. Zygote, 2011, 19(1): 31-45.
[76] BARNES C E, ENGLISH D M, COWLEY S M. Acetylation&Co: an expanding repertoire of histone acylations regulates chromatin and transcription [J]. Essays Biochem, 2019, 63(1): 97-107.
[77] YIN S, JIANG X H, JIANG H W, et al. Histone acetyltransferase KAT8 is essential for mouse oocyte development by regulating reactive oxygen species levels [J]. Development, 2017, 144(12): 2165-74.
[78] DOVEY O M, FOSTER C T, COWLEY S M. Histone deacetylase 1 (HDAC1), but not HDAC2, controls embryonic stem cell differentiation [J]. P Natl Acad Sci USA, 2010, 107(18): 8242-7.

[79] MA P P, SCHULTZ R M. Histone deacetylase 2 (HDAC2) regulates chromosome segregation and kinetochore function via H4K16 deacetylation during oocyte maturation in mouse [J]. PLoS Genet, 2013, 9(3): e1003377.

[80] MONTGOMERY R L, POTTHOFF M J, HABERLAND M, et al. Maintenance of cardiac energy metabolism by histone deacetylase 3 in mice [J]. J Clin Invest, 2008, 118(11): 3588-97.

[81] WANG F, KOU Z, ZHANG Y, et al. Dynamic reprogramming of histone acetylation and methylation in the first cell cycle of cloned mouse embryos [J]. Biol Reprod, 2007, 77(6): 1007-16.

[82] ZHAO J, ROSS J W, HAO Y, et al. Significant improvement in cloning efficiency of an inbred miniature pig by histone deacetylase inhibitor treatment after somatic cell nuclear transfer [J]. Biol Reprod, 2009, 81(3): 525-30.

[83] BUI H T, WAKAYAMA S, KISHIGAMI S, et al. Effect of trichostatin A on chromatin remodeling, histone modifications, DNA replication, and transcriptional activity in cloned mouse embryos [J]. Biol Reprod, 2010, 83(3): 454-63.

[84] LAMBROT R, SIKLENKA K, LAFLEUR C, et al. The genomic distribution of histone H3K4me2 in spermatogonia is highly conserved in spermdagger [J]. Biol Reprod, 2019, 100(6): 1661-72.

[85] SANTOS F, PETERS A H, OTTE A P, et al. Dynamic chromatin modifications characterise the first cell cycle in mouse embryos [J]. Dev Biol, 2005, 280(1): 225-36.

[86] HAO N, XIN H, SHI X, et al. Paternal reprogramming-escape histone H3K4me3 marks located within promoters of RNA splicing genes [J]. Bioinformatics, 2021, 37(8): 1039-44.

[87] XIAO C, LIU Y, XIE C, et al. Cadmium induces histone H3 lysine methylation by inhibiting histone demethylase activity [J]. Toxicol Sci, 2015, 145(1): 80-9.

[88] KIZER K O, PHATNANI H P, SHIBATA Y, et al. A novel domain in Set2 mediates RNA polymerase II interaction and couples histone H3 K36 methylation with transcript elongation [J]. Mol Cell Biol, 2005, 25(8): 3305-16.

[89] GUENTHER M G, LEVINE S S, BOYER L A, et al. A chromatin landmark and transcription initiation at most promoters in human cells [J]. Cell, 2007, 130(1): 77-88.

[90] MEI H, KOZUKA C, HAYASHI R, et al. H2AK119ub1 guides maternal inheritance and zygotic deposition of H3K27me3 in mouse embryos [J]. Nat Genet, 2021, 53(4): 539-50.

[91] TESSADORI F, GILTAY J C, HURST J A, et al. Germline mutations affecting the histone H4 core cause a developmental syndrome by altering DNA damage response and cell cycle control [J]. Nat Genet, 2017, 49(11): 1642-6.

[92] FANG Y, XU X, DING J, et al. Histone crotonylation promotes mesoendodermal commitment of human embryonic stem cells [J]. Cell Stem Cell, 2021, 28(4): 748-63,e7.

[93] ZHANG X, LIU X, ZHANG M, et al. Peptidylarginine deiminase 1-catalyzed histone citrullination is essential for early embryo development [J]. Sci Rep, 2016, 6(1): 38727.

[94] SWATEK K N, KOMANDER D. Ubiquitin modifications [J]. Cell Res, 2016, 26(4): 399-422.

[95] WANG H, WANG L, ERDJUMENT-BROMAGE H, et al. Role of histone H2A ubiquitination in polycomb silencing [J]. Nature, 2004, 431(7010): 873-8.

[96] YUAN G, MA B, YUAN W, et al. Histone H2A ubiquitination inhibits the enzymatic activity of H3 lysine 36 methyltransferases [J]. J Biol Chem, 2013, 288(43): 30832-42.

[97] MA T, KELLER J A, YU X C. RNF8-dependent histone ubiquitination during DNA damage response and spermatogenesis [J]. Acta Bioch Bioph Sin, 2011, 43(5): 339-45.

[98] CHEN Z, DJEKIDEL M N, ZHANG Y. Distinct dynamics and functions of H2AK119ub1 and H3K27me3 in mouse preimplantation embryos [J]. Nat Genet, 2021, 53(4): 551-63.