刘洪彬，山东大学教授，博士生导师。近5年围绕配子减数分裂的分子调控机制进行研究，在*Genome Biol*、*EMBO J*、*Curr Biol*、*Sci Adv*、*Nucleic Acids Res*及*Protein Cell*等期刊发表研究论文20余篇。陆续获得中华医学青年科技奖、全国妇幼健康科学技术奖一等奖等荣誉。

组蛋白翻译后修饰在减数分裂中作用机制的研究进展

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摘要　减数分裂是有性生殖生物产生单倍体配子和遗传多样性的基础。在这一过程中, DNA复制一次, 细胞连续分裂两次, 形成四个染色体数目为母细胞一半的配子。在减数分裂前期, 同源染色体依次进行配对、联会、重组和分离, 亲本的染色体被正确分配到配子中, 实现遗传物质在生物世代间的稳定传递。组蛋白翻译后修饰是重要的表观遗传调控机制之一, 包括组蛋白甲基化(methylation, me)、酰基化(acylation, ac)、磷酸化(phosphorylation, ph)、泛素化(ubiquitination, ub)等。组蛋白修饰的建立、识别、擦除以及不同组蛋白修饰间的交叉会话揭示了一种“组蛋白密码”, 参与了DNA复制、损伤修复、基因表达和染色质构象改变, 在减数分裂多个阶段发挥重要作用。该文综述了近年来对组蛋白翻译后修饰参与减数分裂重要生物学事件的研究进展, 并为后续研究内容和方向提供了新的见解。

关键词　减数分裂; 组蛋白修饰; 精子发生; 同源重组

Research Progress on the Mechanism of Histone Post-Translational Modifications in Meiosis

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Abstract　Meiosis is the basis for the production of haploid gametes and genetic diversity in sexual reproductive organisms. During this process, DNA replicates once and the cell divides continuously twice, forming four

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gametes with half of the mother cell's chromosomes. In the early stage of meiosis, homologous chromosomes undergo pairing, synapsis, recombination, and separation in sequence, and the parental chromosomes are correctly assigned to gametes, achieving stable transmission of genetic material between biological generations. Post-translational modification of histones is one of the important epigenetic mechanisms, including histone methylation (me), acylation (ac), phosphorylation (ph), ubiquitination (ub), and so on. The establishment, recognition, erasure, and cross talk between different histone modifications reveal a "histone code" that participates in DNA replication, damage repair, gene expression, and chromatin conformational changes, playing important roles in multiple stages of meiosis. This article reviews the recent research progress on the involvement of histone post-translational modifications in important biological events related to meiosis, and provides new insights for subsequent research contents and directions.

Keywords meiosis; histone modification; spermatogenesis; homologous recombination

减数分裂是有性生殖生物体产生单倍体配子的特殊分裂方式, 减数分裂的有序进行: 一方面保证了遗传物质在生物世代间的稳定传递, 另一方面通过同源重组产生等位基因的新组合, 增加了遗传多样性[1]。近年来, 组蛋白翻译后修饰因其富含多样化的遗传密码信息受到广泛关注。研究发现组蛋白翻译后修饰在哺乳动物减数分裂中扮演重要角色, 具有广阔的研究前景。在减数分裂过程中, 组蛋白翻译后修饰作为染色质中心调节器, 广泛参与减数分裂多个重要生物学事件, 包括减数分裂启动、程序性DNA双链断裂、同源重组修复、性染色体沉默等[2]。本综述着重于组蛋白翻译后修饰参与减数分裂关键生物学事件的研究进展, 概述组蛋白翻译后修饰在其中的动态变化及其对基因组的调控作用, 并梳理其分子机制, 最后简述组蛋白修饰交叉会话在减数分裂中的作用。本综述将为理解减数分裂的调控机制和探索男性不育的潜在治疗靶点提供有益参考。

1 减数分裂启动与组蛋白修饰

在哺乳动物精子发生中, 精原细胞历经多次有丝分裂扩增细胞群体, 之后停止有丝分裂, 启动减数分裂进程, 称为有丝分裂–减数分裂转换(mitosis-to-meiosis transition), 也被称减数分裂启动(meiosis entry)。减数分裂启动是一个染色质结构高度动态变化的过程, 伴随着大量减数分裂相关基因的转录激活, 该过程受到多个分子的精准调控。减数分裂起始因子STRA8在视黄酸的靶向诱导下启动减数分裂, 然而STRA8并不足以独立诱导减数分裂发生[3-6]。近年来发现, MEIOSIN、ZNHIT1等分子协同参与减数分裂启动, 丰富了该领域的理论基础[7-8]。

多梳抑制复合物(polycomb-repressive complex, PRC)是一类高度保守的表观调控因子, 通过改变组蛋白修饰和染色质结构, 在细胞命运的维持和转变中发挥至关重要的作用[9]。在发育过程中, 当基因需要由转录沉默向激活状态改变时, PRC复合物及其催化的H2AK199ub1和H3K27me3会被去除, 基因才会被激活转录[10-11]。研究发现在减数分裂正式启动之前, PRC复合物介导了一组减数分裂相关基因, 包括减数分裂特异性黏连蛋白、联会复合物亚基、以及进入减数分裂必需的*Stra8*基因的沉默[12-13]。研究者在原始生殖细胞中检测到PRC1复合物催化亚基RNF2以及H3K27me3修饰富集于*Stra8*基因启动子处。*Rnf2*基因敲除小鼠中的原始生殖细胞表现为*Stra8*基因的异常激活, 提前进入减数分裂, 甚至已经开始联会复合物的组装[13]。而另一项研究绘制了精子发生过程中超级增强子动态变化的景观, 并发现SCML2作为PRC1复合物生殖系亚基, 沉默精原细胞特异性超级增强子, 从而驱动了有丝分裂向减数分裂的转换[14]。

PRC复合物在减数分裂后续进程中也发挥重要功能。PRC1核心组分CBX2的缺失会导致雌性小鼠生殖细胞显著减少, 同源染色体发生错配[15]。SCML2还可以促进H3K27me3在雄性生殖细胞中的形成, 从而建立二价染色质结构域, 对雄性种系分化必不可少[16]。这些研究表明PRC复合物通过建立特定的表观遗传印记调控减数分裂基因表达时序性, 是减数分裂启动及后续事件顺利进行的重要保障。

2 减数分裂同源重组中组蛋白修饰的重要功能

2.1 重组热点处独特的组蛋白修饰景观

组蛋白修饰的动态变化在减数分裂中已有广

泛研究。生殖细胞体外培养尚与体内自然发生有一定差异，各时期初级精母细胞缺乏特异性标志物，难以对减数分裂过程中全基因组水平组蛋白修饰动态变化进行研究[17]。近年来，微量建库测序等新兴技术的开发应用使得研究这一过程中潜在的分子机制成为可能。通过DAPI、H1T、SCP1和STRA8的共同标记，研究者成功获取了纯度高于73%的各时期精母细胞，并进行了微量细胞的ChIP-seq[18]。研究发现，H3K4me3、H3K9ac、H3K36me3、H3K4me2、H3K4me1、H3K27ac和H4K5ac显著富集在偶线期精母细胞的重组热点处；而H4K8ac、H4K12ac、H4K20me3、H3K4ac、H3K79me1、H3K79me3、H3K27me1、H3K9me2、H3K9me3和H3K27me3在重组热点处缺失[18]。另一项研究通过精子发生同步化与标签小鼠联合应用，将初级精母细胞分为6个时期，分析了包括H3K4me3在内的8种组蛋白修饰，发现了H3K27ac也富集于重组热点，而H3K9me2在重组热点处缺失[19]。系统鉴定重组热点处的组蛋白修饰景观，为后续开展组蛋白修饰调控同源重组修复的分子机制研究奠定了坚实的理论基础。

值得注意的是，重组热点处富集的组蛋白修饰具有独特的动态变化图谱。H3K4me3最早出现于细线期，于偶线期达到高峰，在粗线期中后期被擦除。而相较于H3K4me3，H3K4me1出现的时期更早，在前细线期已有信号富集，消失的时期更晚，在双线期被擦除。有趣的是，H3K4me1在DNA双链断裂(DNA double strand breaks, DSB)核心区域的信号强度明显弱于周围区域，且偶线期可以明显观察到重组热点处H3K4me1被H3K4me3取代的现象。而H3K9ac出现的时间较H3K4me3稍晚，但集中在DSB核心区域[18-19]。

重组热点处独特的组蛋白修饰景观是同源重组顺利进行的表观遗传学基础，未来对这类修饰如何被催化、识别和擦除的进一步分子机制进行研究，将有助于更好地理解同源重组中表观遗传对遗传物质交换的调控机制(表1)。

2.2 组蛋白甲基转移酶PRDM9催化的H3K4me3与同源重组命运决定

减数分裂重组是通过程序性DSB形成来启动的[38]。在大多数哺乳动物中，PRDM9介导的H3K4me3控制着DSB的非随机分布[27,39-44]。PRDM9羧基端含有长的、遗传上高度可变的锌指结构域，该结构域决定了PRDM9在基因组上的结合位置。这些重组位点并不在基因启动子区域，而是位于基因间区或内含子区域[45]。PRDM9作为一种DNA结合蛋白，通过其SET结构域的组蛋白三甲基转移酶活性[27,46-48]，介导附近核小体上H3K4me3和H3K36me3形成，从而改变局部染色质结构，并在其结合位点附近募集形成DSB所需的其他分子[49-50]。在*Prdm9*基因敲除小鼠中，重组位点处的DSB无法形成，而是错误地出现在基因的启动子区域，导致减数分裂同源重组缺陷，最终导致功能性配子无法形成[49]。

2.3 组蛋白修饰阅读器ZCWPW1保证DSB正常修复和同源重组顺利进行

众所周知组蛋白甲基化修饰一般不直接发挥生物学功能，而是依靠与甲基化修饰识别分子的结合参与下游生物学事件。在酿酒酵母(*Saccharomyces cerevisiae*)中，研究人员提出了Spp1介导的“环/轴结构”假说[51]。Spp1通过植物同源结构域(plant homeodomain, PHD)与重组热点处的H3K4me3结合，并同时与定位于染色体轴的Spo11辅助蛋白Mer2相互作用，促进减数分裂DSB的形成[21,52]。Spp1在哺乳动物中的同源蛋白是CXXC1，该分子含有识别H3K4me3的PHD结构域[53]。研究发现，CXXC1在体外分别与PRDM9和IHO1(酵母Mer2直系同源物)存在相互作用[54-55]。令人意外的是，尽管在生殖细胞中特异性敲除*Cxxc1*基因会导致雄性小鼠不育，DSB修复异常和全基因组H3K4me3修饰水平的降低，但在基因组水平并没有检测到CXXC1在重组热点处的富集[56]。由此可以推测，哺乳动物中可能已经进化出将重组位点处的H3K4me3和H3K36me3与DSB形成和同源重组联系起来的新型减数分裂相关因子。

ZCWPW1通过其zf-CW结构域和PWWP结构域分别特异性识别H3K4me3和H3K36me3修饰。从基因进化的角度，通过生物信息学分析发现，哺乳动物中PRDM9与ZCWPW1、ZCWPW2协同进化，这提示它们的分子生物学功能高度相关[57]。*Zcwpw1*基因敲除雄鼠不育，精母细胞减数分裂阻滞在偶线期阶段，并伴有DSB修复异常和同源重组缺陷；而*Zcwpw1*基因敲除雌鼠表现为继发性卵巢早衰[58]。研究者进一步利用*Prdm9*基因敲除小鼠模型和ZCWPW1蛋白CW结构域点突变小鼠模型，证实ZCWPW1特异性识别PRDM9催化的重组位点附近的H3K4me3和H3K36me3，是减数分裂同源重组修复的重要保

表1 与减数分裂进程有关的主要组蛋白修饰

Table 1 Summary of major histone modifications implicated in meiosis

组蛋白修饰 Histone modifications	功能/减数分裂中的作用 Functions/roles in meiosis	书写器 Writers	擦除器 Erasers	阅读器 Readers	参考文献 References
Methylation					
H3K4me1/me2/me3	Chromatin recombination				
H3K4me3	Related to transcriptional activation/meiotic recombination hotspots	PRDM9	Uncertain	ZCWPW1	[20-22]
H3K9me1/me2	Transcription silencing	G9a; SUV39H1	Uncertain	HP1γ	[23]
H3K9me3	Heterochromatin modification of pericentromere	SETDB1			[24]
H3K27me3	Transcription silencing	PRC2	Uncertain	PRC1	[25-26]
H3K36me3	Meiotic recombination	PRDM9		ZCWPW1	[22,27]
H3K79me2	Transcription activation	DOTL1	Uncertain	Uncertain	[28-29]
H3K79me3	Transcriptional silencing of centromere and sex bodies	DOTL1	Uncertain	Uncertain	[28-29]
H4R3me2a		PRMT1			[30]
Acetylation					
H3K18ac, H3K23ac	The division of meiotic cells				[26]
H3K9ac	Gene transcription/meiotic recombination hotspots				[31]
H3K14ac, H4K5ac, H4K8ac, H4K12acH4K16ac	Open chromatin during gene expression in GV oocytes	Tip60/KAT5 CBP/KAT3A	HDAC	Uncertain	[32]
H4K5ac, H4K12ac	Transcription of genes in leptotene and zygotene spermatocytes				
H4K8ac	Chromatin remodeling during meiosis of oocytes				[33]
H4K16ac	Meiotic recombination checkpoint	CBP/KAT3A	SIR	Uncertain	[34]
H4K44ac	Promote homologous recombination				[35]
Phosphorylation					
γH2AX	DNA double strand breaks	ATM; ATR	Uncertain	MDC1	[36]
Ubiquitination					
H2AK199ub	Transcription silencing	RNF8; PRC1	USP7	Uncertain	[14]
H2BK123ub	Meiosis entry and DSB formation				[37]

障[22]。

3 组蛋白修饰在性染色体沉默中的功能

精母细胞进入粗线期后, 与常染色体粗线期完全联会不同的是, XY染色体只在拟常染色体区域(pseudoautosomal region, PAR)联会, 性染色体基因因此具有特殊的表达模式, 即发生减数分裂性染色体沉默(meiotic sex chromosome inactivation, MSCI)。MSCI是哺乳动物粗线期精母细胞中的独有现象。在MSCI过程中, 沉默的XY染色体历经染色质结构重塑, 浓缩为致密的异染色质, 形成XY body[59-63]。在这一过程中涵盖了剧烈的组蛋白修饰改变: (1) ATR-TOPBP1复合物催化H2AX 139位点的丝氨酸磷酸化, 形成γH2AX, 并招募其识别分子MDC1, MDC1结合γH2AX, 从而促进更多的ATR和TOPBP1结合, 由此形成一个正反馈环路, 将γH2AX信号迅速扩散覆盖至整个XY body区域, 从而介导MSCI的起始[64-67]; (2) γH2AX可通过TRIM28招募甲基转移酶SETDB1, 在早粗线期的XY body上建立抑制性组蛋白修饰H3K9me3, HP1家族分子作为H3K9me3阅读器, 驱动异染色质形成并负责基因沉默[68]; (3) PRC1复合物介导的H2AK119位点的泛素化修饰出现于γH2AX之后, 协同发挥转录沉默的功能, 并于粗线期结束之前在SCML2与去泛素化酶USP7的共同作用下被擦除[14,69]; (4) 在进入中粗线期后, XY染色体上的经典组蛋白变体H3.1和H3.2被H3.3所替换, 该过程伴随着组蛋白H3上的甲基化和乙酰化修饰的大量丢失, 部分修饰直至晚双线期才在XY body上重新定位[70-71]。然而是否是这些特殊表观遗传状态的构建, 导致MSCI及XY body的形成, 仍有待进一步研究。

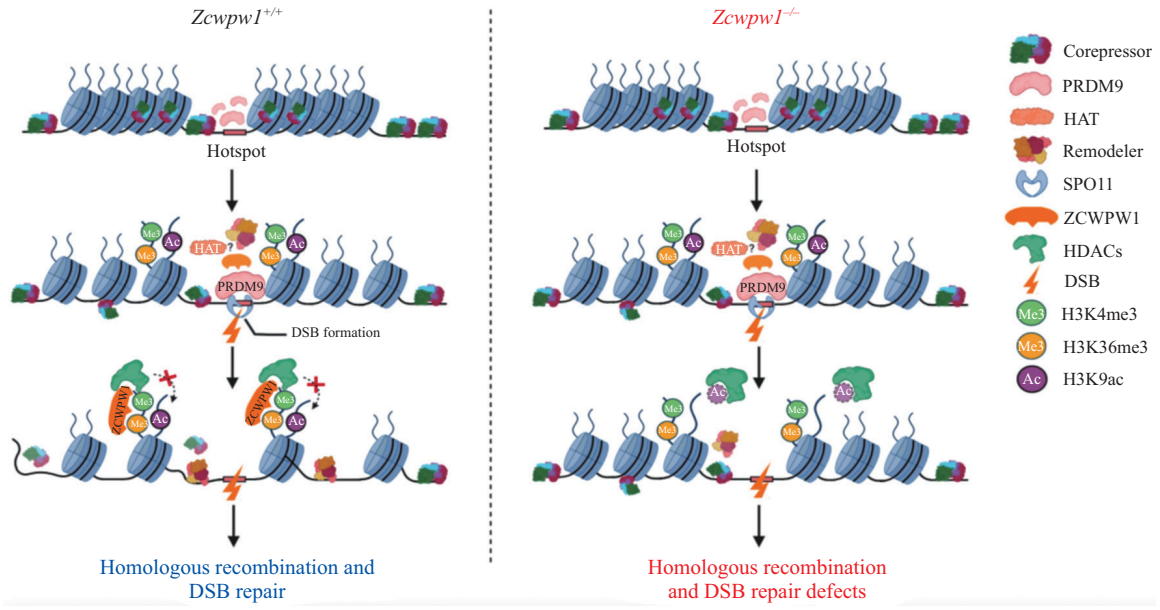

图1　组蛋白甲基化修饰阅读器ZCWPW1在减数分裂中的功能模式图

Fig.1　Diagram of histone methylation modification reader ZCWPW1 during meiosis

4　减数分裂组蛋白修饰间的交叉会话

组蛋白的翻译后修饰由特定的修饰酶催化完成，然而有一些修饰状态的建立还需要其他位点上已有修饰的协助，这种现象被称为组蛋白修饰交叉会话(histone modification crosstalk)。组蛋白修饰交叉会话是一类重要的表观调控机制，在表观遗传景观建立和基因开关切换等细胞进程中扮演重要角色，彰显了表观调控的层次性和精密性。研究人员在*Cxxc1*基因敲除小鼠模型中同时检测到了减数分裂前期H2AK119ub1水平的变化[72]。与此同时在卵母细胞中也有报道H3K4me3水平的降低会影响H2AK119ub1在基因组上的分布以及DNA甲基化水平等[73]。未来有待通过基因编辑小鼠、内源性蛋白降解系统、生物素邻近蛋白标记和结构生物学技术，解析减数分裂中组蛋白修饰交叉会话的精细分子机制。

重组热点处组蛋白修饰之间也存在交叉会话。研究发现重组位点附近H3K9ac信号和染色质开放性的建立依赖于PRDM9及ZCWPW1。进一步研究发现，ZCWPW1通过拮抗HDAC蛋白的去乙酰化酶活性来维持重组位点处的H3K9ac水平，并进一步促进和维持重组位点处的染色质开放状态，最终促进减数分裂DSB的同源重组修复(图1)[50,74]。组蛋白修饰交叉会话在基因组特定区域建立独特的表观遗传景观，使得不同组蛋白修饰及其识别和调控分子协同发挥作用。

5　展望

组蛋白翻译后修饰是表观遗传学研究的重要内容。近年来，人们对于组蛋白修饰在减数分裂中的作用有了更加深刻的认识。一方面组蛋白修饰本身可以改变染色质结构和状态，并串联多种不同修饰形成调节网络，组成“组蛋白密码”；另一方面，组蛋白修饰可作为活化或抑制信号招募多种效应分子，构成表观修饰分子网络，协同发挥功能。总之，在未来深入探究组蛋白翻译后修饰对减数分裂的调控作用，尚有以下主要问题亟待解决：(1) 减数分裂中新型组蛋白修饰(如乳酸化、琥珀酰化、巴豆酰化、β-羟基丁酰化)的鉴定和功能；(2) 减数分裂中组蛋白修饰交叉会话的精细分子机制；(3) 减数分裂组蛋白修饰调控染色质结构状态的效应器及其下游通路；(4) 如何利用动物模型、单细胞多组学技术等筛选组蛋白修饰相关不育症候选基因并明确其机制，指导临床应用。对这些问题的深入探索，一方面有助于加深我们对减数分裂表观遗传景观的理解，为阐明组蛋白密码在减数分裂中的作用奠定基础；另一方面，减数分裂过程中伴随大量基因精确有序的调控，组蛋白翻译后修饰异常会导致减数分裂染色

体行为改变, 从而引发精子缺失、精子畸形或少弱精子等病症。因此进一步加强减数分裂过程中组蛋白修饰调控作用的研究, 将为临床上男性不育的诊断和治疗提供新的靶点。

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