综述

植物组蛋白变体生物学功能

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摘要 组蛋白变体是重要的表观遗传调控因子, 能够在染色质特定位置替换常规组蛋白, 维持染色质结构进而保证转录激活或抑制的顺利进行。目前, 组蛋白变体的调控功能已成为植物学研究领域的一个热点。近年来, 随着植物组蛋白变体生物学功能研究的不断深入, 发现组蛋白变体能够在植物生长发育和环境应答调控等多个生物学过程中发挥重要作用。该文简要介绍了已知的植物组蛋白变体的种类, 系统综述了各类组蛋白变体在植物多个生命进程中的生物学功能及调控过程, 以期为深入认知植物组蛋白变体的作用机制提供参考。

关键词 组蛋白变体; 生物学功能; 转录调控

Biological Functions of Plant Histone Variants

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Abstract Histone variants are important epigenetic regulators, which can replace canonical histones at specific sites on chromatin, to maintain chromatin structure and ensure transcriptional activation or repression. At present, the regulatory function of histone variants has become a research hotspot in plant biology. The recent studies on the biological functions of plant histone variants have shown that histone variants can play critical roles in multiple biological processes such as plant growth and development, as well as environment responses. This review briefly introduces the known plant histone variants, and systematically reviews the biological functions and regulatory processes of various histone variants in multiple biological processes of plants, providing a reference for deeply understanding the regulatory mechanism of plant histone variants.

Keywords histone variants; biological function; transcriptional regulation

组蛋白是染色质基本结构单位——核小体的主要蛋白质组分, 除了常规组蛋白核心成员H2A、H2B、H3和H4以及连接组蛋白H1外, 还有一类特殊的核小体组分即组蛋白变体, 组蛋白变体和它的翻译后修饰共同参与染色质表观遗传调控[1-3]。组蛋白变体是常规组蛋白的变异体, 具有与常规组蛋白不同的编码基因, 它们的氨基酸序列及大小亦有别于常规组蛋白[4]。在植物中除H2B和H4外, 已发现H1、

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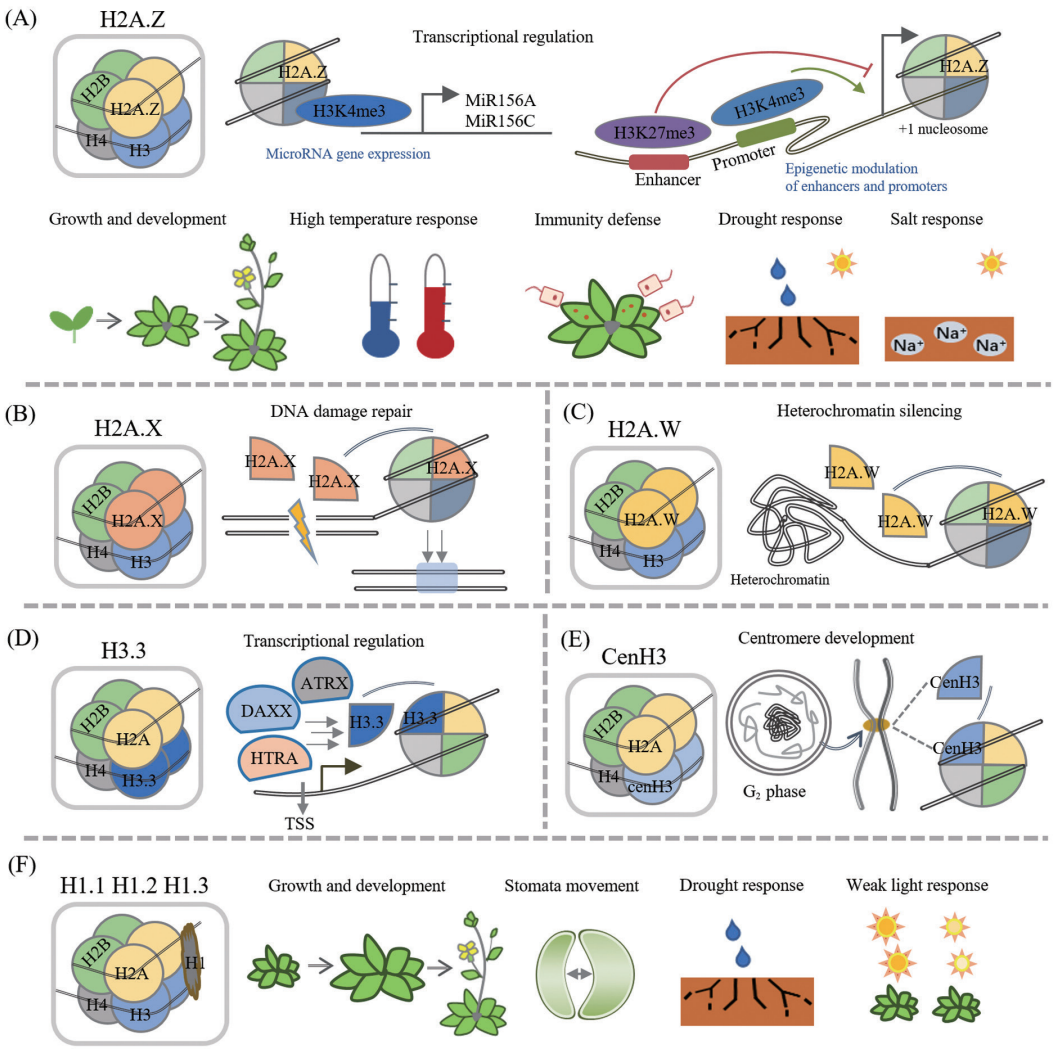


A~F: 植物组蛋白变体H2A.Z、H2A.X、H2A.W、H3.3、CenH3和H1.1 H1.2 H1.3的功能研究进展。H3K4me3: H3K4三甲基化; H3K27me3: H3K27三甲基化; MiR: 小RNA; DAXX: 死亡结构域相关蛋白; ATRX: X关联α地中海贫血迟缓综合征; HTRA: 组蛋白调节因子A; TSS: 转录起始位点。

A-F: the research advances in the functions of plant histone variants H2A.Z, H2A.X, H2A.W, H3.3, CenH3, and H1.1 H1.2 H1.3. H3K4me3: H3K4 tri-methylation; H3K27me3: H3K27 tri-methylation; MiR: MicroRNA; DAXX: death domain associated protein; ATRX: alpha thalassemia retardation syndrome X-linked; HTRA: histone regulator A; TSS: transcription start site.

图1 拟南芥组蛋白变体生物学功能

Fig.1 The biological functions of the histone variants in *Arabidopsis thaliana*

H2A、H3均具有特殊的组蛋白变体, 目前的报道多集中于H2A和H3的变异体, 包括H2A.Z、H2A.X、H2A.W、H3.3和CenH3, 还有少数研究涉及到组蛋白H1的变体H1.1、H1.2和H1.3[5-6]。组蛋白变体可以在染色质伴侣分子的辅助下, 在染色质特定位置替换常规组蛋白, 改变核小体动力学, 进而通过调节核小体结构稳定性维持染色质结构, 对保障转录激活或抑制至关重要。随着研究的不断深入, 组蛋白变体参与转录调控、DNA损伤修复和异染色质沉默等生物学功能的研究已取得一系列进展(图1), 其是植物发育与环境应答过程中至关重要的表观遗传调控因子[7-9]。本文在对已知植物组蛋白变体作简要介绍的基础上, 重点对各类组蛋白变体的生物学功能及其参与的调控过程等的相关研究进行系统综述。

1 组蛋白变体H2A.Z

1.1 H2A.Z编码及核小体装载

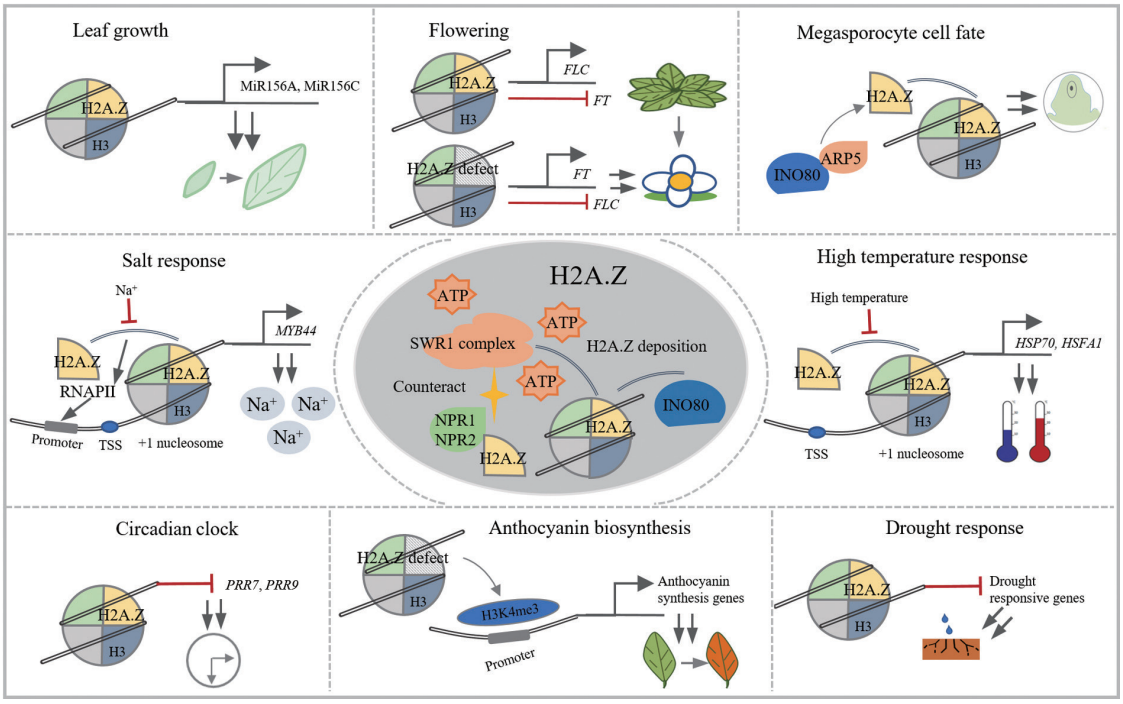
H2A.Z是一类在真核生物中高度保守的组蛋白变体, 在植物多个生物学进程中发挥重要作用(图2)。H2A.Z与H2A主要在C末端结构存在差异, H2A.Z的C末端尾部短于H2A, 且其40%的氨基酸序列不同于H2A[10]。植物中H2A.Z的编码基

因现已在拟南芥和水稻中被明确鉴定，拟南芥基因组共有13个*HTA*(histone H2A)基因编码H2A组蛋白，其中*HTA8*、*HTA9*和*HTA11*负责编码组蛋白变体H2A.Z[11]，而水稻中编码H2A.Z的基因则为*HTA705*、*HTA712*、*HTA713*[12-13]。

H2A.Z在核小体中的装载主要由SWR1(SWi2/snf2-related 1)蛋白复合物负责，该复合物成员主要包括ARP6(actin-related protein 6)、PIE1(photoperiod-independent early flowering 1)、SEF(serrated leaves and early flowering)、SWC4(SWR complex subunit 4)、MBD9(methyl-CpG-binding domain 9)、ATPase亚基、YAF9(yeast all1-fused gene from chromosome 9)[14-18]。SWR1复合物与核小体结合后分解DNA与核小体(图2)，在ATP驱动下改变核小体构象，将H2A.Z/H2B二聚体运送到DNA-(H3/H4)四聚体上，形成核小体核心结构[19-20]。近些年的研究表明，INO80(inositol requiring 80)复合物也参与了H2A.Z在核小体中的组装过程[21](图2)。INO80具有行使组蛋白交换的活性，能够依赖ATPase将游离H2A/H2B二聚体替换为H2A.Z/H2B，完成H2A.Z的装载[21-22]。最新研究表明，NRP1(NAP1-related protein 1)和NRP2能够移除核小体中的H2A.Z(图2)，它们通过干扰SWR1复合物活性，将H2A.Z/H2B替换成H2A/H2B，从而实现H2A.Z的卸载，防止H2A.Z在染色质中的过度积累[23]。

1.2 H2A.Z介导转录调控

H2A.Z对基因的转录调控与其在基因区域内的位置分布有关。目前研究认为，H2A.Z若分布在+1核小体位点则激活转录，若分布在编码区则抑制转录，说明H2A.Z在基因转录调控中具有双重作用[24]。研究显示，在拟南芥和水稻的高水平表达的基因中，H2A.Z主要在TSS下游+1核小体位点高度富集，而在相对低水平表达的基因中，H2A.Z则主要在基因编码区高度富集[25-27]。另外，有研究指出，H2A.Z调控基因转录与组蛋白修饰有关。H3K4me3和H3K27me3是常见的组蛋白甲基化修饰标记，在表观遗传调控中分别起转录激活和转录抑制作用[28-29]。最近的研究表明，



H3K4me3: H3K4三甲基化; MiR: 小RNA; TSS: 转录起始位点; FLC: 开花位点C; FT: 开花位点T; INO80: 肌醇80; ARP5: 肌动蛋白相关蛋白5; RNAPII: RNA聚合酶II; MYB44: MYB结构域蛋白44; NRP1: NAP1相关蛋白1; NRP2: NAP1相关蛋白2; SWR1: SWi2/snf2相关1; HSP70: 热激蛋白70; HSFA1: 热激转录因子A1; PRR7: pseudo响应调节因子7; PRR9: pseudo响应调节因子9。

H3K4me3: H3K4 tri-methylation; MiR: MicroRNA; TSS: transcription start site; FLC: flowering locus C; FT: flowering locus T; INO80: inositol requiring 80; ARP5: actin-related protein 5; RNAPII: RNA polymerase II; MYB44: MYB domain protein 44; NRP1: NAP1-related protein 1; NRP2: NAP1-related protein 2; SWR1: SWi2/snf2-related 1; HSP70: heat shock protein 70; HSFA1: heat shock transcription factor A1; PRR7: pseudo-response regulator 7; PRR9: pseudo-response regulator 9.

图2 拟南芥H2A.Z参与多个生物学途径

Fig.2 The *Arabidopsis thaliana* H2A.Z involved in multiple biological processes

H2A.Z能够促进基因启动子区H3K4me3的富集, 诱导基因表达; 另外H2A.Z通过促进H3K27me3富集和阻止H3K4me3富集来抑制增强子活性, 进而阻止基因表达[28]。CARTER等[15]通过染色质免疫共沉淀, 揭示了PIE1和PKL(PICKLE)介导H3K27me3累积, 参与调控基因表达。PIE1在核小体中装载H2A.Z后, 使DNA与染色质重塑因子PKL相结合, 促进了H3K27me3在启动子区的富集进而抑制基因转录。最近的研究也进一步揭示了H2A.Z和H3K4me3在拟南芥花青素合成基因的表达调控中存在拮抗关系, H2A.Z负向调节花青素生物合成基因的表达, 而在H2A.Z功能缺陷突变体中花青素生物合成基因上调表达, 这归因于突变体中H2A.Z的积累减少并伴随着H3K4me3的富集增加, 从而促进了花青素合成基因的表达[29]。

与所有常规组蛋白类似, 组蛋白变体H2A.Z也存在翻译后修饰, 其中H2A.Z的乙酰化、泛素化也参与了基因转录调控。有研究显示, H2A.Z在+1核小体位置富集并行使转录调控作用取决于不同的修饰类型, 其中H2A.Zub对转录起抑制作用, 而H2A.Zac则促进转录激活[30]。此外, H2A.Z介导的转录调节与DNA甲基化也存在相互关联。研究显示, 在拟南芥中当转录活跃的基因编码区和转座子区域发生DNA甲基化时, 会在相应区域呈现低水平的H2A.Z[25]。此外, 最新研究表明, SWR1复合物成员ARP6和PIE1可以阻止DNA超甲基化和基因沉默, 其中SWR1将H2A.Z召集在DNA甲基化区, 通过招募DNA糖基化酶ROS1(repressor of silencing 1)与H2A.Z相互作用, 启动具有转录活性的DNA去甲基化, 进而防止基因沉默[31]。综上, H2A.Z调控基因转录涉及多个表观遗传修饰方式的复杂作用机制。

1.3 H2A.Z参与调控植物生长发育

最新研究表明, 组蛋白变体H2A.Z在调控植物器官发育和开花时间等过程中发挥了重要的作用, 参与调控的主要因子有ARP6、ARP5、SEF、PIE1、YAF9、INO80、MBD9等, 其中ARP5属于INO80复合物成员[32-33]。

很多研究表明, H2A.Z对植物生长发育的调节与一些重要MicroRNA的转录水平有关。拟南芥HTA9、HTA11、ARP6和SEF的功能缺失, 显著降低了MiR156a和MiR156c的表达, 进而导致出现叶片伸长、叶边缘呈锯齿状且有毛状体形成的表型[34]。抑制叶片发育的MiR396在*arp6*和*pie1*功能缺失突变体中下调表达, 加速了植物叶片的生长[35]。这些研究表明, H2A.Z在MicroRNA转录调控植物生长发育过程中发挥着重要作用。AtINO80(*Arabidopsis* inositol requiring 80)也参与了对植物生长发育的调控, 其功能缺失突变体表现出植株矮小和器官发育缺陷等特征[36], 进一步研究表明, AtINO80可以与AtARP5蛋白相互作用, 共同调控植物的胚胎发生和胚后器官发育[32]。此外, 参与H2A.Z装载的SWC4功能缺失后也会导致胚胎发育缺陷, 进而影响植物的生长发育[37]。

H2A.Z通过介导开花相关基因的转录调控, 参与调节植物开花时间。*FT*(flowering locus T)和*FLC*(flowering locus C)是调节拟南芥开花时间的2个关键基因, 分别为正向和反向调控因子[35,38]。当*FT*基因区域内核小体中不含H2A.Z时, FT上调表达, 促进开花[39-40]。另外, *ARP6*和*PIE1*突变使得FLC表达降低, 是由于核小体中H2A.Z的装载产生缺陷, 进而出现早花表型[41-44]。MARCH-DÍAZ等[14]报道, H2A.Z装载复合物成员SEF是一个新被发现的FLC正调控因子, 研究人员推测SEF、ARP6和PIE1可能是通过介导*FLC*启动子和调节子区H2A.Z的富集分布, 从而促进一些染色体重塑因子或转录调控因子在基因区域的募集, 诱导*FLC*基因表达进而抑制植物开花。YAF9和MBD9也参与了FLC表达的调节, 控制植物开花。MBD9的功能缺失导致了H2A.Z的装载缺陷, 使得*FLC*表达降低, 加速了开花时间进而出现早花表型[18,45]。同样, *yaf9*的缺失突变体也发生早花现象, 这是由于在+1核小体位置的H2A.Z乙酰化水平下降, 导致FLC表达下调[16]。此外, NRP1和NRP2蛋白可以负向调节拟南芥中H2A.Z的积累, 进而调节*FLC*基因表达来影响植物开花时间, WANG等[23]研究报道, *nrp1-1 nrp2-2*双突变体在全基因组范围内表现出H2A.Z的过度积累, *arp6*突变体的FLC表达下调出现早花现象, 与*nrp1-1 nrp2-2*双突变体杂交后*arp6*的表型会增强。上述研究表明, H2A.Z在开花相关基因*FLC*和*FT*中的富集, 直接关系到两者的表达, 从而在调控植物开花时间中发挥关键作用。

1.4 H2A.Z参与调节环境应答

已有研究表明, H2A.Z通过介导相关基因的转录参与调节植物对高温、干旱、盐渍等环境胁

迫因素的应答。热胁迫调节因子HSP70(heat shock protein 70)、HSFA1(heat shock transcription factor A1)对高温的响应与H2A.Z在其基因中的富集有关, 高温条件抑制了HSP70和HSFA1的+1核小体位点上H2A.Z的积累, 激活两者的转录, 进而应对高温胁迫, 这也说明了H2A.Z可能是植物响应高温胁迫的一个负向调节因子[24,39,46]。同时, 也有报道发现, H2A.Z还参与调节高温条件下植物的开花时间, 但在不同植物中所体现出的作用截然相反[47]。较高温度的生长环境使得拟南芥*FT*基因内的H2A.Z积累水平降低, 导致FT的高表达, 加快了植物的开花时间, 然而在油菜中, 高温环境促进了FT在+1核小体位置的H2A.Z富集水平, 从而抑制了油菜FT表达, 使植物开花时间延迟[47]。此外, TONG等[48]最新发现, H2A.Z介导植物对环境温度的应答与EC(evening complex)组分ELF3(early flowering 3)也存在关联。EC是调控拟南芥生物钟的一个蛋白复合物, 其组分ELF3在夜间低温下通过与SWR1复合物相互作用控制H2A.Z核小体积累, 从而调控夜间基因的转录而响应昼夜环境温度变化。其中, EC-SWR1与核心时钟基因*PRR7*(pseudo-response regulator 7)和*PRR9*相互作用, 促进H2A.Z的富集并抑制这些基因在夜间的表达进而响应夜间低温环境[48]。

除调节环境温度应答外, H2A.Z同时还参与了植物对干旱胁迫和盐胁迫的响应。拟南芥响应干旱胁迫基因表达谱的研究显示, 干旱胁迫应答基因的转录与基因区域内H2A.Z的富集程度紧密相关, 富含H2A.Z核小体的基因其转录受到了明显抑制[24]。AtMYB44(*Arabidopsis* MYB domain protein 44)是调控拟南芥响应盐胁迫的重要转录因子, NGUYEN等[49]发现盐胁迫下H2A.Z的富集水平显著降低, 加速了RNAPII在启动子和TSS区域的募集, 从而诱导了*AtMYB44*的转录, 调控植物应答盐胁迫。

1.5 H2A.Z在其他途径中的作用

近些年, 有一些报道指出H2A.Z在植物响应缺磷环境以及免疫防御中具有一定作用[50-51]。在磷缺乏条件下水稻H2A.Z全基因组的富集分析显示, H2A.Z的富集分布与缺磷响应基因的表达水平呈负相关, 表明H2A.Z在其中可能发挥负调控作用[50-51]。在菠萝中, AcSWC6即AcSEF通过H2A.Z的沉积在免疫防御和抗病中也起到一定作用, JAKADA等[52]研究发现, 病原体侵染叶片后会促进*AcSWC6*的转录, 使植物呈现感病表型。

2 组蛋白变体H2A.X

H2A.X是H2A发生磷酸化修饰形成的组蛋白变体, 其C末端含有保守的SQEF基序。H2A.X产生于常染色质中, 主要参与DNA的损伤修复[53-59]。以拟南芥为例, H2A.X是在H2A的Ser138位点发生磷酸化的组蛋白变体[60]。H2A.X在核小体中的组装, 需要组蛋白伴侣的帮助, 其中FACT(facilitates chromatin transcription)是装载H2A.X的重要分子伴侣。当细胞受到DNA损伤信号刺激时, FACT能够增强损伤部位的H2A.X水平, 加速损伤部位的信号转导, 该信号经由H2A.X磷酸化被放大, 进而通过在修复位点积累H2A.X, 协调DNA损伤修复与转录重启[61]。

FACT包含2个重要的亚基SPT16(suppressor of Ty 16)和SSRP1(structure-specific recognition protein 1), 它们在转录调控过程中发挥重要作用。拟南芥*ssrp1*和*spt16*突变体在植物营养生长和生殖发育多个方面具有表型缺陷, 如植株叶片生长缓慢、胚珠不育[62-63]。此外, SSRP1和SPT16都与*FLC*基因编码区结合并诱导FLC表达, 进而抑制植物开花[62-63], 但这些过程是否与FACT亚基介导的H2A.X在相关基因中的积累有关, 还需进一步深入研究。

3 组蛋白变体H2A.W

H2A.W蛋白的C末端尾部长于H2A, 且含有特异的KSPKK基序[27]。H2A.W主要位于异染色质区域, 能够促进异染色质缩合, 对于维持异染色质沉默有重要作用。在拟南芥中, H2A.W主要由*HTA6*、*HTA7*、*HTA12*基因编码。H2A.W与异染色质修饰标记H3K9me2及DNA甲基化协同作用, 维持异染色质的沉默[27]。H3K9me2修饰是异染色质转录沉默的重要标志, 主要由KYP(KRYPTONITE)介导积累[64]。研究显示, *KYP*的突变会导致H3K9me2积累减少, 但不会对植物生长产生明显影响, 但H2A.W编码基因*HTA6*、*HTA7*以及*KYP*三者同时突变会导致植株出现严重的生长缺陷, 且使得含有去浓缩异染色质的细胞核比例增加[27]。此外, H2A.W与CHG甲基化也有特殊联系。H2A.W与DNA甲基转移酶CMT3(chromomethylase 3)介导的CHG甲基化协同作用, 抑制转座元件[65], 且CMT3能够与H3K9me2结

合, 可以使CHG位点(H为A、C或T)的胞嘧啶残基甲基化[66-67]。在*h2a.w*突变体中, CHG甲基化在转座因子和富含H3K9me2的区域显著增加, 弥补了H2A.W缺失引起的功能缺陷, 使转座因子的转录抑制得以维持[27]。

4 组蛋白变体H3.3

关于H3组蛋白变体的研究大多集中在动物中, 而对于植物的相关报道较少。拟南芥组蛋白变体H3.3同常规组蛋白H3.1存在4个氨基酸位点的变异, 分别是第31、41、87和90位氨基酸残基。其中, H3.3第87和90位的氨基酸残基是其在构成染色质部分的核仁rDNA累积的关键, 能够促进转录激活, 而第31和41位氨基酸残基则负责引导H3.3从rDNA中去除, 促进转录沉默[68]。STROUD等[69]对拟南芥组蛋白H3.1和H3.3变体进行了全基因组分析, 发现H3.1作为常规组蛋白主要在基因组的沉默区富集, 而组蛋白变体H3.3主要富集在基因组的转录活跃区, 并与能够激活基因表达的组蛋白修饰标志存在关联。

目前研究表明, DAXX(death domain-associated protein)、ATRX(alpha thalassemia retardation syndrome X-linked)、HTRA(histone regulator A)是介导组蛋白变体H3.3在核小体中累积的的重要分子伴侣[70-72]。DAXX主要在异染色质着丝粒周围和端粒上富集H3.3, ATRX也参与H3.3的富集, 并调节基因表达, 其中ATRX的缺失会导致特异性45S rDNA序列的改变, 进而导致基因表达发生下调[71]。NIE等[70]报道, 在拟南芥中HIRA与H3.3共定位于常染色质区域, 促进了编码核糖体RNA基因的表达, 从而为HIRA在常染色质积累H3.3提供了证据。

H3.3在转录调控中同样也具有重要作用。研究显示, 基因转录受到抑制与TTS附近H3.3水平较低有关, 而转录激活与TTS附近H3.3水平升高相关, 表明TTS附近H3.3富集水平与基因表达呈正相关[69,73]。

5 组蛋白变体CenH3

CenH3具有特异的N末端结构域, 是定位于着丝粒区域的组蛋白变体[74]。CenH3对于着丝粒的建立至关重要, CenH3核小体组装发生在有丝分裂G_2期[75-77]。CenH3与组蛋白H2A、H2B和H4组装成核小体复合物, 取代了常规组蛋白H3复合物, 从而完成CenH3核小体的组装[78]。在拟南芥中, KNL2(kinetochore null 2)和NASP(nuclear autoantigenic sperm protein)介导CenH3的积累, 并影响着丝粒组蛋白的装载。研究表明, NASP功能下降会导致CenH3在着丝粒的装载产生缺陷, 此外, 在拟南芥中敲除*KNL2*会导致着丝粒CenH3数量减少, 细胞分裂发生异常[77,79-80]。

着丝粒功能的改变与染色体的消除有关, 能够诱导单倍体植株的形成。研究发现, *cenh3*突变体与野生型拟南芥杂交可以诱导单倍体产生, 这是由于着丝粒大小与单倍体形成有关, 较小或有缺陷的着丝粒被选择性地降解, 导致*cenh3*突变体的染色体消除, 从而产生了单倍体后代[81-83]。

6 组蛋白H1变体

拟南芥基因组编码三种H1变异体: H1.1、H1.2和H1.3, 三者N、C末端均具有富含赖氨酸的尾巴, 但含量存在差异[5]。H1.1和H1.2氨基酸序列相似程度高, 亲缘关系较近, H1.3属干旱胁迫诱导的组蛋白变体, 其N末端和C末端较短, 缺少与DNA结合的(S/T) PXK基序[84]。

H1的组蛋白变体在调控植物生长发育和响应非生物胁迫中起着重要作用。拟南芥*h1.1 h1.2 h1.3*三突变体植株在生长发育中出现多方面缺陷, 如种子休眠时间延长、早花现象、侧根数量和根毛密度明显增加、保卫细胞的气孔复合体之间的间距变小[85]。在正常生境下, *h1.3*与野生型植株大小相似, 但CO_2同化率和气孔开度显著降低, 而在轻度缺水条件下, *h1.3*气孔关闭, 生物量积累减少, 导致生长迟缓。此外, H1.3参与植物对弱光、干旱和ABA的响应。研究显示, 在干旱和弱光胁迫条件下, *H1.3* mRNA表达水平显著增加, 但在ABA信号缺陷的植株中, *H1.3*的表达受到抑制[86]。这似乎与胁迫条件下H1组蛋白变体介导DNA的甲基化水平有关, 有报道显示, H1.1和H1.2能够阻止DNA甲基转移酶进入染色质, 而H1.3的表达则与植物在胁迫条件下的DNA超甲基化水平直接相关[87]。

7 结语和展望

组蛋白变体种类繁多且具有重要的生物学功能。目前, 有关植物组蛋白变体的研究多数围绕H2A.Z开展, 尤其是对组蛋白变体介导转录调控的

研究成为了热点。已有研究虽让我们对组蛋白变体种类及其生物学功能甚至作用机制有了一定认识, 但仍有很多研究工作有待深入和完善。(1) 目前研究多集中在组蛋白变体H2A.Z上, 人们对其他组蛋白变体的认知还很有限, 多数组蛋白变体生物学功能仍处于空白或探索的初级阶段; (2) 植物在特定生长阶段或处于特殊生境下, 组蛋白变体的组装与卸载经历复杂的、动态的调控过程, 组蛋白变体的伴侣分子如何接受并识别植物内源或外部环境信号, 进行相应变体组装与卸载的作用机制还有待挖掘; (3) 组蛋白变体调节基因的转录涉及多种表观修饰方式, 以H2A.Z为例, 组蛋白变体在染色体中的富集与其他表观修饰大多存在拮抗关系, 但相应调控因子如何协作实现这一表观遗传调控尚不清楚; (4) 组蛋白变体作为重要的表观遗传调控因子, 在植物生长发育、逆境耐受能力中具有关键作用, 但相关育种研究还未见报道。随着现代分子生物学分析技术的快速发展, 未来对组蛋白变体生物学功能的深入探索及作用机制的研究, 有望为作物育种提供更多的重要参考。

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