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Functions and mechanisms of plant histone deacetylases

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Lysine acetylation, one of the major types of post-translational modifications, plays critical roles in regulating gene expression and protein function. Histone deacetylases (HDACs) are responsible for removing acetyl groups from lysines of both histone and non-histone proteins. While tremendous progress has been made in understanding the function and mechanism of HDACs in animals in the past two decades, nearly half of the HDAC studies in plants were reported within the past five years. In this review, we summarize the major findings on plant HDACs, with a focus on the model plant *Arabidopsis thaliana*, and highlight the components, regulatory mechanisms, and biological functions of HDAC complexes.

epigenetics, histone deacetylases, development, stress response, plants

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Overview of histone deacetylases

In eukaryotes, ~147 bp of DNA is wrapped around octamers of histone proteins to form repeating units of nucleosomes, which are the functional units of chromatin. Each histone octamer contains two copies of histones H2A, H2B, H3, and H4 (Kornberg, 1974; Luger et al., 1997; Wang et al., 2018). Histone tails hanging out of the nucleosome are subject to various post-translational modifications (PTMs), including acetylation, methylation, phosphorylation, and sumoylation (Kouzarides, 2007). Histone modifications play critical roles in regulating various chromatin-templated activities, including DNA replication, DNA repair, and RNA transcription (Gong and Miller, 2013; Kouzarides, 2007; Lu et al., 2015; Unnikrishnan et al., 2010; Zentner and Henikoff, 2013; Zhong, 2016). Abnormal regulation of histone modifications are often associated with developmental defects and diseases (Cheng et al., 2018; Haberland et al., 2009; Hollender and Liu, 2008; Marks et al., 2001; Sanders et al., 2017; Zhou et al., 2019). Histone modifications carry out functions mainly through altering chromatin structure and/or recruiting regulatory factors (Lin et al., 2018; Liu et al., 2018; Qian et al., 2018; Yang et al., 2018). For instance, with acetylation, one of the most well-studied PTMs, the negative charges on the acetyl groups neutralize the positive charges of histones. This results in weakened interactions between histones and DNA, thus making chromatin more accessible (Grunstein, 1997). Acetyl groups can also act as recognition anchors for acetylation binding proteins, which may then recruit additional regulatory factors (Marmorstein and Zhou, 2014).

Acetyl groups are deposited by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs). The first *bona fide* HDAC, human HDAC1, was isolated in 1996 (Taunton et al., 1996). HDAC1 is a homolog of yeast RPD3 (Reduced Potassium Deficiency), which was previously identified as a transcriptional repressor (Vidal and Gaber, 1991). Together with HDAC1, subsequently discovered human HDACs were grouped into four classes. Class I HDACs

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(HDAC1, HDAC2, HDAC3, and HDAC8) show most sequence similarity to RPD3, while Class II HDACs (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10) show more similarity to yeast HDA1 (Histone Deacetylase-A 1) than to RPD3. Class III HDACs (SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7) are homologs to the yeast sirtuin protein SIR2 (Silent Information Regulator 2). HDAC11, the only member of Class IV HDACs, is similar to both RPD3 and HDA1. All members of Class I, II, and IV HDACs harbor one or two classical deacetylase domains, which require zinc as a cofactor for deacetylase activity, while Class III SIRT deacetylases remove acetyl groups through a NAD^+-dependent manner (Seto and Yoshida, 2014; Verdin and Ott, 2015). Since their discovery, HDACs have been found to play critical roles in many biological processes, including embryonic development, diseases, genome stability, and RNA transcription (Bosch-Presegue and Vaquero, 2015; Haberland et al., 2009; Hayakawa and Nakayama, 2011; Marks et al., 2001; Seto and Yoshida, 2014).

HDACs are conserved from yeast to human, and similar members are also found in plants. In the dicot model plant *Arabidopsis thaliana*, there are 12 RPD3-like HDACs (Figure 1A). Six are Class I members (HDA6, HDA7, HDA9, HDA10, HDA17, and HDA19), five are Class II members (HDA5, HDA8, HDA14, HDA15, and HDA18), and one is a Class IV member (HDA2) (Alinsug et al., 2009). Compared to the seven sirtuin-like HDACs in human cells, there are only two Class III sirtuin-like members in *Arabidopsis* (SRT1 and SRT2) (Figure 1B). Interestingly, there are four plant-specific Histone Deacetylase 2 (HD2) members (HD2A, HD2B, HD2C, and HD2D) (Figure 1C). Similar number of HDACs are found in the model monocot plants maize (*Zea mays*) and rice (*Oryza sativa* subsp. *japonica*) (Figure 1). Genetic and physiological studies have shown that plant HDACs play important roles in various biological processes, including seed germination, organ development, flowering, biotic and abiotic stress response, and leaf senescence (Figure 2) (Chen et al., 2016; Hollender and Liu, 2008; Kang et al., 2015; Kim et al., 2012; Kim et al., 2013; Park et al., 2019; van Zanten et al., 2014; Yuan et al., 2019; Zheng et al., 2016).

Class I HDACs

In *Arabidopsis*, HDA6, HDA7, HDA9, HDA10, HDA17 and HDA19 are Class I HDACs (Figure 1A). HDA10 and HDA17 are virtually identical in terms of amino acid sequences. Sequence alignment reveals that HDA10 and HDA17 are nearly duplicates of the C-terminal sequences of HDA9, which could be caused by an incomplete duplication of the *HDA9* gene during evolution. Furthermore, HDA10 and HDA17 do not contain deacetylase domain, suggesting that they are likely not functional. HDA7 has only been found to be essential for proper female gametophyte development and embryogenesis (Cigliano et al., 2013). HDA6, HDA9, and HDA19 are the most extensively studied HDACs in plants.

HDA6

HDA6 has been tightly connected with DNA methylation since its discovery (Aufsatz et al., 2007; Liu et al., 2012a). HDA6 was first identified by a genetic screen searching for repressors of transgene expression (Murfett et al., 2001). Soon after that, another genetic screen identified HDA6 as an important factor for the maintenance of RNA-induced CHG (H=A, T, or C) DNA methylation (Aufsatz et al., 2002). Additionally, a recent study showed that HDA6 interacts with the H3K9 methyltransferases SUVH4/5/6 (SU(VAR)3-9 HOMOLOG 4/5/6) to maintain transposable element (TE) silencing (Yu et al., 2017). These findings, together with the positive feedback loop that exists between H3K9me2 and CHG DNA methylation (Du et al., 2012), suggest that HDA6 may regulate DNA methylation through H3K9me2. HDA6 also regulates CG methylation through directly interacting with CG methyltransferase MET1 (Liu et al., 2012b). Consistently, loci that were derepressed in *hda6* knockout mutant significantly overlapped with those upregulated in *met1* mutant (To et al., 2011). Interestingly, additive hyperacetylation was found at activated TEs in *hda6 met1* double mutants (Liu et al., 2012b). These findings suggest that HDA6 and MET1 have both overlapped and independent functions in silencing TEs. HDA6 also plays similar roles as MET1 does in maintaining epigenetic memory at certain loci. Part of the derepressed loci caused by *hda6* or *met1* mutation were unable to be recovered by the re-introduction of HDA6 or MET1 protein (Blevins et al., 2014; Hristova et al., 2015). Small RNA sequencing showed that 24 nt siRNA was not recovered at loci that had lost silencing memory in *hda6* mutants, indicating that the siRNA-DNA methylation loop may be disrupted at those loci in *hda6*. However, the siRNA production deficiency by RNA polymerase IV (Pol IV) mutation was totally restored by Pol IV complementation (Blevins et al., 2014). These data indicate that HDA6, together with MET1, may preserve the silent identity that is memorized during cell division.

Its capability to silence TEs and repetitive elements enable HDA6 to regulate ribosomal RNA transcription. In the nucleolar organization region, HDA6 is required for the maintenance of CG and CHG DNA methylation and repressive histone marks in the intergenic region of rDNA repeats (Earley et al., 2010). HDA6 promotes chromatin condensation, DNA methylation and histone deacetylation to maintain silencing of rDNA repeats (Probst et al., 2004). In

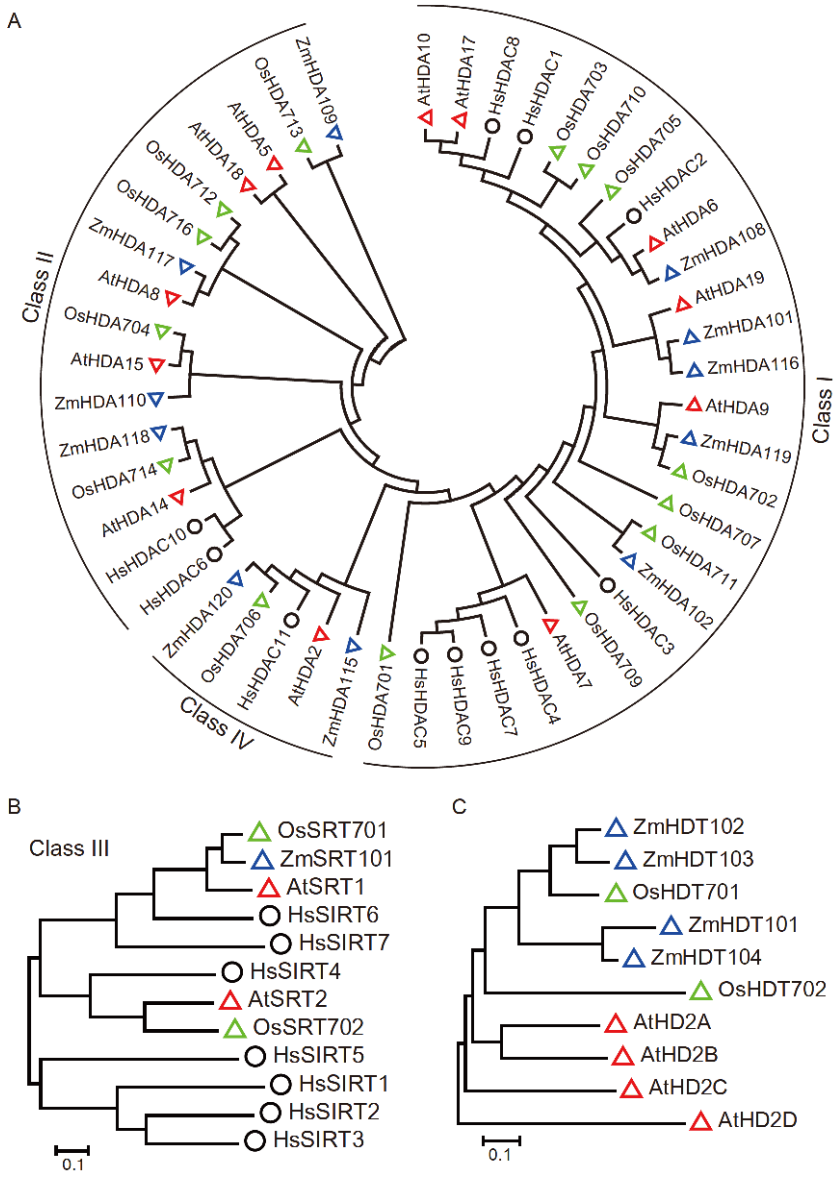

Figure 1 Phylogenetic trees of HDACs. Phylogenetic trees were constructed based on amino acid sequences of RPD3-like (A), Sirtuin (B), and plant-specific HD2 (C) by Mega 7. This analysis includes HDACs from *Homo sapiens* (black circle), *Arabidopsis thaliana* (red triangle), *Oryza sativa* subsp. *japonica* (green triangle), and *Zea mays* (blue triangle).

hybrids, one parental set of ribosomal RNA (rRNA) genes is active, while the other parental set is silent, a phenomenon known as Nucleolar Dominance (Pikaard, 2000). In the hybrid *Arabidopsis suecica* (*A. thaliana* × *A. arenosa*), HDA6 is required for the selective silencing of *A. thaliana* derived rDNA loci during development (Earley et al., 2006; Pontes et al., 2007). The mechanism that guides HDA6 to rDNA from one particular parent, however, is unknown.

The functions of HDA6 in regulating plant physiology have been reviewed (Kim et al., 2012). Recent studies have revealed new functions of HDA6 in regulating plant development and environmental response. In *Arabidopsis*, morning-expressed *CCA1* (*CIRCADIAN CLOCK ASSOCIATED 1*) gene, *LHY* (*LATE ELONGATED HYPOCOTYL*) gene, and evening-expressed *TOC1* (*TIMING OF CAB EXPRESSION 1*) gene, negatively regulate each other's expression to ensure proper circadian rhythms. In this negative feedback loop, a repressive complex consisting of HDA6 and H3K4 lysine-specific histone demethylase (LDL1/2-HDA6) interacts with either CCA1/LHY to repress *TOC1* or TOC1 to repress *CCA1/LHY* expression (Hung et al., 2019; Hung et al., 2018). HDA6 also participates in the brassinosteroid (BR) signaling pathway by regulating a key component BIN2 (BR-INSENSITIVE 2), through deacetylation at lysine 189 to repress its kinase activity (Hao et al., 2016). This is the first identification of a non-histone substrate for HDA6. Interestingly, the acetylation level of BIN2 is regulated by glucose, suggesting a potential connection between metabolism

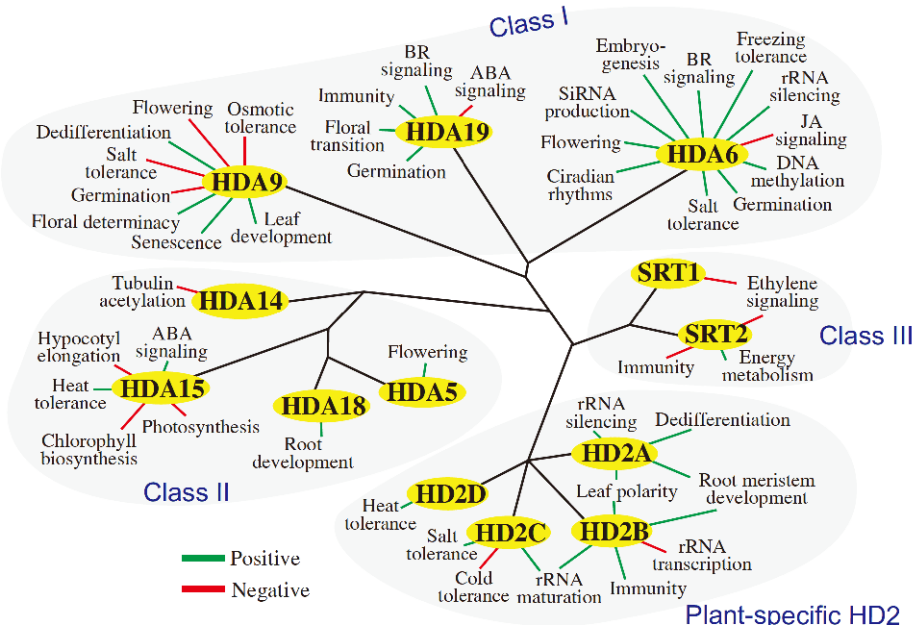

Figure 2 Brief summary of functions of histone deacetylases in *Arabidopsis*. The green line represents positive regulation, and the red line represents negative regulation.

and histone deacetylase in plants (Hao et al., 2016). The proper function of HDA6 also requires precise regulation of HDA6 *per se*. A recent study showed that the silencing function of HDA6 can be negatively regulated by a nuclear export receptor, XPO1A, which directly interacts with HDA6 and promotes HDA6 nuclear exportation (Zhu et al., 2019).

HDA19

Together with *HDA6*, HDA19 is one of the earliest identified RPD3-like HDACs in *Arabidopsis* (Wu et al., 2000). As a general chromatin regulator, HDA19 can carry out functions in specific biological pathways through interaction with various co-factors (Table 1). Two basic-leucine zipper transcription factors, SCARECROW and SCARECROW-LIKE15, interact with HDA19 and recruit it to specific loci to regulate root development and seed maturation, respectively (Gao et al., 2015; Gao et al., 2004). Regulation of seed dormancy by HDA19 is also achieved through interaction with PAH (Paired Amphipathic Helix) domain-containing protein SNL1 (Wang et al., 2013). Besides, HDA19 is found to interact with a WD40 repeat-containing protein, TPL (TOPLESS). HDA19 is required for TPL function in regulating shoot pole differentiation (Long et al., 2006). This HDA19-TPL complex appears to be stable and can be recruited to target genes with the aid of additional factors. For example, an A-class organ identity transcription factor, APETALA2, recruits HDA19-TPL to B-class and E-class target genes to regulate floral development (Krogan et al., 2012). In a separate context, HDA19-TPL is recruited to targets by the BR signaling protein BES1 (BRI1-EMS-SUPPRESSOR 1) to regulate ABA (abscisic acid) and BR signaling cascades (Hong et al., 2019; Kim et al., 2019; Ryu et al., 2014).

In addition to its pivotal role in development, HDA19 is also heavily involved in stress response. Two *Arabidopsis* WRKY transcription factors, WRKY38 and WRKY62, function to repress plants' basal pathogen infection response. This repression is impaired when WRKY38 and WRKY62 form complexes with HDA19 (Kim et al., 2008). A TOPLESS-related protein TRP1, suppressor of *pr1* mutation in pathogen infection, also interacts with HDA19 to regulate immunity related genes (Niu et al., 2019). Interestingly, this interaction is impaired by sumoylation at K282 and K721 in TRP1 (Niu et al., 2019).

HDA19 and HDA6, also known as AtRPD3A and AtRPD3B respectively, were cloned together because of sequence similarity (Wu et al., 2000). Thus, unsurprisingly, HDA19 and HDA6 have partially redundant functions in regulating seed germination, embryo development, and salt resistance (Chen and Wu, 2010; Tanaka et al., 2008). Additionally, both HDA19 and HDA6 can interact with HDC1 (Histone Deacetylase Complex 1), SNLs (SIN3-like proteins), and MSI1 (MULTICOPY SUPPRESSOR OF IRA1) to repress gene expression and regulate plant development (Ning et al., 2019; Perrella et al., 2013).

HDA9

HDA9 is a relatively newly studied HDAC in *Arabidopsis*. It was first reported to be a negative regulator of flowering by deacetylating chromatin at *AGL19* (*AGAMOUS-LIKE 19*)

Table 1 Summary of interacting proteins of HDACs in *Arabidopsis*

HDACs	Co-factors	Functions	References
HDA6	MET1	Maintain DNA methylation	Liu et al., 2012b
	SUVH4/5/6	Maintain TE silencing	Yu et al., 2017
	LDL1/2-TOC1	Regulate circadian clock by repressing *CCA1/LHY*	Hung et al., 2019
	LDL1/2-CCA1/LHY	Regulate circadian clock by repressing *TOC1*	Hung et al., 2018
	FVE, FLD	Repress *FLC* expression	Yu et al., 2017; Yu et al., 2011
	BIN2	Deacetylate BIN2 to repress its kinase activity	Hao et al., 2016
	AS1	Repress *KNOX* expression in leaf development	Luo et al., 2012a
	HD2C	Regulate ABA and salt stress response	Luo et al., 2012b
	AHL22	Regulate flowering through *FT*	Yu et al., 2011
	EXPORTIN 1A	Regulate nucleo-cytoplasmic partition of HDA6	Zhu et al., 2019
HDA9	PWR	Promote leaf aging and dormancy; Repress PIF4 and YUC8 to regulate thermomorphogenesis;	Chen et al., 2016; Mayer et al., 2019; Tasset et al., 2018
	HOS15	Repress *GI* expression to regulate flowering time; Promote leaf development	Mayer et al., 2019; Park et al., 2019; Suzuki et al., 2018
	ELF3	Repress *TOC1* expression in circadian clock	Lee et al., 2019
	AHL22	Regulate flowering through *FT*	Yu et al., 2011
HDA19	TRP1	Pathogen defense	Niu et al., 2019
	HDC1-SNL1-MSI1	Delay flowering time in short-day	Ning et al., 2019
	SCARECROW	Determine cell fate of root cortical cell	Chen et al., 2019
	MSI1	Repress ABA responsive gene expression	Mehdi et al., 2016
	SCARECROW-LIKE15	Repress seed maturation	Gao et al., 2015
	BES1-TPL1	Regulate ABA signaling by repressing ABI3 Regulate BR-signaling	Ryu et al., 2014; Kim et al., 2019
	HSL1	Repress seed maturation	Zhou et al., 2013
	SNL1	Regulate ABA-ethylene antagonism to affect dormancy	Wang et al., 2013
	HDC1	Promote plant growth	Perrella et al., 2013
	APETALA2	Flower development	Krogan et al., 2012
	WRKY38, WRKY62	Pathogen defense	Kim et al., 2008
	LEUNIG	Repress gene expression	Gonzalez et al., 2007
	TOPLESS	Regulate apical embryonic fate	Long et al., 2006
HDA15	HY5	Repress hypocotyl cell elongation	Zhao et al., 2019
	MYB96	Promote ABA signaling	Lee et al., 2019
	NF-YC	Regulate light-controlled hypocotyl elongation	Tang et al., 2017
	PIF1	Regulate germination in dark	Gu et al., 2017
	PIF3	Repress chlorophyll biosynthesis and photosynthesis	Liu et al., 2013b
HDA5	FVE-FLD-HDA6	Regulate flowering time	Luo et al., 2015
HD2B	DMT2	Not described	Song et al., 2010
	HDA6, HDA19	Not described	Luo et al., 2012b
	RPS6	Repress rRNA expression	Kim et al., 2014
	HD2C	Ribosome RNA maturation	Chen et al., 2018
	MPK3	Plant immunity	Latrasse et al., 2017
HD2C	HDA6	Regulate ABA and salt stress response	Luo et al., 2012b
	BRM	Repress heat stress responsive gene expression	Buszewicz et al., 2016
	HD2B	Ribosome RNA maturation	Chen et al., 2018
	HOS15	Cold stress response	Park et al., 2018
SRT1 SRT2	ENAP1	Ethylene signaling	Zhang et al., 2018

and *FT* (*FLOWERING LOCUS T*) (Kang et al., 2015; Kim et al., 2013). Recently, HDA9 has also been found to regulate flowering by interacting with the circadian clock evening complex component ELF3 (EARLY FLOWERING 3). The ELF3-HDA9 complex associates with the *TOC1* promoter and suppresses *TOC1* expression (Lee et al., 2019). HDA9 also regulates germination and stress response. Loss-of-function *hda9* mutants showed deficient seed dormancy and increased resistance to salt and osmotic stress (van Zanten et al., 2014; Zheng et al., 2016). Recent studies identified a core HDA9 repressive complex containing a WD40 repeat protein, HOS15 (HIGH EXPRESSION OF OSMOTICALLY RESPONSIVE GENES 15), and a SANT (Swi3, Ada2, N-Cor, and TFIIIB) domain-containing protein, PWR (POWERDRESS) (Chen et al., 2016; Kim et al., 2016; Mayer et al., 2019). HOS15 was previously identified as a positive regulator of cold stress response and PWR controls floral meristem termination and flowering time (Yumul et al., 2013; Zhu et al., 2008). Both PWR and HOS15 are required for nuclear accumulation and chromatin association of HDA9 (Chen et al., 2016; Mayer et al., 2019). Disruption of either *HOS15* or *PWR* phenotypically resembles a *hda9* mutant, and no additive effects were observed in double or triple mutants compared to single mutants (Mayer et al., 2019). This suggests that HDA9, PWR, and HOS15 mainly act within the same complex. The HDA9-PWR-HOS15 complex is involved in regulating numerous biological processes, including seed germination, plant development, flowering, and leaf senescence (Chen et al., 2016; Kim et al., 2016; Mayer et al., 2019; Park et al., 2019; Suzuki et al., 2018; Tasset et al., 2018). Additionally, HOS15 interacts with several other HDACs, including the plant-specific HD2 member HD2C, to regulate cold response (Park et al., 2018). This suggests that there may be crosstalk between different groups of HDACs. In mammalian cells, there is a homolog of HDA9-PWR-HOS15 complex, known as HDAC3-NCoR/SMRT-TBL1 complex (Guenther et al., 2000; Karagianni and Wong, 2007; Wang and Brendel, 2004). This indicates the conservation of HDACs between plants and mammals.

A previous study profiling the genome-wide binding sites of HDA9 revealed that HDA9 generally binds to euchromatic regions and is depleted in heterochromatic regions (Chen et al., 2016). Surprisingly, though HDA9 is a transcriptional repressor, HDA9 tends to bind to the promoters of active genes and DNase hypersensitive regions (Chen et al., 2016). This phenomenon was also observed for maize HDA101 and other HDACs in human cells (Wang et al., 2009; Yang et al., 2016). The exact mechanisms of this distribution pattern are unknown. It is possible that HDACs are required for repression of antisense transcription in the promoters to ensure proper transcription of sense RNA. Another possibility is that HDACs may be pre-deposited on target genes to await specific stimuli before initiating gene repression. The latter hypothesis could also explain why only a small subset of HDAC bound-genes were upregulated in HDAC mutants (Chen et al., 2016; Yang et al., 2016).

Class II HDACs

Class II members include HDA5, HDA8, HDA14, HDA15 and HDA18. HDA5, HDA8, and HDA14 are localized to the cytoplasm (Alinsug et al., 2012). In support of this notion, HDA14 has been found to associate with and deacetylate α-tubulin (Tran et al., 2012). HDA14 protein is also found in plastids (Hartl et al., 2017). Disruption of *HDA14* resulted in the hyperacetylation of 26 lysine residues corresponding to 26 proteins in plastids (Hartl et al., 2017), suggesting that HDA14 may regulate acetylation of non-histone proteins in chloroplast or mitochondria.

The subcellular localization of HDA15 is dynamically regulated by light. White light promotes nuclear localization of HDA15 protein, whereas dark treatment facilitates its nuclear exportation (Alinsug et al., 2012). In dark condition, the retained nuclear HDA15 interacts with PIF3 (PHYTOCHROME INTERACTING FACTOR 3) to repress chlorophyll biosynthesis and photosynthetic genes. Degradation of PIF3 upon exposure to red light disrupts HDA15's association with the target genes (Liu et al., 2013b). HDA15 also interacts with HY5 (ELONGATED HYPOCOTYL 5) in the nucleus and represses cell wall organization and auxin signaling genes (Zhao et al., 2019). These interacting proteins or post-translational modifications may play important roles in determining the localization of HDA15. HDA15 is also involved in regulating stress response. In the nucleus, HDA15 is responsible for repressing high temperature response genes in normal condition by directly binding to their promoters and deacetylating histones, while high temperature conditions impair the association of HDA15 (Shen et al., 2019).

HDA18 localizes to both the nucleus and cytoplasm (Liu et al., 2013a). HDA18 can directly bind to and regulate the expression of several root cellular patterning related kinase genes (Liu et al., 2013a).

Class III sirtuin-like HDACs

Class III sirtuin-like HDACs require NAD^+ as a cofactor for their enzymatic activity. In humans, there are seven sirtuin-like HDACs that localize to multiple organelles, including nucleus, nucleolus, cytosol, and mitochondria (Seto and Yoshida, 2014). This multi-pattern localization is consistent with their multiple functions in deacetylating numerous non-histone and histone proteins (Seto and Yoshida, 2014). By contrast, only one or two sirtuin-like (SRT) proteins are present in the model organism plants such as *Arabidopsis*,

rice, and maize (Figure 1B). Interestingly, multiple alternative splicing transcripts of sirtuin proteins were found in these plant species. For example, *Arabidopsis* AtSRT2 is predicted to generate seven kinds of transcripts through alternative splicing (At5g09230.1–At5g09230.7, TAIR10). One of the transcripts, coding sequence 3 (*AtSRT2-CDS3*, At5g09230.3), encodes a form of nuclear-localized AtSRT2 with a shortened C-terminus. Disruption of *AtSRT2-CDS3* resulted in increased *PR1* (*PATHOGENESIS-RELATED GENE 1*) expression and enhanced resistance to *Pst*DC3000 (Wang et al., 2010). A longer form of the AtSRT2 protein, encoded by At5g09230.1, At5g09230.2, At5g09230.5 or At5g09230.7, was found predominantly at the inner mitochondrial membrane. It interacts with and deacetylates inner membrane protein complexes to regulate energy metabolism and metabolite transport (Konig et al., 2014). A recent study showed that AtSRT1 and AtSRT2 are also involved in ethylene signaling. Both AtSRT1 and AtSRT2 can interact with ENAP1 (EIN2 NUCLEAR ASSOCIATED PROTEIN 1) and repress ethylene-induced gene expression (Zhang et al., 2018). Interestingly, like the HDA9-interacting protein PWR, ENAP1 also contains a SANT domain, which is capable of binding histones (Kim et al., 2016). This indicates that the SANT domain may have broad functions in regulating histone deacetylases.

In rice, knockdown of *OsSRT1* resulted in DNA fragmentation and programmed cell death (Huang et al., 2007). This may be caused by the activation of TEs that are normally repressed by OsSRT1. Consistent with this notion, genome-wide OsSRT1 binding assays showed that OsSRT1 targets several families of TEs (Zhong et al., 2013). OsSRT1 also deacetylates non-histone proteins. For example, OsSRT1 interacts with and deacetylates glyceraldehyde-3-phosphatedehydrogenase to repress its activity. Thus, OsSRT1 exhibits a functional connection between lysine acetylation and energy metabolism (Zhang et al., 2017).

Plant-specific HD2 (histone deacetylase 2) HDACs

Plant-specific HD2 histone deacetylases were first identified in maize (Lusser et al., 1997). There are four HD2 members (HD2A, HD2B, HD2C, and HD2D) in *Arabidopsis*. The mechanisms of HD2 deacetylase activity are not yet fully understood. It has been reported, however, that the N-terminus of HD2 deacetylases is highly conserved and necessary for deacetylase activity (Bourque et al., 2016). Variable regions within HD2 proteins are potentially subject to post-translational modifications that are important for the proper function of HD2 proteins (Bourque et al., 2016). This is exemplified by the pathogen-triggered phosphorylation of HD2B at Thr249 and Ser266 residues, which drives HD2B from the nucleolus to the nucleoplasm (Latrasse et al., 2017). Mimicking constant phosphorylation of HD2B by mutating Thr249 to Glu and Ser266 to Asp resulted in similar HD2B nucleoplasm localization in normal condition and increased pathogen resistance (Latrasse et al., 2017). Whether other HD2 proteins are also subject to specific posttranslational modifications triggered by environmental stimuli, and what the functions of these modifications are, remain unknown. A rice HD2 member, HDT701, is also involved in immune defense (Ding et al., 2012). Knockdown of *HDT701* enhanced pathogen resistance (Ding et al., 2012). In addition to biotic stress, HD2 members are broadly involved in abiotic stress. *Arabidopsis* HD2C interacts with HDA6 and positively regulates ABA and salt stress response (Luo et al., 2012b). HD2C also interacts with the SWI/SNF chromatin remodeling complex and negatively regulates heat stress resistance (Buszewicz et al., 2016). Plants overexpressing HD2C showed more sensitivity to cold stress due to the repression of several cold responsive genes (Park et al., 2018). In cold conditions, HD2C is degraded through a ubiquitin-proteasome system mediated by HOS15 (Park et al., 2018). Like HD2C, HD2D is also involved in temperature response. Overexpression of HD2D significantly enhanced defense to heat in *Arabidopsis* (Han et al., 2016).

Another unique feature of plant-specific HD2 HDACs is their subcellular localizations. HD2 proteins predominantly localize to the nucleolus. This suggests that this class of HDACs may play important roles in rRNA production. Indeed, *HD2A* (*HDT1*) knockdown plants lost their heterochromatinization ability in nucleolus organizer regions during early embryo development (Pontes et al., 2007). Furthermore, HD2B interacts with ribosomal protein S6 to repress rRNA transcription (Kim et al., 2014). A recent study has shown that HD2B and HD2C form a complex and repress the expression of genes involved in rRNA processing. At the post-transcriptional level, the HD2B-HD2C complex directly binds to pre-rRNA and small nucleolar RNAs, and regulates rRNA methylation, potentially through competition with RNA methyltransferase for binding sites (Chen et al., 2018). Disruption of *HD2B* and/or *HD2C* resulted in abnormal rRNA processing, coupled with short root, and narrow leaf phenotypes. These phenotypes are typical ribosome-deficient phenotypes, which may be caused by delayed cell division due to abnormal protein synthesis. Interestingly, many stress response related genes were downregulated in *hd2b hd2c* mutants in normal condition (Chen et al., 2018). This raises the possibility that HD2B and HD2C may regulate the balance between development and stress response by controlling rRNA processing.

Future perspectives

After two decades of studies, plant HDACs have been found

to participate in almost all biological processes. Compared to the most studies that focus on downstream targets and the biological outputs of HDACs, however, the mechanisms through which HDACs regulate chromatin activities remain largely unknown. Many important questions remain unanswered. For example, how are HDACs targeted to specific genomic regions given their lack of DNA binding motifs? Additionally, how do HDACs sense environmental and developmental cues? One way to begin answering these questions is to mechanically characterize HDAC-interacting proteins given that the formation of protein complexes is a hallmark feature of HDACs (Joshi et al., 2013; Yang and Seto, 2003). These proteins could be chaperones, chromatin association proteins, or transcription factors that are critical for correct protein folding, importation into specific organelles, and recruitment to target sites (Table 1). Recent studies have already revealed several important cofactors for plant HDACs; however, many more complexes remain to be discovered. Furthermore, the exact relationship between transcription and HDAC-mediated deacetylation is not fully understood. HDACs are normally considered transcription suppressors. However, almost all genome-wide chromatin association assays of HDACs revealed a tendency for these proteins to bind to active regions (Chen et al., 2016; Wang et al., 2009; Yang et al., 2016). Interestingly, one study in yeast showed that the Class I HDAC member HOS2 worked with the histone methyltransferase SET3 to ensure active transcription of galactose-inducible genes (Wang et al., 2002), suggesting that HDACs could also be transcription activators. Whether this holds true in other species will require further investigation.

Although they are named “histone deacetylases”, HDACs can remove acetyl groups from non-histone proteins. In human cells, many non-histone substrates of HDACs have been identified. Besides sirtuin HDACs, many plant Class II group RPD3-like HDACs are predicted to be localized to the cytoplasm, indicating that their targets may be non-histone proteins. However, only a few examples have been reported. Furthermore, human sirtuin proteins have been found to execute numerous other modifications in addition to acetylation, such as succinylation and myristoylation (Jiang et al., 2013; Park et al., 2013). Additional studies will be needed to determine whether plant HDACs are also able to remove such modifications.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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