REVIEW

Histone deacetylases and their functions in plants

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Abstract Histone deacetylases (HDACs) mediate histone deacetylation and act in concert with histone acetyltransferases to regulate dynamic and reversible histone acetylation which modifies chromatin structure and function, affects gene transcription, thus, controlling multiple cellular processes. HDACs are widely distributed in almost all eukaryotes, and there have been many researches focusing on plant HDACs recently. An increasing number of HDAC genes have been identified and characterized in a variety of plant species and the functions of certain HDACs have been studied. The present studies indicate that HDACs play a key role in regulating plant growth, development and stress responses. This paper reviews recent findings on HDACs and their functions in plants, especially their roles in development and stress responses.

Keywords Histone deacetylase · Histone acetylation · Development · Stress

Introduction

Chromatin is composed of nucleosomes, each of which consists of a histone octamer (two molecules of the core histones H2A, H2B, H3 and H4) wrapped around by 147 bp of DNA. Chromatin structure is regulated by processes such as DNA methylation and histone post-translational modifications, including acetylation, methylation, phosphorylation, ubiquitation, propionylation, butyrylation, sumoylation, ADP ribosylation, glycosylation, biotinylation, and carbonylation (Hildmann et al. 2007). Of these post-translational modifications, histone acetylation is the earliest (1964) (Allfrey et al. 1964) and the most well characterized. Histone acetylation majorly occurs at the amino groups of lysine residues within the histone N-terminal tails which protrude out of the nucleosomes, whereas some lysines within the histone globular domains, such as H3K56 and H4K91, can also be acetylated (Shahbazian and Grunstein 2007). All four core histones can be acetylated/deacetylated and a nucleosome contains 26 putative acetylation sites (Lusser et al. 2001). The lysine residues 9, 14, 18 and 23 of H3 and the lysine residues 5, 8, 12, 16 and 20 of H4 were reported to be acetylated and deacetylated in plants (Fuchs et al. 2006). Histone acetylation changes chromatin structure and regulates gene transcription, DNA replication, and DNA repair (Bertos et al. 2001).

Histone acetylation and deacetylation is a dynamic and reversible process and is mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. HATs attach acetyl moiety of acetyl-CoA to the ε-amino group of specific lysine residues on histones, while HDACs remove acetyl group from histones. Histone acetylation was initially suggested to neutralize the positive charges on lysine residues and reduce electrostatic interactions between histones and phosphate groups of DNA, making the DNA more accessible for transcription factor complexes (Henikoff 2005; Shahbazian and Grunstein 2007). However, growing evidence indicates that histone acetylation decreases the interactions between neighboring nucleosomes and prevents the compaction of nucleosomes into 30 nm chromatin fibers, thus leading to a looser structure of chromatin (Shahbazian and Grunstein 2007). In

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addition to changing the chromatin structure, histone acetylation alters the surface of nucleosomes and shapes the binding surface for the proteins involved in gene transcription (Berger 2007; Shahbazian and Grunstein 2007). Therefore, hyperacetylation of histones is associated with a more 'open' structure of chromatin and facilitates the binding of transcription factor complexes to the promoter region of genes, thus, resulting in activation of gene transcription. Hypoacetylation mediated by HDACs is associated with a more compact chromatin structure, which blocks the accessibility of transcription factors to target genes and leads to the repression/silencing of genes (Hollender and Liu 2008). In 1996, the first histone deacetylase gene (HD1), now called human HDAC1, was cloned from human Jurkat T cell (Taunton et al. 1996). Since then HDACs have been identified in almost all eukaryotes including fungi, animals (such as fruit-fly, mice, chicken and human) and plants. Homologous proteins also exist in archaebacteria and eubacteria (Gregoretti et al. 2004; Johnson and Turner 1999). In the past 10 years, plant HDACs have drawn considerable research attention and an increasing number of HDACs were purified, identified and characterized from plants such as maize, Arabidopsis, rice, barley (Demetriou et al. 2009), potato (Lagace et al. 2003), grape (Busconi et al. 2009) and tobacco (Bourque et al. 2011). Even in woody plant *Populus Trichocarpa*, HDACs have been identified (http://www.chromdb.org). Current available evidence indicates that HDACs play an important role in plant growth, development, and stress responses. This paper reviews recent findings on HDACs and their functions in plants.

Classification

HDACs are widely distributed in eukaryotes from yeast to mammals and plants. To date, at least 18 HDACs have been identified in human with functions in transcription, cell cycle progression, gene silencing, differentiation, DNA replication, and DNA damage repair (Thiagalingam et al. 2003). These HDAC proteins can be classified into three main classes (e.g., RPD3, HDA1 and SIR2) based on the homology to yeast HDACs (Thiagalingam et al. 2003). Plant HDAC homologues with histone deacetylase activity were first characterized from peas in 1988 (Sendra et al. 1988). Recently, there are more studies focusing on HDACs and different HDAC genes have been identified in plants. Based on the sequence homology to yeast HDACs, the plant HDACs are classified into three distinct groups, including RPD3/HDA1-like family, SIR2-like family and HD2 family (Fig. 1) (http://www.chromdb.org; Pandey et al. 2002). Members of the RPD3/HDA1-like family are related to yeast RPD3 and HDA-1. Members of the SIR2-

like family are homologous to yeast SIR2 proteins. The HD2 proteins were identified initially in maize and are plant-specific histone deacetylases which have not been found in animals (Dangl et al. 2001; Lusser et al. 1997).

RPD3/HDA1-like histone deacetylases

The first cDNA encoding homolog of RPD3 in plants was isolated from maize and designated *ZmRPD3* (Rossi et al. 1998), which complemented the *rpd3* null mutant of yeast
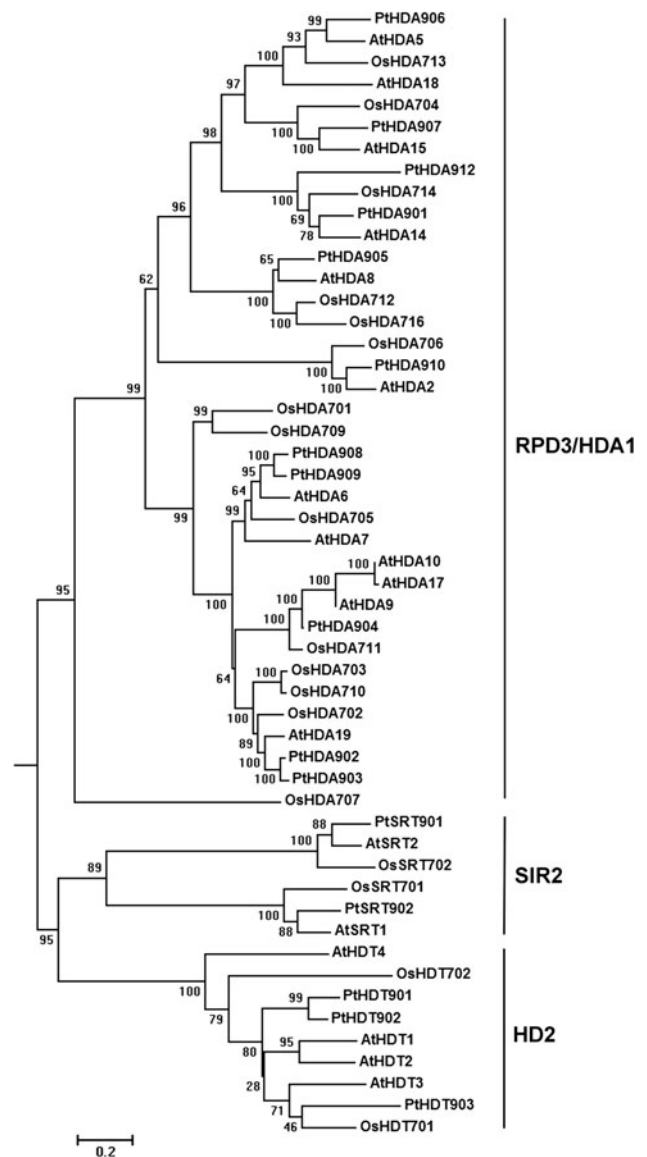

Fig. 1 Phylogenetic analysis of HDACs in plants. The neighbor joining phylogenetic tree of HDACs from Arabidopsis, rice and populus was reconstructed using MEGA5.1 program. The protein sequences of these HDACs are obtained from plant chromatin database (http://www.chromdb.org). Organism abbreviations are as follows: *Arabidopsis thaliana* At, *Oryza sativa* Os, *Populus trichocarpa* Pt

(*Saccharomyces cerevisiae*). HD1A protein, now designated as ZmHda1, was first purified from maize germinating embryo (Brosch et al. 1996a) and is the best characterized HDA1-type histone deacetylase (Pipal et al. 2003). HD1A is subject to phosphorylation resulting in significant activation of enzyme activity and a change in substrate specificity (Graessle et al. 2001). RPD3/HDA1-like histone deacetylases require a zinc (Zn) metal ion for catalytic activity. The active site of RPD3/HDA1-like histone deacetylases consists of a curved-tubular shape and the catalytic Zn^{2+}-ion locates at the bottom of the pocket. The Zn^{2+}-ion and several adjacent conserved residues (including two adjacent histidine residues, two aspartic residues, and one tyrosine residue) are essential for catalyzing the removal of an acetyl group (de Ruijter et al. 2003). The enzyme activities of RPD3-like histone deacetylases can be inhibited by HDAC specific inhibitor trichostatin A (TSA) or sodium butyrate (Hollender and Liu 2008), which displaces the zinc ion at the active site and, thereby, inactivates HDAC catalytic activity.

HD2

HD2 proteins are plant-specific histone deacetylases which are different from RPD3/HDA1 proteins in structure, but are homologous to peptidyl-prolyl cis-transisomerases (PPIases) in sequence (Dangl et al. 2001). HD2 was first detected (Lopez-Rodas et al. 1991) and purified (Brosch et al. 1996b) from maize and identified to be an acidic nucleolar phosphoprotein that may regulate ribosomal chromatin structure and function (Lusser et al. 1997). Amino acid sequence alignment analysis of HD2 proteins from Arabidopsis, maize and rice revealed that HD2 proteins are composed of three domains: an N-terminal domain containing a conserved pentapeptide motif (ME-FWG), a high charged central acidic domain, and a variant C-terminal domain (Dangl et al. 2001). For the C-terminal domain, six of eight analyzed HD2 proteins contain a single, putative zinc-finger motif which is possibly involved in protein–protein interactions.

SIR2-like histone deacetylases

SIR2-like proteins, also known as sirtuins, are nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases. SIR2-like proteins do not share sequence or structural homology with the other HDAC family members and the enzyme activities cannot be inactivated by TSA or sodium butyrate (Hollender and Liu 2008). Thus, SIR2 proteins are regarded as a new type of histone deacetylase. SIR2-like histone deacetylases are conserved from bacteria to human and control basic cellular processes such as gene expression, apoptosis, cell cycle, cell survival, metabolism,

and aging (Denu 2005; Grubisha et al. 2005). Plants have reduced number of genes encoding SIR2 proteins compared with fungi and animals. For example, yeast has five SIR2 genes and mammalian cells have seven SIR2 genes (Frye 2000). While Arabidopsis and rice each has two SIR2 genes, and maize has one SIR2 gene. The functions of SIR2 proteins in plants are not fully understood.

Substrate specificity

All core histones including H2A, H2B, H3 and H4 are substrates of histone deacetylases, whereas HDACs have different specificities for different histones. For example, HD1-A, HD1-B and HD2 from germinating maize embryos showed preference for histone H3. HD1-A and HD1-B can deacetylate H2A and H4 with almost equal specificity, but were least active with H2B. HD2 protein deacetylated H2A and H2B equally, but was least active with H4 (Kolle et al. 1999). In addition, Brosch et al. (1992) described for the first time that HDACs were regulated by phosphorylation which may change the substrate specificity of HDACs. After phosphorylation, maize HD1-A specificity for H2A was twofold increased and its specificity for H3 was decreased to approximately 60 % (Brosch et al. 1992). Native maize HD1-A only partially deacetylated tri- and tetra-acetylated H4, but dephosphorylated HD1-A completely deacetylated di-, tri- and tetra-acetylated H4 (Kolle et al. 1999). HDACs also have distinct specificity for lysines at different sites of histones. For example, pea HD1 preferred lysine 5 (K5) than lysine 16 (K16) of H4 histone, and the preferred residues in H3 are K4 » K18 ≈ K9. For HD2 protein, however, the preferred residues in H4 are K8 ≈ K5 > K16, and the preferred sites in H3 are K4 and K18 (Clemente et al. 2001). The specificity of HDACs for different histones may be related to their different functions in transcription. For example, in yeast, both Hos2 and Rpd3 deacetylate the GAL genes, but exert opposing effects on transcription. Rpd3 represses but Hos2 activates the transcription of gene *GAL1*. The different roles of Hos2 and Rpd3 may be due to their different lysine specificities. Rpd3 deacetylated all lysines examined in the core histones H3, H4, H2A and H2B except for H4K16, while Hos2 preferred to deacetylate histone H3 and H4 including H4K16 (Wang et al. 2002). The specific deacetylation of certain lysines may be important for the binding of effector proteins, or may influence chromatin condensation and folding, thus affecting transcription.

In recent years, some non-histone substrates of HDACs were identified from human cells including nuclear transcription factors p53 and E2F3 and cytoplasmic heat shock protein (Hsp90), Ku70, α-tubulin, and β-catenin (Ma et al. 2009). Proteomics analysis identified 388 acetylation sites

in 195 proteins from HeLa cells and mouse liver mitochondria (Choudhary et al. 2009). The identified proteins were classified into RNA splicing factors, chaperones, structural proteins, signaling proteins and energy metabolic proteins. To date, little is known about non-histone substrates of HDACs in plants. Nevertheless, in Arabidopsis, studies showed that a wide range of non-histone proteins in various subcellular compartments can be acetylated (Finkemeier et al. 2011; Tran et al. 2012; Wu et al. 2011). Proteomics analysis using chromatography-tandem mass spectrometry (LC–MS/MS) identified 74 organellar and cytosolic proteins from Arabidopsis that can be acetylated. These identified proteins included four Calvin cycle enzymes, some central metabolic enzymes and the large subunit of Rubisco (Finkemeier et al. 2011). Wu et al. (2011), using immunoblotting with generic anti-LysAc antibodies, identified 64 lys-acetylation sites on 57 proteins, which were localized in various cellular compartments including the chloroplast, nucleus, and plasma membrane, and so on. The identified lys-acetylated proteins are involved in a wide variety of processes, but a number of them are associated with photosynthesis. These photosynthesis-related proteins include photosystem II (PSII) subunits, light-harvesting chlorophyll a/b-binding proteins (LHCb), Rubisco large and small subunits, and chloroplastic ATP synthase (b-subunit), suggesting that acetylation may be an important post-translational modification in chloroplasts (Wu et al. 2011). Very recently, HDA14, using microcystin-affinity chromatography, was purified from *Arabidopsis thaliana* and was identified to deacetylate α-tubulin (Tran et al. 2012). Thus, not only core histones but non-histone proteins in various compartments are substrates of plant HDACs.

Subcellular localization

HDACs are localized in the nucleus, cytoplasm, or shuttling between nucleus and cytoplasm. HDACs are also distributed in organelles such as mitochondria, chloroplasts and endoplasmic reticulum (ER) (Table 1). The different subcellular localization of HDACs may be associated with their different cellular functions. HDACs are primarily localized in the nucleus to regulate core histone structure and function. In the nucleus, HDACs may exist as soluble, chromatin-bound or nuclear matrix-associated forms and the proportion of each form may be different. During maize embryo germination HD-1A predominantly existed as a soluble form, HD-2 was chromosome-bound, while HD-1B existed as soluble and chromosome-bound forms depending on the germination stage (Grabher et al. 1994). While very low enzyme activities (below 5 %) could be detected in the nuclear matrix.

Current available data indicate that RPD3/HDA1-like histone deacetylases are distributed in the nucleus, cytoplasm, or some organelles. Different members of RPD3/HDA1-like family may have different subcellular localization (Alinsug et al. 2012). For instance, rice OsHDAC6 was localized exclusively in the chloroplasts, while OsHDAC10 was localized in both mitochondria and chloroplasts (Chung et al. 2009). The localization of HDACs in the chloroplasts and mitochondria implies their roles in central metabolic pathways including photosynthesis. HD2 proteins, unlike RPD3/HDA1-like histone deacetylases, were specifically localized in the nucleolus and may be involved in the regulation of ribosomal chromatin structure and function (Lusser et al. 1997; Zhou et al. 2004). HDAC localizations are variable in different plant tissues. For an instance, maize ZmHDA108, also known as HD1B-II or ZmRpd3/108, was localized in the nucleus and cytoplasm in anthers/endosperm, while it mainly exists in the cell cytoplasm in shoot apexes (Varotto et al. 2003). Environmental factors also affect the localization of HDACs. Arabidopsis HDA15 imported into the nucleus in the presence of light, but exported out of the nucleus in the absence of light, implying its possible functions in the light signaling pathway (Alinsug et al. 2012).

In addition, subcellular localization may be a mechanism that regulates HDAC activities, especially for those HDACs that localize to the nucleus and cytoplasm. For example, class II HDACs 4, 5, 7 and 9 shuttle between the nucleus and cytoplasm. The conserved N-terminal serine residues of HDACs 4, 5, 7 and 9 are phosphorylated by CaMK protein kinases and the phosphorylation promotes the binding of 14-3-3 proteins to the N-terminal domain. The binding of 14-3-3 proteins results in the sequestration of the HDACs to the cytoplasm, thus decreasing the amount of the HDACs in the nucleus so that HDAC activities were negatively regulated (Sengupta and Seto 2004).

Expression

Expression of HDACs in different tissues

HDACs are widely expressed in almost all types of analyzed tissues including callus, vegetative tissues, roots, flowers, and seeds. Hollender and Liu (2008) examined the expression profiles of 16 Arabidopsis HDAC genes in 79 different tissues by using microarray analysis (Hollender and Liu 2008). HD2 and RPD3-like HDAC genes are found to be highly expressed in inflorescences and young floral tissues, but at low level in vegetable tissues. The expression profiles of RPD3-like HDAC genes (*AtHDA6*, *AtHDA9* and *AtHDA19*) were highly similar. The members in HD2 family exhibited very similar expression patterns as

Table 1 Subcellular localization of plant HDACs

HDAC family	Enzymes	Plants	Localization	References
RPD3/HDA1-like	ZmRPD3/101	Maize	Cytoplasm, nucleus	Grabher et al. (1994), Varotto et al. (2003)
	ZmRPD3/102	Maize	Cytoplasm, nucleus	Varotto et al. (2003)
	ZmRPD3/108	Maize	Cytoplasm, nucleus	Grabher et al. (1994), Varotto et al. (2003)
	ZmHD1A	Maize	Nucleus	Grabher et al. (1994)
	AtHDA5	Arabidopsis	Cytoplasm (ER)	Alinsug et al. (2012)
	AtHDA6	Arabidopsis	Nucleolus	Chen and Tian (2007), Earley et al. (2006)
	AtHDA8	Arabidopsis	Cytoplasm	Alinsug et al. (2012)
	AtHDA14	Arabidopsis	Mitochondria, chloroplasts	Alinsug et al. (2012)
	AtHDA15	Arabidopsis	Cytoplasm, nucleus	Alinsug et al. (2012)
	AtHDA19	Arabidopsis	Nucleus (not nucleolus)	Fong et al. (2006)
	OsHDAC6	Rice	Chloroplasts	Chung et al. (2009)
	OsHDAC10	Rice	Mitochondria, chloroplasts	Chung et al. (2009)
HD2	AtHD2A	Arabidopsis	Nucleolus	Zhou et al. (2004)
	AtHD2B	Arabidopsis	Nucleolus	Zhou et al. (2004)
	AtHD2C	Arabidopsis	Nucleolus	Zhou et al. (2004)
	ZmHD2	Maize	Nucleolus	Lusser et al. (1997)
SIR2-like	OsSIR2b	Rice	Mitochondria	Chung et al. (2009)
	OsSRT1	Rice	Nucleus	Huang et al. (2007)

well. However, the expression profiles of SIR2 genes (*AtSRT1* and *AtSRT2*) were markedly different, implying that SRT1 and SRT2 may be involved in different cellular processes and function in different tissues. To study the expression profiles of rice HDAC genes, serial Affymetrix microarray data were analyzed by Hu et al. (2009). Rice HDAC genes were found to be differentially expressed in various tissues (Hu et al. 2009). The closely related HDAC genes showed very similar expression patterns. Several RPD3/HDA1-like genes were expressed in a tissue-specific manner. For instance, *OsHDA703* was mainly expressed in calli and imbibed seeds, while *OsHDA710* was specifically expressed in seedlings and stamens. *OsHDA706* and *OsHDA714* were highly expressed in shoots and leaves, which is consistent with their respective localization in the chloroplasts and the mitochondria (Hu et al. 2009). Rice OsSRT701 is localized in the nucleus, while OsSRT702 is localized in the mitochondria. Maybe due to their different subcellular localizations, the expression patterns of the two genes are different (Hu et al. 2009). In potato (*Solanum chacoense*), an HD2-type histone deacetylase gene *ScHD2a* was identified. The transcription of *ScHD2a* was highly induced after pollination in pistils and the transcripts were mostly accumulated in the micropylar region of the ovules, implying the possible role in seed development (Lagace et al. 2003). The different expression levels of HDACs in various tissues suggest that HDACs may play a different role in different tissues.

In addition to different spatial expression, HDACs may be expressed differently dependent on developmental stages. For example, maize *ZmHDA101* (e.g., *ZmRpd3I* or *HD1B-I*) is expressed during the entire germinating process, while *ZmHDA108* is expressed when meristematic cells enter S-phase of the cell cycle (Lechner et al. 2000).

Expression of HDACs in response to stresses

The expression of HDAC genes is in response to stresses and is regulated by stress-related hormones like salicylic acid (SA), jasmonic acid (JA) or abscisic acid (ABA) (Fu et al. 2007; Hu et al. 2009). The microarray data obtained from the rice treated with salt, drought and cold showed that the expression of most HDAC genes was regulated by salt and drought, but less affected by cold (Hu et al. 2009). Two RPD3-like HDAC genes (*OsHDA703* and *OsHDA710*) were upregulated, while a large proportion of HDAC genes (i.e., *OsHDA701*, *OsHDA702*, *OsHDA704*, *OsHDA705*, *OsHDA706*, *OsHDA712*, *OsHDA714*, *OsHDA716*, *OsHDT701* and *OsHDT702*) were repressed by drought and salt (Hu et al. 2009). In another study, rice *OsHDA702* was found to be upregulated by salt and drought, while the expression of most HDAC genes (*OsHDA704*, *OsHDA706*, *OsHDA712*, *OsHDT701*, *OsSRT701*, *OsSRT702* and *OsPR10a*) was decreased (Fu et al. 2007). These results suggest that HDACs may be involved in abiotic stress responses and different members of the HDAC family may have different functions.

SA and JA mediate plant defense responses, while ABA is involved in water stress response to regulate plant water balance and osmotic stress tolerance. In Arabidopsis, the

expression of *AtHDA6* and *AtHDA19* was induced by JA (Zhou et al. 2005), and the expression of *AtHD2C* was repressed by ABA (Sridha and Wu 2006). In rice, different HDAC family members respond differently to plant hormones. JA induced the expression of leaf *OsHDA705*, *OsHDT701* and *OsHDT702*, SA induced the expression of *OsHDT702*, while ABA repressed the expression of *OsHDT701*, *OsHDT702*, *OsSRT701* and *OsSRT702* (Fu et al. 2007). Barley HD2 genes *HvHDAC2-1* and *HvHDAC2-2* were also induced by JA, but responded differently to ABA (Demetriou et al. 2009). *HvHDAC2-1* was induced by ABA, while *HvHDAC2-2* was downregulated by ABA, implying the possible different functions of the two HD2 members in response to ABA. These studies indicate that some HDACs may function as a component in hormone signaling pathways in response to stresses.

Functions

Deacetylation mediated by HDACs, the same as acetylation, is recognized to play a vital role in regulating gene expression and biological processes. Histone deacetylation is generally associated with transcriptional repression and/or gene silencing, though the detailed mechanisms by which HDACs exert the regulatory roles remain to be further studied. HDACs, in general, act as components of large complexes to regulate gene expression. In recent years, several proteins that can interact with HDACs have been identified in plants (Table 2). The proteins include DNA methyltransferases, phosphatase, and transcription factors. Plant HDACs represent a large family with multiple gene members. Different subcellular localizations and different expression profiles of various HDACs suggest their functional diversity. Increasing data indicate that HDACs play a key regulatory role in plant growth, development, and responses to abiotic and biotic stresses (Table 3).

Functions of HDACs in plant growth and development

Reproductive development

Altered expression of HDAC genes may affect the plant growth and development producing visible and various phenotypes. Arabidopsis AtHDA19 is presumably localized in the nuclear euchromatic regions and is responsible for global transcriptional regulation (Fong et al. 2006). Antisense expression of *AtHDA19* in transgenic Arabidopsis increased levels of tetra-acetylated histone H4 and the transgenic plants exhibited various developmental abnormalities, including early senescence, serration, aerial rosette formation, floral abnormalities, and delay of

flowering (Tian and Chen 2001). Some of the phenotypic changes may result from ectopic expression of the tissue-specific genes like *Superman* (*SUP*), which is associated with flower development (Tian and Chen 2001). Arabidopsis AtHDA6, the closest homolog of AtHDA19, is involved in flower development. In Arabidopsis, Flowering Locus C (FLC), a MADS-box transcription factor, acts as a flowering repressor that inhibits the transition from vegetative growth to reproductive development. AtHDA6 can repress the expression of *FLC* to control flowering time. Flowering Locus D (FLD), an ortholog of the human protein Lys-Specific Demethylase 1 (LSD1), and FEV (MSI4), a homolog of the human histone-binding proteins Retinoblastoma-Associated Protein 46/48 (RbAp46/48), are also involved in the regulation of *FLC* expression. The N-terminal region of FLD was found to interact with the C-terminal region of AtHDA6 (Yu et al. 2011). *Athda6* mutant *axe1-5* and (or) *fld-6* mutant plants displayed a late-flowering phenotype (Yu et al. 2011). In these mutants, the expression of flowering-related genes such as *FLC*, *Mads Affecting Flowering 4* (*MAF4*) and *MAF5*, was upregulated and the level of acetylated histone H3 in the first exon of these genes was increased (Yu et al. 2011). FVE was recently reported to directly interact with *FLC* locus, form a complex with AtHDA6 and repress the *FLC* expression (Gu et al. 2011). *FVE* mutation increased the acetylation level of *FLC* locus (He et al. 2003). Therefore, to control flowering time, HDACs may form a complex with the other proteins (such as LSD and FVE) and are recruited to the target genes that are involved in flower development (e.g., FLC), leading to the deacetylation of the target loci and repression/silencing of the genes.

In maize, overexpression and antisense expression of a RPD3-type *ZmHDA101* rendered the transgenic maize a slow growth and late flowering (Rossi et al. 2007). Moreover, adult transgenic plants also displayed altered phenotypes such as changed inflorescence morphology and differentiation, abnormal anther dehiscence, and reduced fertility. These abnormal phenotypes were considered to be related to defects in controlling vegetative-to-reproductive phase transition. Indeed, the expression of genes involved in this transition control *liguleless 2* (*lg2*), *knotted 1* (*kn1*) and *rough sheath 2* (*rs2*) was found to be impaired in *hda101* overexpression and antisense transgenic plants (Rossi et al. 2007). It was recently reported that overexpression of *OsHDT1*, a rice HD2-type HDAC, in hybrid rice led to early flowering probably by suppressing the overdominance expression of key flowering repressors *Heading date 1* (*Hd1*) and its upstream activator *OsGigantea 1* (*OsG1*) (Li et al. 2011).

In addition, HDACs are involved in seed development. Antisense silencing of *AtHD2A* resulted in aborted seed development (Wu et al. 2000a). Rice RPD3-type HDA703

Table 2 Proteins associated with HDACs

Enzymes	Plants	Associated protein factors	Functions	References
AtHDA6	Arabidopsis	F-box protein COL1	Regulate expression of jasmonate responsive genes	Devoto et al. (2002)
		Flowering locus D (FLD)	Regulate flowering	Yu et al. (2011)
		DNA methyltransferase (MET1)	Regulate locus-directed heterochromatin silencing; maintains transposable element silencing	Liu et al. (2012), To et al. (2011b)
AtHDA14	Arabidopsis	Protein phosphatase PP2A-A	Tubulin deacetylation	Tran et al. (2012)
AtHDA19	Arabidopsis	Transcription co-repressor LEUNIG	Disease resistance, DNA damage response and cell signaling	Gonzalez et al. (2007)
		Transcription factor WRKY38, WRKY62	Basal defense responses	Kim et al. (2008)
		Pathogenesis-related1 (PR1), PR2	Basal defense responses	Choi et al. (2012)
		AtSin3	ABA and drought stress responses	Song et al. (2005)
ZmRpd3I	Maize	Retinoblastoma-related homologues (ZmRBR1)	Regulate gene transcription in the cell cycle	Rossi et al. (2003)
AtHD2A	Arabidopsis	DNA methyltransferase 2 (AtDNMT2)	Repress gene expression	Song et al. (2010)
AtHD2B	Arabidopsis	DNA methyltransferase 2 (AtDNMT2)	Repress gene expression	Song et al. (2010)
AtHD2C	Arabidopsis	DNA methyltransferase 2 (AtDNMT2)	Repress gene expression	Song et al. (2010)
		Histone deacetylase 6 (HDA6)	ABA and salt stress responses	Luo et al. (2012)

was also found to be involved in reproductive development and seed morphology. RNAi-mediated downregulation of *HDA703* reduced elongation of the peduncle and fertility (Hu et al. 2009). These above findings suggested that histone deacetylases are required for the transition of plants from vegetative growth to reproductive phase and subsequent reproductive development.

Vegetative development

In addition to reproductive development, HDAC genes are also involved in the regulation of plant vegetative growth and development. In seed plants, the shoot apical and root apical meristem form at the apical and basal poles of the embryonic axis. Arabidopsis AtHDA19 is expressed throughout the embryogenesis and act in conjunction with Topless-1 (TPL-1), a transcriptional co-repressor, to ensure proper development of the shoot poles (Long et al. 2006). In *tpl-1* mutants, the embryo shoot pole was converted into a second root pole. While in *AtHDA19* mutant seedlings, similar apical defects were also observed. Arabidopsis HD2A and HD2B acted independently with Asymmetric Leaves 2 (AS2) or AS1 to control the development of adaxial–abaxial leaf polarity (Ueno et al. 2007). Inhibition of HDAC activity with TSA caused aberrant distribution of miR165/166 on the adaxial side of young leaves and resulted in abaxialized filamentous leaves during leaf development in *as1* and *as2* mutant plants (Ueno et al. 2007). HDAC is also involved in root development (Ueno

et al. 2007). TSA treatment of Arabidopsis seedlings altered the cellular patterning of root epidermis and induced hair cell development at non-hair positions (Xu et al. 2005). Moreover, the expression levels of three patterning gene *CPC*, *GL2* and *WER* were changed significantly in response to TSA. By screening HDAC mutants, Arabidopsis HDA18 was found to be a key regulator of cellular patterning in the root epidermis (Xu et al. 2005). Several rice HDACs were recently studied for their effects on plant development. Overexpression of rice HDACs did not lead to altered visible phenotypes, nevertheless, downregulation of HDACs (i.e., *OsHDA704*, *OsHDA710* or *OsHDT702*) produced phenotypic defects (Hu et al. 2009). RNAi-mediated downregulation of *OsHDA710* reduced vegetative growth. Lowered expression of *OsHDA704* and *OsHDT702* impaired plant growth and leaf morphology. In another study, overexpression of *OsHDAC1* increased the growth rate of rice and changed the architecture of the roots and shoots (Jang et al. 2003). These studies in Arabidopsis and rice demonstrate that HDACs are important regulators in plant growth and vegetative development. Nevertheless, the target genes and interacting proteins of HDACs still need to be defined to understand the regulation mechanism of HDACs in plant development.

Functions of HDACs in stress responses

Plants are subjected to various abiotic (e.g., high salinity, cold, heat, drought and heavy metals) or biotic (pathogens)

Table 3 HDAC functions in plants

HDAC family	Enzymes	Plants	Functions	Reference
RPD3/ HDA1-like	AtHDA19	Arabidopsis	*Antisense phenotype* various developmental abnormalities; late flowering	Tian and Chen (2001), Wu et al. (2000a)
			Mutant phenotype hypersensitive to ABA and NaCl; increased tolerance to *P. syringae*	Chen and Wu (2010), Choi et al. (2012)
			Overexpression phenotype enhanced resistance to pathogens *A. Brassicicola* and *P. syringae*	Kim et al. (2008), Zhou et al. (2005)
	AtHDA6	Arabidopsis	*Mutant phenotype* late flowering; hypersensitive to ABA and NaCl; decreased tolerance to freezing temperature after cold acclimation; the expression of JA responsive genes was downregulated	Chen et al. (2010), To et al. (2011b), Wu et al. (2008), Yu et al. (2011)
			RNA interference phenotype the expression of jasmonate responsive genes was downregulated	Wu et al. (2008)
	AtHDA18	Arabidopsis	Root cellular patterning. TSA treatment: hair cell development at non-hair positions	Xu et al. (2005)
	ZmHDA101	Maize	*Overexpression phenotype* grew slowly and late flowering	Rossi et al. (2007)
			Antisense phenotype: grew slowly and late flowering	Rossi et al. (2007)
	OsHDAC1	Rice	*Overexpression phenotype* increased the growth rate and changed the root and shoot architecture	Jang et al. (2003)
HD2	AtHD2A	Arabidopsis	*Antisense phenotype* resulted in aborted seed development	Wu et al. (2000b)
			RNA interference phenotype produced radicalized leaves in the T1 and T2 generation	Ueno et al. (2007)
	AtHD2B	Arabidopsis	*RNA interference phenotype* produced radicalized leaves in the T1 and T2 generation	Ueno et al. (2007)
	AtHD2C	Arabidopsis	*Overexpression phenotype* insensitive to ABA and increased tolerance to salt and drought stresses	Sridha and Wu (2006)
			Mutant phenotype increased the sensitivity to salt	Luo et al. (2012)
	OsHDT1	Rice	*Overexpression phenotype* early flowering	Li et al. (2011)
	NtHD2a/2b	Tobacco	*RNA interference phenotype* distal necrosis occurred on one-half of the leaf or as mosaic of small necrotic spots	Bourque et al. (2011)
			Overexpression phenotypes strongly reduced the cell death induced by an elicitor cryptogein	Bourque et al. (2011)
SIR2-like	AtSRT2	Arabidopsis	*Knock-out phenotype:* increased resistance to pathogen *P. syringae*	Wang et al. (2010)
			Overexpression phenotype decreased resistance to pathogen *P. syringae*	Wang et al. (2010)
	OsSRT1	Rice	*RNA interference phenotype* induced DNA fragmentation and cell death	Huang et al. (2007)

stresses. Histones were epigenetically modified by acetylation (Kim et al. 2010) and/or methylation (Feng and Jacobsen 2011) upon exposure to stresses. Recent studies reveal that histone deacetylases are involved in the responses of plants to stress-related hormones and stress stimuli such as salt, drought, cold, and pathogen.

Salt and drought stresses

The functions of HDACs, especially AtHDA6 and AtHDA19, were most well studied in Arabidopsis. AtHDA6 and AtHDA19 were recently reported to be involved in

ABA response and are required for salt stress tolerance. AtHDA6 mutant *axe1-5* and *AtHDA6* RNA-interfering plants were hypersensitive to ABA and salt stress, at least in part due to the reduced expression of ABA and abiotic-responsive genes including *ABA Insensitive 1* (*ABI1*), *ABI2*, *3-Keto-Acyl-coa Thiolase 1* (*KAT1*), *KAT2*, *Dehydration-Responsive Element-Binding Protein 2A* (*DREB2A*), *Responsive to Desiccation 29A* (*RD29A*), and *RD29B* (Chen et al. 2010). Arabidopsis *HDA19* T-DNA insertion mutant, *HDA19-1*, was also hypersensitive to ABA and NaCl (Chen and Wu 2010). Upon exposure to ABA and NaCl, the percent germination of mutant seeds

was much lower than wild-type. Moreover, the expression of ABA and abiotic stress-responsive genes (i.e., *ABI1*, *ABI2*, *KAT1*, *KAT2*, and *RD29B*) was decreased in the *HDA19-1* mutant plants upon ABA treatment, suggesting that HDA19 is required for full induction of ABA-responsive genes (Chen and Wu 2010). AtHDA19 was proposed to form a complex with AtERF7 and AtSin3 to regulate the expression of ABA and stress-responsive genes (Song et al. 2005). AtERF7, a transcriptional repressor in ABA response, interacts with AtSin3, a homolog of a human global co-repressor. AtHDA19 can interact with AtSin3 and may be recruited to the target genes. Therefore, AtERF7 may repress gene expression through chromatin modification mediated by histone deacetylation. RNAi-mediated downregulation of *AtERF7* increased Arabidopsis sensitivity to ABA during seed germination (Song et al. 2005), which was consistent with the phenotype of *HDA19-1* mutant (Chen and Wu 2010).

HD2 proteins are plant-specific histone deacetylases. AtHD2C, an Arabidopsis HD2 protein, was involved in ABA and stress responses. The overexpression of *AtHD2C* in Arabidopsis rendered the transgenic plants insensitive to ABA and tolerant to salt and drought stresses (Sridha and Wu 2006). After high NaCl treatment for 20 days, about 60 % of *AtHD2C* transgenic leaves survived, whereas only 5 % of wild-type leaves were alive. The enhanced tolerance of transgenic plants may be due to the increased expression of ABA-responsive LEA-like genes, such as *Rd29B* and *RAB18*, and the decreased expression of some stress-responsive genes including *ABI2*, *Alcohol Dehydrogenase 1* (*ADH1*), *KAT1*, *KAT2* (*K+ inward rectifier*), and *Stelar K+ Outward Rectifier* (*SKOR*, K+ outward rectifier). In contrast, *AtHD2C* T-DNA insertion mutants (*hd2c-1* and *hd2c-3*) were more sensitive to ABA and salt during seed germination (Luo et al. 2012). AtHD2C was identified to bind to histone H3 and physically interact with AtHDA6 in vitro and in vivo to regulate the expression of abiotic stress-responsive genes. In *hd2c-1*, *hda6* and *hd2c-1/hda6* double mutants, the expression of ABA-responsive genes, such as *ABI1*, *ABI2* and *AtERF4*, was increased (Luo et al. 2012).

Cold stress

Histone acetylation and deacetylation also play a critical role in cold acclimation and tolerance in plants. HOS15, a WD40-repeat protein, is a component of the protein complex for histone deacetylation. Arabidopsis *hos15* mutation increased the acetylation level of histone H4 and *hos15* mutant plants were hypersensitive to freezing temperature but not to salt, ABA, or oxidative stress (Zhu et al. 2008). A recent report gave direct evidence for the role of histone deacetylase in cold acclimation and freezing tolerance (To

et al. 2011a). In this study, Arabidopsis AtHDA6 was transcriptionally upregulated at low temperature (2 °C) and, compared with wild-type, *hda6* mutant *axe1-5* was highly sensitive to freezing temperature (−18 °C) after cold acclimation. Microarray analysis showed that many genes were aberrantly expressed in the *axe1-5* mutant plants after cold acclimation, which may lead to the sensitivity of mutants to subsequent freezing. In maize, HDACs (e.g., *ZmHDAC101*, *ZmHDAC102*, *ZmHDAC103*, *ZmHDAC106*, *ZmHDAC108* and *ZmHDAC110*) were also highly induced by cold stress, and global deacetylation of histones H3 and H4 was observed (Hu et al. 2011). Under cold stress conditions, TSA treatment inhibited the induction of cold responsive genes such as *ZmDREB1* and *ZmCOR413*, implying that HDAC activity is required for cold stress tolerance and may activate transcription of some cold-inducible genes (Hu et al. 2011).

Biotic stress

Histone deacetylases are also involved in biotic stress responses. Jasmonates (JAs) generally inhibit plant growth and promote defense responses against insect pests and pathogens. Arabidopsis COL1, which is required in jasmonate response, was found to interact with RPD3-type histone deacetylase AtHDAC6 (Devoto et al. 2002). In *AtHDA6* mutant *axe1-5* and *AtHDA6-RNAi* plants, the expression of JA responsive genes including *PDF1.2*, *VSP2*, *JIN1* and *ERF1* was decreased (Wu et al. 2008), suggesting that AtHDA6 is a candidate regulator of JA responsive genes. Another RPD3-type HDAC, AtHDA19, was also involved in pathogen responses. Transcription of Arabidopsis *AtHDA19* was induced by pathogen-related hormones (e.g., JA and ethylene) and fungal pathogen *Alternaria brassicicola* (Zhou et al. 2005). Overexpression of *AtHDA19* in Arabidopsis increased the expression of *Ethylene Response Factor 1* (*ERF1*), a key element in defense response, and enhanced the resistance of transgenic plants to the pathogen *A. brassicicola*. Moreover, the expression of pathogenesis-related genes, *Basic Chitinase* and *β-1-3-Glucanase*, was upregulated in *AtHDA19* transgenic plants, and downregulated in *AtHDA19-RNAi* plants, implying the positive role of *At*HDA19 in plant-pathogen resistance (Zhou et al. 2005). Arabidopsis *AtHDA19* could also be induced by another species of bacterial pathogen, *pseudomonas syringae*. Kim et al. (2008) showed that overexpression of *AtHDA19* rendered transgenic Arabidopsis resistant to *P. syringae* (pv *tomato* strain DC3000, *Pst*DC3000). AtHDA19 was found to interact with transcription factors WRKY38 and WRKY62, negative regulators of plant disease resistance, and abolished their gene activator activity. These studies indicated that HDACs are required in pathogen defense responses.

In maize, HDACs are required for tolerance to fungus pathogen and associated with plant-pathogen interactions. Upon exposure to pathogenic filamentous fungus *C. carbonum*, the maize HDAC activity was found to be inhibited in vitro (Brosch et al. 1995) and in vivo (Ransom and Walton 1997) in susceptible maize line (hm/hm), but not in resistant line (Hm/Hm). Further studies showed that fungus *C. carbonum* can produce HC-toxin, an HDAC inhibitor, and inhibit maize HDAC activity in susceptible maize line (hm/hm). Resistant maize line (Hm/Hm) can express *Hm* gene which encodes an NADPH-dependent carbonyl reductase that detoxifies HC-toxin and protects HDACs from inhibition (Ransom and Walton 1997). In the susceptible maize line, due to the inhibition of HDACs, histone H3 and H4 hyperacetylation was induced by HC-toxin treatment or pathogen infection and the expression of pathogen defense genes was postulated to be interfered, which led to disease symptoms (Ransom and Walton 1997).

The above studies indicated that HDACs play a positive role in pathogen defense responses, whereas in some occasions HDACs seem to play a negative role in defense responses. AtHDA19 was very recently reported by Choi et al. (2012) to play a negative role in basal defense mediated by the SA-dependent signaling pathway in Arabidopsis (Choi et al. 2012). In *AtHDA19* mutant, SA was accumulated, the expression of *PR1* and *PR2*, two well-known markers of the SA-mediated defense systems, was upregulated, and the tolerance to *P. syringae* (*Pst*DC3000) was enhanced. In Choi's experiment, the concentration of *P. syringae* used for inoculation was tenfold than that used in Kim's study, possibly implying that the role of AtHDA19 (positive or negative) in resistance to *P. syringae* may be related to the concentration of pathogen used for infection. Arabidopsis SIR2-type histone deacetylase AtSRT2 was also shown to have a negative role in plant basal defense against the pathogen *Pst*DC3000 possibly by suppressing SA biosynthesis (Wang et al. 2010). The expression of *AtSRT2* was downregulated in response to the pathogen infection. The resistance against pathogen *Pst*DC3000 was increased in *AtSRT2* knock-out plants, but decreased in *AtSRT2*-overexpressing plants. Altogether, different members of the HDAC family may have different roles, positive or negative, in pathogen response. The mechanisms for their different roles in response to pathogen infection need to be further investigated.

Gene silencing

HDACs are also involved in gene silencing. Arabidopsis RPD3-like histone deacetylase AtHDA6 was found to mediate silencing of transgene, transposable element and rRNA genes. In eukaryotes, rRNA genes are repeated head to tail at nucleolus organizer regions (NORs) and each rRNA gene can be transcribed to produce a 45S pre-rRNA primary transcript. In Arabidopsis, mutations in *AtHDA6* gene resulted in a heterochromatin-to-euchromatin transition at the NOR regions, which was characterized by the hyperacetylation of histone H4, hypermethylation at lysine four of histone H3 (H3K4met), and DNA hypomethylation (Probst et al. 2004). RNAi-mediated knockdown of *AtHDA6* also induced a heterochromatin-to-euchromatin transition at underdominant NORs and derepression of silenced rRNA genes in Arabidopsis (Earley et al. 2006). The derepression of silenced rRNA genes was accompanied by epigenetic changes including loss of promoter cytosine methylation and replacement of histone H3 Lys 9 (H3K9) dimethylation with H3K4 trimethylation, H3K9 acetylation, H3K14 acetylation, and histone H4 tetra-acetylation (Earley et al. 2006). The recent study on Arabidopsis *Athda6* mutants revealed the detailed mechanisms by which AtHDA6 mediates rRNA gene silencing (Earley et al. 2010). In Arabidopsis, rRNA gene repeats are separated by an intergenic spacer (IGS) that contains multiple regulatory elements, and the major role of AtHDA6 is to suppress spurious RNA polymerase II (Pol II) transcription throughout the IGS (Earley et al. 2010). In *Athda6* mutants, the transcription of IGS mediated by spurious RNA polymerase II (Pol II) was elevated and the IGS siRNAs, diced from dsRNAs that were generated from bidirectional IGS transcripts, were overproduced (Earley et al. 2010). The overproduction of IGS siRNA directed de novo cytosine methylation of corresponding genes. Nevertheless, the maintenance of DNA methylation at CG and CHG motifs was reduced in *Athda6* mutants (Earley et al. 2010). Therefore, the combination of spurious transcription throughout the IGS, losses of maintenance cytosine methylation and absence of HDAC activity were suggested to disrupt the histone modifications needed for the repression of rRNA genes during development.

In plants, transposable elements (TEs) were first discovered in maize by Barbara McClintock in the 1940s. The silencing of TE loci may be controlled by the combination of histone acetylation, histone methylation and DNA methylation. AtHDA6 is involved in RNA-directed DNA methylation (RdDM) pathway for stable silencing of TEs and repetitive sequences. FVE and MSI5, the plant RbAp46/48 relatives from animal counterparts, are also associated with the silencing of RdDM target loci *AtSN1*, *AtMu1*, *FWA* and *IG/LINE* in Arabidopsis (Gu et al. 2011). Both FVE and MSI5 can form a complex with AtHDA6 and can interact with the examined target loci, leading to histone deacetylation and transcriptional silencing of these loci. Meanwhile, FVE and MSI5 are required for the de novo CHH methylation and maintenance of CHG methylation at the target loci. Loss of HDA6 activity or loss of

functional FVE and MSI5 led to re-activation of the four target loci (Gu et al. 2011). Thus, histone deacetylation and cytosine methylation are required for the silencing of TEs and repetitive sequences. In addition, a recent study showed that AtHDA6 interacted directly and acted in concert with MET1 to silence TEs by modulating histone acetylation, histone methylation and DNA methylation status (Liu et al. 2011). In *Athda6* mutant *axe1-5*, a subset of TEs was transcriptionally reactivated and TE re-activation was accompanied by elevated histone H3 and H4 acetylation, increased H3K4Me3 and H3K4Me2, and decreased DNA methylation of the TEs (Liu et al. 2011).

Other functions of HDACs

In addition to their functions in plant growth, development, stress responses and gene silencing, HDACs are also involved in other cellular processes such as cell death and cell cycle. Downregulation of rice *OsSRT1*, a SIR2-like histone deacetylase, induced DNA fragmentation and cell death (Huang et al. 2007). Microarray analysis revealed that transcription of many genes involved in hypersensitive response and/or programmed cell death was activated. In tobacco, NtHD2a and NtHD2b were found to act as negative regulators of cell death induced by elicitor cryptogein (Bourque et al. 2011). However, the mechanism by which tobacco HD2 proteins regulate the cell death was unknown.

In mammalian cells, the overexpression of mouse *HD1* can reduce cell growth rate and cause a delay at the G2/M phases of the cell cycle (Bartl et al. 1997). In plants, HDACs are also associated with cell cycle progression. Maize ZmRPD3 proteins (ZmHDA101, ZmHDA102 and ZmHDA108) were able to interact with Rb-related protein ZmRBR1, a key regulator of the G1/S transition (Varotto et al. 2003), and the interaction of ZmHDA101 with ZmRBR1 repressed gene transcription in tobacco protoplasts (Rossi et al. 2003). Thus, histone deacetylases were proposed to be targeted to the genes that are required for cell cycle entry (De Veylder et al. 2007) and regulate the transcription of these genes. In addition, maize *ZmHDA108* gene started to be expressed when meristematic cells enter S-phase of the cell cycle (Lechner et al. 2000), implying that HDACs may function at a certain phase of the cell cycle.

Conclusions

It is becoming evident that histone acetylation regulated by HDACs and HATs works with other modifications such as histone methylation and DNA methylation to regulate gene transcription or gene silencing. HDACs are generally recruited to the target genes, modify the chromatin structure at the loci, and regulate gene transcription. To date, however, the study of plant HDACs is still new in the beginning and many questions remain to be addressed. HDAC upstream regulators, downstream target genes and gene regulatory network largely remain to be investigated. Researches in these fields will contribute to the understanding of mechanisms by which HDACs regulate plant development and stress responses. Rapid and reversible epigenetic regulation is an important mechanism that regulates the responses of plants to biotic and abiotic stresses. However, except for the best studied AtHDA6 and AtHDA19 in Arabidopsis, it is largely unknown whether HDACs have adaptive advantages. Therefore, the studies to clarify the roles of HDAC family members in stress tolerance would be of great value not only for basic science, but also for breeding practices.

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