



Review

The roles of histone acetylation in seed performance and plant development

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ABSTRACT

Histone acetylation regulates gene transcription by chromatin modifications and plays a crucial role in the plant development and response to environment cues. The homeostasis of histone acetylation is controlled by histone acetyltransferases (HATs) and histone deacetylases (HDACs) in different plant tissues and development stages. The vigorous knowledge of the function and co-factors about HATs (e.g. GCN5) and HDACs (e.g. HDA19, HDA6) has been obtained from model plant *Arabidopsis*. However, understanding individual role of other HATs and HDACs require more work, especially in the major food crops such as rice, maize and wheat. Many co-regulators have been recently identified to function as a component of HAT or HDAC complex in some specific developmental processes. The described findings show a distinctive and interesting epigenetic regulation network composed of HATs, HDACs and co-regulators playing crucial roles in the seed performance, flowering time, plant morphogenesis, plant response to stresses etc. In this review, we summarized the recent progresses and suggested the perspective of histone acetylation research, which might provide us a new window to understand the epigenetic code of plant development and to improve the crop production and quality.

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1. Introduction

In eukaryotes, histone acetylation is a reversible biological process in chromatin and considered as one of the major factors that facilitate the chromatin relaxation and gene transcription regulation (Waterborg, 2011). The acetylation at lysine residues of histones through the action of histone acetyltransferases (HATs) and histone deacetylases (HDACs) is in rapid response to the developmental and environmental clues (Waterborg, 2002). Up to now, many HATs or HDACs have been identified as transcriptional activators or repressors to be involved in a variety of biological processes in plants.

The active HATs have been isolated and partially or fully characterized since the early 1970's. Two types of taxonomy have been adopted. First, by the substrate specificity and intracellular localization, HATs have been grouped into two classes: A-type enzymes (HAT-A), which are localized into nucleus and acetylate the nucleosome core histones; B-type enzymes (HAT-B), which are localized in the cytoplasm with specificity to free histones (Eberharter et al., 1996). Second, on the basis of the sequence

characterization and preliminary experimental data *in silico*, all the plant HATs are divided into four categories: (1) HAG for HATs of the GNAT (GCN5-related N-terminal acetyltransferases) superfamily, (2) HAM for HATs of the MYST superfamily, (3) HAC for HATs of the CREB-binding protein (CBP) family, (4) HAF for HATs of the TATA-binding protein-associated factor (TAF_{II}250) family. In *Arabidopsis*, four (HAG1–HAG3, MMC1), two (HAM1 and HAM2), five (HAC1, HAC2, HAC4, HAC5 and HAC12), and two (HAF1 and HAF2) HAT genes have been identified (Pandey et al., 2002; Perrella et al., 2010).

HDACs can be classified into three families. The first family is homologous to the yeast Reduced Potassium Deficiency 3 (RPD3), which is present throughout eukaryotes and is most widely studied (Hollender and Liu, 2008). The second family, HD-tuins (HDT), is originally determined in maize (Lusser et al., 1997) and appears to be present only in plants (Dangl et al., 2001; Wu et al., 2000). The structurally-distinct third family, sirtuins, is homologous to the yeast Silent Information Regulator 2 (Sir2), which is a nicotinamide adenine dinucleotide (NAD)-dependent enzyme (Frye, 2000). Both HDACs and HATs can function in protein complexes as transcriptional co-repressors and co-activators or associated with chromatin remodelers as modulators of the accessibility of DNA to different machineries.

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Table 1
The genes encoding HATs and HDACs in Arabidopsis, rice, maize and tomato.

HAT or HDAC families	Gene name	Locus	Species	Co-factors	Functional analysis	References
GNAT	HAG1(GCN5)	At3g54610	<i>Arabidopsis thaliana</i>	–	Root and shoot development miRNA production Flower development	Long et al. (2006), Kornet and Scheres (2009) Kim et al. (2009)
	HAG2	At5g56740	<i>A. thaliana</i>	–	Light signaling Low temperature response	Vlachonasios et al. (2003), Long et al. (2006), Kornet and Scheres (2009) Benhamed et al. (2006, 2008) Vlachonasios et al. (2003)
	HAG3	At5g50320	<i>A. thaliana</i>	–	Cell proliferation	Nelissen et al. (2005)
	MCC1	At3g02980	<i>A. thaliana</i>	–	Leaf and flower development, male and female gametes development	Perrella et al. (2010)
	OsHAG702	Os10g0415900	<i>Oryza sativa</i> L.	–	High temperature response and ABA pathway	Liu et al. (2012)
	OsHAG703	Os04g0484900	<i>O. sativa</i> L.	–	High temperature response, High salt stress response and ABA pathway Drought stress response	Liu et al. (2012)
	OsHAG704	Os09g0347800	<i>O. sativa</i> L.	–	Temperature response and ABA pathway	Fang et al. (2014) Liu et al. (2012)
	SIHAG1	–	<i>Solanum lycopersicon</i>	–		
	SIHAG2	–	<i>S. lycopersicon</i>	–		
	SIHAG3	–	<i>S. lycopersicon</i>	–		
	SIHAG4	–	<i>S. lycopersicon</i>	–		
	SIHAG5	–	<i>S. lycopersicon</i>	–		
	SIHAG6	–	<i>S. lycopersicon</i>	–	Reproductive development	Aiese-Cigliano et al. (2013b)
	SIHAG7	–	<i>S. lycopersicon</i>	–		
	SIHAG8	–	<i>S. lycopersicon</i>	–	Vegetative development	Aiese-Cigliano et al. (2013b)
	SIHAG9	–	<i>S. lycopersicon</i>	–		
	SIHAG10	–	<i>S. lycopersicon</i>	–		
	SIHAG11	–	<i>S. lycopersicon</i>	–		
	SIHAG12	–	<i>S. lycopersicon</i>	–		
	SIHAG13	–	<i>S. lycopersicon</i>	–		
	SIHAG14	–	<i>S. lycopersicon</i>	–		
	SIHAG15	–	<i>S. lycopersicon</i>	–		
	SIHAG16	–	<i>S. lycopersicon</i>	–		
	SIHAG17	–	<i>S. lycopersicon</i>	–		
	SIHAG18	–	<i>S. lycopersicon</i>	–	Reproductive development	Aiese-Cigliano et al. (2013b)
	SIHAG19	–	<i>S. lycopersicon</i>	–		
SIHAG20	–	<i>S. lycopersicon</i>	–			
SIHAG21	–	<i>S. lycopersicon</i>	–			
SIHAG22	–	<i>S. lycopersicon</i>	–	Vegetative development	Aiese-Cigliano et al. (2013b)	
SIHAG23	–	<i>S. lycopersicon</i>	–			
SIHAG24	–	<i>S. lycopersicon</i>	–			
SIHAG25	–	<i>S. lycopersicon</i>	–			
SIHAG26	–	<i>S. lycopersicon</i>	–			
MYST	HAM1	AT5G64610	<i>A. thaliana</i>	–	Flowering time regulation and gamete formation	Latrasse et al. (2008), Xiao et al. (2013)
	HAM2	AT5G09740	<i>A. thaliana</i>	–	Flowering time regulation and gamete formation	Latrasse et al. (2008), Xiao et al. (2013)
	OsHAM701	Os07g0626600	<i>O. sativa</i> L.	–	High salt stress response and ABA pathway Drought stress response	Liu et al. (2012) Fang et al. (2014)
CBP	SIHAM1	–	<i>S. lycopersicon</i>	–	Seed and/or fruit development, gametogenesis	Aiese-Cigliano et al. (2013b)
	HAC1	At1g79000	<i>A. thaliana</i>	–	Sugar response Flowering time regulation	Deng et al. (2007), Heisel et al. (2013) Heisel et al. (2013)
	HAC2	At1g67220	<i>A. thaliana</i>	–		
	HAC4	AT1G55970	<i>A. thaliana</i>	–		
	HAC5	At3g12980	<i>A. thaliana</i>	–		
	HAC12	At1g16710	<i>A. thaliana</i>	–		
	OsHAC701	Os01g0246100	<i>O. sativa</i> L.	–	ABA pathway, temperature response, High salt stress	Liu et al. (2012)
	OsHAC703	Os02g0137500	<i>O. sativa</i> L.	–	ABA pathway, low temperature response, High salt stress response and SA pathway Drought stress response	Liu et al. (2012)
	OsHAC704	Os06g0704800	<i>O. sativa</i> L.	–	Temperature response and high salt stress response	Fang et al. (2014) Liu et al. (2012)
	SIHAC1	–	<i>S. lycopersicon</i>	–		Aiese-Cigliano et al. (2013b)
SIHAC2	–	<i>S. lycopersicon</i>	–		Aiese-Cigliano et al. (2013b)	
SIHAC3	–	<i>S. lycopersicon</i>	–		Aiese-Cigliano et al. (2013b)	
SIHAC4	–	<i>S. lycopersicon</i>	–	Fruit development	Aiese-Cigliano et al. (2013b)	
TAF _{II} 250	HAF1	At1g32750	<i>A. thaliana</i>	–		
	HAF2	At3g19040	<i>A. thaliana</i>	HY5	Light signaling	Bertrand et al. (2005)
	OsHAF701	Os06g0645700	<i>O. sativa</i> L.	–	Drought stress response Low temperature response	Fang et al. (2014) Liu et al. (2012)
HAT-A	SIHAF1	–	<i>S. lycopersicon</i>	–	Fruit maturation	Aiese-Cigliano et al. (2013b)
	HAT-A1	–	<i>Zea mays</i>	–	Embryo germination	Georgieva et al. (1991)
	HAT-A2	–	<i>Z. mays</i>	–	Embryo germination	Georgieva et al. (1991)

Table 1 (continued)

HAT or HDAC families	Gene name	Locus	Species	Co-factors	Functional analysis	References	
HAT-B RPD3/HDA1	HAT-B		<i>Z. mays</i>	–	Seed development and germination	Georgieva et al. (1991)	
	HDA2	AT5G26040	<i>A. thaliana</i>	–	–		
	HDA5	AT5G61060	<i>A. thaliana</i>	–	–		
	HDA6	AT5G63110	<i>A. thaliana</i>	HDC1, HDT3 AS1 PRR9, TPL FLD, MSI4, MSI5 JAZ1	Seed development and germination ABA and salt stress response Leaf morphogenesis Circadian regulation Flowering controlling JA signaling Cold stress response and ethylene pathway Light signaling DNA methylation	Perrella et al. (2013), Tanaka et al. (2008) Luo et al. (2012a) Scofield and Murray (2006), Luo et al. (2012b) Wang et al. (2013a) Gu et al. (2011), Wu et al. (2008), Yu et al. (2011) Thines et al. (2007), Zhu et al. (2011) To et al. (2011) Tessadori et al. (2009) Aufsatz et al. (2002)	
	HDA7	AT5G35600	<i>A. thaliana</i>	–	Seed germination, plant growth, female gametophyte development and embryogenesis	Aiese-Cigliano et al. (2013a)	
	HDA8	AT1G08460	<i>A. thaliana</i>	–	–		
	HDA9	AT3G44680	<i>A. thaliana</i>	AGL19	Flowering time	Kim et al. (2013)	
	HDA10	AT3G44660	<i>A. thaliana</i>	–	–		
	HDA14	AT4G33470	<i>A. thaliana</i>	–	–		
	HDA15	AT3G18520	<i>A. thaliana</i>	PIF3	Phytochrome A/B pathway and hypocotyls growth	Liu et al. (2013b)	
	HDA17	AT3G44490	<i>A. thaliana</i>	–	–		
	HDA18	AT5G61070	<i>A. thaliana</i>	–	Root hair development	Liu et al. (2013a)	
	HDA19	AT4G38130	<i>A. thaliana</i>	HSL1, SNL1, HDC1 LEUNIG	Seed development and dormancy Flower development	Perrella et al. (2013), Wang et al. (2013b), Zhou et al. (2013)	
				–	Leaf morphogenesis,	Gonzalez et al. (2007), Tian and Chen (2001), Tian et al. (2003)	
				–	Light signaling and hypocotyls growth	Tian and Chen (2001), Tian et al. (2003, 2005), Zhou et al. (2005), Tanaka et al. (2008)	
				–	High temperature response	Benhamed et al. (2006)	
				WRKY38, WRKY62	Ethylene, JA, SA pathway and basal defense responses	Long et al. (2006) Zhou et al. (2005), Kim et al. (2008), Choi et al. (2012)	
		HDA701	Os01g40400	<i>O. sativa</i> L.	–	–	
		HDA702 (HDAC1)	Os06g38470	<i>O. sativa</i> L.	–	Root growth	Chung et al. (2009)
		HDA703 (HDAC3)	Os02g12350	<i>O. sativa</i> L.	–	Seed development and germination	Hu et al. (2009)
		HDA704	Os07g06980	<i>O. sativa</i> L.	–	Flag leaf morphogenesis	Hu et al. (2009)
		HDA705	Os08g25570	<i>O. sativa</i> L.	–	–	
		HDA706 (HDAC6)	Os06g37420	<i>O. sativa</i> L.	–	–	
		HDA707	Os01g12310	<i>O. sativa</i> L.	–	–	
		HDA709	Os11g09370	<i>O. sativa</i> L.	–	–	
		HDA710 (HDAC2)	Os02g12380	<i>O. sativa</i> L.	–	Seed germination and root growth	Hu et al. (2009)
		HDA711	Os04g33480	<i>O. sativa</i> L.	–	–	
		HDA712	Os05g36920	<i>O. sativa</i> L.	–	–	
		HDA713	Os07g41090	<i>O. sativa</i> L.	–	–	
		HDA714 (HDAC10)	Os12g08220	<i>O. sativa</i> L.	–	–	
		HDA716	Os05g36930	<i>O. sativa</i> L.	–	Seed development and germination	Hu et al. (2009)
		SIHDA1	–	<i>S. lycopersicon</i>	–	Fruit ripening	Aiese-Cigliano et al. (2013b)
		SIHDA2	–	<i>S. lycopersicon</i>	–	Root and flower meristems	Aiese-Cigliano et al. (2013b)
		SIHDA3	–	<i>S. lycopersicon</i>	–	Fruit ripening	Aiese-Cigliano et al. (2013b)
		SIHDA4	–	<i>S. lycopersicon</i>	–	–	
		SIHDA5	–	<i>S. lycopersicon</i>	–	Fruit development	Aiese-Cigliano et al. (2013b)
		SIHDA6	–	<i>S. lycopersicon</i>	–	Fruit development	Aiese-Cigliano et al. (2013b)
		SIHDA7	–	<i>S. lycopersicon</i>	–	Fruit development	Aiese-Cigliano et al. (2013b)
		SIHDA8	–	<i>S. lycopersicon</i>	–	–	
		SIHDA9	–	<i>S. lycopersicon</i>	–	Root development	Aiese-Cigliano et al. (2013b)
		ZmHDA101	–	<i>Z. mays</i>	–	Plant cell cycle and development	Varotto et al. (2003)
		ZmHDA102	–	<i>Z. mays</i>	–	Plant cell cycle and development	Varotto et al. (2003)
		ZmHDA108	–	<i>Z. mays</i>	–	Plant cell cycle and development	Varotto et al., 2003
	HD-tuins	HDT1	AT3G44750	<i>A. thaliana</i>	AS1, AS2	Leaf morphogenesis	Kidner and Martienssen (2004), Ueno et al. (2007)
		HDT2	AT5G22650	<i>A. thaliana</i>	AS1, AS2	Leaf morphogenesis	Kidner and Martienssen (2004), Ueno et al. (2007)
		HDT3	AT5G03740	<i>A. thaliana</i>	HDA6	Seed dormancy ABA pathway, salt stress and seed germination	Yano et al. (2013) Luo et al. (2012a) Colville et al. (2011)
		HDT4	AT2G27840	<i>A. thaliana</i>	–	–	

(continued on next page)

Table 1 (continued)

HAT or HDAC families	Gene name	Locus	Species	Co-factors	Functional analysis	References
	HDT701	Os05g51830	<i>O. sativa</i> L.	–	–	
	HDT702	Os01g68104	<i>O. sativa</i> L.	–	Leaf and stem development	Hu et al. (2009)
	HD1	–	<i>Z. mays</i>	–	Embryo development and germination	Georgieva et al. (1991)
	HD2	–	<i>Z. mays</i>	–	Seed germination	Georgieva et al. (1991)
	SIHD1	–	<i>S. lycopersicon</i>	–	Fruit development	Aiese-Cigliano et al. (2013b)
	SIHD2	–	<i>S. lycopersicon</i>	–	Fruit development	Aiese-Cigliano et al. (2013b)
	SIHD3	–	<i>S. lycopersicon</i>	–	Fruit development	Aiese-Cigliano et al. (2013b)
Sirtuin	SRT1	AT5G55760	<i>A. thaliana</i>	–	–	
	SRT2	AT5G09230	<i>A. thaliana</i>	–	Basal defense to pathogen mitochondrial energy metabolism	Wang et al. (2010) König et al. (2014)
	SRT701	Os04g20270	<i>O. sativa</i> L.	–	–	
	SRT702	Os12g07950	<i>O. sativa</i> L.	–	–	
	SISRT1	–	<i>S. lycopersicon</i>	–	Early stage of fruit development	Aiese-Cigliano et al. (2013b)
	SISRT2	–	<i>S. lycopersicon</i>	–	Flowering regulation, fruit ripening and gametogenesis	Aiese-Cigliano et al. (2013b)

The diversity of structure and function within HAT or HDAC superfamilies have been discussed in detail for Arabidopsis by Hollender and Liu (2008), for rice by Liu et al. (2012) and Hu et al. (2009), and for tomato (*Solanum lycopersicon*) by Aiese-Cigliano et al. (2013b). However, the recent studies have shown that reversible and rapid changes in histone acetylation play an essential role in seed development such as seed maturation, seed dormancy (Wang et al., 2013b; Zhou et al., 2013). Therefore, our review will highlight the new discoveries on the roles of histone acetylation in seed performance and some important plant developmental events.

2. HATs and HDACs in seed development, dormancy and germination

Many HATs and HDACs have been identified from Arabidopsis, rice, tomato and maize (Table 1), most of which are involved in many plant developmental processes including seed development. It is not shown that HATs play key roles in the seed performance until now. Whereas, most of HATs in rice show a low level expression in imbibed seeds and significantly increased expression in response to abscisic acid (ABA), indicating the possible roles in seed germination (Liu et al., 2012). In *Zea mays*, it was showed that the extensive DNA repair in the initial stage of seed germination is dependent on the chromatin structure remodeling mediated by HAT-B, indicating the possibility of the involvement of HAT-B in seed germination (Georgieva et al., 1991). Furthermore, the latter work showed that HAT-B predominantly acetylates histone H4 up to the diacetylated form (Lusser et al., 1999), so as to regulate gene transcription. But, the particular target genes and co-factors of the HATs in *Z. mays* are still poor understood.

GeneChip arrays showed that trichostatin A (TSA), an inhibitor of HDACs, can activate or repress the expression of many genes during seed germination, thereby indicating that histone acetylation is a key developmental signal in germinating process (Tai et al., 2005). Among the RPD3-like HDACs in Arabidopsis, AtHDA19 and AtHDA6 are best characterized and exhibit divergent and overlapping functions in seed development and seed performance. Depending on the analysis of loss-of-function or gain-of-function transgenic lines, HDA19 was identified as a global regulator of gene transcription in response to development and stress signals (Tian and Chen, 2001; Tian et al., 2003, 2005; Zhou et al., 2005). Some experiments evidenced a redundant role of HDA19 and HDA6 in the repression of embryonic program and embryogenesis-

related genes such as *LEAFY COTYLEDON1 (LEC1)* and *FUSCA3 (FUS3)* (Tanaka et al., 2008). Based on the embryonic lethality of double mutant, the Zhou et al. (2013) reported that HDA19 recruits HSI2-LIKE 1 (HSL1) to inhibit seed maturation gene expression during germination and suggested that HDA19 and HSL1 likely play a crucial role during embryogenesis. The work in our group showed that *hda19-1* (Ws) and *hda19-2* (Ler) display significantly decreased seed dormancy. HDA19 can interact to SIN3-Like 1 (SNL1) to promote seed dormancy by regulating the antagonistic pathways between ABA and ethylene. The double mutant *snl1 snl2* shows distinctly reduced seed dormancy and sensitivity of seed germination to exogenous ABA (Wang et al., 2013b). Moreover, a scaffolding protein, histone deacetylation complex1 (HDC1) that interacts with HDA6 and HDA19, improves seed germination as well as plant growth under stress or ABA and paclobutrazol (PAC) treatments in HDC1-overexpressing plants (Perrella et al., 2013). Silencing of *AtHDA7* also exhibited a significant reduction in seed germination compared with the wild-type (Aiese-Cigliano et al., 2013a). These works show that histone deacetylation mediated by HDA19, HDA6 and HDA7 is involved in seed maturation, dormancy and germination. It also indicated that HDA6 and HDA19 may interact with variant co-factors within multi-functional complexes to play diverse functions during the seed performance (Fig. 1).

For the type II HDACs (HDTs), silencing of *HDT1* expression resulted in aborted seed development in transgenic Arabidopsis plants, suggesting that *HDT1* gene is important in seed development (Wu et al., 2000). A recent report showed that loss-of-function mutant of *HDT3* displayed increased sensitivity of seed germination to ABA and NaCl. *HDT3* interacts with HDA6 to regulate gene expression through histone modifications in response to ABA and salt stress, similarly to HDC1 (Luo et al., 2012a; Perrella et al., 2013). The phenotypic data of mutants suggest that *HDT1* and *HDT3* may have opposing functions in seed germination with the glucose/*HDT1* pathway limiting germination and the *HDT3* pathway promoting germination (Colville et al., 2011). The work combining association mapping and transcriptomics identified *HDT2/HD2B* as a genetic factor associated with seed dormancy in Arabidopsis. The seeds of transgenic Cvi-0 lines carrying a 2.5 kb genomic DNA fragment of *HDT2* cloned from less-dormant Col-0 accession exhibited reduced seed dormancy accompanied by enhanced expression of *HDT2*, suggesting that suppression of *HDT2* expression may be important to maintain seed dormancy in dormant accessions (Yano et al., 2013). In a word, the HDTs play overlapping and different roles in seed formation and germination

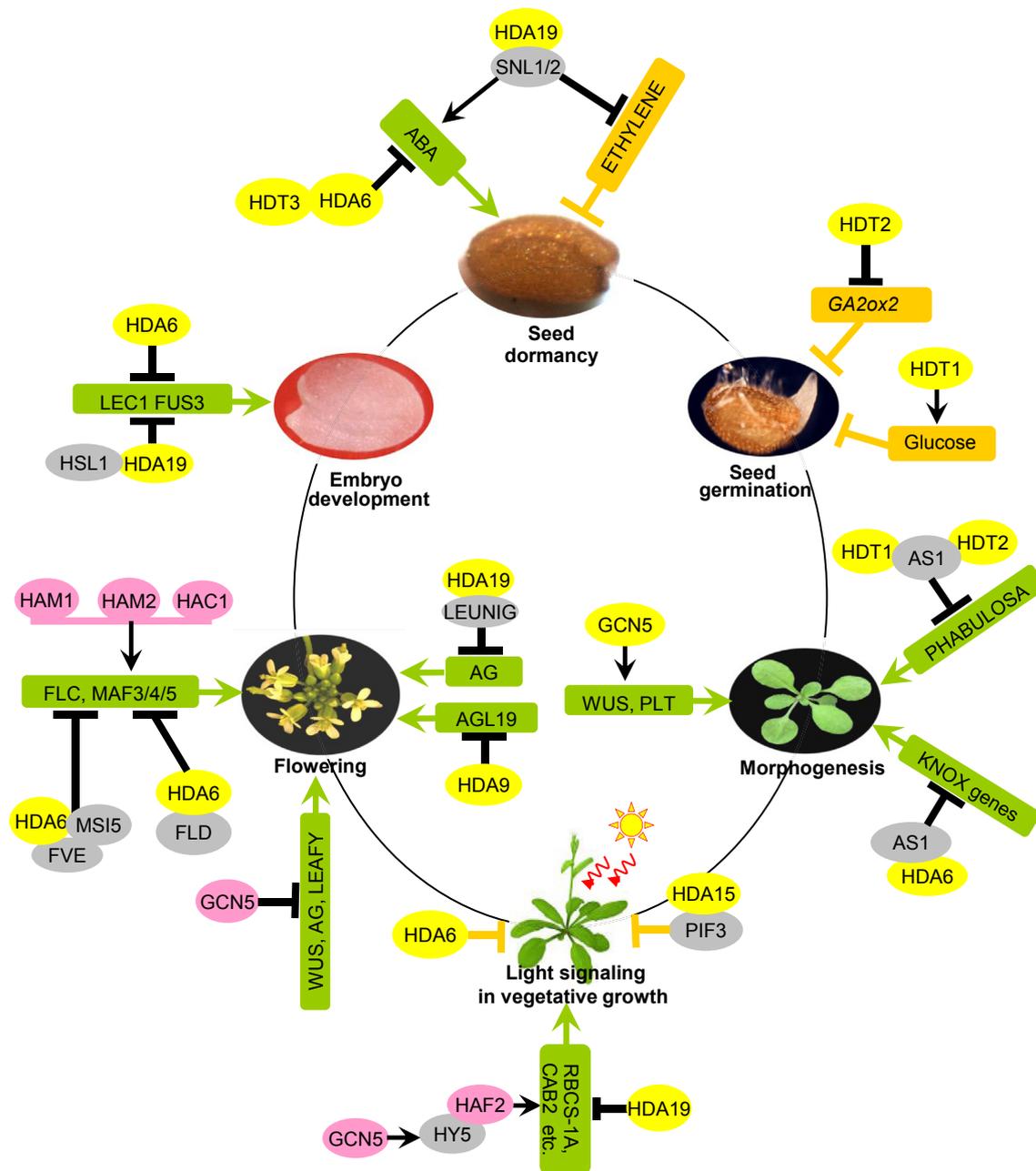


Fig. 1. The model of HATs and HDACs being involved in the Arabidopsis seed performance and development associated with related co-regulators. All the histone acetyltransferases are showed in pink oval, and histone deacetylases are in yellow oval; the gray oval indicated the co-regulators. The green boxes and arrows indicated the positive pathways or regulators associated with related development stages. The light yellow boxes and stop lines indicated the negative pathways or regulators associated with related development stages.

in Arabidopsis. So far, few specific co-regulators of HDTs have been identified in plant.

In rice, 19 HDACs have been identified. By microarray analysis, *HDA716* was found to show a strong expression in developing endosperm and germinating seeds, *HDA710* and *HDA703* displayed higher expression in imbibed and germinating seeds, indicating the possible functions during seed development and germination. Plants with down-regulation of *HDA703* by artificial micro RNA (*amiRNA*) displayed partial or complete sterility and awn seeds related to increased acetylation level of histone H4, suggesting that *HDA703* plays a role in plant seed development and morphology through histone H4 modification (Hu et al., 2009). In *Z. mays*, it was showed that the enzymatic activity of histone deacetylase HD1 is

low in the dry embryo and increases during germination, whereas, HD2 is the predominant enzyme in the dry embryo, and almost disappears at later germination (Georgieva et al., 1991). Furthermore, three Rpd3-type histone deacetylases encoding genes (*ZmHDA101*, *ZmHDA102*, and *ZmHDA108*) were found to have similar expression profiles with higher accumulation in endosperm (Varotto et al., 2003). All these indicate the potential functions of HDACs in seed development and germination of maize.

3. HATs and HDACs in vegetative development and growth

Vegetative development including leaf morphology, root and shoot meristems growth, are tightly linked to histone acetylation

modification. HAG1/AtGCN5, the most widely studied histone acetyltransferase, plays an essential role in many plant development processes, such as meristem function, cell differentiation, leaf and floral organogenesis (Servet et al., 2010). AtGCN5 is necessary for the transformation of apical half into a root. The *gcn5* mutants can suppress the phenotype of *topless-1* (*tpl-1*) that switches the identity of the shoot into that of a root (Long et al., 2006). WUSCHEL (WUS), a key factor in regulating the stem cell fate in the shoot meristem, accumulated mRNA normally in *tpl-1* globular-stage embryo, but not in heart-stage embryo. Mutation of AtGCN5 in the *tpl-1* background restored the expression of WUS to normal level, thereby resuming proper differentiation of the shoot (Long et al., 2006). AtGCN5 is also required for root meristem development. Mutants of AtGCN5 show defects in root quiescent center specification and root meristem differentiation. AtGCN5 increases the expression levels of root stem cell transcription factors PLETHORA (PLT1 and PLT2), indicating that AtGCN5 also plays important role for root stem cell niche maintenance through regulating the PLT pathway (Kornet and Scheres, 2009). MEIOTIC CONTROL OF CROSSOVERS1 (MCC1), a GCN5-related histone N-acetyltransferase, may also play a role in Arabidopsis vegetative development. Analysis of *mcc1* mutant obtained by enhancer activation tagging revealed that over-expression of MCC1 caused several visible vegetative phenotypes including narrower and elongated rosette leaves, faster stem elongation and earlier flowering than wild type (Barra et al., 2012; Perrella et al., 2010). The AtHAG3 is one of the subunits of histone acetyltransferase elongator complex which is required for the process of RNA polymerase II (RNAP_{II})-mediated transcription and responsible for the phenotype of *elongata3* (*elo3*) mutant-narrow leaves and reduced root growth. Whereas, it is not clear how HAG3 stimulates cell proliferation to influence leaf and root growth (Nelissen et al., 2005). Impairment in AtHAC1 also causes shortened primary root. The defects in sugar response and fertility of *hac1* mutants may be partially explained by reduced expression of Arabidopsis *Phaseolus vulgaris42a* (PV42a) and PV42b, encoding two putative components of SNF1-RELATED PROTEIN KINASE1 (SnRK1) complexes, which have been shown to function as central regulators of plant nutrient and energy status (Deng et al., 2007; Heisel et al., 2013). HAC1 being involved in sugar response provides a possibility that nutritional status exert successive effects via epigenetic regulation on plant development and growth.

The loss-of-function *hda19* lines also displayed some defects in vegetative development including shorter plant, asymmetrical development of the first two leaves, and aberrant leaves (Tian and Chen, 2001; Tian et al., 2003, 2005). However, the underlying mechanism is not clear so far. HDA6 interacts with ASYMMETRIC LEAVES 1 (AS1) to regulate the key *KNOTTED-LIKE HOMEODOMAIN* (*KNOX*) genes transcription in the shoot apex (Luo et al., 2012b; Scofield and Murray, 2006). By chromatin immunoprecipitation (ChIP), it was showed that HDA6 and AS1 bind directly to the chromatin of *KNOX* genes, *KNAT1*, *KNAT2*, and *KNATM*. Taken together, these data indicated that HDA6 and AS1 together form an HDAC repressor complex involved in the regulation of *KNOX* expression and leaf development (Fig. 1). Interestingly, the over-expression and silencing of *HDA7* all showed a significant retardation of plant growth rate, although the underlying mechanism is unclear (Aiese-Cigliano et al., 2013a). Additionally, loss-of-function mutants of *HDA18* displayed higher root hair density in the seedlings by influencing the level of acetylation at H3K9, H3K14 and H3K18 of four kinase genes (Liu et al., 2013a). Experimental data suggested that HDT1 and HDT2 can interact with AS1 or AS2 to influence the generation or distribution of *miRNA 165/166*, which targets the *PHABULOSA* (*PHB*) transcripts (Kidner and Martienssen, 2004), afterward regulating leaf polarity determination (Ueno et al.,

2007). So, it is possible that HDA6, HDT1 and HDT2 are involved in the AS1/2 pathway to regulate leaf morphogenesis.

For sirtuin proteins, a recent report indicated that Arabidopsis SRT2 locates in the mitochondrial inner membrane and is involved in energy metabolism and transport (König et al., 2014). In *srt2* mutants, the alteration of metabolite levels such as sugars, amino acids, and ADP contents were observed, some metabolism related genes such as encoding proteins of the ATP synthase and the ATP/ADP carriers showed an increased acetylation level at histone lysine. These results indicate that SRT2 is an important factor in fine-tuning mitochondrial energy metabolism (König et al., 2014).

In rice, HDA702, HDA710 and HDA703 belong to the same clade as AtHDA19 (Fu et al., 2007). Unlike *HDA703* which plays role in the seed development, repression of its close homologue *HDA710* by RNA interference (RNAi) affected vegetative growth (Hu et al., 2009). Over-expression of *OsHDA702* leads to increased growth rate and altered architecture through epigenetically regulating the OsNAC6 which controls seedling root growth (Chung et al., 2009). In addition, the root growth was affected in *HDA702* T-DNA insertion heterozygous lines, but homozygote failed to be obtained, suggesting that the gene may be essential for plant growth (Hu et al., 2009). The parallel expression pattern and phenotypes of *HDA702* and *HDA710* suggest that both genes may play a similar role in root and vegetative growth. Moreover, down-regulation of rice *HDT702* led to the production of narrowed leaves and stems. *HDA704* RNAi altered plant height and flag leaf morphology (Hu et al., 2009). These data suggest that rice HDAC genes may have divergent developmental functions compared with closely related homologues in Arabidopsis.

4. HATs and HDACs in flower development

Flowering is vital for the plant to complete life cycle and reproduce offspring. A lot of histone acetylation factors are identified to be involved in flowering time determination, flower organ development and growth. The loss-of-function of AtGCN5 displayed short petals and stamens, defects in floral organ identity (Vlachonasios et al., 2003). Some key floral meristem regulatory genes *WUS*, *AGAMOUS* (*AG*) and *LEAFY* were up-regulated in the *gcn5* mutants, indicating that AtGCN5 repress the expression of floral meristem related genes in flowering (Long et al., 2006; Kornet and Scheres, 2009; Vlachonasios et al., 2003). The meiotic defects in *MCC1* over-expression mutant led to abortion in about half of the male and female gametes due to histone hyperacetylation (Perrella et al., 2010). In the Arabidopsis MYST superfamily, HAM1 and HAM2 likely affect flowering time through regulating *FLOWERING LOCUS C* (*FLC*) and *MADS AFFECTING FLOWERING 3/4* (*MAF3/4*) expression mediated by histone acetylation. By ChIP, it was found that global H4 hyperacetylation and H4K5ac at *FLC* and *MAF3/4* were decreased in *amiRNA-HAM1/2* lines, but enriched in *HAM1*-OE lines as compared to the wild type (Xiao et al., 2013). Furthermore, both HAM1 and HAM2 play essential roles in gametogenesis redundantly by genetic and cytological analysis (Latrasse et al., 2008). In *S. lycopersicon*, the SIHAM1 was shown the highest expression in flowers, indicating the similar role with AtHAM1/2 in flowering regulation (Aiese-Cigliano et al., 2013b). AtHAC1 is involved in the regulation of flowering time via repression of *FLC*. Lesions in AtHAC1 caused delayed flowering (Deng et al., 2007). The recent data showed that the mutation of HAC1 also resulted in decreased expression of *AtPV42a* and *AtPV42b*, which play redundant roles in regulating male gametogenesis (Heisel et al., 2013). So, the flowering regulation is generally tightly associated with gametogenesis regulation through histone acetylation in plant.

A variety of flower developmental aberrations were observed in the loss-of-function *hda19* lines including abnormal flowers,

reduced female fertility, and smaller siliques (Tian and Chen, 2001; Tian et al., 2005; Zhou et al., 2005). HDA19 interacts with the LEUNIG/SEUSS co-repressor complex involved in the suppression of carpel and stamen identity by repressing AG expression (Gonzalez et al., 2007). The similar floral phenotype was observed in loss-of-function *leunig* mutant (Tian and Chen, 2001; Tian et al., 2003). HDA6 also displayed important role in the flowering time control (Wu et al., 2008). Experimental data showed that HDA6 likely directly interact with the histone demethylase FLOWERING LOCUS D (FLD). In both *hda6* and *fld* mutants, it is observed the increased levels of histone H3 acetylation and H3K4 trimethylation (H3K4me3) at some key repressors of flowering such as *FLC*, *MAF4*, and *MAF5*, suggesting functional interaction between histone deacetylase and demethylase in flowering control (Jiang et al., 2007; Yu et al., 2011). Additionally, HDA6 was also found to associate with MULTICOPY SUPPRESSOR OF IRA1 4 (MSI4) and MSI5, two Arabidopsis homologues of the human histone-binding proteins Retinoblastoma-Associated Protein 46/48 (RbAp46/48), to form complexes involved in flowering time control (Gu et al., 2011). Furthermore, HDA9 was shown to regulate flowering time by repressing AGAMOUS-LIKE 19 (AGL19), which promotes flowering through a way independent of the FLC pathway (Kim et al., 2013). In tomato, the higher expression of *SISRT2* in flower indicated that *SISRT2* could play a role in flower development (Aiese-Cigliano et al., 2013b). These results indicate that histone acetyltransferases and deacetylases play diverse roles in the flower organ formation and flowering time control, and some of which function together through the FLC pathway (Fig. 1).

5. HATs and HDACs in plant response to abiotic and biotic conditions

Light specifically increases the acetylation level of histone H4K5 and H3K9 in the promoter and the transcribed region of the maize C(4)-Pepc gene (Offermann et al., 2008), indicating that histone acetylation may play an important role in light-responsive gene activation in plants. In Arabidopsis, Mutation of AtGCN5 resulted in long-hypocotyl phenotype under a far-red light condition and decreased light-inducible gene expression. Genetic analysis showed that AtGCN5 is epistatic to ELONGATED HYPOCOTYL 5 (HY5), the positive regulator of the Phytochrome A (PHYA)-mediated inhibition of hypocotyl elongation (Benhamed et al., 2006). Furthermore, the histone acetyltransferase HAF2 (TAF1) is shown to integrate light signal and acetylating histone to activate light-responsive gene expression by interacting with HY5 (Bertrand et al., 2005). The *haf2-1* can enhance the long hypocotyl phenotype of *elongated hypocotyl 4-1 (hy4-1)* but not *hy1-1* in white light, suggesting that HAF2 may also function in the phytochrome pathways by histone modification. Moreover, the *gcn5 taf1* double mutant shows a further decrease of light-regulated gene expression and a cumulative reduction of H3K9 acetylation (Benhamed et al., 2006; Bertrand et al., 2005). These evidences indicate that both AtGCN5 and HAF2 function in HY5 pathway to regulate light-responsive genes expression in plant development (Benhamed et al., 2008), but they play different roles in response to various light wavelength.

As regards HDACs, loss-of-function mutants of HDA15 showed increased proto-chlorophyllide contents similar to *phytochrome interacting factor 3 (pif3)* (Liu et al., 2013b). In addition, PIF3 recruited HDA15 to the promoters of the light responsive genes (i.e. *GUN5*, *LHCB2.2*, *PSBQ*, and *PSAE1*) and repressed their expression by histone deacetylation. Moreover, longer hypocotyl was observed in *hda15* mutant seedlings under red light and far-red light conditions, indicating that HDA15 might positively regulate PHYA and PHYB-mediated inhibition of hypocotyl elongation. On the contrary, the

mutant of *AtHDA19* showed a shorter hypocotyl phenotype and increased expression of light-responsive genes (Benhamed et al., 2006). Genetic analysis showed that HDA15 and HDA19 may act antagonistically in the regulation of hypocotyl growth (Liu et al., 2013b). Moreover, the double mutant *gcn5 athd1/hda19* resumed the normal photomorphogenic phenotype and expression levels of light-inducible genes. CHIP data revealed that AtGCN5 and HDA19 acetylate and deacetylate histones in the promoter of same genes *CHLOROPHYLL A/B-BINDING PROTEIN 2 (CAB2)*, *RIBULOSE BISPHOSPHATE CARBOXYLASE SMALL CHAIN 1A (RBCS1A)* and *INDOLE-3-ACETIC ACID INDUCIBLE 3 (IAA3)* (Benhamed et al., 2006). Combination of a quantitative trait locus (QTL) analysis and microscopic assay showed that HDA6 and PHYB are involved in the regulation of light-controlled chromatin compaction positively. The *hda6* mutant display decondensed chromatin and decreased methylation levels of DNA and histone H3K9 at the Nucleolar Organizing Regions (NORs) (Tessadori et al., 2009). So, HDA6 is involved in nucleolar dominance (Earley et al., 2006). In addition, in the circadian period regulation, Wang et al. (2013a) showed that PRR9 and TPL form a complex with HDA6, acting as a central repressor of circadian gene expression. Therefore, AtGCN5 and AtHDA19 are likely to be a HAT/HDAC couple operating on light-responsive genes to involve in the photomorphogenesis, which is different to the HDA6 involved in the rRNA expression, NORs activity and circadian period regulation (Servet et al., 2010; Wang et al., 2013a).

Histone acetylation is involved in the temperature regulation of plant development. Mutation of AtGCN5 reduced the expression of cold-inducible genes (Vlachonasis et al., 2003). *hda19-1* also displayed temperature-sensitive phenotype, which developed disorganized root and shoot meristems to form pin or tubular or single cotyledon at a high temperature (29 °C) but not at room temperature (25 °C) (Long et al., 2006). Interestingly, HDA6 regulates the expression of several cold stress induced genes and plays a role in response to freezing stress. After cold-acclimation, *hda6* mutant plants showed a freezing-sensitive phenotype compared with wild type plants (To et al., 2011). This suggested that the plant cold acclimation process is regulated by HDA6-mediated chromatin remodeling. HOS15, a WD40-repeat protein, is crucial for repression of genes associated with cold tolerance through histone deacetylation in Arabidopsis (Zhu et al., 2008). The *hos15* plants are specifically hypersensitive to freezing treatment, thereby indicating HOS15 as a co-factor in the histone deacetylation complex that likely determines the selective function of the complex.

The involvement of histone acetylation in plant responses to other abiotic and biotic stresses has been documented. HDT3/HD2C associates with HDA6 to regulate gene expression in response to ABA and salt stress (Luo et al., 2012a). Compared with wild-type plants, *hd2c-1* and *hd2c-3* plants displayed increased sensitivity to NaCl during germination and decreased tolerance to salt stress. The studies on the *srt2* mutant and *SRT2*-overexpression lines have showed that *SRT2* may be a negative regulator of basal defense to pathogen *Pseudomonas syringae* pv. tomato DC3000 (*PstDC3000*) through repressing salicylic acid (SA) biosynthesis (Wang et al., 2010). Plants overexpressing HDA19 displayed increased expression of ETHYLENE RESPONSE FACTOR1 (ERF1) and PATHOGENESIS RELATED (PR) genes, and further enhanced resistance to pathogen *Alternaria brassicicola*. Consistently, HDA19-RNAi plants showed opposite phenotypes and reduced expressions of corresponding downstream genes (Zhou et al., 2005). Recently, Choi's (2012) work showed that loss of HDA19 activity increased SA content and increased the expression of a group of genes required for accumulation of SA as well as PR genes, resulting in enhanced resistance to *P. syringae*. Furthermore, HDA19 can interact with two WRKY transcription factors WRKY38 and WRKY62, two negative regulators of plant basal defense (Kim et al., 2008). Both WRKY38 and

WRKY62 are transcriptional activators in plant cells, but their activation activities are abolished by overexpressed HDA19. Interaction of WRKY38 and WRKY62 with HDA19 may act to fine-tune plant basal defense responses (Kim et al., 2008). Obviously, HDA19 might play a very complicate role as a positive or negative regulator in pathogen resistance depending on its partners. In addition to HDA19, HDA6 can be induced by jasmonic acid (JA) too. JASMONATE ZIM-DOMAIN 1 (JAZ1), a key regulator of JA signaling, interacts with COI1 in the presence of jasmonoylisoleucine (JA-Ile) conjugate (Thines et al., 2007). A recent study has shown that JAZ1 recruits HDA6 to repress ETHYLENE INSENSITIVE 3 (EIN3)/EIN3-LIKE 1 (EIL1)-dependent transcription, afterward, inhibits JA signaling by chromatin organization and plasticity (Zhu et al., 2011). These data suggest that both HDA19 and HDA6 are involved in the resistance response to abiotic and biotic stresses via JA, SA and/or ethylene signaling pathways.

In rice, although the evidence of stress tolerance involvement for histone acetylation has not been found, four HATs (*OsHAC703*, *OsHAG703*, *OsHAF701* and *OsHAM701*) are induced significantly by drought stress (Fang et al., 2014). The expression of some HDACs genes are also regulated by stress-related hormones such as SA, JA or ABA in rice plants (Fu et al., 2007; Hu et al., 2009), indicating the potential roles of the HATs and HDACs in response to various abiotic and biotic stresses in rice development.

6. Conclusions

Histone acetylation homeostasis regulated by different histone complexes associated with HATs and HDACs (e.g. GCN5, HDA6 and HDA19) play crucial roles during the seed performance, plant development and/or response to biotic and abiotic stresses (Fig. 1 and Table 1). Individual HAT or HDAC frequently execute their functions through combining to various co-factors such as SIN3-Like, HDC1, AS1. HATs or HDACs are the core components in the complex, since the loss of function mutants of HATs or HDACs such as HDA19 or GCN5 cause pleiotropic developmental defects in plant (Fig. 1 and Table 1), and co-factor SNLs or AS1 mutation result in relatively specific effects on seed dormancy or leaf development. Therefore, the HATs or HDACs may be universal and essential components, and diverse co-regulators determine the function specificity of individual histone (de)acetylation complexes. A big challenge in investigating how and why the acetylation or deacetylation complexes based on the co-factors act in some specific plant development process has appeared. Moreover, gene transcription regulation mediated by HAT or HDAC might be the final step of the developmental signals or environmental signals, so far little is known about how the signals are transferred to HATs or HDACs. The work in our group showed that the SNLs are induced by ABA and are involved in the regulation of seed dormancy by histone deacetylation (Wang et al., 2013b), implying that plant hormones may be signaling to the correlative histone (de)acetylation complexes to activate or repress the histone acetylation regulation in plant development. The recent progress about the interaction between histone acetylation and other chromatin modifications such as histone and DNA methylation, miRNA pathway and histone phosphorylation (Aufsatz et al., 2002; Edmondson et al., 2002; Kim et al., 2009; Soppe et al., 2002; Williams et al., 2008; Zhou et al., 2013) also showed the complicated epigenetic regulation in plant and provided us a line to explore the regulation network of epigenetic modifications in the future.

Author contributions

In this review, Z. W. and Y-X L. wrote the manuscript, H. C. and F-Y. C. provided suggestions for the manuscript.

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