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Chromatin remodeling in plant development

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ABSTRACT Plant development results from specific patterns of gene expression that are tightly regulated in a spatio-temporal manner. Chromatin remodeling plays a central role in establishing these expression patterns and maintaining epigenetic transcriptional states through successive rounds of mitosis that take place within a cell lineage. Plant epigenetic switches occur not only at the embryo stage, but also during postembryonic developmental transitions, suggesting that chromatin remodeling activities in plants can provide a higher degree of regulatory flexibility which probably underlies their developmental plasticity. Here, we highlight recent progress in the understanding of plant chromatin dynamic organization, facilitating the activation or repression of specific sets of genes involved in different developmental programs and integrating them with the response to environmental signals. Chromatin conformation controls gene expression both in actively dividing undifferentiated cells and in those already fate-determined. In this context, we first describe chromatin reorganization activities required to maintain meristem function stable through DNA replication and cell division. Organ initiation at the apex, with emphasis on reproductive development, is next discussed to uncover the chromatin events involved in the establishment and maintenance of expression patterns associated with differentiating cells; this is illustrated with the complex epigenetic regulation of the *Arabidopsis* floral repressor *FLOWERING LOCUS C (FLC)*. Finally, we discuss the involvement of chromatin remodeling in plant responses to environmental cues and to different types of stress conditions.

KEY WORDS: *chromatin, Arabidopsis, epigenetics, histone modification*

Introduction

The embryonic development of plants defines the apical-basal axis of the seedling and establishes pools of stem cells that constitute the shoot and root meristems (SAM and RAM respectively), but the development of leaves, stems and flower meristems takes place sequentially during postembryonic stages of plant development. A dynamic balance between cell division and organ initiation in the flanks of the meristems provides the basis for the continuous organogenesis that characterizes plant development. A group of undifferentiated cells is maintained in the centre of each meristem throughout the entire life of the plant, while cells in the periphery give rise to growing primordia that progressively acquire the lateral organ identity. During their life cycle, plants undergo several developmental phases characterized by different types of growing primordia that give rise to particular organs with specific patterns of cell differentiation. The timing of the transition between developmental phases is controlled by a combination of endogenous and environmental signals, generating the characteristic plasticity of plant development that allows plant species to optimize their adaptation to the environment.

As in other multicellular organisms, developmental processes in plants result from specific patterns of gene expression that need to be tightly regulated in a spatial and temporal manner. Chromatin remodeling plays a central role in establishing these

Abbreviations used in this paper: HAT, histone acetyl transferase; HDAC, histone deacetylase; PAF, polymerase associated factor; PcG, Polycomb group; PRC, polycomb repressive complex; PRE, polycomb responsive element; RAM, root apical meristem; SAM, shoot apical meristem; TRE, trithorax responsive element; TrxG, trithorax group; VRE, vernalization response element.

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expression patterns and maintaining epigenetic transcriptional states through the successive rounds of mitosis that take place within a cell lineage (Reyes, 2006; Exner and Hennig, 2008). In contrast to animals where epigenetic states are established early during embryonic development, in plants, epigenetic mechanisms also operate during post-embryonic developmental transitions such as organogenesis and flowering (Henderson and Jacobsen, 2007). This suggests that chromatin remodeling activities in plants provide a higher degree of flexibility that probably underlies their developmental plasticity.

From a developmental perspective, chromatin organization participates in the control of gene expression patterns both in actively dividing undifferentiated cells and in differentiated cells. Meristems maintain stem cells, proliferating cells and differentiating cells that are progressively fate-restricted. In proliferating cells, meristem-specific gene expression needs to be maintained through mitosis and therefore conserved throughout DNA replication. Similarly, differentiating cells require maintaining stable repression of meristem genes and expression of transcriptional programs responsible for organ identity (Guyomarc´h *et al.,* 2005; Köhler and Villar, 2008). At the same time, all cells need to be able to transcriptionally respond to specific environmental cues, either periodic such as light-dark cycles or random as stress conditions. Plant chromatin must display a very dynamic organization to activate or repress specific sets of genes involved in different developmental responses, allowing the integration of developmental programs with the response to environmental signals.

Nucleosomes are the basic structural units of chromatin in eukaryotic cells. Each nucleosome is composed of two turns of DNA wound around a histone octamer containing two H2A-H2B dimers and one H3-H4 tetramer, and is connected to the next nucleosome by linker DNA. The nucleosome chains can be packaged into more condensed chromatin fibre structures, often found in transcriptionally inactive chromosomal regions. Proteins participating in chromatin remodeling fall in three major classes: histone chaperones, DNA and histone modification enzymes and ATP-dependent chromatin remodeling enzymes.

Histone chaperones prevent misfolding and aggregation of histones, facilitating their interaction with other molecules (Loyola and Almouzni, 2004; Ramirez-Parra and Gutierrez, 2007). They are often associated with other chromatin modifiers and with the DNA replication machinery, participating in chromatin remodeling processes and nucleosome deposition.

Both DNA and histones can be covalently modified in chromatin (Vaillant and Paszkowski, 2007). DNA methylation has been classically associated to gene silencing in inherited epigenetic events, and heterochromatin and transposons are heavily methylated (Hsieh and Fischer, 2005; Zhang *et al.,* 2006). Covalent modifications of specific residues in the N-terminal tails of the core histones such as acetylation, phosphorylation, methylation and ubiquitination affect nucleosome positioning and compaction, playing important roles in gene regulation (Kouzarides, 2007). The spectrum of histone modifications at a given locus is often referred to as the histone code, because the specific combination of modifications is thought to create a unique state of gene transcriptional activity (Strahl and Allis, 2000; Jenuwein and Allis, 2001; Pfluger and Wagner, 2007). Several histone acetyltransferases (HATs) are associated with transcription coactivators whereas histone deacetylases (HDACs) are often components of corepressor complexes in yeast and animal cells, indicating that histone acetylation is an integral part of transcriptional regulatory systems (Lee and Workman, 2007). Consistent with these findings hyperacetylation of histones is associated with transcriptional activation, whereas hypoacetylation of histones induces inactive chromatin conformations and gene repression (Carroza *et al.,* 2003). Similarly, trimethylation of H3K4 (H3K4me3) and H3K36me3 are hallmarks of active genes (Rando, 2007; Xu *et al.,* 2008) whereas H3K9me3 and H3K27me3 are present in repressed regions of chromatin (Ringrose and Paro, 2007). These latter modifications can lead to mitotically stable repressed states of target genes through the recruitment of repressor complexes that may establish autoregulatory loops that propagate the silenced state throughout rounds of DNA replication (Pien and Grossniklaus, 2007). Moreover, several proteins and functional domains involved in recognition and translation of the histone code into patterns of gene expression have been recently identified, and this is likely to be an area of active research in the near future (Becker, 2006; Mellor, 2006).

In addition, ATP-dependent chromatin-remodeling enzymes can modify the interactions between the DNA and the histone octamer, destabilizing nucleosome structure and allowing the transcriptional machinery to access the DNA (Smith and Peterson, 2005; Kwon and Wagner, 2007; van Vugt *et al.,* 2007). Finally, recent findings indicate the relevance of the spatial distribution of genes within the nucleus in their transcriptional control (Sexton *et al.,* 2007; Singh *et al.,* 2008). The topology of the chromatin where a particular gene is located could determine its proper expression in the context of a developmental program, revealing a mechanistic link between gene position, and gene expression (Sexton *et al.,* 2007). The combined action of all these mechanisms modulates the structural dynamics of chromatin and defines the transcriptional state on target loci.

In this review, we highlight recent progress made in the understanding of the role of chromatin modification in plant development, using Arabidopsis as a model species. Plant developmental processes are considered in the context of cell proliferation and differentiation. Developmental processes at the meristem are first considered as they involve chromatin events that need to be stable through DNA replication and cell division. Organ differentiation at different stages of development will be then discussed to review the available information on chromatin events involved in establishment and maintenance of expression patterns associated to differentiated cells. These will be illustrated in depth with recent progress concerning the regulation of the Arabidopsis floral repressor *FLC*. Finally, we will describe the current information on the involvement of chromatin remodeling in the response to environmental cues such as light and temperature and to different types of abiotic stress.

Chromatin modification events required to establish and maintain proper meristem activity

The SAM and RAM are responsible for the continuous growth and development of the aerial and underground structures of the plant. Both meristems contain groups of pluripotent stem cells (Verdeil *et al.,* 2007). In the SAM, stem cells are located in the central region of the meristem and pluripotency is maintained by signals generated by cells of the so-called *organizing centre*, that

TABLE 1

GENES CITED IN THE TEXT AS INVOLVED IN CHROMATIN REMODELLING

Gene	Homology and function	References
ADA2a, ADA2b	TRANSCRIPTIONAL ADAPTOR 2a and 2b; coactivator proteins that interact with GCN5; involved in the stimulation of cold-regulated gene expression by CBF1	Stockinger et al., 2001; Vlachonasios et al., 2003
AtBRM	AtBRAHMA; SWI/SNF (SWITCH/SUCROSE NONFERMENTING) ATP-dependent chromatin remodeling enzyme with a role in SAM maintenance and also required for proper acquisition of floral organ identity	Farrona et al., 2004; Hurtado et al., 2006; Kwon et al., 2006; Su et al., 2006
AtCHR12	AtCHROMATIN-REMODELING PROTEIN 12; SNF2/Brahma-type ATPase; mediates the establishment of a temporary growth arrest that allows adaptation to adverse conditions	Mlynarova et al., 2007
AtCZS	Plant-specific C2H2 Zinc finger-SET domain protein; interacts to AtSWP1 and regulates K9 and K27 dimethylation of histone H3 and hyperacetylation of histone H4 within the *FLC* locus	Krichevsky et al., 2007
AtSWC6/SEF1	AtSWC6/SERRATED AND EARLY FLOWERING 1*;* a HIT-Zinc finger containing protein of the SWR1 complex; regulates *FLC* and *FLC*-like expression	Choi et al., 2007; March-Diaz et al., 2007; Lazaro et al., 2008
AtSWI3c, AtSWI3d	AtSWI3; SWI/SNF ATPases that perform nonredundant regulatory functions that affect embryogenesis and both the vegetative and reproductive phases	Sarnowski et al., 2005
AtSWP1/LDL1	AtSWIRM domain polyamine oxidase protein; member of the Lysine Demethylase LSD1 family; regulates K9 and K27 dimethylation of histone H3 and hyperacetylation of histone H4 within the *FLC* locus	Jiang et al., 2007; Krichevsky et al., 2007
ATX-1	TRITHORAX 1; SET domain protein that displays H3K4 methyl transferase activity; activates flower homeotic genes	Alvarez-Venegas et al., 2003
BRU1/MGO3/ TSK	BRUSHY1/MGOUN3/TONSOKU; possesses leucine-glycine-asparagine (LGN) and leucine-rich repeats (LRR); could be part of a nuclear protein complex involved in SAM and RAM organization	Guyomarc'h et al., 2004; Takeda et al., 2004; Suzuki et al., 2005
CLF	CURLY LEAF; PRC2 component; putative E(z) homologue with a SET domain responsible for H3K27me3 activity; necessary for stable repression of *AGAMOUS* floral homeotic gene	Goodrich et al., 1997
DET1	DE-ETIOLATED1*;* part of a protein complex (CDD) containing DDB1, a protein that interacts with HAT complexes; controls light regulated gene expression through chromatin remodeling	Pepper et al., 1994
EBS	EARLY BOLTING IN SHORT DAYS; plant-specific nuclear protein that contains BAH and PHD Zn finger motifs; represses *FT* and vegetative expression of floral organ identity genes as well as germination during the dormancy period	Piñeiro et al., 2003
EFS/SDG8	EARLY FLOWERING IN SHORT DAYS; SET domain-histone methyltransferase associated to the PAF1 complex; may antagonize PcG repression of developmental master genes	Kim et al., 2005; Zhao et al., 2005
ELF7	EARLY FLOWERING 7; relative of yeast RNA polymerase II (Pol II) Associated Factor 1 (PAF1); regulates *FLC* and *FLC*-like expression	He et al., 2004; Oh et al., 2004
ELF8	EARLY FLOWERING 8; relative of yeast CLN Three Requiring 9 (CTR9), component of PAF1 complex; regulates *FLC* and *FLC*-like expression	He et al., 2004; Oh et al., 2004
EMF2	EMBRYONIC FLOWER 2; PRC2 component; putative Su(z)12 homologue; involved in shoot development and repression of flowering	Yoshida et al., 2001
ESD1/SUF3/ ARP6	EARLY IN SHORT DAYS1/SUF3/ACTIN RELATED PROTEIN 6*;* component of the SWR1 complex that catalyzes the replacement of nucleosomal H2A by the H2A.Z variant; related to ARP6; regulates *FLC* and *FLC*-like expression	Choi et al., 2005; Deal et al., 2005; Martin-Trillo et al., 2006
FAS1	FASCIATA1*;* subunit of the CAF1, involved in *de novo* nucleosome assembly during DNA replication; participates In RAM and SAM organization	Kaya et al., 2001
FAS2	FASCIATA2*;* subunit of the CAF1, involved in *de novo* nucleosome assembly during DNA replication; participates in RAM and SAM organization	Kaya et al., 2001
FIE	FERTILIZATION INDEPENDENT ENDOSPERM; PRC2 component; putative Enhancer of Zeste (E(z) homologue; WD-40 protein involved in the repression of endosperm development in the absence of fertilization	Kinoshita et al., 2001; Katz et al., 2004;
FIS2	FERTILIZATION INDEPENDENT SEED 2*;* PRC2 component; putative Suppressor of Zeste12 (Su(z)12) homologue; C2H2 zinc-finger protein involved in the repression of endosperm development in the absence of fertilization	Ohad et al., 1999
FLD	FLOWERING LOCUS D; homologue to human KIAA0601/Lysine Demethylase 1 (LSD1); also present in HDAC complexes and involved in the deacetylation of the *FLC* locus	He et al., 2003
FVE/MSI4	MULTICOPY SUPPRESSOR OF IRA 4*;* a MSI-like protein involved in the deacetylation of the *FLC* locus; also acts as a negative regulator of the CBF pathway	Ausin et al., 2004; Kim et al., 2004
GCN5	GENERAL CONTROL OF AMINO ACID SYNTHESIS PROTEIN 5-LIKE 2; a histone acetyl transferase acting at several light-responsive genes; also interacts with CBF1 and could be involved in the stimulation of cold-regulated gene expression by CBF1	Bertrand et al., 2005; Benhamed et al., 2006
HD1	HISTONE DEACETYLASE 1; deacetylase acting at several light-responsive genes	Bertrand et al., 2005; Benhamed et al., 2006
LHP1/TFL2	HETEROCHROMATIN PROTEIN 1 /TERMINAL FLOWER 2; may perform PRC1 functions in Arabidopsis*;* it associates in vivo with genes marked by H3K27me3; involved in the regulation of euchromatic genes such as *FLC*, *AP3*, *PI*, *AG* and *FT*	Gaudin et al., 2001; Mylne et al., 2006; Sung et al., 2006b; Turck et al., 2007; Zhang et al., 2007b
MEA	*MEDEA*; PRC2 component; putative E(z) homologue with a SET domain responsible for H3K27me3 activity; regulates embryo, endosperm and seed development	Grossniklaus et al., 1998
MSI1	MULTICOPY SUPPRESSOR OF IRA1; subunit of the CAF1, involved in *de novo* nucleosome assembly during DNA replication; participates in RAM and SAM organization; also PRC2 component, putative p55 homologue	Kaya et al., 2001
NRP1, NRP2	NAP1-RELATED PROTEIN 1 and *2*; homologues of the NUCLEOSOME ASSEMBLY PROTEIN1; bind histones H2A and H2B and associate with chromatin in vivo; participate in root patterning	Zhu et al., 2006
PIE1	PHOTOPERIOD INDEPENDENT EARLY FLOWERING 1; ATPase subunit of the SWR1 complex; regulates *FLC* and *FLC*-like expression	Noh et al., 2003
PKL	PICKLE; SWI/SNF involved in the suppression of embryonic and meristematic characteristics during development, and in the control of gene expression during primordia initiation and floral patterning	Ogas et al., 1999
REF6	RELATIVE OF EARLY FLOWERING 6; member of Arabidopsis jumonji-containing factors related to mammalian proteins involved in demethylation of K residues in different positions of histone H3	Noh et al., 2004
SKB1/AtPRMT5	SHK1 BINDING PROTEIN 1; homolog of a human arginine methylase (PRMT5) that catalyses the symmetric dimethylation of H4R3 (H4R3sme2) and binds to the *FLC* promoter	Pei et al., 2007; Wang et al., 2007; Schmitz et al., 2008
SUF4	SUPPRESSOR OF FRIGIDA 4; a C2H2-type zinc finger protein that represses flowering by transcriptional activation of *FLC*; could function as an intermediate to recruit the PAF1 complex to *FLC* chromatin	Kim and Michaels, 2006; Kim et al., 2006
SWN	SWINGER; PRC2 component; putative E(z) homologue with a SET domain responsible for H3K27me3 activity; controls initiation of seed development and flowering	Chanvivattana et al., 2004
SYD	SPLAYED; SWI/SNF ATP-dependent chromatin remodeling enzyme required to maintain shoot meristem function	Wagner and Meyerowitz, 2002
TAF1	TATA-BINDING PROTEIN (TBP)-ASSOCIATED FACTOR 1; a histone acetyl transferase acting at several light-responsive genes	Bertrand et al., 2005; Benhamed et al., 2006
VIL1/VRN5	VIN3-LIKE1/ VERNALIZATION INSENSITIVE 5*;* a VIN3-interacting protein required for a proper vernalization response	Sung et al., 2006a; Greb et al., 2007
VIN3	VERNALIZATION INSENSITIVE 3; a PHD-containing protein required for histone deacetylation in the *FLC* region following vernalization; it is found as part of the VRN2-PRC2	Sung and Amasino, 2004
VIP4	VERNALIZATION INDEPENDENT 4*;* relative of yeast Leo1, a component of PAF1 complex; regulates *FLC* and *FLC*-like expression	Zhang and van Nocker,, 2002
VRN2	VERNALIZATION 2; PRC2 component; putative Su(z)12 homologue; it represses *FLC* expression in response to vernalization	Gendall et al., 2001

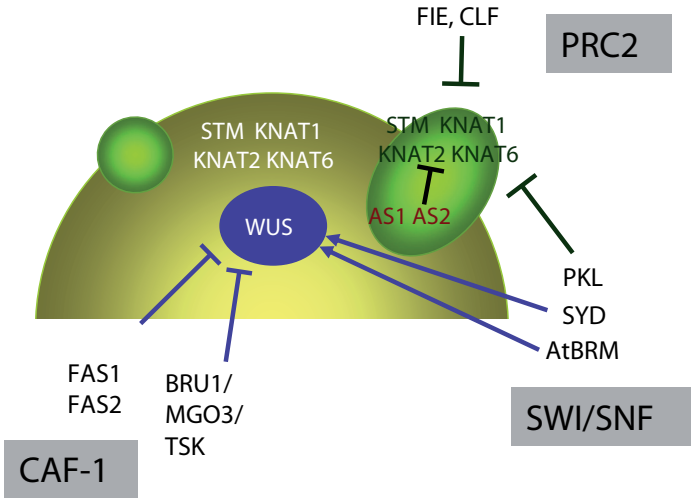

Fig. 1. Chromatin remodeling factors control the correct expression of meristem-specific genes. *FASCIATA 1 (FAS1) and FAS2, members of the Chromatin Assembly Factor (CAF-1) complex and BRU1/MGO3/TSK are required to determine the correct spatial expression of* WUSCHEL (WUS)*, preventing its ectopic expression outside the organizing centre. The SWI/SNF factor SPLAYED (SYD) and, probably AtBRAHMA (AtBRM), ensure high levels of* WUS *within its expression domain. The SWI/SNF protein PICKLE (PKL) also acts, together with ASYMMETRIC LEAVES1 (AS1), to repress the KNOX genes* STM, KNAT1, KNAT2 *and* KNAT6 *in developing lateral organs while the polycomb-group proteins CURLY LEAF (CLF) and FERTILIZATION-INDEPENDENT ENDOSPERM (FIE) participate in this repression in newly formed primordia.*

prevent differentiation of the stem cells (Scheres, 2007). Daughter cells, surrounding the stem cells, divide more rapidly and provide the *founder cells* that will generate lateral organs and the main stem. Underlying the stem cells, a group of cells expressing the homeobox gene *WUSCHEL (WUS)* form the organizing centre (Figure 1; See Table I for a list of genes involved in chromatin remodeling). A feedback loop between these cells and the stem cells, expressing the signaling gene *CLAVATA3 (CLV3)*, maintains the constant size of the stem cell niche. In the RAM, stem cells are arranged around the organizing cells of the *quiescent centre* that express the gene *WOX5* (*WUSCHEL-RELATED HOMEOBOX 5,* Haecker *et al.,* 2004; Sarkar *et al.,* 2007). Stem cells generate regular files of daughter cells which divide rapidly in a stereotyped manner. Descendants of these cells stop dividing and begin to elongate. In the SAM, in addition to the *CLV–WUS* pathway, *KNOX* genes *(SHOOTMERISTEMLESS (STM)*, *KNOTTED1-like ARABIDOPSIS THALIANA* 1 *(KNAT1)*, *KNAT2* and *KNAT6)* act in the meristem cells to prevent premature cell differentiation (Figure 1).

It is not yet known how stem cells are maintained in a pluripotent state and, at the same time, are able to generate a progeny in which differentiation pathways are rapidly activated. However, increasing evidence, both in plants and animals, indicate that chromatin modifications help restrict and stabilize expression patterns in the stem cells progeny (Sablowski, 2004; Scheres, 2007). Recent experiments in animals indicate that stem-cell chromatin maintains genes involved in cell differentiation repressed whereas it allows transcription of proliferation factors and stem-cell regulators (Boyer *et al.,* 2006; Lee *et al.,* 2006a; Scheres, 2007; Verdeil *et al.,* 2007). In plants, mutations at different genes coding for chromatin factors that preserve epigenetic marks through cell division, dramatically affect meristem size and organization as well as expression patterns of meristem genes suggesting that chromatin structure plays an important role in controlling this dynamic process (Goodrich and Tweedie, 2002). This is the case of mutants altered in the Chromatin-Assembly Factor-1 (CAF1), a histone-binding protein complex which participates in *de novo* nucleosome assembly during DNA replication (Ramírez-Parra and Gutiérrez, 2007). CAF1 is formed by three subunits conserved in all eukaryotes that in Arabidopsis are encoded by *FASCIATA1 (FAS1)*, *FAS2* and *MULTICOPY SUPPRESSOR OF IRA1 (MSI1)* (Kaya *et al.,* 2001; Hennig *et al.,* 2003; Kirik *et al.,* 2006; Ono *et al.,* 2006). CAF1 seems to be necessary to ensure the stable inheritance and maintenance of epigenetic states during DNA replication (Kaya *et al.,* 2001). Indeed, *fas1* mutants display a stochastic release of Transcriptional Gene Silencing (TGS) and overexpression of genes located in heterochromatic genomic regions (Ono *et al.,* 2006). In addition, the expression of stem-cell regulatory genes such as *WUS* is severely altered (Figure 1; Kaya *et al.,* 2001). In *fas* mutants, epigenetic repressing signals in *WUS* chromatin are stochastically lost and *WUS* transcription occurs in ectopic patches. As a result, *fas* mutants display overproliferation and fasciation of the SAM, aberrant SAM organization and defects in the stem cell pool size (Kaya *et al.,* 2001; Ono *et al.,* 2006). Mutants in another Arabidopsis gene *BRUSHY1(BRU1)/MGOUN3 (MGO3)/TONSOKU (TSK),* are strikingly similar to *fas* mutants (Guyomarc'h *et al.,* 2004; Takeda *et al.,* 2004; Suzuki *et al.,* 2005). The structure of the BRU1/MGO3/TSK protein suggests that it could also be part of a nuclear protein complex involved in chromatin organization. Epistatic analyses suggest that *BRU1* and *FAS1* might also have common targets (Guyomarc'h *et al.,* 2004; Suzuki *et al.,* 2004; Takeda *et al.,* 2004).

A different type of histone chaperones have been proposed to be involved in RAM maintenance and organization. The Arabidopsis homologues of the *NUCLEOSOME ASSEMBLY PROTEIN1 (NAP1)* gene, *NAP1-RELATED PROTEIN1* and *2 (NRP1* and *NRP2)* encode proteins that bind histones H2A and H2B and associate with chromatin *in vivo*. Double mutants *nrp1 nrp2* display impaired post-embryonic root growth, arrest of cell cycle progression at G2/M and disordered cellular organization in root tips; these mutants also exhibit perturbed expression of genes involved in root proliferation and patterning, and release of TGS (Zhu *et al.,* 2006). All these data indicate that the correct functions of CAF1 and other histone chaperone complexes involved in the maintenance of chromatin epigenetic marks are essential for meristem function.

In contrast to the CAF1 complex, necessary to spatially restrict *WUS* expression to the organizing centre, SWI/SNF ATP-dependent chromatin remodeling enzymes are required to maintain shoot meristem function by ensuring appropriate levels of *WUS* transcript within its normal expression domain (Kwon and Wagner, 2007). The SWI/SNF protein SPLAYED (SYD) is recruited to the *WUS* promoter and controls its transcription thus directly affecting the stem cell pool maintenance (Figure 1; Kwon *et al.,* 2005). *syd* plants exhibit decreased *WUS* expression, premature termination of the SAM, and carpelloid structures are formed after the inflorescence meristem has produced a few flowers (Wagner and Meyerowitz, 2002). Mutations in *BRAHMA* (*AtBRM*), mostly ex-

pressed in meristems and proliferating tissue, also show reduction in size of the inflorescence meristem and in the number of flowers, suggesting that AtBRM also might have a role in SAM maintenance (Figure 1; Farrona *et al.,* 2004; Hurtado *et al.,* 2006; Kwon *et al.,* 2006; Su *et al.,* 2006). All these observations confirm the crucial role of chromatin remodeling in the regulation of meristem activity.

Chromatin organization mediates the establishment and maintenance of gene expression patterns associated with organ initiation and cell differentiation

As cell proliferation proceeds in the growing primordia at the peripheral zone of the SAM, chromatin remodeling processes also play a central role in establishing transcriptional programs required for organ initiation and differentiation. First, it is important for the sequential production of lateral organs to keep meristem genes stably repressed outside the meristematic region. Second, it is necessary to ensure steady expression of differentiation genes in developing tissues and organs (leaf primordia, floral organs etc.), and repression of these genes in the domains where they have to be silenced so that the correct identity of growing organs is achieved. The Polycomb-Group (PcG) and Trithorax-group (TrxG) genes play key roles in these repressive and activating activities, respectively (Pien and Grossniklaus, 2007; Table I). The PcG proteins act as memory factors to stabilize repressive states of homeotic gene expression and the TrxG proteins establish transcriptionally active state of differentiation genes. SWI/SNF chromatin remodelers also play key roles in the control of the expression of genes involved in organ initiation and cell differentiation.

Establishment of repressive states

A pivotal level in the control of primordium fate is established by PcG protein complexes. Two types of Polycomb Repressive Complexes (PRC) have been described in animals, PRC1 and PRC2 which are responsible for the establishment of gene repression (PRC2) and maintenance of the repressive state (PRC1). The PRC2 complex promotes H3K27 methylation in target loci (Pien and Grossniklaus, 2007). These histone modifications regulate the accessibility of the transcriptional machinery to target genes leading to gene repression. The PRC2 complex in *Drosophila* is formed by four core proteins: Enhancer of Zeste (E(z)), Extra Sex Comb (ESC), p55 and Suppressor of zeste 12 (Su(z)12) (Muller *et al.,* 2002). The proteins that constitute the PRC2 complex in animals are conserved in plants. However, contrary to what has been observed in animals, in plants some of the subunits of these protein complexes are encoded by small gene families, which suggests the existence of different PRC complexes regulating diverse developmental programs. In Arabidopsis, the *ESC* homolog is encoded by a single copy gene *FERTILIZATION INDEPENDENT ENDOSPERM (FIE);* however, the other PRC2 subunits have more than one homolog: EMBRYONIC FLOWER 2 (EMF2), FIS2 and VERNALIZATION 2 (VRN2) are homologs of Su(z)12, while MEDEA (MEA), CURLY LEAF (CLF) and SWINGER (SWN) are homologs of the E(z) protein that contains a SET domain responsible for the Histone MethylTranferase (HMTase) activity of PRC2 complexes. Finally, the p55 homolog is encoded by *MSI1*, a gene belonging to a five member gene family, although only MSI1 has been proposed to be part of the PRC2 complex (Calonje and Sung, 2006; Köhler and Villar, 2008).

During organ initiation, the PcG-proteins FIE, encoding a WD-40 protein, and CLF are required to maintain the meristem-specific genes *STM, KNAT1, KNAT2* and *KNAT6* repressed in the newly formed primordia (Figure 1). In *fie* mutants, these genes are ectopically expressed in leaves while in *clf* mutants *STM* and *KNAT2* are de-repressed (Goodrich *et al.,* 1997; Katz *et al.,* 2004). Moreover, it has been demonstrated that CLF binds to the *STM* locus and that CLF and SWN have partially redundant functions in the H3K27 trimethylation of the *STM* gene (Makarevich *et al.,* 2006). Besides their role in repressing the homeobox gene *STM*, CLF and to some extent SWN, probably provide the HMTase activity required for the repression of the floral homeotic gene *AGAMOUS* (*AG*) in vegetative tissues (Goodrich *et al.,* 1997; Katz *et al.,* 2004). Recently both *STM* and *AG* were shown to constitute direct targets of CLF, and also to carry dispersed H3K27me3 and localised H3K27me2 in leaf tissues; methylation in H3K27 was present in the *AG* locus throughout leaf development and was strictly dependent on CLF activity that is required for persistent silencing of this gene in leaves (Schubert *et al.,* 2006). In contrast to animals where H3K27me3 occupies large genomic regions, in Arabidopsis H3K27me3 enriched domains are essentially restricted to the transcribed regions of particular genes, suggesting that the mechanisms underlying the establishment and spreading of H3K27me3 might be significantly different in plants and animals (Zhang *et al.,* 2007a). CLF and SWN have been shown to interact with EMF2, suggesting that either CLF or SWN and EMF2 could be part of a PRC2-like complex involved in the repression of *AG* (Chanvivattana *et al.,* 2004). FIE is also likely to be a component of this complex and recent findings support this view. The embryo lethal phenotype of *fie* mutants prevented for a long time the identification of any possible role of FIE during postembryonic development; however, plants partially depleted of FIE activity by means of cosuppression or partial complementation have revealed additional roles for FIE in the repression of homeobox genes, in the maintenance of root identity or in the repression of floral homeotic genes such as *AG*, *APETALA3 (AP3)* and *PISTILLATA (PI)* (Kinoshita *et al.,* 2001; Katz *et al.,* 2004).

Another PRC2 complex that plays a central role in the regulation of gametophyte, embryo and endosperm development was originally defined on the basis of Arabidopsis mutations that cause the development of seed-like structures in the absence of fertilization (reviewed in Kohler and Makarevich, 2006). The identified loci collectively referred to as FERTILIZATION INDEPENDENT SEED (FIS) class of genes, included *MEA*, *FIE*, *MSI1* and *FIS2*. This PRC2-MEA complex is required to repress the expression of the *PHERES1 (PHE1)* MADS box gene and other genes normally expressed during early stages of endosperm development (Makarevich *et al.,* 2006; Pien and Grossniklaus, 2007); *PHE1* repression is at least partly dependent on MEA activity, although CLF and SWN appear to have partially redundant roles in this repression (Kohler *et al.,* 2003; Makarevich *et al.,* 2006). All these observations provide evidence for the existence of different types of PRC2 complexes in plants that *in vivo* methylate H3K27 residues in the genomic regions of their target genes (Calonje and Sung, 2006; Pien and Grossniklaus, 2007). FIE is probably present in all these complexes while other components with different spatio-temporal expression patterns change

during plant development, providing a way to regulate different target genes at specific stages of development. Moreover, the analyses of double mutants affected in more than one PcG gene have revealed severe defects in development suggesting that partial redundancy and embryo lethality had masked until now some of the key roles that PRC2 protein complexes play in the regulation of plant developmental transitions.

Maintenance of repressive states

Once a given repressive state is established by PRC2, maintenance of this state in animals depends on a second Polycomb Repressive Complex (PRC1) (Köhler and Villar, 2008, Schwartz and Pirrota, 2008). This complex contains four core subunits and is proposed to bind H3K27me3 marks established by PRC2 in target loci; the activity of PRC1 is responsible for the monoubiquitination of residue K119 of histone H2A, a modification that generates the stable silencing of target genes (Pien and Grossniklaus, 2007). In Arabidopsis neither homologues of the PRC1 components nor ubiquitinated H2AK119 have been identified so far, suggesting that plants could use a different mechanism to maintain stable silencing. In fact, recent reports have provided evidence that LIKE HETEROCHROMATIN PROTEIN 1 (LHP1)/TERMINAL FLOWER 2 (TFL2), a plant homologue of HP1, may perform PRC1 functions in Arabidopsis (Mylne *et al.,* 2006; Sung *et al.,* 2006b; Turck *et al.,* 2007; Zhang *et al.,* 2007b). Animal HP1 is a chromodomain protein that binds methylated H3K9 and is strongly associated with constitutive heterochromatin (Hediger and Gasser, 2006), although is not involved in Polycomb repression. However, Arabidopsis LHP1 does not appear to have a role in the maintenance of constitutive heterochromatin (Libault *et al.,* 2005; Nakahigashi *et al.,* 2005), and seems to be involved in the regulation of euchromatic genes, such as *FLC*, *AP3*, *PI*, *AG* and *FT* (Nakahigashi *et al.,* 2005; Germann *et al.,* 2006; Sung *et al.,* 2006b; Turck *et al.,* 2007). LHP1 specifically associates *in vivo* with genes marked by the trimethylation of H3K27, although it is not involved in this histone modification (Turck *et al.,* 2007; Zhang *et al.,* 2007b), suggesting that LHP1 might contribute to PcG–mediated silencing in a PRC1-like analogous manner.

Establishment of active states of gene expression

Groups of genes repressed by PcG complexes need to be active at particular developmental stages to promote the differentiation of specific organs. In animals, this activity, required to antagonize PRC repression and promote developmental processes, is provided by the TrxG group of proteins (Pien and Grossniklaus, 2007). As for PcG proteins, some TrxG proteins are also conserved in plants and several homologues have been identified in Arabidopsis; among them, TRITHORAX 1 (ATX-1) contains a SET domain and displays H3K4 methyl transferase activity *in vitro* (Alvarez-Venegas *et al.,* 2003); consistent with this, *atx1* mutants have moderately low levels of genomic H3K4 methylation. This partial reduction of H3K4 methylation observed in *atx1* mutants suggests that other Trx proteins could contribute to overall H3K4 methylation levels. In addition, *atx1* mutants show reduced levels of expression of floral homeotic genes repressed by PcG proteins such as *AG*, *AP3* and *PI*, indicating that ATX1 is necessary for proper activation of these genes in developing flowers (Alvarez-Venegas *et al.,* 2003; Saleh *et al.,* 2007). Moreover, ATX1 is required for *FLC* expression (Pien *et al.,* 2008). Thus, as in animals, plant Trx

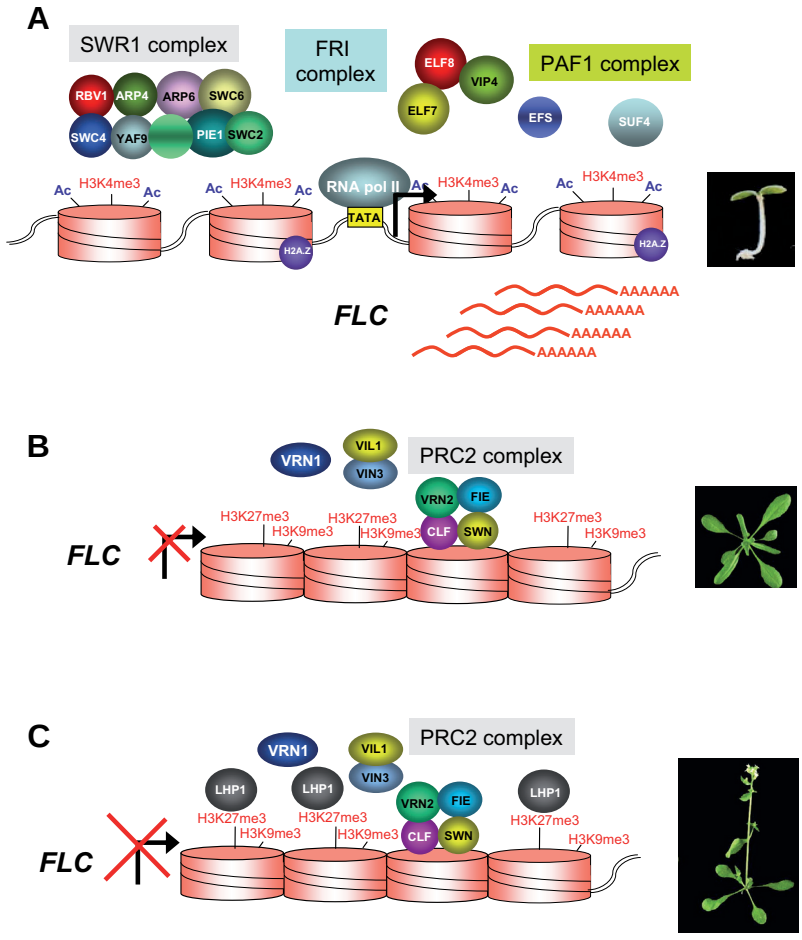

Fig. 2. Hypothetical models for chromatin-dependent regulation of *FLOWERING LOCUS C (FLC)* expression. FLC *chromatin might exist in at least three different configurations: the active state required for the establishment of the winter-annual habit of* Arabidopsis **(A)**, *the repressed state that occurs under prolonged exposure to cold during the winter season* **(B)**, *and the stably silenced state* **(C)**, *where Like Heterochromatin Protein1 (LHP1) is involved in the maintenance of stable* FLC *repression by vernalization. In the fall season, components of the SWR1, FRIGIDA (FRI), and Polymerase Associated Factor (PAF) complexes are required to maintain* FLC *chromatin activated* **(A)**. *Histone modifications associated with active* FLC *such as acetylation of histone H3 and H4 and H3K4me3 decrease in* FLC *chromatin following vernalization, and additionally, the level of repressive marks like H3K9 and H3K27 trimethylation increases. Winter low temperature promotes Vernalization-Insensitive3 (VIN3) (and maybe VIL1) proteins to interact with an* Arabidopsis *PRC2 complex to epigenetically silence* FLC **(B)**.*This silencing is maintained by VRN1 and LHP1 together with the VIN3-PRC2 complex* **(C)**; *LHP1 might contribute to PcG–mediated silencing in a PRC1-like analogous manner. Ac, acetylated lysines of histones H3 and H4; H3K4me3, trimethylated lysine 4 of histone H3; H3K9me3, trimethylated lysine 9 of histone H3; H3K27me3, trimethylated lysine 27 of histone H3; H2A.Z, Histone H2 variant; RNA pol II, RNA polymerase II.*

proteins may function in antagonizing the repressor activity of PcG complexes. The mechanism directing both Trx and PcG complexes to the target genes remains essentially unknown and so far no Polycomb or trithorax Responsive Elements (PRE/TREs) have been identified in plants.

Role of other chromatin remodeling factors

Chromatin remodeling factors belonging to the SWI/SNF family previously discussed for their role in meristem maintenance are also involved together with PcG and Trx complexes in the control of gene expression during primordia initiation and floral patterning. *PICKLE (PKL)* encodes an ATP-ase of the CHD3 class containing a CHROMODOMAIN (CHD) and a PLANT HOMEODOMAIN (PHD), two motifs normally found in chromatin remodeling factors, and contributes to the repression of meristem-specific genes in new primordia. *PKL* is involved in the suppression of embryonic and meristematic characteristics during development, and in leaf primordia PKL cooperates with ASYMMETRIC LEAVES 1 (AS1) and AS2 to repress *KNOX* genes or their target genes (Ogas *et al.,* 1999; Ori *et al.,* 2000). AS1 contains a SANT motif, also found in SWI3 proteins, which interact with a SWI/SNF chromatin remodeling factor (Sarnowski *et al.,* 2005). Apart from this role in repression of meristem-specific genes, other SWI/SNF proteins play crucial roles in floral patterning. *AtBRM* is required for proper acquisition of floral organ identity since *brm* mutants show severe flower abnormalities including homeotic transformations and reduced expression levels of AP2, AP3, PI and NAC-LIKE, ACTIVATED BY AP3/PI (NAP) (Hurtado *et al.,* 2006). BRM and AtSWI3c show strong interactions, and *atswi3c* mutants display similar defects to *brm* mutant plants, suggesting that both components might act in a common genetic pathway or even are part of the same protein complex during floral homeotic gene activation (Sarnowski *et al.,* 2005; Hurtado *et al.,* 2006; Farrona *et al.,* 2007). *swi3d* mutants also show defects in floral development although the phenotypic alterations are clearly distinguishable from those present in *swi3c* mutants, and BRM does not interact with ATSWI3D. SYD is also involved in the repression of the floral transition and floral development (Wagner and Meyerowitz, 2002) and can interact with different SWI3 ATPases. Gene expression profiling has revealed that these two ATPases control the expression of a limited number of genes in different developmental processes, and that they are specific transcriptional co-regulators (Kwon *et al.,* 2005; Kwon *et al.,* 2006). *SYD* and *AtBRM* have unique and shared targets and interaction partners, and they have a remarkable degree of regulatory specificity (Sarnowski *et al.,* 2005; Bezhani *et al.,* 2007). Altogether, the emerging picture is starting to suggest that a number of SWI/SNF complexes containing different SWI3 subunits coexist in plants; these different combinations and their interaction with other components provide specificity to regulate different target genes and processes along development.

Chromatin organization in the control of flowering time. A model for epigenetic regulation of gene expression

In Arabidopsis, growth in long days (LD) accelerates flowering, while short days (SD) delay the floral transition. Two major Arabidopsis growth habits can be distinguished in natural populations: summer annual plants which germinate in the spring and flower in late spring or early summer and winter annual plants which germinate in the fall but will not flower till the next spring (Sung and Amasino, 2006). In most winter-annual plants, the acquisition of competence to flower requires an extended period of cold exposure (vernalization), and the floral repressor gene *FLC* plays a central role in this adaptive response. The winter-annual habit of Arabidopsis is mainly established by the ability of *FRIGIDA (FRI)* to promote high levels of expression of the floral repressor *FLC*, a MADS-box gene that inhibits the expression of the floral integrators *FT* and *SUPPRESSOR OF OVEREXPRESSION OF CO* (*SOC1)* (Sung and Amasino, 2006; Dennis and Peacock, 2007). Accumulation of the FLC protein prevents plants from flowering, but a prolonged exposure to cold causes *FLC* repression, which is maintained for the rest of the plant life cycle in a mitotically stable manner (Baurle and Dean, 2006). The regulation of *FLC* expression and its stable repression in response to winter temperatures involves a number of chromatin remodeling processes that have become a model for epigenetic regulation of gene expression in plants (reviewed in Schmitz and Amasino, 2007; Farrona *et al.,* 2008). Moreover, chromatin remodeling processes are also involved in the negative control of *FT*, *SOC1* or *AGL19* genes during vegetative development and their expression upon flowering induction, reinforcing the role of chromatin dynamics in the control of flowering time (Piñeiro *et al.,* 2003; Takada and Goto, 2003; Bouveret el al., 2006; Germann *et al.,* 2006; Imauzumi and Kay, 2006).

Establishment of the winter-annual habit

The establishment of the winter-annual habit of Arabidopsis requires high levels of *FLC* expression during the first growing season in order to block flowering before winter. For that, the *FLC* switch must be reset to the active state as it passes to the next generation and this resetting, postulated to occur during meiosis (Sheldon *et al.,* 2008), is necessary to perpetuate the vernalization requirement in successive generations (reviewed in Schmitz and Amasino, 2007). The isolation of early flowering mutants in winter annual genetic backgrounds showing reduced levels of *FLC* expression has led to the identification of genes required to activate *FLC* at the beginning of the life cycle. These genes encode components of two different putative chromatin remodeling complexes, the PAF1 and the SWR1 complexes (Figure 2A; Table I).

Genes encoding proteins related to components of the yeast transcriptional activating Polymerase Associated Factor 1 (PAF1) complex include *early flowering 7* (*elf7)*, *elf8* and *vernalization independent 4 (vip4)* (He *et al.,* 2004; Oh *et al.,* 2004, 2008). In yeasts, this complex interacts with SET1 and SET2 HMTases involved in methylation of H3K4 and H3K36 respectively (Krogan *et al.,* 2003; Ng *et al.,* 2003). There is a correlation between *FLC* expression and high levels of H3K4 methylation at *FLC* chromatin (He *et al.,* 2004; Kim *et al.,* 2005; Martin-Trillo *et al.,* 2006). Mutants in the SET domain-histone methyltransferase *EARLY FLOWERING IN SHORT DAYS (EFS/SDG8)* also flower early and display reduced levels of *FLC* expression, like PAF1 complex mutants (Kim *et al.,* 2005; Zhao *et al.,* 2005), suggesting that PAF1 complex and EFS may act directly on *FLC* to maintain high levels of expression. EFS/SDG8 H3 methyltransferase seems to

antagonize PcG repression of developmental master genes and shows homology to *Drosophila* TrxG proteins such as Absent, Small and Homeotic Discs 1 (ASH1). Thus, this SET domain protein has been proposed to perform TrxG proteins functions in plants. Consistently, two different reports have provided evidence that EFS/SDG8 is required for high levels of either H3K4me3 or H3K36me2 in the region of *FLC* (Kim *et al.,* 2005; Zhao *et al.,* 2005). One additional factor, SUPPRESSOR OF FRIGIDA 4 (SUF4), could function as an intermediate to recruit the PAF1 complex to *FLC* chromatin (Kim and Michaels, 2006; Kim *et al.,* 2006).

Genes encoding putative orthologues of the yeast SWR1 complex include *EARLY IN SHORT DAYS1*/*SUF3*/*ACTIN RELATED PROTEIN 6 (ESD1/SUF3/ARP6)* (Choi *et al.,* 2005; Deal *et al.,* 2005; Martin-Trillo *et al.,* 2006), *PHOTOPERIOD INDEPENDENT EARLY FLOWERING 1 (PIE1)*, (Noh *et al.,* 2003), and AtSWC6/SEF1 *(SERRATED AND EARLY FLOWERING 1)* (Choi *et al.,* 2007; March-Diaz *et al.,* 2007; Lazaro *et al.,* 2008). The SWR1 complex in yeast catalyzes the replacement of nucleosomal H2A by the H2A.Z variant, ensuring full activation of underlying genes. This H2A.Z histone variant has recently been identified within *FLC* chromatin (Deal *et al.,* 2007) and loss of H2A.Z from *FLC* chromatin in *esd1*/*suf3*/*arp6* and *pie1* mutants results in reduced *FLC* expression and premature flowering. In addition, H2A.Z interacts with both PIE1 and AtSWC2, and knockdown of the H2A.Z genes by RNA interference or artificial microRNA (miRNA) caused a phenotype similar to that of *esd1*/*suf3*/*arp6* mutants (Choi *et al.,* 2007). These observations support the existence of a SWR1-like complex in plants that is targeted to different loci including *FLC*, and show that the presence of the H2A.Z histone variant in the chromatin of specific genes enhance their transcriptional activation in plants. The fact that H2A.Z remains associated with chromatin throughout mitosis suggests that it may serve as an epigenetic memory function marking active genes and poising silenced genes for reactivation (Deal *et al.,* 2007).

FLC *repression, the vernalised state*

Under prolonged exposure to cold during the winter season, *FLC* expression is progressively repressed. This state of *FLC* that will later facilitate flowering induction in spring is maintained for the rest of the plant life cycle in a mitotically stable manner, even after cold exposure ends, suggesting the involvement of a mechanism conferring cellular memory for remembering winter (Sung and Amasino, 2006). Recent studies have confirmed that vernalization of Arabidopsis plants causes a number of changes in the array of histone modifications present in the *FLC* locus, providing further evidence for the involvement of chromatin remodeling processes in the mitotic stability of the vernalized state (Figure 2B). Histone modifications associated with active genes such as acetylation of histone H3 and H4 and H3K4me decrease in *FLC* chromatin following vernalization (Sung and Amasino, 2004; Sung *et al.,* 2006a). Additionally, the level of repressive marks like H3K9 and H3K27 di and trimethylation increases during vernalization (Bastow *et al.,* 2004; Sung and Amasino, 2004; Sung *et al.,* 2006a). The involvement of PcG proteins in *FLC* repression during vernalization was first revealed by the molecular characterization of *VRN2* that encodes a homologue of the PRC2 component Su(z)12 (Gendall *et al.,* 2001). Recent results have shown that a PRC2 complex containing VRN2 also includes other PcG homologues such as FIE and the E(z) homologues CLF and SWN (Wood *et al.,* 2006; De Lucia *et al.,* 2008) (Figure 2B). This complex is probably responsible for methylation of H3K27 in the *FLC* locus (Bastow *et al.,* 2004; Sung and Amasino, 2004). However, methylation of H3K27 mediated by the VRN2-PRC2 complex is not sufficient to maintain stable *FLC* repression after vernalization. Methylated H3K9 also appears to be an important histone mark during vernalization because *vrn1* mutants lack H3K9 methylation but not H3K27me3 in the chromatin of *FLC*, and *FLC* repression is not stably maintained in these plants. This observation is consistent with the involvement of VRN1 in H3K9 methylation after the VRN2-complex methylates H3K27 (Bastow *et al.,* 2004; Sung and Amasino, 2004). The PHD-containing protein VERNALIZATION INSENSITIVE 3 (VIN3) is also necessary to accelerate flowering in response to prolonged cold exposure (Sung and Amasino, 2004). *VIN3* mRNA accumulates only after a period of cold sufficient to trigger vernalization and its expression domain overlaps with that of *FLC*. VIN3 appears to be required for histone deacetylation in the *FLC* region following vernalization (Sung and Amasino, 2004). None of the repressive marks associated to vernalization are present in *vin3* mutants, suggesting that VIN3-mediated deacetylation of *FLC*-chromatin may facilitate histone methylation by a VRN2-PRC2 or other histone methylation complexes.

The mechanism by which high expression chromatin marks such as H3K4me3 are reduced by cold exposure remains obscure, but specific demethylases may be involved. Recent results have shown that the PHD domain can bind trimethylated H3K4 and bring chromatin remodeling complexes to target genes and modulate their level of expression (Becker, 2006; Mellor, 2006). This raises the possibility that recognition of trimethylated H3K4 by the PHD finger of VIN3 could contribute to the recruitment or modulate the activity of a silencing chromatin remodeling complex or complexes. A VIN3-interacting protein referred to as VIN3-LIKE1 (VIL1)/VRN5 is also required for a proper vernalization response (Sung *et al.,* 2006a; Greb *et al.,* 2007) (Figure 2B). Similarly to *vin3*, *vil1* mutations result in a vernalization-insensitive phenotype and absence of repressive histone modifications in *FLC* (Sung *et al.,* 2006a; Greb *et al.,* 2007). VIN3 and VIL1 belong to a small gene family, and the possible role of the other members in the vernalization response is still unknown. Thus vernalization appears to require a chromatin remodeling complex that contains at least two PHD finger proteins. Recently, VIN3, VIL1 and VIL2/VEL1 were found as part of the VRN2-PRC2 complex mentioned above, that is likely to be involved in the initial stages of vernalization-mediated *FLC* repression (Wood *et al.,* 2006; De Lucia *et al.,* 2008). The abundance of the complex increases during vernalization and declines after plants are returned to warm temperatures. VRN2 associates throughout the *FLC* locus independently of the cold, whereas association of VIL1 to a specific domain in *FLC* intron 1 is dependent on cold and VIN3 (De Lucia *et al.,* 2008). The VRN2-VIN3 complex may bring histone deacetylase and histone methyltransferase activities together at *FLC* chromatin, providing a coordinated mechanism for the epigenetic modifications associated with the vernalization-mediated repression of *FLC* gene. Vernalization has been proposed to be a two-step process, with an initial downregulation of *FLC* followed by maintenance of the repressed state by a Polycomb

complex. In fact, the deletion of a sequence of the *FLC* first intron referred to as vernalization response element (VRE), required for maintenance of the repressed state, does not prevent the initial repression of *FLC* by cold (Sung *et al.,* 2006b). Thus, the initial response maybe separable and is mediated by other sequence elements residing in the promoter or along the first intron of the gene. Recently it has been suggested that the VRN2-containing PRC2 complex determines the extent of downregulation but not the maintenance of *FLC* repression (Sheldon *et al.,* 2006). In addition, a reverse genetics approach has revealed that LHP1 is involved in the maintenance of stable *FLC* repression by vernalization (Mylne *et al.,* 2006; Sung *et al.,* 2006b) (Figure 2C) and is associated with regions methylated at H3K9 of *FLC* chromatin during vernalization, including the region encompassing the VRE (Sung *et al.,* 2006b). Moreover, LHP1 is required for maintaining increased H3K9 methylation at *FLC*, but not for the initiation of this methylation during cold exposure (Sung *et al.,* 2006b), suggesting that in addition to VRN2-PRC2 complex, there might be two different histone methylating components involved in the vernalization response.

In spring habit (summer annual) plants, *FLC* is frequently silenced as the result of the lack of function of *FRI* but also with the contribution of other factors involved in chromatin remodeling which participate in the negative regulation of *FLC* expression. These include proteins such as FVE and FLOWERING LOCUS D (FLD) that show similarity to mammalian chromatin remodeling factors. Both factors are components of the so-called autonomous floral promotion pathway, defined on the basis of the phenotype of Arabidopsis late flowering mutants responsive to both photoperiod and vernalization (for reviews see Ausin *et al.,* 2005; Baurle and Dean, 2006; Schmitz and Amasino, 2007). The homologue of *FVE* in animals is found in Nucleosome Remodeling Factor (NuRF) and HDAC complexes and is likely to function as a histone chaperone (Ausin *et al.,* 2004; Kim *et al.,* 2004). FLD is highly homologous to human KIAA0601/Lysine Demethylase 1 (LSD1) also present in HDAC complexes (Lee *et al.,* 2006b). LSD1 is a polyamine oxidase (PAO) that can demethylate H3K4 (Shi *et al.,* 2004). Consistent with the nature of these proteins, the increased expression of *FLC* in *fve* and *fld* mutants is correlated with hyperacetylation of histones H3 and H4 (He *et al.,* 2003; Ausin *et al.,* 2004), a modification associated to transcriptionally active chromatin conformations.

Besides these classical members of the autonomous pathway, new components of chromatin remodeling complexes that participate in *FLC* repression are beginning to emerge. That is the case of AtSWP1/LDL1, another member of the family of PAO/LSD1 proteins found in Arabidopsis, and therefore a homologue of FLD. AtSWP1 can interact with a plant-specific C2H2 zinc finger-SET domain protein named AtCZS. Knock-out (KO) mutations in the genes encoding any of these two proteins result in hyperacetylation of histone H4 and reduced methylation of H3K9 and H3K27 in the genomic region of *FLC*. Consistent with these observations *swp1* and *czs* mutants show increased *FLC* expression and a moderate delay in flowering (Krichevsky *et al.,* 2007). Recently, AtSWP1/LDL1 and its homolog LDL2 have also been shown to reduce the levels of H3K4 methylation in the chromatin of *FLC* and *FWA* (Jiang *et al.,* 2007). These results suggest that AtSWP1/LDL2 and AtCZS represent components of a plant specific repressor complex involved in the fine tuning of *FLC* expression. Confirming the central role of chromatin remodeling processes in the regulation of *FLC*, two additional chromatin associated factors have been recently proposed as components of the autonomous pathway: RELATIVE OF EARLY FLOWERING 6 (REF6) and SHK1 BINDING PROTEIN 1(SKB1). *REF6* encodes a member of a large family of Arabidopsis jumonji-containing factors related to mammalian proteins involved in the demethylation of lysine residues in different positions of histone H3. *ref6* mutants display a modest delay in flowering as compared to other autonomous pathway mutants, although this late flowering is suppressed by *flc* mutations (Noh *et al.,* 2004). SKB1 is a homolog of a human arginine methylase (PRMT5) that catalyses the symmetric dimethylation of H4R3 (H4R3sme2) and binds the *FLC* promoter; *skb1* loss-of-function mutations result in upregulation of *FLC* and late flowering that can be reversed by vernalization. Furthermore *skb1* mutants show decreased H4R3sme2 in regulatory regions of *FLC*, suggesting that this histone covalent modification is also required for the induction of flowering mediated by *FLC* repression (Pei *et al.,* 2007; Wang *et al.,* 2007; Schmitz *et al.,* 2008).

Finally, small RNA-mediated chromatin silencing also appears to be required for the regulation of *FLC*, and 3´end regions of this locus constitute targets of si-RNAs and are enriched in H3K9me2 in a DICER dependent way (Schmitz *et al.,* 2007; Swiezewski *et al.,* 2007). All these observations highlight the importance of chromatin remodeling processes in the regulation of the central Arabidopsis floral repressor *FLC*.

Regulation of flowering signal integrator genes by chromatin remodeling

FLC epigenetic regulation is the best known example of the role of chromatin remodeling in the control of flowering time, but it is not the only one (Farrona *et al.,* 2008). *AGAMOUS-LIKE19 (AGL19)* is another MADS box gene recently shown to be controlled by mechanisms involving chromatin remodeling processes mediated by PcG proteins (Alexander and Hennig, 2008). This floral activator acts to promote flowering in response to prolonged cold exposure (Schonrock *et al.,* 2006). In contrast to *FLC*-mediated repression of flowering, this, so far, poorly understood pathway does not require *SOC1* to promote the floral transition. In the absence of cold, the expression of *AGL19* is maintained at very low levels and the chromatin of this locus is heavily enriched in H3K27me3 repressive marks. Plant PRC2 polycomb proteins such as MSI1, CLF and EMF2, but not VRN2, appear to be necessary for those high levels of H3K27me3 and *AGL19* repression in the absence of cold. Following vernalization, the levels of H3K27me3 decrease in the promoter and ATG regions of *AGL19* relieving its repression by a mechanism that requires VIN3. The induction of *AGL19* results in activation of floral meristem identity genes *LEAFY (LFY)* and *AP1* and subsequent flowering (Schonrock *et al.,* 2006).

Silencing of the SWI/SNF chromatin remodeling ATPase gene *AtBRM* using RNA interference strategies revealed that this protein is involved in the regulation of different aspects of plant development, including floral transition (Farrona *et al.,* 2004). *AtBRM* silenced plants flower earlier than wild-type plants and show increased levels of *CONSTANS (CO)*, *FT* and *SOC1* expression under non-inductive photoperiodic conditions, suggesting that *AtBRM* contributes to the repression of these genes that participate in the long day promotion pathway (Imaizumi and

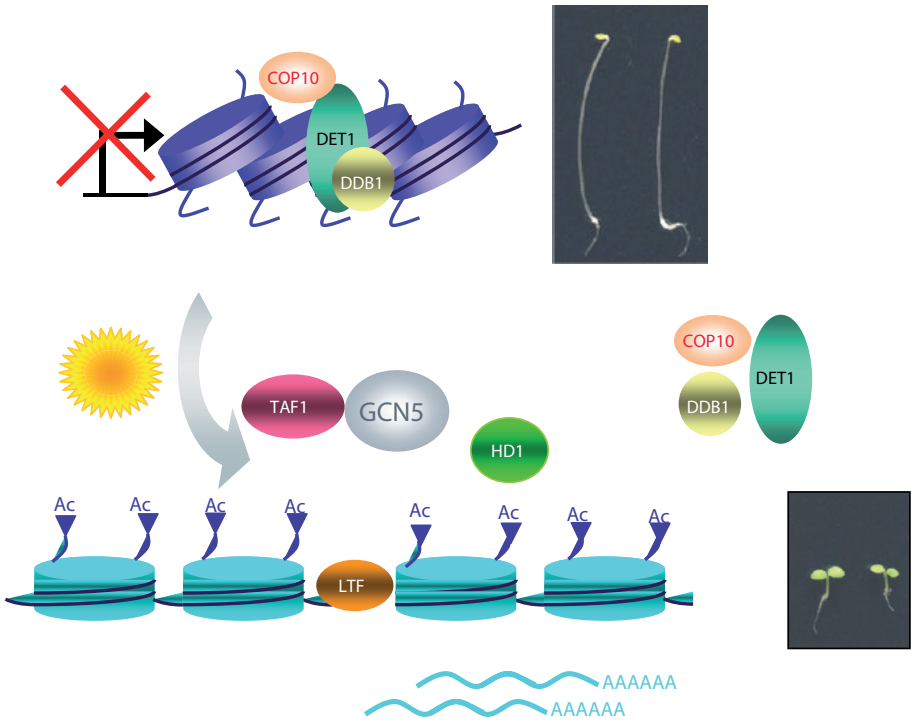

Fig. 3. Chromatin remodeling plays a central role in the control of light-responsive gene expression and photomorphogenesis. *In darkness, seedlings follow a skotomorphogenesis developmental pathway generating a long hypocotyl phenotype. Under these conditions, the DET1/DDB1/COP10 complex may bind to non-acetylated H2B (and maybe other histones) to repress the expression of light-responsive genes. In response to light, the DET1/DDB1/COP10 complex might recruit histone acetyltransferase (HAT) activities, such as TAF1 and GCN5, causing acetylation of histones H3 and H4 (and maybe others) at the promoter of light-inducible genes and the release of the DET1/DDB1/COP10 complex. This is accompanied by changes in nucleosome accessibility at the promoter region and correlates with light-induced transcription mediated by specific light-responsive transcription factors (LTF). HD1 may play an opposing role to GCN5 to fine-tune and balance light regulation of gene expression during photomorphogenesis.*

Kay, 2006). Modifications of chromatin structure are also likely involved in the regulation of the expression of floral integrator *FT*. At least a PRC2-like complex containing CLF, EMF2 and FIE (Jiang *et al.,* 2008), as well as two additional factors involved in chromatin remodeling processes are required to repress *FT* expression, LHP1/ TFL2 and EARLY BOLTING IN SHORT DAYS (EBS) (Piñeiro *et al.,* 2003; Takada and Goto, 2003). Mutations in the genes encoding any of these proteins cause early flowering and upregulation of *FT*, especially under non-inductive photoperiods, suggesting that these proteins are required in the establishment of a non-active chromatin conformation at the *FT* locus under non inductive short day photoperiods (reviewed in Imaizumi and Kay, 2006). As discussed above, LHP1/TFL2 is involved in the silencing of euchromatic genes related to developmental processes; in addition to its role in maintaining vernalization-induced silencing of *FLC*, LHP1 is targeted to the promoter and transcribed regions of *FT* to repress its expression, and also participates in the repression of vegetative expression of floral organ identity genes (Gaudin *et al.,* 2001; Kotake *et al.,* 2003; Takada and Goto, 2003; Nakahigashi *et al.,* 2005; Libault *et al.,* 2005; Germann *et al.,* 2006). EBS is a plant-specific nuclear protein that contains a BAH (BromoAdjacent Homology) and a PHD Zn finger motif (Piñeiro *et al.,* 2003); both types of domain are present in chromatin remodeling factors, and as for LHP1/ TFL2, the role of EBS in the regulation of plant development is not restricted to the floral transition. *ebs* mutants show pleiotropic developmental alterations including defects in the expression of floral organ identity genes as well as a reduction in seed dormancy, which suggests a role for chromatin organization in the repression of germination during the dormancy period (Gomez-Mena *et al.,* 2001; Liu *et al.,* 2007).

Confirming the central role of chromatin remodeling in the control of flowering time, plants with reduced levels of *MSI1* show late flowering and delayed induction of the floral integrator *SOC1*. MSI1-mediated activation of *SOC1* is independent of *FLC* and is correlated with increased levels of histone modifications such as K4H3me2 and H3K9 acetylation in the *SOC1* locus; these histone marks are associated to actively transcribed chromatin, suggesting that epigenetic mechanisms operate in the genomic region of this floral activator during the induction of flowering (Bouveret *et al.,* 2006).

Chromatin-mediated responses to environmental cues

As discussed above, different chromatin remodeling mechanisms in plants generate epigenetic modifications which provide a mechanism for the stable propagation of gene activity states from one cell generation to the next. These mechanisms provide a cell memory for past environmental events such as vernalization or stabilize specific developmental phases and patterns of differentiation. Chromatin remodeling mechanisms also participate in the regulation of gene expression which takes place in differentiated cells in response to environmental cues either when they represent expected regular variations, such as light-dark cycles, or unpredictable stress conditions.

Chromatin remodeling processes during photomorphogenesis

Many of the physiological modifications induced by light are the result of changes in gene expression (Jiao *et al.,* 2007). In addition to the regulation mediated by transcription factors that bind a number of defined light-responsive regulatory elements, chromatin remodeling processes play a central role in the control of light-responsive gene expression and photomorphogenesis. Increased acetylation of histones H3 and H4 at the promoter of a pea plastocyanin (*PetE)* gene correlates with light-induced transcription (Chua *et al.,* 2001), and is accompanied by changes in nucleosome accessibility at the promoter region. Furthermore, transcriptional enhancers associated with the nuclear matrix seem to trigger the light-induced acetylation of histones in promoter and nearby coding regions to activate transcription (Chua

et al., 2003). More recently a pivotal role of Arabidopsis histone acetyl transferases TAF1 and GCN5 and deacetylases such as HD1 in the control of histone acetylation at several light-responsive genes has been established (Bertrand *et al.,* 2005; Benhamed *et al.,* 2006). Mutants of *TAF1* displayed reduced H3 acetylation in light-responsive promoters, altered expression of about 9% of genes in young leaves and developmental abnormalities (Bertrand *et al.,* 2005). Furthermore, loss of function mutations of the *GCN5* HAT resulted in a long-hypocotyl phenotype and reduced light-inducible gene expression, whereas mutants of *HD1* displayed opposite effects. A detailed analysis revealed that TAF1, GCN5 and HD1 have distinct and specific effects on the acetylation of particular lysine residues present in H3 and H4 histones of promoter regions required for light regulation of gene expression (Benhamed *et al.,* 2006) (Figure 3; Table I). Indeed, variations in histone modifications have been demonstrated as important physiological components of plant responses to changing light environments (Guo *et al.,* 2008).

Arabidopsis *DE-ETIOLATED1* (*DET1*) also seems to control light regulated gene expression through chromatin remodeling. *det1* mutants show photomorphogenesis in the dark and nearly half of the genes induced by light in the wild type show enhanced expression in the *det1* mutant (Schroeder *et al.,* 2002). In contrast to the enhanced expression observed in dark-grown seedlings and roots, *det1* mutants show reduced expression of *CAB* genes in light-grown leaves. DET1 is part of a protein complex (CDD) containing the homolog of UV-Damaged DNA Binding Protein 1 (DDB1), a protein that interacts with HAT complexes (Schroeder *et al.,* 2002), and COP10 (Yanagawa, *et al.,* 2004). DDB1 binds HAT complexes in other species, and therefore a suggestive possibility is that in darkness DET1 binds H2B and DDB1 to repress transcription. In response to light, the DET1/DDB1 complex might recruit HAT activities, causing acetylation of H2B (and maybe other histones) and the release of the DET1/DDB1 complex to promote transcription (Benvenuto *et al.,* 2002; Schroeder *et al.,* 2002). Binding of DET1 to specific promoter sequences to induce or repress gene transcription could be mediated by transcription factors like CCA1 and HY5. The dual activity of DET1, working as a repressor and promoting transcription via recruitment of HAT complexes would be consistent with the contrasting effects of *det1* mutations on gene expression. Thus, it appears that chromatin modifications are convergent points in light regulated transcription (Figure 3) and are likely to act as downstream switches of multiple photoreceptors in regulatory networks. Consistent with the role of light in chromatin remodeling processes, inductive photoperiods cause a CRY2 dependent extensive reduction in chromocenters of rosette leaves chromatin prior to bolting, which is followed by a recovery of the heterochromatin domains after elongation of the floral stem. A blue light triggered decondensation of chromatin in gene-rich regions suggests the existence of a light-signalling pathway mediating large scale chromatin modulation (Tessadori *et al.,* 2007).

Signaling to the circadian clock: plasticity by chromatin remodeling

Circadian rhythms are driven by endogenous biological clocks that confer a 24-hour rhythm on many biochemical and physiological processes and are also relevant on seasonal rhythms, such as flowering (Imaizumi and Kay, 2006). In higher plants, as in animals and fungi, endogenous biological clocks are based on autoregulatory negative-feedback loops, which are synchronized by entraining stimuli, in particular light and temperature. The complex program of gene expression that characterizes circadian physiology involves dynamic changes in chromatin structure that ensure the proper timing and extent of circadian regulation. In this way, the animal transcription factor CLOCK was recently found to have intrinsic HAT activity (Doi *et al.,* 2006) and transcriptional activation of clock-controlled genes by CLOCK-BMAL1 has been shown to be coupled to circadian changes in histone acetylation at their promoters (Etchegaray *et al.,* 2003; Ripperger and Schibler, 2006). Indeed, CLOCK-mediated acetylation of BMAL1 controls circadian function (Hirayama *et al.,* 2007). Thus transcription-permissive chromatin states are dynamically established in a circadian-time-specific manner. A direct connection between chromatin remodeling and the plant circadian clock has also been recently reported. The circadian induction of the Arabidopsis clock component *TIMING OF CAB EXPRESSION 1 (TOC1)* is accompanied by cycles of histone acetylation that favor a transcriptionally active chromatin conformation at the *TOC1* locus. In contrast, CCA1-mediated repression of *TOC1* at dawn is facilitated by HDAC activities that promote the switch to an inactive chromatin structure (Perales and Mas, 2007; Stratmann and Mas, 2008).

Cold acclimation

Gene expression events underlying cold acclimation of plants to low temperatures, whereby exposure to low non-freezing temperatures results in protection from subsequent exposure to freezing temperatures, may be also regulated by chromatin remodeling (Vlachonasios *et al.,* 2003; Mao *et al.,* 2006). In *Arabidopsis*, a family of transcription factors known as CBF1, CBF2 and CBF3 are induced by low temperatures and direct the expression of a set of cold-regulated (COR) genes. Different reports have identified coactivator proteins such as *GCN5* HAT and *ADA2* homologs (*ADA2a* and *ADA2b*) that interact with CBF1 and could be involved in the stimulation of cold-regulated gene expression by CBF1 (Stockinger *et al.,* 2001; Vlachonasios *et al.,* 2003). The yeast homologous proteins are components of HAT complexes (Lee *et al.,* 2007), suggesting that CBF1 might stimulate transcription through the recruitment of the ADA/SAGA-like complexes to the promoters of its target genes (Stockinger *et al.,* 2001). Indeed, cold-regulated gene expression was diminished in *gcn5-1* and *ada2b-1* mutant plants (Vlachonasios *et al.,* 2003). Furthermore, FVE, an MSI-like protein involved in the deacetylation of the *FLC* locus, has also been identified as a negative regulator of the CBF pathway (Kim *et al.,* 2004). Thus, it is tempting to speculate that the induction of genes that respond to cold is mediated by HAT activities that are antagonized by HDAC FVE-containing complexes, and therefore histone acetylation mediates transcriptional activation by CBF proteins during cold acclimation in Arabidopsis. HOS15, a component of a repressor protein complex involved in histone deacetylation is also required for cold tolerance in Arabidopsis (Zhu *et al.,* 2008).

Chromatin remodeling in response to stress

Responses to abiotic stress require the modulation of gene expression, which is also mediated by the alteration of chromatin

structure (Arnholdt-Schmitt, 2004). One basic response of plants to environmental stress is the establishment of a temporary growth arrest that allows adaptation to adverse conditions and AtCHR12 SNF2/Brahma-type ATPase seem to play a vital role in mediating this response (Mlynarova *et al.,* 2007; Table I). Exposing an *AtCHR12* overexpressing mutant to stress conditions leads to rapid growth arrest of normally active primary buds, as well as to reduced growth of the primary stem. In contrast, the AtCHR12 KO mutant shows less growth arrest than the wild-type when exposed to moderate stress. Without stress, *AtCHR12* KO mutant plants are indistinguishable from the wild-type, and the growth arrest response seems to depend on the severity of the stress applied. Modulation of AtCHR12 expression also correlates with changes in expression of dormancy-associated genes. This is in agreement with the participation of AtCHR12 in priming plants for growth arrest in the case of stress conditions. By priming their growth response, plants do not repress growth before they actually perceive stress, permitting flexible modulation of growth in adverse and/or otherwise limiting environments. Growth arrest upon stress is thought to be advantageous for plants (Achard *et al.,* 2006) since slower growth might allow plants to redirect resources to overcome or temporarily cope with stress. Apart from this basic growth retardation response, chromatin-remodeling would likely be involved in transcriptional responses to any environmental factor. This is the case of the maize response to UV-B radiation where RNAi transgenic plants with lower expression of four chromatin-associated genes exhibited hypersensitivity to UV-B and altered UV-B regulation of selected genes (Casati *et al.,* 2006), suggesting that genes involved in chromatin remodeling are crucial for UV-B acclimation. Moreover, H3 and H4 histone acetylation and chromatin remodeling are required for proper UV-B dependent activation of genes in maize (Casati *et al.,* 2008). Recently, alterations of lysine modifications on histone H3 N-tail and patterns of nucleosome changes under drought stress have been reported (Kim *et al.,* 2008).

Concluding remarks

The molecular genetic analysis of plant development has reached to the level of epigenetic modification of chromatin. Chromatin structure, determined by a large number of factors which provide epigenetic histone marks, strongly influence the transcriptional activity of master regulatory genes controlling the development of organs and tissues as well as response to environmental cues such as light and temperature. Proper inheritance of chromatin modifications throughout cell division ensures the maintenance of transcriptional states in daughter cells, the proper establishment of cell fates and correct response to changes in the environmental stimuli.

Chromatin remodeling mechanisms and complexes are widely conserved among plants, animals and yeast, indicating that ancient mechanisms evolved in a common eukaryote ancestor. However, the continuous post-embryonic development of plants and its plasticity modulated by environmental cues suggest that chromatin modification must have a higher flexibility in plants than in animals. This flexibility requirement could be responsible for the higher redundancy of complex components observed in plants, allowing the viability of loss-of-function mutants.

Genomic advances in plants such the sequencing of a growing number of genomes, the feasibility of high-throughput genomic, transcriptomic and proteomic analyses and the wide range of reverse genetic tools available are allowing the identification of complete families of plant chromatin modifier factors, making it possible to elucidate the nature of chromatin complexes and facilitating the study of their effect in the transcriptional activity of key regulatory loci. These approaches should provide important insights on how chromatin modifications and epigenetic marks are established and maintained, how chromatin factors interact with each other and how different combinatorial chromatin complexes directly influence the developmental plasticity of plants.

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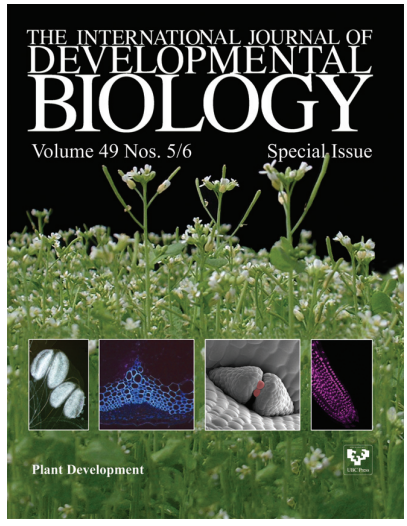

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