Physiologia Plantarum 126: 484–493. 2006

REVIEW

Chromatin-mediated regulation of flowering time in *Arabidopsis*

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Received 20 August 2005; revised 27 October 2005

doi: 10.1111/j.1399-3054.2006.00639.x

Both the transcriptional activation and repression of the major floral repressor *FLOWERING LOCUS C* (*FLC*) are under the control of numerous chromatin modifiers. Some of these modifiers are involved in histone modification or chromatin remodeling that is generally linked to the transcriptional activation. Other modifiers are required for the formation of repressive *FLC* chromatin, which involves histone deacetylation and methylation processes. Epigenetic memory of vernalization is also recorded as a histone modification in *FLC* chromatin. Many proteins that resemble known chromatin modifiers have been proven to regulate gene expressions in the photoperiodic flowering pathway. Therefore, chromatin modification might also act as a mechanism for plants to recollect the experience of exposure to inductive photoperiods.

Floral regulatory network in *Arabidopsis*

Flowering is a switch from vegetative to reproductive growth in plants. Reproductive success can be achieved by a proper control of flowering time; therefore, each plant species has developed sophisticated mechanisms for floral transition. The process of floral transition involves the co-ordinated integration of external or environmental cues with internal regulatory factors such as the developmental status and age of plants. Environmental cues such as temperature, photoperiod, and light quality exert profound effects on the regulation of flowering time. Among temperature effects, the floral promotive role of a long-term cold treatment known as vernalization is best understood. The vernalization effect is more significant in winter-annual type of *Arabidopsis* than in the rapid-cycling summer-annual varieties. In the absence of vernilization in long days (LDs), the winter-annual varieties flower late, whereas the summer-annual varieties flower early.

The winter-annual versus summer-annual habit among different *Arabidopsis* accessions is determined by natural allelic variations in *FRIGIDA* (*FRI*; Johanson et al. 2000) and *FLOWERING LOCUS C* (*FLC*; Gazzani et al. 2003, Michaels et al. 2003). Dominant functional alleles of *FRI* and *FLC* confer winter-annual habit, whereas non-functional *fri* alleles or weak *flc* alleles abolish vernalization requirement for rapid flowering under LD conditions. Therefore, both *FRI* and *FLC* act as floral repressors in *Arabidopsis*. It was observed that the *FLC* transcript level is increased by *FRI* but decreased by vernalization (Michaels and Amasino 1999, Sheldon et al. 1999). Therefore, in comparison with *FRI*, vernalization has an antagonistic effect on *FLC* expression. *FRI* encodes a novel nuclear protein (Johanson et al. 2000), and a genetic study by Michaels et al. (2004) revealed that an *FRI*-related gene, *FRI LIKE 1* (*FRL1*), is also required for the activation of *FLC* transcription by *FRI*.

Some of the induced late-flowering mutants showed flowering time behaviors similar to those of *FRI*-containing accessions (Koornneef et al. 1991). The

Abbreviations – *FLC*, *FLOWERING LOCUS C*; *FRI*, *FRIGIDA*; LD, long day; SD, short day.

genes responsible for the late-flowering behaviors of these mutants normally act as *FLC* repressors. However, the presence of *FRI* overrides the repressive role of these genes and allows the activation of *FLC* transcription (e.g. Michaels and Amasino 1999). This *FLC*-repressive pathway was named the autonomous pathway (Koornneef et al. 1991). The autonomous pathway is mainly composed of two protein classes: the first includes putative RNA-binding proteins, whereas the second includes chromatin modifiers (He and Amasino 2005, He et al. 2003). Therefore, *FLC* acts as a convergence point of multiple floral regulatory signals that include *FRI*, vernalization, and the autonomous pathway.

In *Arabidopsis*, flowering is accelerated by LD conditions but delayed by shorter light periods (Koornneef et al. 1998). Light quality also exerts significant effects on flowering (recently reviewed in Boss et al. 2004). Generally, far-red and blue lights promote flowering in *Arabidopsis*; however, red light delays flowering. The ability to sense the photoperiod and light quality primarily depends on photoreceptors. In *Arabidopsis*, phytochromes A through E (Quail 2002) and cryptochromes 1 and 2 (Lin 2000) are responsible for light perception. Different light qualities, i.e. wavelengths, are perceived by different photoreceptors, and wavelength-specific signals are generated. Light and dark signals are first perceived by the photoreceptors, and the duration of the day and night, i.e. the photoperiod, is then measured by the circadian clock. Therefore, it is natural that many photoreceptors and circadian clock mutants show altered photoperiodic flowering behaviors. Light signals that are used for measuring photoperiods are mediated to flowering time through the key linker protein CONSTANS (CO, reviewed in Hayama and Coupland 2003).

Floral regulatory signals that converge on *FLC* are further integrated with the photoperiodic floral regulatory signals to control the expression of a few common downstream floral integrators such as *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1* (*SOC1*) and *FT* (e.g. Boss et al. 2004, Simpson and Dean 2002). The role of FLC is to repress the expressions of these floral integrators, whereas that of the CO-mediated photoperiodic signals is to activate the integrators. The induction of the expression of floral integrators results in the activation of floral meristem identity genes such as *LEAFY* and *APETALA 1* (Boss et al. 2004), which in turn allows the transition of the vegetative shoot apical meristem (SAM) to inflorescence SAM. Thus, FLC acts as a major floral repressor in *Arabidopsis*, and the photoperiodic floral regulatory signals antagonize this FLC-mediated floral repressive activity.

Activation of *FLC* transcription by chromatin modifiers

Molecular genetic studies using an *FRI*-containing winter-annual *Arabidopsis* have led to the identification of numerous factors required for the elevated expression of *FLC*. One of these factors, *FRL1* (Michaels et al. 2004), is specifically required for the *FRI*-dependent activation of *FLC* transcription, but not for *FLC* activation due to mutations in the autonomous pathway. However, the remaining factors are required for the elevated expression of *FLC* by the mutations in the autonomous pathway as well as by *FRI*. Many of these factors resemble chromatin modifiers that have been studied in yeast or animal systems. VERNALIZATION INDEPENDENCE 2 (VIP2, also known as EARLY FLOWERING 7, ELF7) is a homolog of yeast RNA polymerase II-associated factor 1 (PAF1; Squazzo et al. 2002) and is required for the elevated expression of *FLC* in the autonomous-pathway late-flowering mutants and in an *FRI*-containing winter-annual ecotype (He et al. 2004, Oh et al. 2004). In yeast, PAF1 forms a complex with LEO1, RTF1, CTR9, and CDC73 (He and Amasino 2005, Mueller and Jaehning 2002). It was observed that *Arabidopsis* homologs of LEO1 (VIP4), RTF1 (VIP5), and CTR9 (VIP6 or ELF8) are also required for the transcriptional activation of *FLC*, and VIP6 interacts with VIP4 *in vivo* (He et al. 2004, Oh et al. 2004). Therefore, it is believed that the *Arabidopsis* PAF1-like complex is required for the general activation of *FLC* transcription.

The PAF1 complex together with serine-5 phosphorylation of the C-terminal domain of RNA Polymerase II (RNA POLII) is required for the recruitment of SET1, a histone methyltransferase, in yeast (Hampsey and Reinberg 2003). The recruited SET1 catalyzes the trimethylation reaction of histone 3 (H3) at lysine 4 (H3-K4) in the 5′ region of the target gene, and this trimethylation is believed to be a hallmark of active chromatins (Ng et al. 2003). A recent study indicates that EARLY FLOWERING IN SHORT DAYS (EFS), an *Arabidopsis* homolog of SET1, is also required for the activation of *FLC* transcription in the *FRI*-containing winter-annual ecotype or in the autonomous-pathway late-flowering mutants (Kim et al. 2005). The H3-K4 trimethylation of *FLC* chromatin is reduced in *vip2* and *vip6* as well in *efs* mutants (He et al. 2004, Kim et al. 2005). Therefore, not only an SET1 homolog (EFS) but also a PAF1-like complex is required for the elevated H3-K4 trimethylation of *FLC* chromatin and for the increased *FLC* transcription in winter-annual type late-flowering *Arabidopsis*.

Lesions in *PHOTOPERIOD-INDEPENDENT EARLY FLOWERING 1* (*PIE1*), a gene encoding an ISWI family

ATP-dependent chromatin remodeling protein, also cause the conversion of winter-annual habit to rapid-flowering summer-annual habit, which accompanies a large reduction in *FLC* transcript levels (Noh and Amasino 2003). With regard to the report that Isw1p, a yeast PIE1 homolog, can bind di- and trimethylated H3-K4 (Santos-Rosa et al. 2003), it might be speculated that PIE1 might bind the trimethylated H3-K4 that is generated by EFS and the PAF1-like complex and remodel *FLC* chromatin to allow active transcription.

In conclusion, molecular genetic studies on *Arabidopsis* have identified multiple chromatin modifiers involved in the activation of *FLC* transcription. Yeast counterparts of many of these factors are known to induce H3-K4 trimethylation at the 5′ region of the target gene chromatin. *FLC* chromatin is believed to be affected by these chromatin modifiers in a similar manner. Hence, a scenario similar to that depicted as a model in Fig. 1 might govern chromatin modification during the activation of *FLC* transcription.

Repression of *FLC* chromatin in the absence of *FRI*

Lesions in the autonomous floral regulatory pathway derepress *FLC* expression in a non-functional *fri* background (Michaels and Amasino 2001). Thus far, approximately eight members are known to act as *FLC* repressors in the autonomous pathway. These include LUMINIDEPENDENS (LD; Lee et al. 1994), FCA (Macknight et al. 1997), FPA (Schomburg et al. 2001), FY (Simpson et al. 2003), FLOWERING LOCUS D (FLD; He et al. 2003), FVE (Ausin et al. 2004), FLOWERING LOCUS K (FLK; Lim et al. 2004), and RELATIVE OF EARLY FLOWERING 6 (REF6; Noh et al. 2004). The molecular nature of some of these autonomous pathway members suggests that they may regulate *FLC* expression through chromatin remodeling. Hyperacetylation of H3 or H4 tails usually allows active transcription of the target gene (Iizuka and Smith 2003). Consistent with this general concept, hyperacetylation of H3 or H4 tails in *FLC* chromatin was observed in *fld* (He et al. 2003), *fve* (Ausin et al. 2004), and *ref6* (Noh et al. 2004) mutants in which *FLC* transcription is derepressed. However, mutations in other autonomous pathway genes such as *ld*, *fpa*, and *fca* do not result in similar hyperacetylation in *FLC* chromatin (He et al. 2003).

FLD encodes a polyamine oxidase that is similar to human KIAA0601 (He et al. 2003). KIAA0601 was reported to be a member of a human histone deacetylase (HDAC) complex (Humphrey et al. 2001). However, a study by Shi et al. (2004) showed that KIAA0601 is a histone demethylase, which is specific to dimethylated H3-K4. Therefore, hyperacetylation of H3 or H4 tails of *FLC* chromatin in *fld* mutants might be an indirect effect of a chromatin modification complex that might contain FLD as well as HDACs that are yet to be identified. *FVE* encodes a homolog of mammalian retinoblastoma-associated proteins RbAp46 and RbAp48 that are known to function as transcriptional repressors by recruiting HD1/RPD3 HDACs (Ausin et al. 2004). Hence, the hyperacetylation of *FLC* chromatin in *fve* mutants (Ausin et al. 2004) might have occurred due to the lack of recruitment of an HDAC complex to *FLC* chromatin. REF6 is a nuclear-localized putative DNA-binding protein that contains four copies of C2H2-type zinc-finger (ZnF) domains as well as jumonji N- (JmjN) and C-terminal (JmjC) domains (Noh et al. 2004). As a yeast Jmj-domain-containing protein Epe1 was shown to be required for the modulation of heterochromatin formation, the hyperacetylation of H4 tails in the *FLC* locus was observed in *ref6* mutants (Noh et al. 2004).

Therefore, a possible scenario for the repression of *FLC* chromatin in the absence of *FRI* might involve REF6 binding to the *FLC* locus, which results in the recruitment of FVE (Fig. 2). The WD-repeat motif of FVE may act as a platform for the assembly of other chromatin modifiers that include FLD and the unidentified HDACs. The chromatin remodeling activity driven by this complex may result in the hypoacetylation of H3 or H4 tails as well as the reduced H3-K4 methylation of *FLC* chromatin.

Vernalization-induced repression of *FLC* chromatin

The acceleration of flowering by vernalization in winter-annual type of *Arabidopsis* is largely mediated by the downregulation of *FLC* expression (Michaels and Amasino 2000). One of the interesting characteristics of vernalization is the stable maintenance or memory of the long-term cold effect in the warm growth conditions that follow. Downregulated *FLC* expression is also maintained stably in the absence of the inducing cold signal after vernalization (Sheldon et al. 2000). Therefore, vernalization-dependent regulation of *FLC* expression has an epigenetic nature in which the experience of cold exposure is recollected and inherited stably in cell lineages during the following growth period. However, this 'memory-of-cold' is reset in the next generation following meiotic cell division.

Three mutants that are less sensitive or insensitive to the floral promotion effect of vernalization have been isolated, and their target genes have been confirmed. In two of these mutants, *vernalization 1* (*vrn1*; Levy et al. 2002) and *vrn2* (Gendall et al. 2001), *FLC* expression is downregulated

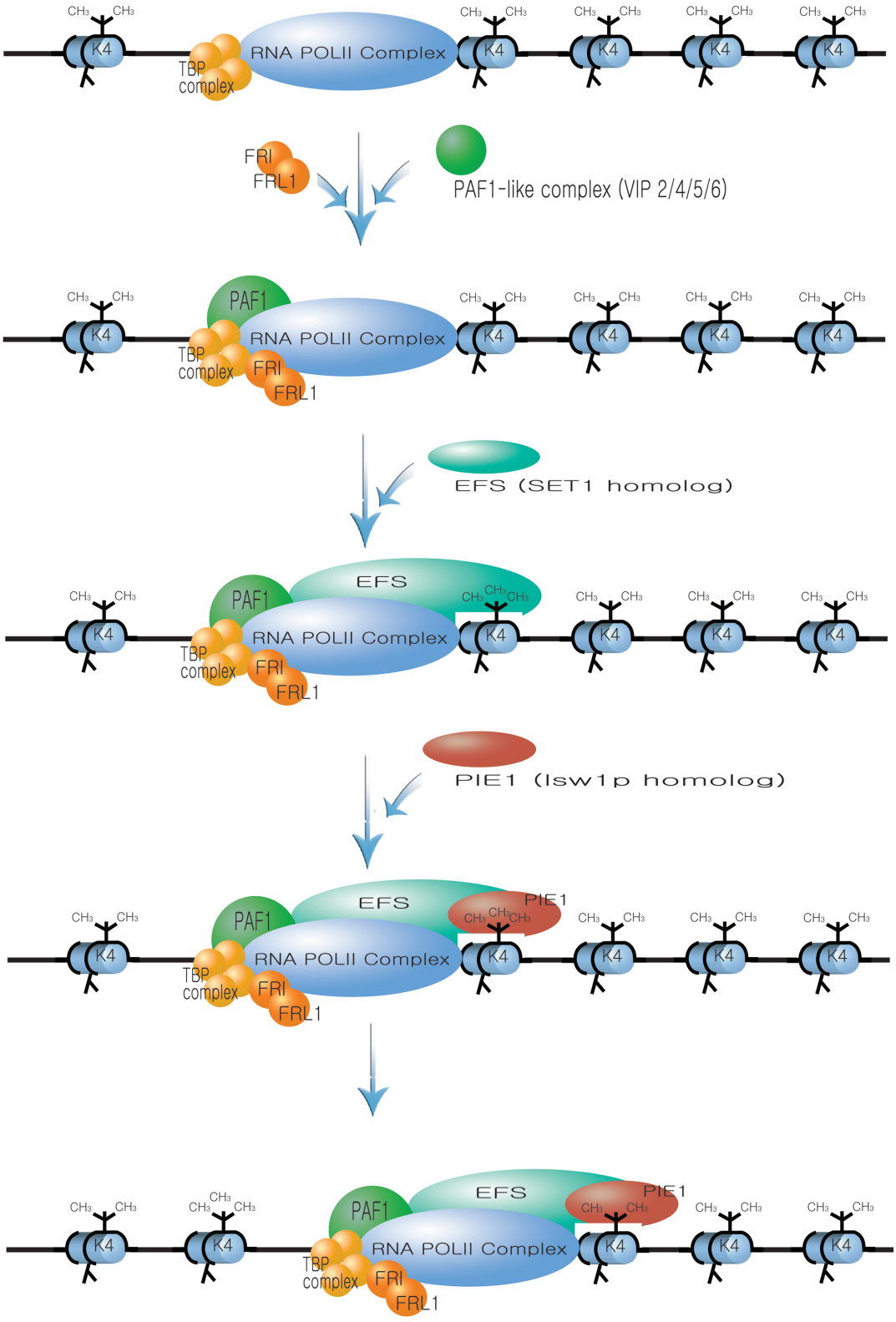

Fig. 1. Model of the *FLC* transcription activation. TBP, TATA box-binding protein. Refer to text for details.

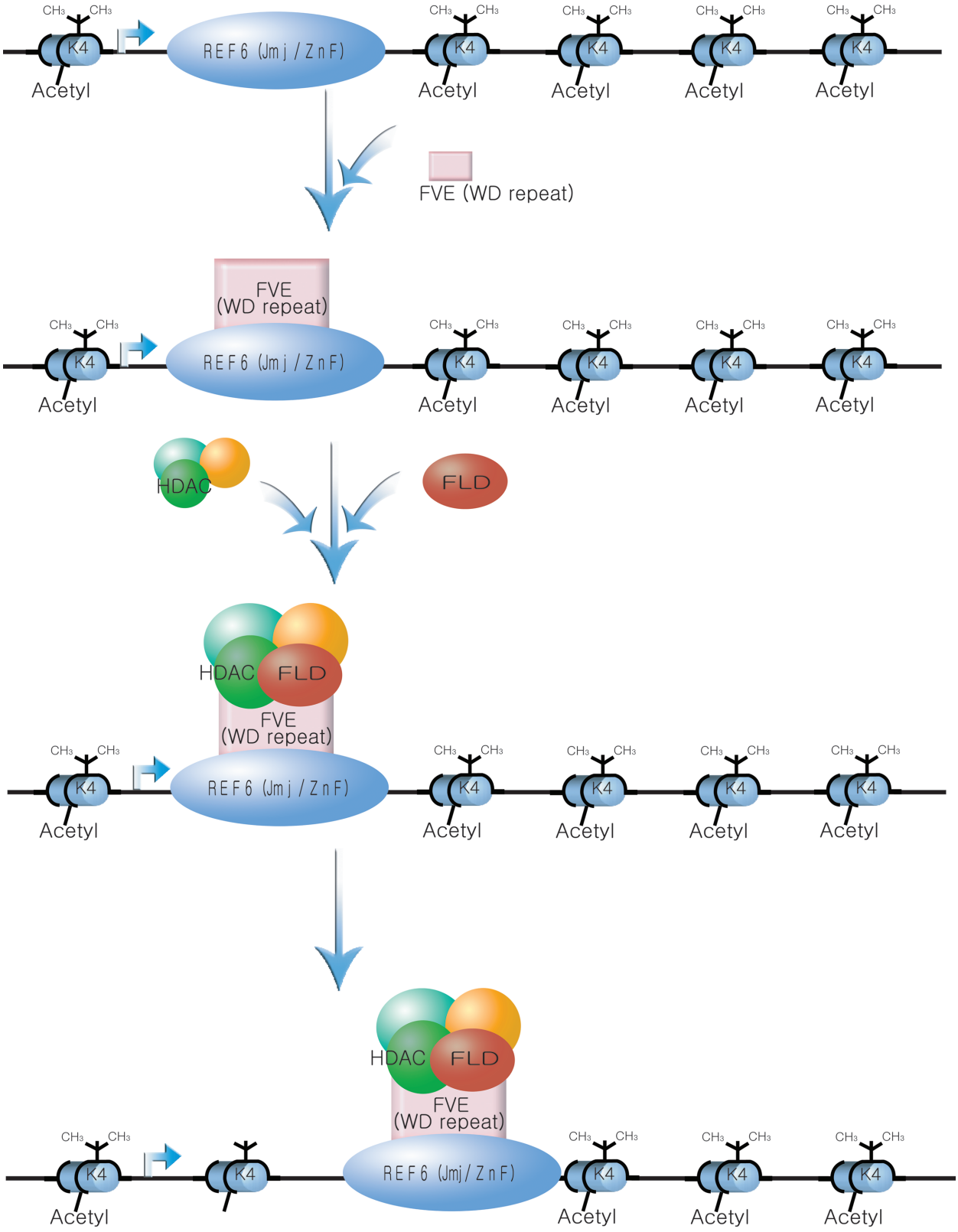

Fig. 2. Model of the repression of *FLC* chromatin in the absence of functional *FRI*. Refer to text for details.

during the course of vernalization; however, the repressed expression level is not maintained stably during the warm growth period that follows, thereby resulting in the derepression of *FLC* expression and late flowering. Therefore, *VRN1* and *VRN2* are required for the stable maintenance of the floral promotion effect of vernalization. In the third mutant, *vernalization insensitive 3* (*vin3*; Sung and Amasino 2004), *FLC* expression is not repressed during the long cold treatment period; this suggests that *VIN3* plays a role in early vernalization stages.

VIN3 encodes a protein containing a PLANT HOMEODOMAIN (PHD) finger (Sung and Amasino 2004). *VIN3* expression is specifically induced during the course of vernalization and repressed upon returning to warm growth conditions. *FLC*-independent floral promotion effect of vernalization is also disrupted in *vin3* mutants. Therefore, *VIN3* might have a specific role in the initial perception of a long-term cold exposure. Consistent with this view, neither deacetylation of histone tails nor an increase in H3-K27 and H3-K9 methylation of *FLC* chromatin, which are known to occur during vernalization (Bastow et al. 2004, Sung and Amasino 2004), is observed in *vin3* mutants. VRN2 is similar to a *Drosophila* polycomb group protein, Suppressor of Zeste-12 (Gendall et al. 2001), and is required for H3-K27 methylation of *FLC* chromatin (Bastow et al. 2004, Sung and Amasino 2004). *VRN1* encodes a B3-domain-containing DNA-binding protein (Levy et al. 2002) that plays a role in H3-K9 methylation of *FLC* chromatin (Bastow et al. 2004, Sung and Amasino 2004). The level of trimethylation at H3-K4, which is a hallmark of an active chromatin, is also known to be reduced in *FLC* chromatin due to vernalization (He and Amasino 2005).

In conclusion, studies using the winter-annual type of *Arabidopsis* indicate that *FLC* chromatin is remodeled into a heterochromatin-like structure by vernalization. This long-term cold-induced chromatin modification process may accompany the dissociation of a chromatin remodeling complex that is required for the activation of *FLC* transcription (Fig. 3). Furthermore, a VIN3-containing vernalization-specific complex may associate with *FLC* chromatin and reduce the H3-K4 trimethylation and the acetylation levels of histone tails. Epigenetic memory of vernalization with a greater stability may then be achieved through VRN2- and VRN1-dependent methylation of histone tails within *FLC* chromatin.

Regulation of photoperiodic flowering by chromatin modifiers

Early studies on photoperiodic flowering led to the development of the 'florigen hypothesis' in which leaves perceive inductive photoperiods and subsequently produce a signal that is translocated from the leaves to the SAM to initiate the floral transition (Chailakhyan 1936). This signal has been referred to as florigen, although its chemical nature remains to be clarified. In some plant species, a detached leaf can be photoperiodically induced and then grafted onto uninduced plants several times, thereby causing the recipient plants to flower (Zeevaart 1984). This indicates that the photoperiodically induced leaves might have a memory of floral promotion.

Molecular genetic studies on *Arabidopsis* flowering have led to the discovery of several chromatin modifier proteins that act on the photoperiodic pathway. ELF6 contains Jmj/ZnF domains and shares maximum homology with REF6 in the *Arabidopsis* genome (Noh et al. 2004). Although the direct target of ELF6 has not been defined, genetic studies indicate that ELF6 represses the photoperiodic pathway at the upstream of *GIGANTEA*. A chromatin modifier in the SWI/SNF-class ATPase, *Arabidopsis thaliana* BRAHMA, is known to regulate the expression of *CO*, *FT*, and *SOC1* but not *FLC*, indicating that it is involved in the photoperiodic floral regulation at the upstream of *CO* (Farrona et al. 2004). Lesions in *EARLY BOLTING IN SHORT DAYS* (*EBS*), a gene encoding a bromoadjacent homology domain- and PHD-containing protein, result in an increased expression of *FT*, but not *CO* mRNA (Pineiro et al. 2003). Similarly, when the function of TERMINAL FLOWER 2 (TFL2 or LHP1, a homolog of yeast chromodomain-containing protein HETEROCHROMATIN PROTEIN 1) was disrupted, the expression of *FT*, but not *CO*, was increased significantly (Kotake et al. 2003, Takada and Goto 2003). Therefore, both *EBS* and *TFL2* might be required for the repression of *FT* chromatin through direct or indirect mechanisms.

Recent studies have suggested that FT might be a component of the mobile floral inductive signal (Abe et al. 2005, Wigge et al. 2005). *FT* is expressed in the leaf vascular cells; however, FT protein can interact with the transcription factor FD that is specifically expressed in shoot and root apical meristems, and this interaction is required for the proper control of floral transition in *Arabidopsis*. Furthermore, a study by another group showed that the transcript of *FT* moves from the leaf to the shoot apex (Huang et al. 2005). A local induction of *FT* in a single *Arabidopsis* leaf resulted in the movement of *FT* mRNA to the shoot apex, and this induction was sufficient to trigger flowering. The induced *FT* could stably maintain its expression, irrespective of the day-length conditions that follow. This finding explains the classical observation in which a photoperiodically induced leaf continues to generate a graft-transmissible signal(s) (Zeevaart 1984).

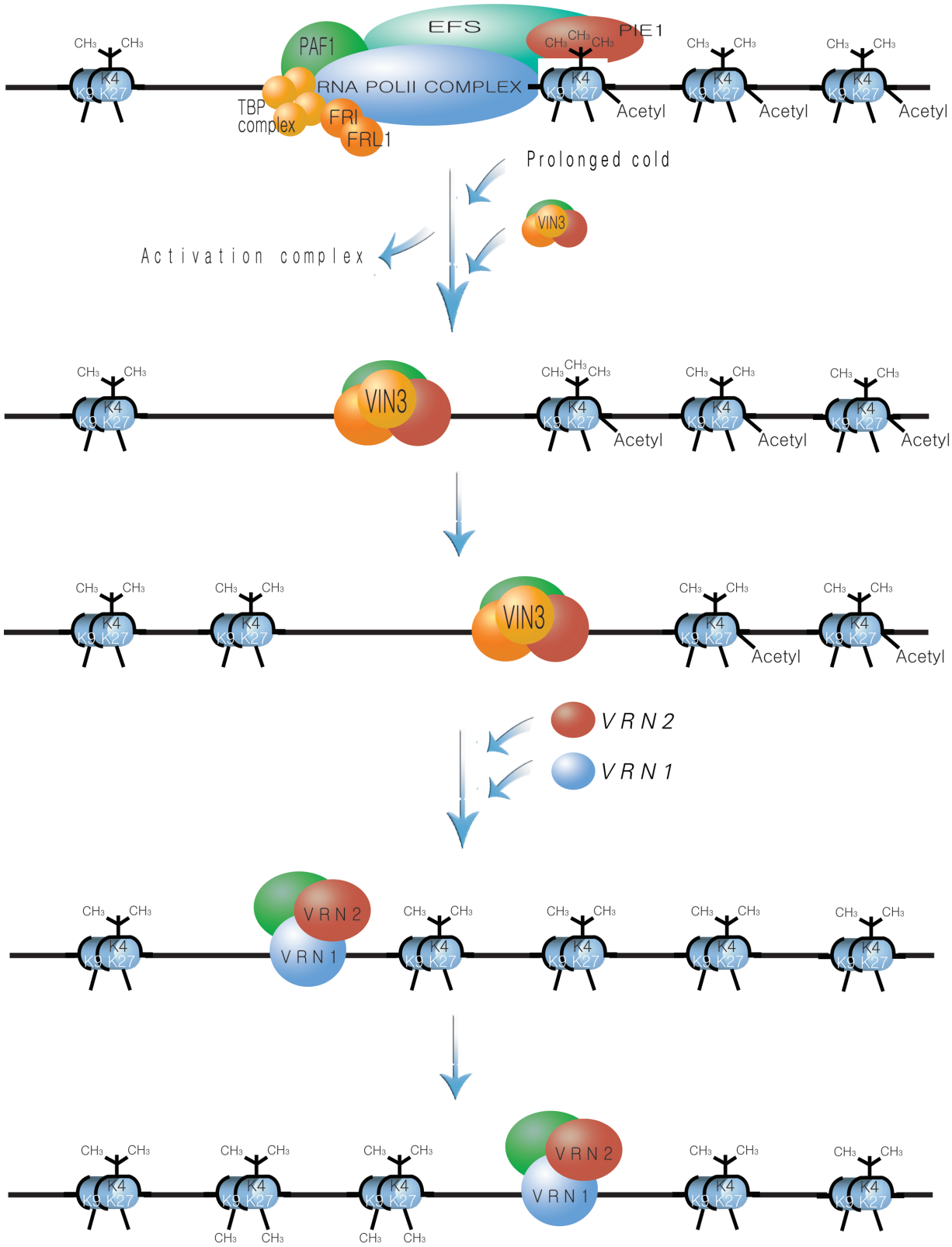

Fig. 3. Model of the repression of *FLC* chromatin by vernalization. TBP, TATA box-binding protein. Refer to text for details.

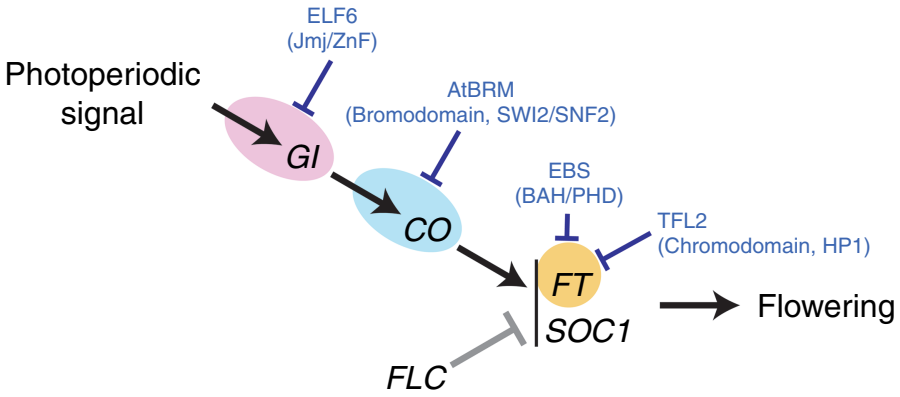

Fig. 4. Chromatin modifier proteins acting on the photoperiodic flowering pathway. Refer to text for details.

Taken together, early physiological studies implied the existence of a mechanism that allows an epigenetic floral induction in leaves by inductive photoperiods. A recent study on *FT* also suggested that the photoperiodic induction of *FT* is recollected in leaves, irrespective of the photoperiodic conditions that follow (Huang et al. 2005). As *FLC*, another epigenetic floral regulatory point, is controlled by a variety of chromatin modifiers, the photoperiodic floral regulatory pathway is also under the control of many chromatin modifiers (Fig. 4). Hence, chromatin modification could be a mechanism to recollect the experience of exposure to inductive photoperiods in plant leaves.

Concluding remarks

Growing evidences indicate that the major floral repressor *FLC* is under the control of numerous chromatin modifiers. Some of these chromatin modifiers are required for the activation of *FLC* transcription, whereas others repress *FLC* transcription either in the absence of functional *FRI* or during vernalization-induced floral activations. It is evident that H3-K4 trimethylation plays an important role in the activation of *FLC* transcription. Histone deacetylation and methylation processes are clearly involved in the transcriptional repression of *FLC*. Further, it is believed that 'histone codes' act as a mechanism for the cellular memory of vernalization. However, the catalytic components and biochemical details of these deacetylation or methylation processes of *FLC* chromatin have to be thoroughly studied in the future. Physiology of photoperiodic floral induction in leaves and the stable maintenance of *FT* expression after a single photoperiodic induction suggest the existence of a mechanism to recollect the experience of exposure to inductive photoperiods. Because the photoperiodic flowering pathway is also under the control of numerous chromatin modifiers, it is possible that the exposure to inductive photoperiods might be recollected in the leaf cells through the modification of the chromatin of key regulatory genes in the photoperiodic flowering pathway.

Acknowledgements – We are grateful to the Molecular and Cellular Biodiscovery Research Program (M10301000060-05N0100-06010) from the Ministry of Science and Technology of Korea, the BioGreen21 Program (20050401-034-753-145-02-00 and 20050401-034-753-145-03-00) from the Rural Development Administration of Korea, and the Environmental Biotechnology National Core Research Center for their support to our research on flowering and chromatin.

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Edited by V. Hurry