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HIGHLIGHT

# Regulation of Flowering Time by MicroRNAs

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The shoot apical meristem (SAM) continuously produces lateral organs in plants. Based on the identity of the lateral organs, the life cycle of a plant can be divided into two phases: vegetative and reproductive. The SAM produces leaves during the vegetative phase, whereas it gives rise to flowers in the reproductive phase (reviewed in Poethig, 2003). The floral transition, namely the switch from vegetative to reproductive growth, is controlled by diverse endogenous and exogenous cues such as age, hormones, photoperiod, and temperature (reviewed in Bäurle and Dean, 2006; Srikanth and Schmid, 2011; Andres and Coupland, 2012).

The model annual *Arabidopsis thaliana* has been extensively used for the dissection of the molecular mechanism underlying the floral transition during the last two decades. The molecular and genetic analyses have revealed five flowering time pathways, including age, autonomous, gibberellins (GAs), photoperiod and vernalization (reviewed in Amasino and Michaels, 2010). Growing lines of evidence indicate that there are extensive crosstalks, feedback or feed-forward loops between the components within these pathways, and that these multiple floral inductive cues are integrated into a set of floral promoting MADS-box genes including *APETALA 1* (*AP1*), *SUPPRESSOR OF OVEREXPRESSION OF CO 1* (*SOC1*), *FRUITFULL* (*FUL*) and *LEAFY* (*LFY*) (Amasino and Michaels, 2010; Lee and Lee, 2010; Srikanth and Schmid, 2011).

The onset of flowering in *Arabidopsis* is accelerated when the length of daylight is prolonged compared with darkness. Seasonal changes in day length are measured by CONSTANS (CO), which activates the expression of *FLOWERING LOCUS T* (*FT*) in the vascular tissues of the leaves (Samach et al., 2000; An et al., 2004; Kobayashi and Weigel, 2007). In long day, *CO* expression coincides with light, which leads to stabilization of CO. By contrast, the expression of *CO* peaks after dusk in short day, so that CO protein is subjected to degradation (Yanovsky and Kay, 2002; Valverde et al., 2004). The FT protein, as the output of the photoperiodic cue, moves from the leaves to the shoot apex, where it binds to the 14-3-3 protein and the transcription factor FD to activate the expression of *LFY* and MADS-box genes, such as *AP1* and *SOC1* (Abe et al., 2005; Wigge et al., 2005; Corbesier et al., 2007; Jaeger and Wigge, 2007; Lin et al., 2007; Mathieu et al., 2007; Taoka et al., 2011).

In addition to long day, the flowering of *Arabidopsis* is accelerated by 2-month exposure to cold temperatures, a treatment known as vernalization. Genetic screen has identified *FLOWERING LOCUS C* (*FLC*), a floral repressor MADS-box gene, as the key factor in vernalization pathway. Transcription of *FLC* rapidly decreases in the cold through a polycomb-based switching mechanism (Heo and Sung, 2011; reviewed in Song et al., 2012). Tissue-specific expression experiments further indicate that FLC delays flowering through repressing *FT* in the leaves and MADS-box genes at shoot apex (Searle et al., 2006).

GAs are diterpenoid acids that regulate many aspects of plant growth and development, including stem elongation, germination, dormancy, and leaf senescence. The plant deficient in GA biosynthesis never flowers under non-inductive short day conditions (Wilson et al., 1992). GA signaling transduction is mediated by ubiquitin-proteasome degradation (Harberd, 2003; Schwechheimer and Willige, 2009). GIBBERELLIN INSENSITIVE DWARF1 (GID1), a nuclear-localized GA receptor, binds to GA and promotes the degradation of the transcriptional repressor, DELLA. In the *Arabidopsis* genome, there are five DELLA proteins: REPRESSOR OF GA1-3 (RGA), GA INSENSITIVE (GAI), RGA-LIKE1 (RGL1), RGL2 and RGL3 (Murase et al., 2008).

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The degradation of DELLA proteins is mediated by 17 amino acids, called DELLA motif (Dill et al., 2001). The *gai* mutant, which carries the deletion of the DELLA motif, is insensitive to GA-induced proteolysis and delays flowering (Peng et al., 1997; Dill et al., 2001).

miRNAs are 21−24 nt long, noncoding RNAs widely distributed in animals and plants (Bartel, 2009). Plant miRNAs are generated by endonuclease DICER1 (DCL1) in the nucleus (Papp et al., 2003). The mature miRNA is then exported to the cytoplasm and loaded into the RNA-induced silencing complex (RISC), where it regulates gene expression, through distinct mechanisms including transcript cleavage (Llave et al., 2002; Reinhart et al., 2002), translational inhibition (Chen, 2004; Brodersen et al., 2008) or DNA methylation (Bao et al., 2004). In this review, we summarize the recent progress in understanding how miRNAs regulate the floral transition and how these small gene regulators are integrated into flowering time pathways by feedback or feed-forward loops.

## miR156-SPL DEFINES AGE PATHWAY

miR156 targets a group of transcription factors, called SQUAMOSA PROMOTER BINDING LIKEs (SPLs) (Cardon et al., 1999; Rhoades et al., 2002). In the *Arabidopsis* genome, there are 11 *SPLs* targeted by miR156. These *SPL* genes can be divided into two major clades, represented by *SPL3* and *SPL9*. SPL3 differs from SPL9 as it lacks the putative protein−protein interaction domain in the C-terminal.

Expression of miR156 is regulated by age: it is highly accumulated at seedling stage, and gradually decreased with time (Wu and Poethig, 2006; Wang et al., 2009; Wu et al., 2009). This temporal expression pattern is observed not only in *Arabidopsis*, but also in other plants, including maize, rice, and poplar (Chuck et al., 2007; Wang et al., 2011; Xie et al., 2012). The age-dependent decline of miR156 results in an increase in SPLs that promote flowering through activating *FT*, MADS-box genes, and *LFY* (Wang et al., 2009; Yamaguchi et al., 2009; Kim et al., 2012). Interestingly, SPL is able to activate another miRNA, miR172, which targets APETALA2 (AP2), a group of transcriptional repressor of *FT* (Mathieu et al., 2009; Wu et al., 2009). This feed-forward loop ensures an irreversible vegetative-to-reproductive transition.

SPLs not only act as the upstream activators of the floral promoting MADS-box genes but also serve as their downstream targets (Fig. 1). The expression of three miR156-targeted *SPLs*, namely *SPL3*, *SPL4* and *SPL5*, is highly induced by photoperiod in a *PENNYWISE* (*PNY*) and *POUND-FOOLISH* (*PNF*) dependent manner (Schmid et al., 2003; Lal et al., 2011). Consistent with this, *SPL3* has been shown to be directly regulated by SOC1 (Jung et al., 2011) and the transcript level of *SPL4* is reduced in the shoot apical meristem of the *soc1 ful* double mutant (Torti et al., 2012).

miR156 is present in nearly all plant taxa (Axtell and Bowman, 2008). Overexpression of miR156 in rice results in severe dwarfism, strongly reduced panicle size, and delayed flowering (Xie et al., 2006). In maize, the dominant mutation in *Corngrass1*, which overproduces miR156, causes a delay in flowering (Chuck et al., 2011). The similar flowering phenotype is observed in the transgenic *Solanum lycopersicum* (Zhang et al., 2011), indicating an evolutionarily conserved role of miR156 in flowering.

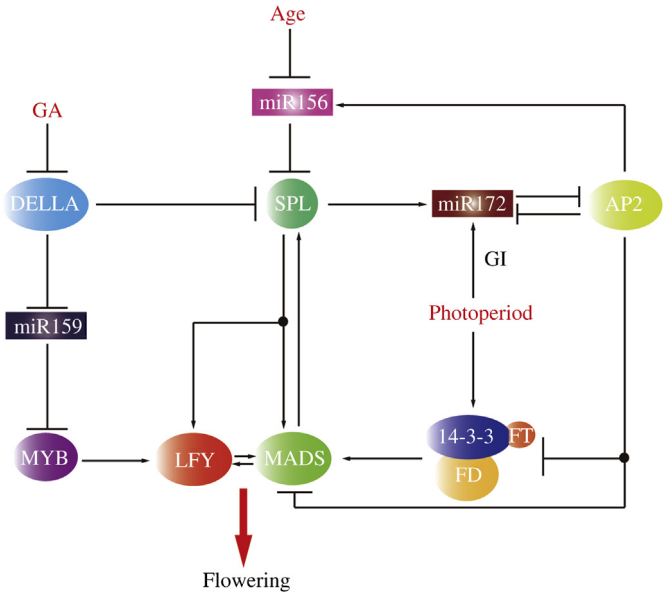


Fig. 1. miRNA-mediated flowering time pathways.
The flowering time pathways are governed by three miRNAs, miR156, miR172 and miR159. The targets of these miRNAs (SPL, AP2 and MYB) regulate the floral transition through modulating the expression of the key floral promoting genes, such as *FT*, MADS-box genes and *LFY*. Note the role of miR159 and its targets in flowering is controversial (see text for details).

## miR172 INTEGRATES DIVERSE FLORAL INDUCTIVE CUES

The targets of miR172 encode a family of AP2-like transcription factors, including *AP2*, *SCHLAFMUTZE* (SMZ), *SCHNARCHZAPFEN* (SNZ), *TARGET OF EAT1* (*TOE1*), *TOE2* and *TOE3* (Aukerman and Sakai, 2003). Overexpression of miR172 causes an extremely early flowering phenotype under both short day and long day conditions (Jung et al., 2007). The plant in which *TOE1* is constitutively expressed responds to vernalization and GA treatments, but impairs the day-length perception. Expression analyses indicate that miR172 is regulated by photoperiod through GIGANTEA (GI) (Jung et al., 2007), which positively regulates *CO* transcription (Fowler et al., 1999; Park et al., 1999). Mature miR172 level is significantly reduced in *gi* mutant, whereas the primary transcript of *MIR172* (*pri-MIR172*) is elevated, suggesting that GI promotes miR172 accumulation at the miRNA processing level (Fig. 1).

Whole-genome mapping of AP2 binding sites demonstrates that miR172-AP2 module not only regulates *FT* in leaves, but also represses many other flowering time regulators acting downstream of *FT* in the shoot apex (Mathieu et al., 2009). Intriguingly, AP2 also negatively regulates miR172 and

positively regulates miR156, suggesting a miR156-miR172 feedback loop in fine tuning the flowering response (Yant et al., 2010).

In addition to being regulated by GI-mediated miRNA processing, the level of miR172 is also affected by FCA, an RNA-binding protein (Jung et al., 2012). FCA is less abundant at 16°C than at 23°C. FCA binds to the flanking sequences of the stem-loop within the *pri-MIR172* transcripts and promotes its processing *via* the RNA recognition motif.

SHORT VEGETATIVE PHASE (SVP) encodes a MADS box protein that regulates flowering in response to ambient temperature (Lee et al., 2007). Recently, it is found that the level of miR172 correlates with SVP expression. SVP protein directly represses miR172 transcription through the binding of CArG motif in the promoter of *MIR172A* (Cho et al., 2012).

Being endogenous flowering time pathways, age and GA pathways play the predominant roles under non-inductive short day conditions. Misexpression experiments have revealed that DELLA represses flowering in both leaves and shoot apex (Galvao et al., 2012; Yu et al., 2012). GA and age pathways are integrated through a direct physical interaction between DELLA and miR156-targeted SPLs. The binding of DELLA to SPLs interferes with SPL transcriptional activities: DELLA delays flowering through reducing *FT* expression *via* repressing of miR172 in leaves; whereas it delays flowering *via* repressing MADS-box genes in the shoot apex (Fig. 1). Thus, miR172 and its targets act as a central hub for integration of photoperiod, age and GA pathways.

## OTHER FLOWERING TIME RELATED miRNAs

Another miRNA-mediated flowering time pathway is governed by miR159, which targets at least three *MYB* genes in *Arabidopsis*, including *MYB33*, *MYB65* and *MYB101* (Achard et al., 2004). The role of miR159 and its targets in flowering is controversial. It has been shown that the transcript level of *MYB33* is elevated by short to long-day shift or GA treatment and MYB33 promotes the floral transition through activation of *LFY* (Gocal et al., 2001). In addition, expression analyses indicate that DELLA represses miR159 and GA promotes miR159 accumulation by overcoming DELLA-mediated repression (Achard et al., 2004). The impact of miR159 in flowering is pronounced in non-inductive condition since increased level of miR159 delays flowering only in short day. However, another two labs reported contradictory results. Schwab et al. (2005) showed that overexpression of miR159 results in anther defects, but no alteration in flowering time. In agreement with these findings, Alonso-Peral et al. (2010) revealed that *mir159a mir159b* double mutant confers normal GA response and does not exhibit early flowering phenotype in short day. Thus, whether *MYB33* and its related *MYB* genes play a role in flowering time awaits further investigation.

In addition to miR156, miR172 and miR159, some other miRNAs have been shown to play important role in flowering. In rice, the targets of miR393 encode auxin receptors, OsTIR1 and OsAFB2 (Xia et al., 2012). Increased level of miR393 not only shows hyposensitivity to auxin, but also promotes flowering (Xia et al., 2012), suggesting a potential role of auxin signaling in flowering. Similarly, miR399 and its target gene *PHOSPHATE 2* (*PHO2*) are known to regulate flowering time, in addition to a role in the maintenance of phosphate homeostasis (Kim et al., 2011). In *Arabidopsis*, miR399-overexpressing plants and *pho2* mutants exhibit early flowering phenotype only at normal temperature (23°C), but not at lower temperature (16°C). Expression analyses suggest that the acceleration of flowering is likely due to an increased expression of *TWIN SISTER OF FT* (*TSF*).

## FUTURE DIRECTIONS

With the identification of a number of flowering-time related miRNAs, the challenge is now to understand their precise roles in the floral transition. For example, how these miRNAs and their targets are integrated into flowering time pathways? Whether these miRNAs exert a conserved role in flowering between annual and perennial plants, or between dicot and monocot? Flowering time is sensitive to endogenous cues such as age and nutrition, and environmental fluctuations including temperature, photoperiod and light quality. Thus, another challenge is to explore the molecular mechanism by which these miRNAs are regulated by these diverse cues.

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