FLOWERING NEWSLETTER REVIEW

Genetic and molecular basis of floral induction in Arabidopsis thaliana

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Received 13 October 2019; Editorial decision 13 January 2020; Accepted 3 February 2020

Editor: Frank Wellmer, Trinity College Dublin, Ireland

Abstract

Many plants synchronize their life cycles in response to changing seasons and initiate flowering under favourable environmental conditions to ensure reproductive success. To confer a robust seasonal response, plants use diverse genetic programmes that integrate environmental and endogenous cues and converge on central floral regulatory hubs. Technological advances have allowed us to understand these complex processes more completely. Here, we review recent progress in our understanding of genetic and molecular mechanisms that control flowering in Arabidopsis thaliana.

Keywords: Ageing pathway, epigenetics, gene regulatory networks, miRNAs, photoperiod, phytohormone, vernalization.

Introduction

Flowering time control in plants is essential for their reproductive success and is also an important trait in agriculture. Plants have adapted several mechanisms to synchronize flowering so that they can maximize seed yields by carrying out fertilization and seed development at the optimal time (Purugganan and Fuller, 2009). In the model plant Arabidopsis thaliana, flowering is promoted by distinct environmental cues, such as daylength (photoperiod), winter (vernalization), and high ambient temperatures, as well as endogenous cues, such as plant age (ageing), the phytohormone gibberellin (GA), and the carbohydrate status (Ponnu et al., 2011; Andrés and Coupland, 2012; Capovilla et al., 2015). These signalling cues are perceived in the leaves and the shoot apical meristem (SAM) to induce flower formation. Over the last decades, extensive genetic studies have identified key regulators for flowering that function in the discrete flowering pathways (Koornneef et al., 1998). Notably, these key regulators are encoded by transcription factors (TFs), cofactors for TFs, and chromatin remodellers. Furthermore, these genetic and epigenetic elements interact with each other to form a complex gene regulatory network (GRN).

In this review, we highlight the recent findings on photoperiod, age-related, and phytohormone-based mechanisms that sustain the plasticity in flowering time. This review is especially aimed to present a comprehensive summary of the recently characterized components that play important roles in the complex GRNs for flowering time control in Arabidopsis.

Floral induction by the photoperiod pathway

Plants have evolved intricate mechanisms to measure fluctuations in daylength to accurately time the onset of flowering throughout seasonal progression, particularly at higher latitudes, and this phenomenon is known as photoperiodism.
(Garner and Allard, 1925). On the basis of their responses to photoperiod, plants are classified under three major groups: short-day (SD) plants initiate flowering when the night exceeds a critical length (normally in autumn); long-day (LD) plants flower when the night falls below a critical length (normally in late spring and summer); and day-neutral plants flower after attaining a certain developmental stage independently of daylength (Andrés and Coupland, 2012).

Regulatory network of long-day signals in the model plant Arabidopsis

Arabidopsis late flowering time mutants were initially isolated based on their increased total number of leaves (Rédei, 1962; Koornneef et al., 1991). Genes that have been isolated from these screens are key regulators in the process of floral induction in LDs, such as FLAVIN-BINDING, KELCH REPEAT, F-BOX1 (FKF1), GIGANTEA (GI), CRYPTOCHROME2 (CRY2), FLOWERING LOCUS E (FE), CONSTANS (CO), and FLOWERING LOCUS T (FT) (Andrés and Coupland, 2012; Song et al., 2015). Photoperiodic perception occurs in leaves, a tissue where these genes are expressed (Takada and Goto, 2003; An et al., 2004; Wigge et al., 2005). Although FKF1 and GI display a broad expression pattern, they overlap with that of CO and FT in the vascular tissue of leaves (Song et al., 2013).

Molecular basis of long-day-dependent transcriptional activation of CONSTANS

LD-dependent flowering is associated with the activation of the photoperiodic pathway through the transcriptional regulator CO, a member of the B-box (BBX) zinc family which contains two N-terminal B-boxes and a C-terminal CONSTANS, CONSTANS-LIKE, TIMING OF CAB EXPRESSION1 (TOC1) (CCT) DNA-binding domain (Fig. 1) (Strayer et al., 2000; Robson et al., 2001; Khanna et al., 2009; Gangappa and Botto, 2014).

Transcriptional activation of CO is light dependent and controlled through the formation of a complex between the ubiquitin ligase FKF1 and GI in late afternoon (regarded as external coincidence) (Mizoguchi et al., 2005; Sawa et al., 2007, 2008). Although the circadian clock-regulated genes FKF1 and GI have differently entrained expression rhythms depending on daylength, they have the same phase in LDs (regarded as internal coincidence) but not in SDs (Sawa et al., 2008). GI protein accumulates in late afternoon and stabilizes FKF1 in a circadian manner to target its substrate CYCLING DOF FACTORS (CDFs) for proteasomal degradation (Fowler et al., 1999; Park et al., 1999; Fornara et al., 2009). CDFs contribute to the correct interpretation of the seasonal information by forming a repressor complex with TOPELESS (TPL) (Liu and Karmarkar, 2008; Goralogia et al., 2017). The rhythmic light-controlled turnover of CDFs releases the transcriptional repression on CO which peaks in its expression at dusk (Imaizumi et al., 2005; Fornara et al., 2009). The vascular-expressed and photoperiod-specific FLOWERING BHLH (FBH) proteins form an activator complex with the otherwise miRNA319 (miR319)-sensitive TEOSINTE BRANCHED/CYCLOIDEA/PCF (TCP) TFs and bind to a CO proximal promoter region (Palatnik et al., 2003; Ito et al., 2012; Kubota et al., 2017; Liu et al., 2017). PHOTOTROPE AND FLOWERING TIME1/MEDIATOR25 (PFT1/MED25), a Mediator complex component required to orchestrate RNA polymerase II-dependent transcription, conveys regulatory information from the FBF–TCP complex to activate photoperiodic expression of CO in LDs (Cerdán and Chory, 2003; Íñigo et al., 2012; Ito et al., 2012; Liu et al., 2017). However, it is of major interest to explore the genetic interaction between FBHs and TCPs in the regulation of CO expression since both transcriptional activators may function cooperatively and/or independently.

Molecular mechanisms regulating CONSTANS protein stability and function

Post-translational control of CO protein is an important determinant for floral induction in response to LDs. The phosphorylated form of the CO protein is preferentially degraded in the dark by the 26S proteasome through the activity of the E3 ubiquitin ligase complex CONSTITUTIVE PHOTOMORPHOGENIC 1 (COP1) and SUPPRESSOR OF PHYTOCHROME A-105 (SPA) (Hoecker et al., 1999, 1999; Laubinger et al., 2006; Jang et al., 2008; Liu et al., 2008; Sarid-Krebs et al., 2015). While light-activated FKF1 conveys daylength-dependent transcriptional activation of CO and FT, FKF1 also increases the protein level of CO by inhibiting functional COP1 homodimerization (Song et al., 2012; Lee et al., 2017). In addition, CO protein stability is increased through a blue-light-dependent binding to FKF1 (Nelson et al., 2000; Demarsy and Fankhauser, 2009; Song et al., 2012). The blue light photoreceptors CRY1 and CRY2 enhance CO protein stability through sequestration of SPA1 from the COP1–SPA1 complex, whereas the CRY2–COP1 interaction reduces COP1–SPA catalytic activity under blue light (Liu et al., 2008; Lian et al., 2011; Zuo et al., 2011; Holtkotte et al., 2017). On the other hand, COP1 and SPA proteins most probably contribute to the blue-light-dependent proteasomal degradation of CRY2 (Shalitin et al., 2002; Liu et al., 2016). Similarly, far-red light activation of the phytochrome A (phyA) photoreceptor directly disrupts SPA1–COP1 interaction in the late afternoon, whereas the red/far-red light photoreceptor phytochrome B (phyB) facilitates CO protein degradation in the morning (Valverde et al., 2004; Sheerin et al., 2015). An attenuation of the phyA-dependent inhibition of the COP1–SPA complex is mediated through a COP1-dependent proteolysis of phyA, thereby creating an autoregulatory feedback loop on COP1 E3 ubiquitin ligase function (Seo et al., 2004). Likewise, a light-dependent (auto)-ubiquitylation pathway for the COP1–SPA2 complex has been proposed, where COP1 mediates ubiquitylation and degradation of SPA2 (Chen et al., 2015).

Alternative splicing of CO mRNA produces the CCT-truncated variant COβ that promotes HIGH EXPRESSION OF OSMOTICALLY RESPONSIVE GENE 1 (HOS1), a RING-finger-containing E3 ubiquitin ligase, and COP1-dependent
proteasomal turnover of the full-length protein COα, whereas COβ is resistant to the activity of these E3 ubiquitin ligases (Gil et al., 2017). The HOS1-mediated reduction in COα protein depends on phyB in the morning (Lazaro et al., 2012, 2015). Plants overexpressing COβ are strongly delayed in flowering, which is due to a loss of interaction between COα and the CO-stabilizing protein FKF1 on one hand and the inhibition of COα–NUCLEAR FACTOR-Y (NF-Y) complex formation on the other hand (Wenkel et al., 2006; Gil et al., 2017).

The destabilization of CO protein in the morning is attenuated through the formation of a complex with PSEUDO RESPONSE REGULATOR9 (PRR9), a central component of the circadian clock, whereas the related family members TOC1/PRR1, PRR5, and PRR7 engage in interactions with CO mainly in the late afternoon (Strayer et al., 2000; Farré and Liu, 2013; Hayama et al., 2017). PRRs repress CDF1 transcription, thus allowing CO mRNA to rise in the late afternoon (Nakamichi et al., 2007). In addition to its main function as an E3 ubiquitin ligase to control proteasomal degradation of central clock proteins TOC1 and PRR5, ZEITLUPE (ZTL) enhances destabilization of CO protein in the morning and changes intracellular localization of FKF1 in the late afternoon (Somers et al., 2000; Mas et al., 2003; Han et al., 2004; Kiba et al., 2007; Takase et al., 2011; Song et al., 2014). Thus, it is imperative to understand in detail how PRRs may function to reduce COP1 activity on CO during the day and whether PRRs might also bind to the FT promoter.

Integration of floral transition signals at FLOWERING LOCUS T

As a consequence of the transcriptional and post-translational regulation, CO protein peaks at late afternoon in LDs. CO binds to a proximal CO response element (CORE) in the promoter of FT, and interacts with the NF-Y–FE complex that binds to the distal enhancer element in the FT promoter, to induce DNA looping at FT and to sustain enhanced transcriptional activation of FT in late afternoon (Fig. 1) (Ben-Naim et al., 2006; Wenkel et al., 2006; Adrian et al., 2010; Song et al., 2012; Cao et al., 2014; Gnesutta et al., 2017; Hayama et al.,

![Fig. 1. CONSTANS (CO) controls photoperiodic flowering of Arabidopsis. Left: CO mRNA peaks 12–16 h after dawn in the light under LD conditions and induces floral transition through the activation of FLOWERING LOCUS T (FT) in Arabidopsis. Right: CO mRNA peaks in the dark under short-day conditions and the CO protein is targeted for proteasomal degradation through the activity of the COP1–SPA ubiquitin ligase complex. In the morning, CO protein is degraded by the PHYB pathway.](https://academic.oup.com/jxb/article-abstract/71/9/2490/5739814?redirectedfrom=fulltext)
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A recent study identified another crucial enhancer with additive effects on flowering time in inductive conditions that is located downstream of *FT* and most probably contributes to photoperiod-dependent activity (Zicola et al., 2019).

In addition to the photoperiod-specific *FT* regulation, several mechanisms regulate proper timing of flowering, most probably by maintaining the intricate balance between floral repressors and activators (Fig. 2). The two functionally redundant genes *TEMPRANILLO1* (*TEM1*) and *TEM2* act in the early developmental stage to block floral transition. Thus, an important mechanism for *FT* regulation is the balance between *CO* and *TEM* genes (Castillejo and Pelaz, 2008). Both *TEM1* and *TEM2* directly bind to *FT*, whereas *TEM2* shows a specific binding to the *FT* homologue *TWIN SISTER OF FT* (*TSF*) under low ambient temperatures (Yamaguchi et al., 2005; Castillejo and Pelaz, 2008; Marín-González et al., 2015).

A morning-specific inhibition of *CO* function occurs through an interaction with the miR172-sensitive *APETALA2* (AP2)-type transcriptional regulator TARGET OF EAT1 (TOE1), whereas FKF1 relieves this repressive constraint by binding TOE1 (Zhang et al., 2015). Other miR172-sensitive subfamilies of AP2-like transcriptional regulators, including AP2, TOE2, TOE3, SCHRARCHZAPFEN (SNZ), and SCLAFMUTZE (SMZ), also contribute to the repression of flowering under inductive and non-inductive photoperiod conditions (Schmid et al., 2003; Yant et al., 2010). However, a direct binding to a region downstream of *FT* was shown only in plants overexpressing SMZ or TOE1 (Mathieu et al., 2009; Zhai et al., 2015).

The major advances in the understanding of the complex GRNs contributing to *FT* activation were made over the last years under standard laboratory growth conditions. Interestingly, a recent report showed that the *FT* expression is actually induced not only in the evening but also in the morning under natural LD conditions. The morning-specific increases in *CO* protein stability and *FT* transcript level were reproduced under refined laboratory conditions, in which the ratio of far-red light to red light and the daily temperature are modified (Song et al., 2018). Thus, recreating natural plant growth conditions in laboratories will help to identify previously uncharacterized mechanisms contributing to floral induction.

**Epigenetic regulation of FLOWERING LOCUS T**

Epigenetic modifications are important for a widespread set of biological and developmental processes in higher eukaryotes. Epigenetic information involves covalent modifications of chromosomal histones that translate into changes in chromatin structure and are associated with either gene repression or activation (Steffen and Ringrose, 2014). In Arabidopsis, *FT* is a target of the Polycomb repressive complex 2 (PRC2) component CURLY LEAF (CLF), a methyltransferase that catalyses the deposition of histone H3 lysine 27 tri-methylation (H3K27me3), one of the repressive marks, and is associated with gene silencing (Fig. 2) (Goodrich et al., 1997; Jiang et al., 2008; Lopez-Vernaza et al., 2012). The B3-domain-containing TF VIVIPAROUS1/ABSCISIC ACID INSENSITIVE3-LIKE1 (VAL1) binds to two intronic RY (purine and pyrimidine nucleotides) motifs in *FT* and orchestrates recruitment of PRC components before dusk to mediate H3K27me3 deposition on *FT* chromatin (Reidt et al., 2000; Jia et al., 2014; Luo et al., 2018; Jing et al., 2019a). Epigenetic silencing of *FT* is sustained by the activity of LIKE HETEROCHROMATIN PROTEIN1 (LHP1) which binds to H3K27me3 sites in *FT*.
through its chromodomain (Gaudin et al., 2001; Turck et al., 2007; Zhang et al., 2007; Exner et al., 2009; Adrian et al., 2010). In contrast, formation of NF-YB–YC–CO complexes antagonizes CLF binding and deposition of H3K27me3 at FT (Takada and Goto, 2003; Liu et al., 2018; Luo et al., 2018). Similarly, binding of the PRC1 component EMBRYONIC FLOWER1 (EMF1) to FT is disrupted by the photoperiodic activity of CO, thus resulting in the activation of FT (Sung et al., 1992; Calonje et al., 2008). A physical interaction between CO and the CHD3 chromatin-remodelling factor PICKLE (PKL) enhances the binding of both regulators to FT chromatin and thus promotes floral transition (Ogas et al., 1997, 1999; Jing et al., 2019). Although genome-wide studies demonstrate that PKL predominantly co-localizes with the repressive epigenetic mark H3K27me3, PKL was also found to be associated with gene activation (Zhang et al., 2008, 2012; Jing et al., 2013; Zhang et al., 2014). A recent study suggested that PKL might act as a pre-nucleosome maturation factor and promotes retention of epigenetic marks after DNA replication and/or transcription, which can provide a plausible explanation for its dual role as activator and repressor in gene transcription (Carter et al., 2018). PKL also contributes to the relaxation of chromatin at FT through the formation of a complex with the H3K4me2/3–specific methyltransferase ARABIDOPSIS HOMOLOGOUS OF TRITHORAX1 (ATX1), thus preventing the H3K4me2/3-specific methyltransferase ARABIDOPSIS FACTOR 4 (PIF4) induced activation at high ambient temperatures (Kumar et al., 2012; Gómez-Zambrano et al., 2018). Notably, a thermosensorial function has been assigned to PIF proteins (Jung et al., 2016a; Légris et al., 2016). Although rather speculative, these findings imply a possible scenario in which phyB modulates the floral response under changing environmental conditions. Moreover, the photoperiodic, thermosensorial, and GA pathways converge on the CO–PIF4/5–DELLA module to promote flowering at high temperatures in SDs (Galvão et al., 2015; Fernández et al., 2016). Sliding and eviction of nucleosomes are promoted by BRAHMA (BRM), a member of SWI2/SNF2 chromatin-remodelling ATPases (Farrona et al., 2007; Ojolo et al., 2018). BRM regulates flowering time through transcriptional repression of FT in LDs (Farrona et al., 2004, 2011). Notably, H2A.Z and BRM cooperate in the control of FT transcription, which is further supported by a recent report that shows context-dependent regulatory roles of BRM and H2A.Z (Torres and Deal, 2019).

**Nucleosomal organization contributes to FLOWERING LOCUS T regulation**

Nucleosome organization and distribution contribute to a tight control over gene transcription. Genome-wide studies have indicated that different levels of the histone variant H2A.Z along the genes contribute to the regulation of gene activity (To and Kim, 2014). Eviction of H2A.Z-containing nucleosomes is crucial for PHYTOCHROME INTERACTING FACTOR 4– (PIF4) induced FT activation at high ambient temperatures (Kumar et al., 2012; Gómez-Zambrano et al., 2018). Although rather speculative, these findings imply a possible scenario in which phyB modulates the floral response under changing environmental conditions. Moreover, the photoperiodic, thermosensorial, and GA pathways converge on the CO–PIF4/5–DELLA module to promote flowering at high temperatures in SDs (Galvão et al., 2015; Fernández et al., 2016). Sliding and eviction of nucleosomes are promoted by BRAHMA (BRM), a member of SWI2/SNF2 chromatin-remodelling ATPases (Farrona et al., 2007; Ojolo et al., 2018). BRM regulates flowering time through transcriptional repression of FT in LDs (Farrona et al., 2004, 2011). Notably, H2A.Z and BRM cooperate in the control of FT transcription, which is further supported by a recent report that shows context-dependent regulatory roles of BRM and H2A.Z (Torres and Deal, 2019).

**Natural variation at FLOWERING LOCUS T**

Although chromatin remodelers facilitate chromatin opening, they have less effect on the binding specificity of TFs. Nevertheless, promoter and cis-regulatory variation are instrumental for gene regulation since they contribute to changes in TF binding and chromatin structure (de Meaux, 2018). An Arabidopsis accession Col-0-specific insertion (Block ID) in FT was identified and shown to contribute to photoperiodic regulation of FT (Adrian et al., 2010; Bao et al., 2019). In more detail, large insertions–deletions (INDELs) overlapping with Block ID correlated with geographical clines which are widespread and account for natural variation at FT (Liu et al., 2014). Likewise, CO-associated flowering time diversity was shown to be linked to natural variation in cis-regulatory sequences of
the CO promoter (Rosas et al., 2014). As for FT, Liu (2014) suggested that cis-regulatory variation could be adaptive by conferring differences in the control of FT which translates into increased fitness (Schwartz et al., 2009; Liu et al., 2014). Cis-regulatory changes in the MYC3-binding site at FT to suppress its activation under non-inductive SD conditions is an elementary pillar of natural variation in the control of photoperiodic flowering responses (Bao et al., 2019). Targeted DNA methylation of cis-regulatory elements and intronic regions in FT helped to further unveil additional cis-regulatory elements with functional roles in the regulation of FT in the photoperiodic response pathway (Deng and Chua, 2015; Zicola et al., 2019). It is noteworthy that these sites are involved in the targeted recruitment of PIF4/5 and the floral repressors FLC, FLOWERING LOCUS M (FLM), and VAL1 (Searle et al., 2006; Gu et al., 2013; Lee et al., 2013; Pedmale et al., 2016; Jing et al., 2019a).

**FT, a leaf-derived systemic signal that moves to the shoot apical meristem**

The concept of florigen was first proposed in the 1930s as a graft-transmissible leaf-derived florigenic signal that is responsive to photoperiodic stimuli and induces floral initiation at the SAM (Chailakhyan, 1936). By virtue of genetic and molecular experiments in *Arabidopsis thaliana* and rice in the past two decades, the FT protein has been characterized as the long-sought florigen (Corbesier et al., 2007; Jäger and Wigge, 2007; Mathieu et al., 2007; Tamaki et al., 2007). FT shares homology with phosphatidylethanolamine-binding proteins (PEBPs) or RAF kinase inhibitor proteins (RKIPs), and its ligand-binding domain is evolutionarily conserved from bacteria to mammals and plants (Kardailsky et al., 1999; Kobayashi et al., 1999). FT protein is expressed in the phloem companion cells of the leaves and is shown to diffuse in the SAM to induce flowering, which indeed fits with the concept of florigen (Corbesier et al., 2007; Jäger and Wigge, 2007; Mathieu et al., 2007; Tamaki et al., 2007). A recent report further confirmed the transport of FT protein from leaves to the SAM, by combining an improved bi-molecular fluorescence complementation (BiFC) assay and a heat shock-inducible gene expression system (Abd et al., 2019). FT protein levels gradually decrease once floral transition occurs, although FT mRNA is still transcribed with its typical peak in expression at dusk, and this post-translational control is mediated by proteases which cleave the C-terminal part of FT (Kim et al., 2016). Trafficking of FT to the vegetative SAM depends on the endoplasmic reticulum (ER) membrane protein FT-INTERACTING PROTEIN 1 (FTIP1), a member of the family of multiple C2 domain and transmembrane region proteins (MCTPs), which facilitates the export of FT from phloem companion cells (CCs) to sieve elements (SEs) (Liu et al., 2012). The plasma membrane-resident syntaxin-like Q-SNARE, SYNTAXIN OF PLANTS 121 (SYP121), interacts with QUIRKY (QKY/MCTP15) to regulate FT movement to the plasmalemma in CCs through the endosomal trafficking pathway (Liu et al., 2019). The long-distance transport of FT from leaves to the SAM through the phloem stream is facilitated by the heavy metal-associated (HMA) domain-containing protein SODIUM POTASSIUM ROOT DEFECTIVE 1 (NaKR1), which is activated by CO and FE in leaf vascular tissue and shown to interact with FT (Zhu et al., 2016; Shibuta and Abe, 2017). Nevertheless, uploading of FT to the phloem and unloading in the SAM are actively regulated processes, at least in cucurbit plants. Furthermore, trafficking of FT is strongly influenced by phloem fluxes and concentrations of major sugars in phloem sap as they exhibit diurnal and developmental changes (Mitchell et al., 1992; Savage et al., 2013; Yoo et al., 2013).

**Formation of the florigen activation complex**

Transport of FT from leaves to the vegetative SAM induces floral transition which is characterized by morphological changes and rewiring of transcriptional networks that culminate in floral induction (Jacquard et al., 2003; Torti et al., 2012). The basic leucine zipper (bZIP) domain TF FD is expressed in the SAM and forms a transient complex with FT/TSF to induce floral meristem identity genes such as APETALA1 (AP1) (Abd et al., 2005, 2019; Wigge et al., 2005). This interaction is indirect since the 14-3-3 protein GF1c bridges the interaction between HEADING DATE 3A (HD3A), the rice orthologue of FT, and rice OsFD1 (Taoka et al., 2011). Phosphorylation of FD by the SAM-expressed CALCIUM-DEPENDENT PROTEIN KINASE 6 (CDPK6) and CDPK33 promotes florigen activation complex (FAC) formation to coordinate floral transition (Kawamoto et al., 2015; Collani et al., 2019). In contrast, the FT-related gene TERMINAL FLOWER1 (TFL1), which is a key floral repressor, interacts with the unphosphorylated form of FD via 14–3–3 proteins. Moreover, it has been suggested that the transcriptionally inactive ternary FD–14–3–3–TFL1 complex represents the ground state at the SAM (Collani et al., 2019). As TFL1 acts through FD, TFL1 counterbalances incoming FT signals to maintain the centre of the SAM in a vegetative state through an interlocking feedback loop (Kobayashi et al., 1999; Hanano and Goto, 2011; Jäger et al., 2013; Lee et al., 2019). Modulation of FAC activity also occurs through the specific binding of FT to diurnally changing molecular species of phosphatidylcholine (PC) (Nakamura et al., 2014). Lipid binding seems to be important for FT function, as several loss-of-function ft alleles carry point mutations within the lipid-binding pocket (Kobayashi et al., 1999). Although FT and TSF are not required for FD binding to DNA, their presence increase the enrichment of FD to a subset of genes that regulate flowering time and floral organ identity (Collani et al., 2019).

**Modulation of the floral response through integration of transcription factors with the FT-FD module**

A recent work has shed light on the importance of the FD–FT protein interaction network and how this relates to the associated transcriptional output (Li et al., 2019). FD was found to interact with class II CINCINNATA (CIN)-like TCP5, TCP13, and TCP17, which facilitate the DNA binding of FD to the floral meristem identity gene *AP1* (Martin-Trillo and Cubas, 2010; Li et al., 2019). This study concluded that the
class II CIN-like TCPs and FD synergistically activate downstream signalling (Li et al., 2019). Similarly, the age-related miR156-sensitive SQUAMOSA PROMOTER-BINDING PROTEIN (SBP)-LIKE (SPL) TFs SPL3, SPL4, and SPL5 hijack the FD–FT signalling module through physical interaction with FD to enhance its DNA binding and to synergistically activate AP1 expression (Jung et al., 2016). It is noteworthy that SPL3 and FT mutually cross-activate each other, thereby creating a coherent feedforward loop (Alon, 2007; Jung et al., 2012; Kim et al., 2012; Lee et al., 2012). Nevertheless, regardless of which protein complexes assemble at AP1 and how they modulate the binding behaviour of FD, a consensus is that these proteins synergistically activate the expression of AP1. Of note, SPL9 was also shown to bind to AP1 to trigger the onset of flower formation and interacts with the mir319-sensitive TCP4 to regulate leaf complexity. It is thus speculated whether TCP4 could cooperate to facilitate recruitment of AP1.

**Age-related floral induction under non-inductive conditions**

Before plants become competent to flower and reproduce, the shoot has to undergo the phase of vegetative growth, which can be further divided into the juvenile and the adult vegetative phase. These phases are accompanied by changes in growth pattern and body forms, and increases in photosynthetic capacity, which are particularly recognizable in perennials rather than in annual species such as Arabidopsis. During the transition from the juvenile to adult phase, miR156 also becomes known as vegetative phase change, plants acquire reproductive competence. Eventually, the reproductive phase change is characterized by the switch from vegetative to reproductive growth, a process in which the SAM adopts an inflorescence meristem identity. It has become increasingly clear in recent years that the juvenile to adult phase and reproductive phase use similar molecular and genetic mechanisms. In particular, the miR156–SPL and miR172–AP2 modules are likely to be the central regulatory hubs and required to coordinate the transitions of the discrete phases in a timely manner (Fig. 3) (Huijser and Schmid, 2011; Hyun et al., 2017).

**Age-related decline in miR156**

Floral induction under non-inductive SD conditions requires the activity of the phytohormone GA and the age-dependent reduction in the levels of miR156, which is one of the most abundant miRNAs in Arabidopsis with the highest levels at the seedling stage (Wilson et al., 1992; Axtell and Bartel, 2005; Schwab et al., 2005). miR156 and miR157, which are encoded by eight and four precursors, respectively, repress SPL gene expression in a threshold-dependent manner (Rhoades et al., 2002; He et al., 2018). Although miR157 is more abundant than miR156, the major role in the regulation of vegetative phase can be attributed to miR156, which is also one of the most conserved miRNAs among various plant species (Zhang et al., 2006; Yang et al., 2011; He et al., 2018). A recent report hypothesized that miR156 diffuses non-cell autonomously from the SAM into leaf primodia to promote juvenile leaf identity (Fouracre and Poethig, 2019). In further support of this notion, previous studies found that miR156 acts as a mobile signal in potato and maize (Poethig, 1988; Dudley and Poethig, 1993; Bhogale et al., 2014). Following the juvenile growth, miR156 is expressed in leaves and increased in abundance as leaves expand (Fouracre and Poethig, 2019). To confer a gradual transition from the juvenile to adult phase, miR156 progressively declines in successively developing shoot-derived leaf primodia (He et al., 2018). The signalling activity of HEXOKINASE1 (HXK1) and sugar,
which acts as a mobile signal, contributes to the reduction in miR156 abundance (Yang et al., 2013; Yu et al., 2013; Buendia-Monreal and Gillmor, 2017). Furthermore, TREHALOSE-6-PHOSPHATE (T6P) SYNTHASE 1 (TPS1) and T6P, which has been suggested to function as a signalling molecule of sugar status in plants, are also likely to contribute to the reduction in miR156 abundance (Lunn et al., 2006; Wahl et al., 2013). In addition, tps1 mutants are extremely late flowering even in LDs, and disable to induce oscillating FT expression during a day (Wahl et al., 2013).

**Epigenetic and transcriptional regulation of MiR156**

The transcription of MIR156a/c is repressed at the adult phase by epigenetic regulators such as BMI1, VAL1/2, CLF, and its homologue SWINGER (SWN), while BRM antagonizes mainly the function of SWN at the juvenile phase (Picó et al., 2015; M. Xu et al., 2016a; Xu et al., 2016; Merini et al., 2017). The ATP-dependent SWR1 chromatin remodelling complex (SWR1-C) contributes to nucleosomal dynamics at MIR156a/c, while ACTIN-RELATED PROTEIN6 (ARP6) promotes H2A.Z incorporation to facilitate ARABIDOPSIS TRITHORAX-RELATED7 (ATXR7)-dependent active chromatin formation at MIR156a/c (Tamada et al., 2009; Choi et al., 2016; Xu et al., 2018).

**SPLs induce developmental transitions**

Two important developmental transitions—the juvenile to adult transition and the vegetative to reproductive transition—in Arabidopsis are controlled through miR156-targeted inactivation of SPL mRNAs by cleavage and translational inhibition (Schwab et al., 2005; Gandikota et al., 2007; Hyun et al., 2017). The SPL family is comprised of 16 genes in Arabidopsis that are divided into two groups (Guo et al., 2008; Xing et al., 2010). miR156 recognition sites were reported for 11 members of these SPL genes. Among them, SPL2, SPL9, SPL10, SPL11, SPL13, and SPL15 were shown to be strongly associated with floral transition, whereas SPL3, SPL4, and SPL5 promote floral meristem identity (Schwarz et al., 2008; Wang et al., 2009; Wu et al., 2009; Yamaguchi et al., 2009; Hyun et al., 2016; M. Xu et al., 2016b).

SPL9 and SPL15 bind to the promoter of the miR172b gene to promote its expression, which is required to inactivate transcripts of floral repressor genes of the AP2-like family (Wu et al., 2009; Zhu and Helliwell, 2011; Hyun et al., 2016; M. Xu et al., 2016b). The inverse relationship of miR156 and miR172 abundance in apices of Arabidopsis plants is likely to be part of an intricate gene regulatory network and is recognized by a feedforward loop as AP2 directly binds to MiR156 and MiR172 to induce and repress their expression, respectively (Yant et al., 2010; Jung et al., 2011). In addition, SPL9/SPL15 functionally cooperate with the MADS-box protein SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1 (SOC1) to activate FRUITFULL (FUL) and TARGET OF FLC AND SVP1 (TFS1) (Wang et al., 2009; Wu et al., 2009; Hyun et al., 2016; Richter et al., 2019). While SOC1 promotes DNA looping and orchestrates the recruitment of the chromatin remodeller REF6 and BRM to FUL and TFS1, SPL9/SPL15 stabilize the DNA loop to induce an epigenetic switch through activation of transcription (Hyun et al., 2016; Richter et al., 2019). Bioactive GAs are important for SPL9/SPL15 function as their interaction with the otherwise GA-labile DELLA proteins inhibits SPL9/SPL15 transcription activity during floral transition (Yu et al., 2012; Hyun et al., 2016). In contrast, the transcriptional activity of SPL9 is potentiated through the interaction with DELLA proteins during reproductive development to enhance the expression of the floral meristem identity gene AP1 (Yamaguchi et al., 2014).

**Phytohormone-dependent floral induction in Arabidopsis thaliana**

Spatially distinct regulatory roles for bioactive GAs have been suggested in the promotion of flowering under non-inductive SD and inductive LD photoperiodic conditions (Galvão et al., 2012; Porri et al., 2012). TEM genes were shown to link photoperiod and GA pathways by directly binding to and repressing the expression of GA metabolic enzyme genes GIBBERELLIN 3-OXIDASE1 (GA3ox1) and GA3ox2 (Hu et al., 2008; Yamaguchi, 2008; Osnato et al., 2012). Similarly, the floral repressors SHORT VEGETATIVE PHASE (SVP) and FLC control GA metabolism through the regulation of GA20- and GA2-oxidases (Andrés et al., 2014; Mateos et al., 2015). GA deficiency leads to the stabilization of the otherwise GA-labile DELLA proteins GIBBERELLIC ACID INSENSITIVE (GAI), REPRESSOR OF ga1-3 (RGA), RGA-LIKE1 (RGL1), RGL2, and RGL3 that inhibit transactivation activity of CO through a physical interaction (Schwechheimer, 2011; Wang et al., 2016; F. Xu et al., 2016).

The WRKY-type TFs WRKY71 and WRKY75 activate the expression of FT in inductive LD conditions through direct binding to W-boxes located within the promoter of FT (Yu et al., 2016; Zhang et al., 2018). The transcription activity of WRKY75 is inhibited by interactions with DELLA proteins, thus leading to a reduced expression of FT (Fig. 2) (Zhang et al., 2018). Similarly, WRKY12 and WRKY13 were also found to interact with DELLA, and oppositely regulate flowering under non-inductive SD conditions. Interestingly, whereas the expression of WRKY12 increases as the plant ages to promote flowering, the expression of the floral repressor WRKY13 concomitantly declines (Li et al., 2016).

Elucidation of GA responses in seedlings revealed that gene expression of virtually all GA-regulated genes depends on the chromatin-remodelling factor PKL (Park et al., 2017). PKL function is inhibited through physical interaction with DELLA, thus reshaping the epigenetic landscape of its immediate downstream target genes (Zhang et al., 2014; Park et al., 2017). It is noteworthy that the ABA-responsive element (ABRE)-binding factor 3 (ABF3) and ABF4 engage in NF-YC interactions to promote flowering by activating SOC1 gene expression in the leaf, whereas they delay flowering by repressing SOC1 transcription in the apex (Riboni et al., 2013, 2016; Hwang et al., 2019). Thus, the spatio-temporal control of SOC1 gene transcription via ABF3/ABF4 and NF-YC modulates
the drought escape response in Arabidopsis. Moreover, the formation of REF6/NF-Y (namely NF-YA–NF-YB–NF-YC) complexes is disrupted through physical interactions between DELLAs and NF-Ys, thus suppressing SOC1 gene activation and the floral response in Arabidopsis (Hou et al., 2014).

FUL and TCP15, but probably also TCP14, bind to the promoter of SOC1 to activate its expression downstream from GA (Torti et al., 2012; Balanzà et al., 2014; Lucero et al., 2017). TCP14 and TCP15 also constitute a point of convergence for GA and cytokinin (CK) signalling as both TCPs interact with DELLA proteins and the O-fucosyltransferase SPINDLY (SPY), which suppresses GA signalling and promotes CK responses (Steiner et al., 2012; Davière et al., 2014; Zentella et al., 2017). Similarly, the GATA-type TF genes GATA, NITRATERINDUCIBLE, CARBON-METABOLISM INVOLVED (GNC), and CYTOKININ-RESPONSIVE GATA FACTOR1 (CGA1)/GNC-LIKE (GNL) are downstream factors of GA and CK signalling and involved in a cross-repressive interaction with SOC1 to regulate floral and greening response (Naito et al., 2007; Richter et al., 2010, 2013). Although GNC and CGA1/GNL were found to interact with the transcriptional co-regulator SNL1 in yeast, which is part of HDAC complexes, both GATAs induce the expression of SMZ and SNZ to regulate flowering (Bowen et al., 2010; Gras et al., 2018). Interestingly, the transcriptional repressor function of TOE1 and TOE2 is inhibited through interactions with the otherwise jasmonate (JA)-labile JASMONATE-ZIM DOMAIN (JAZ) proteins, thus linking JA signalling to flowering time (Zhai et al., 2015). Furthermore, the JA-activated MYC-type TFs directly bind to a promoter-proximal region in FT, further supporting the contribution of JA to the floral response (Wang et al., 2017).

Conclusion

The mechanism underlying seasonal flowering has been attracting a lot of attention for a long time. Initial genetic studies on Arabidopsis have identified many molecular components that either positively or negatively regulate competence to flower downstream of environmental and endogenous cues. Subsequently, further genetic studies together with genome-wide analyses have revealed the crosstalk between these regulators, illustrating the networks that are progressively increasing in complexity over the last years. One of the most important features in this network is the convergence of the regulatory pathways on the integrator genes. As we introduced, recent studies have demonstrated detailed molecular mechanisms by which different signals are integrated into FT expression in leaves. Flowering time control via the vernalization pathway is not explained due to space limitation, but there are a number of articles that review recent findings on the vernalization pathway (Bloomer and Dean, 2017; Xu and Chong, 2018). On the other hand, there is still less information available for the signal integration in the SAM to reorganize its identity upon the arrival of FT protein. Future studies will elucidate such mechanisms more precisely and will deepen our knowledge on developmental plasticity.
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