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GENETIC REGULATION OF TIME TO FLOWER IN *ARABIDOPSIS THALIANA*

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■ **Abstract** In *Arabidopsis thaliana*, the initiation of flowering is carried out by four genetic pathways: gibberellin, autonomous, vernalization, and light-dependent pathways. These processes are integrated by the function of the genes *FD, FE, FWA, PDF2, SOC1*, and *FT* at the integration pathway. The integrated signal of the floral induction is transmitted to the floral meristem identity genes *LFY* and *AP1*, and floral morphogenesis is performed.

CONTENTS

INTRODUCTION

This review focuses on the initial process of genetic aspects of flowering in mainly *Arabidopsis thaliana*. Many good reviews have been published (4, 7, 9, 11, 52, 58). This review tries to abolish duplication and be concise.

Flowering is the developmental turning point from the vegetative to the reproductive phase. For plants, the induction of flowering is the most important part

from the standpoint of reproductive strategy and allocation of limited resouces. Monocarpic plants, in particular, perform the flowering only once in their lifecycle, and the reproductive success depends entirely on this one opportunity. For humans, the problem of flowering has been a long-term interest for the agricultural field as well as for the basic plant science arena.

Strategy of Study

Laboratory strains (known as ecotypes) of *Arabidopsis* are early flowering and the lateness was the initial screening character of flowering mutations. Thus, late-flowering mutants were identified from the initial stage of *Arabidopsis* genetics to study time control of flowering (53). The process of flowering is redundant because late-flowering mutants can be isolated, but nonflowering mutants can not. Ironically, if nonflowering mutants exist we can not apply the tool of genetics. Early-flowering mutants have been also isolated and analyzed (25, 100).

FLORAL DEVELOPMENT IS A REPRESSIBLE PROCESS

Because reproduction requires many resources, it is plausible to think that plants prepare their resouces for the flowering. Flowering is a repressible developmental process. Consistent with this notion, the wild-type counterparts of late-flowering genes collected are positive factors for this repressible developmental function toward flowering (53).

After the Koornneef study in 1991 (53) (described below), Sung and coworkers (90) isolated intriguing mutants in 1992. The embryonic flower mutants immediately formed flowers (or at least flower-like organs) after germination (8, 20). If the flower-like organ is really the flower, the *EMF* gene has the repressible function to prevent plants from immediately flowering after germination. There are two *EMF* genes (6, 99). The *EMF1* gene codes for a novel protein of 121 kD, which is a transcriptional regulator (6). The *EMF2* gene encodes a 71-kD Polycomb group (PcG) protein containing a zinc finger motif and a cluster of tryptophan and methionine-rich sequences (99). PcG proteins are *VERNALIZATION2*, *FERTILIZATION-INDEPENDENT SEED2*, and *Suppressor of zeste12* genes (10, 27, 28, 31, 32, 49, 91, 101). The *EMF1* and *EMF2* genes initially were given central roles for the flowering pathway by the following evidence. The early flowering mutations in *EMF1* and *EMF2* genes are epistatic not only to those in *GI* or *CO* genes but also to those in the *ELF1*, *ELF2*, or *ELF3* genes (21, 37, 97). *AP1*::*uidA*(=GUS) fusion (44) can express beta-glucuronidase in *EMF1* and *EMF2* mutants. However, the *EMF* mutants showed developmental defects other than those related to flowering: The germination was late, the elongation of hypocotyl was poor, the expansion of cotyledon was poor, and the embryogenesis was poor after the late-globular stage (8, 20). Thus, the existence of the *EMF1* and *EMF2* mutants shows that the abnormal developmental terminal revealed unspecified developmental errors. The early flowering might be a side effect of the developmental

terminal, or the blind alley. The weak allele, *emf1-2*, can express the reporter of *AP1*::*uidA* fusion in cotyledon hypoctyl ectopically, but severe allele *emf1-1* can not (20). Currently, we might speculate that the role of *EMF1* and *EMF2* genes are responsible for maintaining the repressible state of flowering-related genes as young vegetative tissues at the shoot apical meristems (SAMs). In a recent paper, Sun's group (70) also proposed that *EMF* genes may function independent of a regular flowering pathway (descibed below) and are developmental repressors that allow plants to stay at a vegetative state.

Other classes of early-flowering mutants were identified among developmetally abnormal mutants. They are mutants in *CURLY LEAF* (*CLF*) and *WAVY LEAVES AND COTYLEDONS* (*WLC*) genes (31, 58). They are also PcG genes (10, 27, 28, 31, 32, 49, 91, 101). It has also been thought that their apparent flowering phenotypes are the secondary and the abnormal developmental stages. Another observation that is difficult to explain is flowering in darkness. It is known that some plants can make flowers (or flower-like structures) in darkness by the supply of sugar (another light-dependent product) (41). Redei (5, 80) found, and we confirmed, flowering in the liquid-shaken culture of *Arabidopsis*. Redei thus thought that flowering was a default state, meaning that the plants precociously make flowers unless the repressors function. Roldan et al. (84) extended these observations: Some (but not all) late-flowering mutants made flowers earlier by the supply of sugars at the SAM region in darkness. The *constitutive photomorphogenesis 1* (*cop1*) mutants can make flowers in darkness if sugar is supplied in media (67). These lines of observations favor the notion that flowering is the repressible developmental pathway. We found that the flowering in darkness in the *cop1-6* mutant may use the regular flowering pathway (light-dependent pathway) described below (M. Nakagawa & Y. Komeda, unpublished results).

Our knowledge of the effect of the sugar for enhancing promotion of floral initiation is still inconclusive (23, 71).

CONSTRUCTION OF GENETIC NETWORK

The working hypothesis was made by the initial construction of a genetic network of flowering control. Koornneef and coworkers (53) performed the study. There are physical, chemical, and biological signals/information for the initiation of flowering. The four constructed pathways corresponded to these signals. In *Arabidopsis* and some model plants the genetics-based framework model can now be assessed by molecularly cloning each member. Currently, there are four pathways established (51); Figure 1 shows the sequence.

GIBBERELLIN PATHWAY

Gibberellic acid (GA) is a sort of florigen for long-day (LD) plants because of the following observation: *ga1* mutants of *Arabidopsis thaliana* never flower under

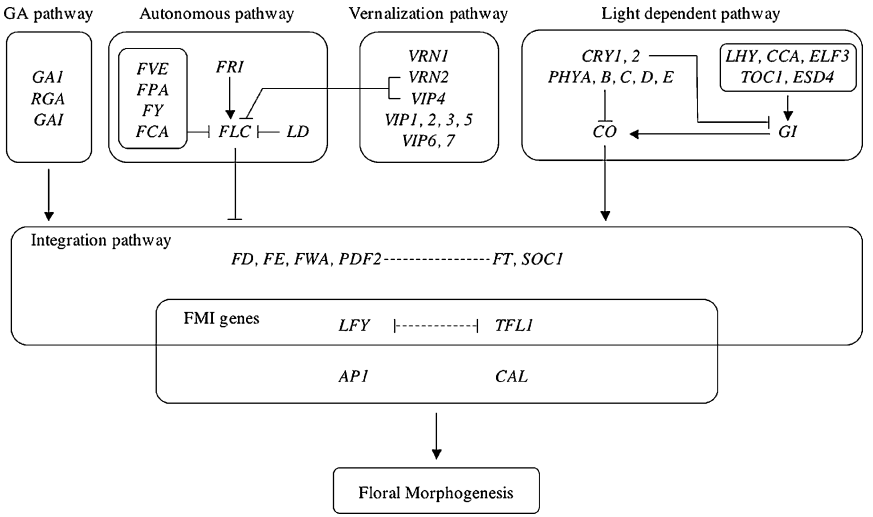

Figure 1 The genetic pathways of flowering in *Arabidopsis thaliana*. See the text for gene descriptions. Positive (*arrows*) and negative (*T-lines*) interactions are described. Dotted lines show undescribed interaction.

short-day (SD) conditions (95). Thus, GA satisfied most criteria for the florigen concept except one, which is universal reagent among LD and SD plant species (24, 48). Blazquez et al. (12) found that the *ga1-3* mutant lost *LFY* activity in SD conditions. When *LFY* is overexpressed by the transgenic method, *ga1-3* mutation could flower under SD conditions. Because the GA-signaling mutations in *RGA* and *GAI* genes rescued the phenotype of *ga1* mutants, the GA signal (not the GA molecule) is the information for the up-regulation of the pathway (24).

AUTONOMOUS PATHWAY

Plants require not only external (environmental) factors but also internal (developmental) factors to promote flowering.

Although the ecotypes used in the laboratory of *Arabidopsis thaliana* flower earlier, many ecotypes flower very late or require the cold treatment, vernalization. Amasino and coworkers (68) shed light on this mystery. The *FRIGIDA* (*FRI*) gene is responsible for the differences of the lateness of flowering among *Arabidopsis* ecotypes (45). The *FRI* codes for a protein with 619 amino acids that has coiled-coil domain in two positions (45). The predicted protein did not show any significant match to known protein domains. The *FRI* is a positive regulator of the *FLC* repressor for flowering. The coiled-coil domains may have a role in regulating the *FLC* gene (68). Early-flowering ecotypes, such as Columbia, Landsberg *erecta*, and WS, have mutations in the *FRI* gene (45). Also, the southern ecotypes

have defective *FRI* alleles. The *FLC* gene encodes the MADS-box protein family belonging to a new subfamily (68, 76). The *FLC* also plays a key role in vernalization (88).

FCA and *LD* are repressible for the expression of the *FLC* gene, thus *FCA* or *LD* loss-of-function mutants are late flowering (53). The *LD* gene codes for a protein carrying nuclear localizing signal, homology to mammalian transcription domain, and homology to plant DNA-binding homeo domain (57). The *FCA* gene codes for a RNA-binding protein and has the domain of WW-protein interaction (63). It has homology to SX-1 and ELAV genes of *Drosophila* (63). The *FCA* gene is transcribed and alternatively spliced as alpha, beta, gamma, and delta products (63, 72). The gamma message is the only functional message because the transgenic plants expressing higher gamma messages flowered earlier (64).

FVE, FPA, and *FY* genes belong to this pathway and have similar functions to the *FCA* gene (72, 87). Whereas *LD* is mainly the repressor of the *FLC* gene, *FVE*, *FPA*, and *FY* have functions to repress the *FLC* gene as well as the direct positive factor for the integration pathway shown below. They are redundant genes in the autonomous pathway that ensure the developmental tuning of flowering. Because the insertional mutations in the *FLC* gene did not induce early flowering (88), the *FLC* is not the only regulatory point nor the master regulatory gene.

VERNALIZATION PATHWAY

There are two genes identified for the process of vernalization, *VRN1* and *VRN2* (19). *VRN2* has the repressible role for expressing the key gene, *FLC* (88). *VRN2* codes for a protein with homology to PcG proteins (28). Thus, *VRN2* may function to keep the *FLC*-chromatin state for down-regulation.

Accordingly, autonomous and vernalization pathways are partially cross-talkable using the *FLC* function. A recent study (101) to isolate vernalization-independent mutants identified *VIP1* to *VIP7* genes. The *VIP4* was cloned and encodes another PcG protein (101), and is a repressor of the *FLC* gene.

LIGHT-DEPENDENT PATHWAY

Red light is accepted by the phytochrome proteins, which are encoded by *PHYA* through *E* genes in *Arabidopsis thaliana* (17, 75, 81). Blue light receptors are named as cryptochrome proteins, which are encoded by *CRY1* and *CRY2* (2, 60). Koornneef et al. (53) identified the mutants in the *CRY2* gene as *fha* mutants. The *fha* mutants were initially identified as late flowering in LD under white light. *PHYA*, *PHYB*, *CRY1*, and *CRY2* are the members of the light pathway of flowering (58).

The *PHYB* loss-of-function mutants are early flowering (75). Because *co phyB* double mutants did not show evidence of early flowering, *CO* is responsible for early flowering in the *PHYB*-minus mutants (77). Under red light, *PHYB* functions

by the repression of the *CO* function (77). Under blue light, *CRY2* inhibits *PHYB* and induces flowering (60). Another cryptochome gene *CRY1* cooperatively functions with the *CRY2* gene to repress the function of the *CO* and *GI* genes (69). The functions of genes *LHY*, *CCA1*, *ELF3*, and *TOC1* process the physical signal (25, 39). The processed signal is transmitted to the *GI* gene and the resultant signal activates the *CO* gene (89). The *early in shortdays 4* mutant belongs to this class (82).

The late-flowering, and thus supervital because of a prolonged vegetative life span, *GI* mutants are defective for a membrane protein with a membrane-spanning region (26, 74). The *GI* protein is expressed with circadian rhythmicity. The *gi* mutants are defective for the expression of *CCA1* and *LHY* genes.

The *co* mutants are late flowering under LD (53). The *CO* gene has homology to the Zn-finger domain proteins of transcriptional factor (77). The quantity of the *CO* message was proportional to the earliness of flowering in transgenic plants and seems to be rate limiting for flowering (86). Thus, *CO* is functional for integrating the light pathway.

The transgenic plants expressing the *CO* gene to some extent ectopically rescued the lateness of flowering by the defect in an autonomous pathway (described below). Thus, the autonomous pathway seems to be partially redundant to that of the light-dependent pathway.

FLORAL MERISTEM IDENTITY GENES

The success of the A-B-C model for floral morphogenesis in the developmental biology of plants attracted many biologists belonging to nonplant sciences and gave impact to this field (22). The model is now extended to be an A-B-C-D-E model for the morphogenesis of floral development (43). The A + B and B + C functions are conserved among many plant species but the interaction including A- or C-specific function is not so simple. The C-function is tightly linked to the fate of the apical shoots, such as the decision for either determinate or indeterminate shoots. The A-function is tightly linked to the floral meristem identiy (FMI) genes.

The studies using mutants predicted that three FMI genes were required ito develop floral primordia (13, 14, 65, 78, 88), *LFY*, *AP1*, and *CAL* (15,18, 33). The phenotype of the loss-of-function-type mutations in *LFY* or *AP1* gene is as follows: Flowers either have vegetative characteristics or have been replaced by vegetative shoots (in severe mutations). The functional redundancies were detected in *AP1-LFY* and *AP1-CAL* genes. *AP1* and *LFY* belong to the MADS domain genes and *LFY* codes for an unrelated transcriptional factor (65, 94). The possible molecular functions in FMI genes are DNA transcriptional factors. Constitutive expression of the *LFY* transgene accelerates the time to flowering (40, 59). In these plants, *AP1* expression was enhanced in floral primordia and also detected in leaf primordia. Thus, the *LFY* induces expression of *AP1*. Molecular interaction was also shown (93). *LFY* is also thought to promote *CAL* expression (93). Hence, a positive feedback model at floral primoria is proposed.

After extensive studies trying to understand FMI genes, the initiation of flowering has been shown as the up-regulation of the FMI genes at shoot apical meristems. The transcription of *LFY* genes is detected high in floral primordia and low in primordia of leaves (93). The expression is increased abruptly, for example by transferring plants from SD to LD. The increase was also detected in continuous LD or even in continuous SD. But the rate of the increase was lined as [SD to LD transfer], [continuous LD], and [continuous SD]. Because this order corresponded to the readiness of flowering, the threshold seems to be in the level of *LFY* transcript for the initiation of flowering. The leafy mutants have an extended vegetative phase and their flowers are often incompletely converted to vegetative shoots. Transgenic plants with *LFY* or *AP1* genes of constitutive expression have very early flowering (13). As speculated above, the plants that express the *CAL* gene constitutively are also the same phenotype, but don't flower as early. The *ap1* mutation nulifies the acceleration by constitutive *LFY* expression. But the *LFY* mutant retains the early-flowering phenotype by constitutively expressing the *AP1* gene. Thus, the function of *LFY* to induce flowering mainly promotes the expression of the *AP1* gene. The reason of the term "mainly" is because the *LFY* mutants can finally make flowers and then LFY is not the only positive factor of the *AP1* gene.

Accordingly, expressing FMI genes is primarily important. In other words, the study of flowering is equal to the study to know the pathway to up-regulate FMI genes.

INTEGRATION PATHWAY

All of the pathways shown above seem to converge in some genes. Four genetical pathways induce the FMI genes for flowering as whole.

The FMI gene *LFY* plays a critical role in this convergence (14). *LFY* regulates the transcription of *AP1*, *AP3*, and *AG* and gives floral identity to the SAM tissues. Thus, *LFY* is the switch of the floral development but is not of the floral evocation, which the flowering initially determines (9).

FT is the important switch of the floral evocation. The *ft* mutants are the late-flowering mutants that Koornneef et al. (53) first described. The enhancement of flowering by *LD* is completely disappeared in *ft* loss-of-function mutants. Thus, they are late flowering especially in LD. The *ft* mutants were unresponsive to vernalization, as in *co*, *gi*, and *fha*($=$*cry2*) mutants. The analysis using *ft* double mutants with *co*, *gi*, and *fha* mutations showed that the defective point is the enhancement of flowering in a light-dependent pathway. Araki's and Detlef's groups (46, 50) isolated the *FT* gene. *FT* has high homology to *TFL1* (16). This *FT* group has six homologous members in the *Arabidopsis* genome. Araki and coworkers (M. Abe & T. Araki, unpublished data) characterized the *ARABIDOPSIS THALIANA CENTRORADIALIS* (*ATC*) gene. The *FT* gene has the following characteristics: It is expressed universally, it is expressed maximumly at the onset of floral induction, it is positvely regulated by the LD condition, and it requires the *CO* gene for positive regulation in the LD condition. The *CO* gene directly interacts with the

FT gene (86). When the *FT* gene was consititutively expressed, transgenic plants flowered very early irrespective of LD or SD. The early flowering of constitutively *CO*-expressed plants was cancelled by the mutation in *FT* genes. Thus, the *FT* is under the light pathway. When grown in a SD condition or in a *CO*-minus condition by the mutation in a *CO* gene, these plants still can express the *FT* message. Thus, the expression of the *FT* gene is controlled not only by a light-dependent pathway, but also by a light-independent pathway. The autonomous pathway may control the expression of the *FT* gene because the expression of the *FT* gene was down-regulated by the mutation of the *FCA* gene. Additionally, the early-flowering transgenic plants by the constitutive expression of the *FT* transgene did not become late flowering after the introduction of an *fca* mutation. As can be predicted by the scheme of the autonomous pathway, the *FT* appears to be regulated by *FLC*, a key of the autonomous and vernalization pathway. *FT* is also repressed during the noninductive phase by the *EBS* gene (30), which shows that *FT* expression is doubly repressed.

How does *FT* induce floral evocation in a molecular mechanism? The protein encoded by the *FT* gene seems to be homologous to the phosphatidylethanolamine-binding protein (PE-BP), and belongs to the same group of *TFL1* and *CEN* genes (16, 78). The crystal structures were proposed in PEBP and CEN proteins, and they appear to have the same 3-dimensional structure. Thus, *FT* and *TFL1* may have the same structure as some of the mutations that reside at the presumptive functional domain of the ultrastructure. Thus, it may be plausible to speculate the same function to the animal PEBP. Biochemical activity of the PEBP is interesting. PEBP is the precursor form of the hippocampal cholinergic neurostimulating peptide (HCNP), is the Raf-1 kinase inhibitor protein, and is the specific inhibitor of thrombin. The TFS protein, a yeast member of the PEBP family, is a specific inhibitor of carboxypeptidase Y. The *SOC1* (=*AGL20*), has critical roles in the convergence (38). *LFY* functions in part downstream of *SOC1* (56).

The expression of *FT* and *SOC1* is controlled positively not only by light pathway, but also by the autonomous pathway acting through *FLC* negatively. The signal of the vernalization increases *SOC1* expression presumably via reduction of *FLC* levels (56), and *SOC1* can be up-regulated by a gibberellin pathway as well (14). Accordingly, *SOC1* and *FT* act as the convergence of all four pathways (38). Therefore, *FT*, *LFY*, and *SOC1* are integral to the process of the flowering pathway (13,14, 56).

The mutations in *TERMINAL FLOWER 1* (*TFL1*) are semidominant and early flowering with determinate inflorescence (3). Thus, *TFL1* codes for a repressor of the flowering. The *tfl1* is an interesting mutation because it has mutations in two aspects for flowering, temporal (early flowering), and spatial (terminal-determinate flowering) regulations. The *TFL1* codes for a protein with homology to *FT*, as above (16). The *TFL2* gene was initially identified as an enhancer mutation of the *tfl1* mutant (54, 55). It codes for a protein with homology to heterochromatin protein 1 (HP1) of animals and Swi6 of fission yeast (92). The *TFL2* functions as a negative repressor of the *FT* expression. Note that we cannot explain the role of the *TFL1* gene (3). Although the *tfl1* mutants flowered earlier than wild type, the

TFL1 transcription is inhibited by the FMI genes. The *tfl1*-minus phenotypes are puzzling; early flowering in *tfl1* single, *fwa tfl1* double, and *ft tfl1* double mutants, but late flowering and vernalization in *fca tfl1*, *fve tfl1*, and *fpa tfl1* double mutants.

As described above, the rescue of lateness of flowering was established in some dark-grown late-flowering mutants but not in other mutants (84). The nonrescued class of mutations were *fd, fe, ft,* and *fwa*. They were originally included in the class of the final stage, which is now called the integration pathway.

Because initially known mutants in *FWA* gene were late flowering, the *FWA* gene's function was thought to be positive for flowering (53). The *FWA* gene codes for a GL2-type homeodomain protein. The semidominant and late-flowering mutants were not loss-of-function types but ectopically expressed types. The *FWA* gene is not expressed in plants of early-flowering Columbia wild type. *ATML1* and *ANTHOSYANINLESS1* (*ANL1*) are the same group of genes, the GL2-type HD gene (1). We identified the *PDF2* gene as a L1 layer-specific gene (1). The overexpressed plants were late flowering (1). We also confirmed that the overexpression of *ATML1* and *ANL1* genes let transgenic plants late flower to some extent. This group of genes is responsible for the repression of flowering if these genes are overexpressed. The study to elucidate the molecular nature is underway.

The *FD* and *FE* genes belong to this integration pathway. *FD* was cloned to have transcriptional sequence identity (T. Araki & M. Abe, unpublished data). The functions of *FWA-FD-FE* genes to express the *FT* gene may be the key to understanding the integration pathway. We would then be able to construct the functional network depicted in Figure 1.

INFORMATION SIGNAL

After constructing the model for a genetic network, the cross-talks among four pathways appear to have been known.

The next step is to figure out the florigenic signal in the flowering pathway. After the florigen hypothesis was proposed, a specific signal was produced and transported (7). The signal should have a very important identity, mobility (29). Since the discovery of Systemin, our knowledge for the mobile signal has been deep but is still poor. The RNA is now transferred as a "morphogen" (47). If the RNA form is the signal of the information, there may be several lines of circumstantial evidence. Note that *FCA* and *FPA* may code for RNA-binding proteins (63, 87).

The tuberization of potatoes was inhibited by the overexpression of the *Arabidopsis CO* gene (66). Thus, the tuberization appears to use the same mechanism as flowering (42) and its signal may be moveable probably via the vascular system. Any form of sucrose may also be a candidate for the signal.

Recent knowledge of microRNA for regulating plant genes favors this RNA-signal "hypothesis" (34–36, 61, 62, 73, 79, 83). The GRAS family genes are included in this class. The GRAS family *GAI* and *RGA* genes are important in the GA pathway (61, 83).

Because there have been many chromatin-structure-related genes in the flowering process, we note the importance of chromatin structure for the process of flowering (27, 28, 31, 49, 54, 101).

There have been many MADS-box genes identified in the flowering system (14, 56, 65, 68, 76). Thus, understanding the precise role of MADS-box genes will be the key to clarifying the process of flowering.

FUTURE PROSPECTS

The above pathways were constructed by the study of mutants and genes in *Arabidopsis*. We speculate this may be applicable to other plant species. However, we should mention the following: The use of other plant species, such as Japanese morning glory, rice, and Lemna, should strengthen our knowledge of flowering. The studies and summation of data using Japanese morning glory should complement the knowledge of the light pathway (85). Those studies using rice will shed new light on SD and genetics-applicable material (98). Those using Lemna will reveal active agents for flowering in SD and LD because the Lemna are very sensitive in a liquid-culture medium (96). Because the grafting was a powerful tool for understanding the movement of the "signal," the use of plant species that are applicable to the grafting technique is also recommended (66).

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