REVIEW: FLOWERING

Arabidopsis, the Rosetta Stone of Flowering Time?

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Multiple environmental and endogenous inputs regulate when plants flower. The molecular genetic dissection of flowering time control in *Arabidopsis* has identified an integrated network of pathways that quantitatively control the timing of this developmental switch. This framework provides the basis to understand the evolution of different reproductive strategies and how floral pathways interact through seasonal progression.

The major developmental transition in flowering plants is the switch from vegetative to reproductive development. The correct timing of this transition is essential to maximize reproductive success given the requirement for synchronous flowering in out-crossing species and the dependence on favorable conditions for optimal seed set (*1*). Distinct reproductive strategies have evolved in different plant species. Many plants respond to environmental cues to control flowering time, particularly those that indicate seasonal change. *Arabidopsis* flowering, for instance, is accelerated by conditions that reliably indicate the passage of winter and the onset of spring and summer, such as a long period of cold temperature, elevated ambient growth temperatures, and increasing day length. In contrast, flowering in rice is promoted by short days. Flowering is also promoted in response to stresses such as overcrowding (perceived as changed light quality input), nutrient deficiency, heat, and drought. In addition, endogenous signals regulate the floral transition. Many plants pass through a juvenile phase, in which flowering cannot occur, to ensure that sufficient reserves accumulate to sustain floral development and seed set.

The multiple inputs converge to regulate the developmental fate of the shoot apical meristem. The capacity to adapt morphological development in response to environmental cues highlights a fundamental difference between plants and animals. In plants, most development occurs postembryonically through the continuous production of stem cells at the shoot and root apical meristems. Leaf and flower primordia emerge from the flanks of the shoot apical meristem, and the transition to floral identity is controlled by the activation of floral meristem identity genes such as *LFY*, *AP1*, *CAL*, and *FUL*, [most recently reviewed in (*2*)]. Images of *Arabidopsis* plants flowering at different times and defective in floral meristem identity function are shown in Fig. 1.

The challenge in flowering time research has been to define the pathways mediating response to multiple environmental and endogenous cues and to understand how they are integrated to effect the up-regulation of the floral meristem identity genes. We review here the regulatory network as it has been established through molecular genetic analysis in *Arabidopsis*. We then describe how changes in the quantitative interactions of the multiple inputs alters the predominance of the different pathways that can account for phenotypic plasticity in response to environmental change and the evolution of distinct reproductive variants adapted to local microclimates. Last, we discuss flowering time control in different plant species. Will the model developed for *Arabidopsis* unlock the complexities of flowering time control in all plants, as the Rosetta stone did for Egyptian hieroglyphics?

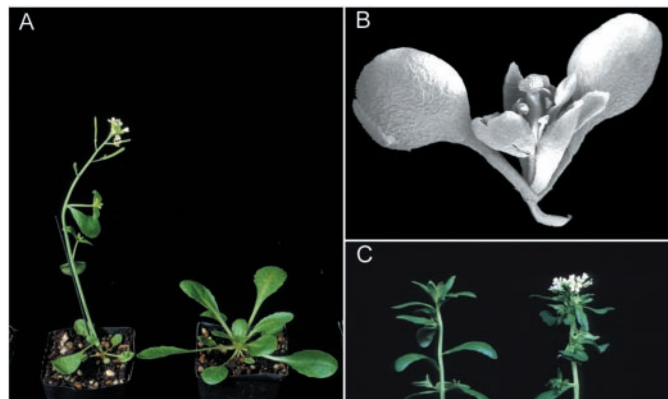

Fig. 1. *Arabidopsis* flowering time. (**A**) Two *Arabidopsis* plants, sown at the same time. The plant on the left is already flowering, whereas the plant on the right is delayed because it carries active *FRI*. (**B**) An electron micrograph of an extremely early flowering transgenic plant overexpressing the floral pathway integrators FT and LFY. (**C**) The consequence of loss of floral meristem identity function. The *lfy* mutant on the left has leaf-like structures in place of the flowers seen in the plant on the right.

Multiple Pathways Control Flowering Time

Genetic pathways have been defined (Fig. 2) that control the well-characterized effects on flowering time of the requirement for and response to a long period of cold temperature, photoperiod, and light quality. However, the molecular basis of other responses, such as the promotion of flowering by age and ambient temperature, is still poorly understood. In addition, the genetic approach has identified floral pathways for which physiological inputs are not yet known.

Vernalization requirement and response. The acceleration of flowering by a long period of cold temperature (1 to 3 months of ~1° to 10°C, depending on species or variant) is a process known as vernalization. A requirement for vernalization is a reproductive strategy adopted by many species and bred into several crops to ensure they overwinter vegetatively and flower in the favorable conditions of spring. In *Arabidopsis*, this can be mapped as a monogenic trait with dominant alleles of *FRI* conferring a vernalization requirement (*3*). *FRI* encodes a novel protein with two predicted coiled-coil domains that functions to promote the accumulation of *FLC* messenger RNA (mRNA) (*4–8*). *FLC* encodes a MADS box transcription factor that is a repressor of the floral transition, and there is a quantitative relation between *FLC* mRNA levels and the timing of flowering (*4*, *5*). By promoting the accumulation of *FLC* mRNA, FRI represses the floral transition to such a degree that it overrides the influence of otherwise favorable conditions (*7*). Vernalization results in a quantitative reduction in *FLC*

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mRNA levels such that the level of *FLC* mRNA correlates with the time of flowering (*4–6*). This observation provides a molecular explanation for the quantitative nature of the vernalization response. *FLC* mRNA levels remain low after plants have been returned to warm temperatures, explaining the mitotic stability of vernalization; however, *FLC* mRNA levels are reset after meiosis. Vernalization can still accelerate flowering in a null *flc* background, indicating that *FLC* is not the only target of this process (*8*, *9*). Vernalization is permissive, not instructive, because it prepares the plant to flower rather than evoking the flowering itself. That is, there is a clear temporal separation between the cold treatment and flowering, suggesting that vernalization has an epigenetic basis.

The mechanism of vernalization has been addressed through the identification of mutants defective in this process (*vrn* mutants). One such mutant, *vrn2*, has been characterized in detail (*10*). The initial cold-dependent reduction in *FLC* mRNA levels is not affected by the *vrn2* mutation. However, *vrn2* mutants cannot maintain low *FLC* mRNA levels through subsequent development at warmer temperatures (*10*). Therefore, *VRN*2 is required for maintenance but not the establishment of *FLC* repression. *VRN2* encodes a nuclear protein with homology to Polycomb-group proteins found in plants and animals (*10*), specifically FIS2, EMF2 of *Arabidopsis*, and Su(z)12 of *Drosophila*. This suggests that *VRN2* functions to maintain transcriptional repression of *FLC* through an effect on chromatin organization in a manner analogous to Polycomb-group protein complexes that maintain repression of *Drosophila* homeotic gene expression (*11*). It is not yet known which molecules are involved in the reduction of *FLC* mRNA levels during the cold, but genes such as *HOS1* (*12*) and *EARL1* (*13*) are candidates for regulatory molecules.

Photoperiod and light quality control. At higher latitudes, changing day length is a fundamental feature of seasonal progression. Acceleration of the floral transition by *Arabidopsis* is observed in response to long days. This ability to sense the lengthening photoperiod requires two components: (i) detection and transduction of the light signal and (ii) an endogenous timer. In *Arabidopsis*, light is perceived by phytochromes A through E (*14*) and cryptochromes (CRY) 1 and 2 (*15*), whilst the duration of the day and night is measured by the circadian clock (oscillator) (*16*). The molecular basis of signal input to the clock and the likely components that constitute the central oscillator have recently been reviewed (*17*). The circadian oscillator controls many aspects of plant biology in addition to flowering time, and several *Arabidopsis* mutants (*lhy*, *cca1*, *gi*, *elf3*, *toc1*, *ztl*, *fkf1*) that affect day length–dependent flowering also disrupt other circadian-regulated processes [see (*17*, *18*)].

The link between the oscillator and flowering time appears to be CO, a transcription factor with two B-box type zinc fingers (*18*). Loss-of-function *co* mutants flower late in inductive long days but like wild type in short days, whereas ectopic overexpression of *CO* promotes early flowering independently of day length (*19*). The level of *CO* expression is reduced in late flowering *gi* loss-of-function and *lhy* gain-of-function mutants (*18*).

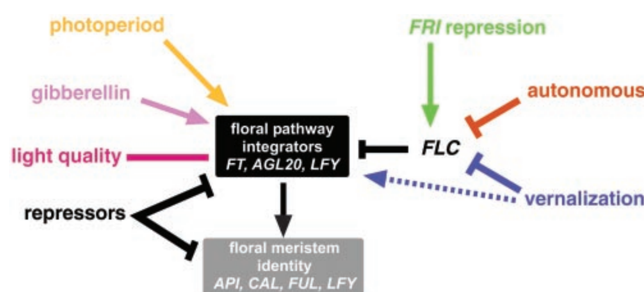

Fig. 2. Multiple input pathways regulating the transition to flowering. The inputs promote or repress activation of genes termed floral pathway integrators. Depending on the wavelength of light, the light quality pathway can repress or promote. The precise molecular events involved are uncertain in most cases, so the pathways have been shown feeding into a black box (and details are provided in Table 1). In turn the floral pathway integrators up-regulate the function of floral meristem identity genes. The components of the different input pathways have been omitted to simplify the diagram. The representation that the input pathways act independently of each other is likely to be an oversimplification.

Both of these mutants flower late and affect other circadian processes. In contrast, the level of *CO* expression is constitutively elevated in early flowering *elf3* mutants (*18*), which also have perturbed clock function but flower early. Their output effects on CO expression can, therefore, explain the opposite effects on flowering time caused by these mutations. Consistent with this, the expression of *FT*, an immediate target of CO (*20*), correlates with changes in *CO* expression in these different mutant backgrounds (*18*).

In addition to being controlled by the clock, *CO* expression is modulated by day length. In long day photoperiods, *CO* mRNA abundance is high at the end and the beginning of the photoperiod, but in short days peak *CO* abundance occurs in darkness (*18*). If the translation, activity, or stability of CO were controlled by light, this might provide the mechanism by which CO activity was effective only in long days; indeed, CO protein appears to be particularly unstable (*18*). Therefore, CO may function in an output pathway that integrates day length perception and time-keeping mechanisms to promote flowering.

Although photoreceptors contribute light input signals to the circadian system, this is not their only role in the photoperiodic control of flowering. A single photoreceptor mutation has little or no effect on circadian rhythms in white light (*21*, *22*), and yet single *phyA*, *phyB*, and *cry2* mutants affect flowering time: *cry2* mutants flower late in long days (*23*) whereas *phyB* mutants flower early (*24*). *phyA* mutants flower slightly late in long days, but are strongly delayed in night break experiments (where night-time dark is interrupted by a light period) (*25*, *26*). Far-red (735 nm) and blue (440 nm) light promote flowering through PHYA and CRY1 and 2, respectively. Red light (660 nm) inhibits flowering through PHYB, D, and E function across a range of species (*27–30*) independently of clock function and not involving transcriptional regulation of *CO* (*31*). PHYB negatively regulates *LFY* expression (*31*), so PHYB may act to compromise the ability of the various floral pathways to activate downstream targets. CRY2 mediates blue light inhibition of PHYB function (*32*) possibly through a direct interaction between the proteins (*33*).

Light quality (the relative intensities of the various wavelengths that reach the plant) is unlikely to provide seasonal information, but it is important for monitoring local environment. An important manifestation of light quality effects is the shade avoidance response. Light reflected from neighboring vegetation exhibits a reduced red/far-red ratio due to absorption of red light by chlorophyll. Far-red enriched light thus serves as a signal of neighborly competition and results in accelerated flowering and life cycle completion in a crowded environment.

The autonomous pathway. Mutants of the autonomous pathway (*fca*, *fy*, *fpa*, *ld*, *fld*, and *fve*) are late-flowering in long days and short days, a phenotype that can be overcome by vernalization (these induced mutations, therefore, confer a vernalization requirement) or growth in far-red enriched light (*23*, *34*). Autonomous pathway components normally function to limit the accumulation of *FLC* mRNA (*4–6*, *35*) and, where tested, this appears to fully account for their late flowering mutant phenotype (*8*). *FCA* and *FPA* both encode RNA binding proteins, so a key question being addressed is whether *FLC* is post-transcriptionally regulated by this pathway

(*36*, *37*). *FCA* and *FPA* transcripts are themselves alternatively processed (*36*, *38*), and in the case of *FCA* this limits the accumulation of active protein and delays flowering (*39*). *LD* encodes a homeodomain protein (*40*) and *FVE* encodes a WD-40 repeat protein (*41*).

The convergence of the autonomous, vernalization, and *FRI* repression pathways on *FLC* raises the question of how pathway predominance is established. Active *FRI* alleles are epistatic (have the predominant effect) to *FCA*, but this epistasis can be reversed through bypassing the posttranscriptional regulation of *FCA* expression (*35*). This quantitative, antagonistic relation of *FRI* with the autonomous and vernalization pathways may have evolved to enable fine-tuning of *FLC* levels. *FLC* is a potent block of the up-regulation of genes that in turn activate the floral meristem-identity genes. Efficient release of this block is a prerequisite for the promotive photoperiod and gibberellin (GA) signal transduction pathways to have an effect.

An unresolved issue is whether there is an endogenous input signal to the autonomous pathway. The autonomous pathway may monitor developmental age; plants must pass through a juvenile phase and reach the adult vegetative phase before they will flower. However, as yet there is no positive evidence for this hypothesis. *flc*-null alleles flower only slightly earlier than wild-type and still pass through a vegetative phase (*4*, *8*). Therefore, *FLC* does not appear to be a central repressor that prevents flowering in an age-dependent manner. The autonomous pathway may not be dynamically regulated but instead may function constitutively to maintain low levels of *FLC* expression throughout development. Some features of this pathway may also be environmentally regulated, as recent findings indicate that the control of flowering by ambient temperature may involve an *FLC*-independent function of the autonomous pathway (*42*).

The gibberellin pathway. All the currently known phytohormones (GAs, auxin, cytokinins, and brassinosteroids) have, at some point, been associated with flowering time control (*1*), but so far the genetic analysis of *Arabidopsis* flowering time has focused on GAs. Flowering is promoted by the application of GA_3 and *Arabidopsis* mutations such as *spindly*, which cause constitutively active GA signaling (*43*). In contrast, mutants that block GA signaling (*gai*) or GA biosynthesis (*ga1-3*) delay flowering, particularly in short days (*44*). The GA pathway is genetically distinct from the PHYB repression (*31*), vernalization (*45*, *46*), autonomous (*45*), and photoperiod (*9*, *47*) pathways. As with the autonomous pathway, the input signal that regulates GA activity in the control of flowering is unknown.

Integration of the Multiple Inputs

A key step forward in our understanding of flowering time control was the identification of genes whose expression or function was regulated by more than one of the input pathways. These genes are termed the floral pathway integrators (Fig. 2); thus far, three genes that function at this level have been identified: *LFY*, *FT*, and *AGL20* (*20*, *48*–*51*). Because *FT* and *AGL20* are immediate targets of the transcription factor CO (*20*), it seems likely that integration takes place through the direct transcriptional control of these genes. Although *LFY* is not an immediate target of CO (*20*), GAs activate the *LFY* promoter through cis elements different from those that are sufficient for the day length response, demonstrating that environmental and endogenous signals controlling flowering time can be integrated at the *LFY* promoter, rather than upstream (*52*). A summary of which pathways affect the expression and function of the different integrators is provided in Table 1. The floral pathway integrators serve similar functions but their redundancy is partial based on several criteria. First, the effect that each pathway has on the expression of a particular integrator is not equal. The expression of *AGL20*, for example, is more strongly affected by loss of autonomous pathway function than loss of the photoperiodic pathway (*20*). Second, the same set of pathways and factors may not control each integrator. Though *LFY* expression is abolished in *ga1co* double mutants, *FT* expression is not (*52*).

The relative importance of these (and other as yet undiscovered) integrators as critical checkpoints in flowering time control and how (and if) they potentiate each other's activity are important questions currently being addressed. *FT* functions in parallel to *LFY* (*53*) and is necessary for *LFY* function (*54*), but the relation of *AGL20* to these integrators has not yet been determined. Plants overexpressing *LFY* or *FT* flower early, illustrating that forced ectopic overexpression of either is sufficient to accelerate flowering time (*49*, *50*, *55*). However, both lines pass through a vegetative phase (*49*, *50*, *55*). In contrast, plants ectopically overexpressing both *LFY* and *FT* flower so early that the seedling has time to develop only cotyledons and occasionally one or two subtending leaves (bracts) (*49*, *50*) (Fig. 1). Because the cotyledons are formed during embryogenesis, these plants flower without passing through a large vegetative phase. This phenotype reveals the combined importance of these integrators and emphasizes the fact that their functions are not redundant.

A missing piece in our understanding of how the multiple floral pathways are integrated involves the input of a relatively large number of floral repressors that were identified from early flowering mutants. In addition to flowering early, many of the mutants exhibit pleiotropic phenotypes and some ectopically express *FT*, *AP1*, and downstream floral organ identity genes, such as *AGAMOUS* and *APETALA 3.* They include *EMF1* and *-2* (*56*, *57*), *TFL1* (*58*), *CLF* (*59*), *WLC1* (*60*), *EBS1* (*61*), *TFL2* (*62*), *ESD4* (*63*), and *FIE* (*64*). The first of these mutants to be described were the *emf* mutants. As a result, some early models of flowering time control invoke EMF as a central repressor of the floral transition with the flowering time pathways converging on its removal, resulting in the default activation of meristem identity genes. However, because the GA and day length response elements on the *LFY* promoter are distinct, this proposition would not appear to be correct (*52*). In addition, *emf* phenotypes are pleiotropic, exhibiting floral organ defects, whereas early flowering lines overexpressing *FT* and *LFY*, for example, are not.

An emerging theme, now that many of the repressors have been cloned, is that they are

Table 1. Floral pathway integrators. + or − signs signify accelerated or delayed integrator expression in response to the specified factor or condition. Light quality control has been analyzed through the action of different phytochromes. TCN, transcription

Integrator	Function	GA	Day length	Light quality	Age	Ambient temp.	FLC	Target of	Target
LFY	Novel TCN factor	+	+ in LDs	Repressed by PHYB	+		– expression in FLC-elevated genotypes		*AP1* *AG*
FT	Putative kinase inhibitor		+ in LDs		+	+ in higher temps	– expression in *FLC*-elevated genotypes	CO	
AGL20	MADS TCN factor	+	+ in LDs		+		– expression in *FLC*-elevated genotypes	CO	

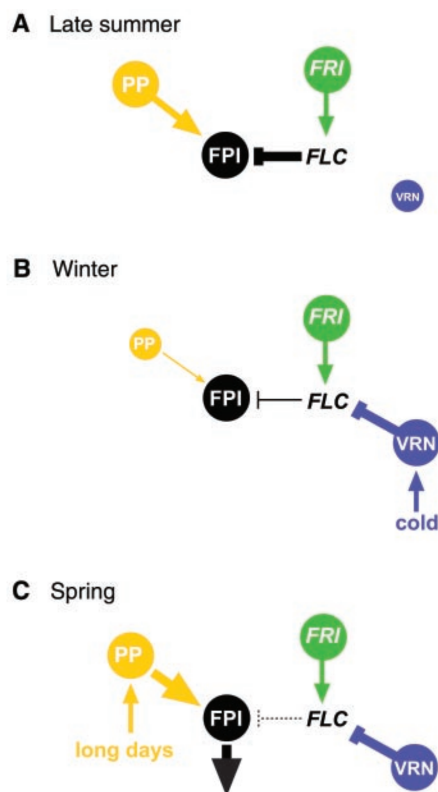

Fig. 3. (**A** to **C**) Model representing changing predominance of the floral pathways through different seasons. Only those input pathways playing a major role in seasonal progression are shown. FRI repression prevents promotive photoperiod (PP) accelerating flowering in late summer or autumn. Vernalization (VRN) antagonizes FRI repression, reducing FLC activity thus enabling long days in spring to up-regulate the floral pathway integrators (FPI). Smaller circles and thinner arrows indicate a lesser role and vice versa.

involved in generic repression of gene expression. Their homology to known proteins suggests they are likely to function in the regulation of chromatin structure and protein degradation (*41*). One of the repressors, *TFL1*, encodes a protein related to the floral pathway integrator FT (*49*, *50*, *65*).

Changing Predominance of Floral Pathways

The ability of a range of input pathways to quantitatively activate an overlapping set of common targets can explain much of the plasticity and diversity of flowering time control. The interactions of the floral pathways change predominance through different seasons (Fig. 3). *Arabidopsis* accessions that overwinter vegetatively can germinate in autumn when conditions may be similar to those of spring. By increasing *FLC* mRNA levels, *FRI* repression overrides otherwise favorable long day conditions (*7*) and functions as a "predictor" that winter has yet to come. The antagonism of *FLC* expression by vernalization removes this repression, conveys the "memory" that winter has passed (by altering *FLC* chromatin structure), and facilitates the ability of the integrators like *FT*, *LFY*, and *AGL20* to respond to subsequent increased temperature and day length, signaling the onset of spring and summer.

Changing predominance of pathways within the network also accounts for evolution of flowering time variants. *Arabidopsis* accessions display two principal reproductive strategies: winter annual and rapid cycling habits, thought to reflect adaptation to different niches. Winter annual accessions germinate in autumn, complete much of their vegetative development in late winter or early spring, and flower in late spring, a trait considered to be adaptive in regions where summers are short or harsh. In contrast, rapid cycling accessions can germinate and flower within a season, a strategy considered to be favored in regions where winter is so severe that germination or seedling survival is prevented or where mild conditions enable more than one life cycle a year. *FRI* is the major determinant of flowering time variation in natural accessions. Molecular analysis of *FRI* alleles revealed that most of the early-flowering *Arabidopsis* accessions carried *FRI* alleles containing one of two different deletions that disrupt the open reading frame (*7*). Rapid cycling thus appears to have evolved independently at least twice from late-flowering progenitors through loss-of-function *FRI* mutations. Loss of *FRI* minimizes the requirement for the vernalization pathway and causes the photoperiod, GA, and autonomous pathways to predominate in controlling flowering in rapid cycling accessions of *Arabidopsis* (Fig. 4).

Can changes in the predominance of the input pathways also explain flowering time control in species other than *Arabidopsis*? A number of components of the clock and photoperiod pathway are conserved between long day–induced *Arabidopsis* and short day–induced rice. Cloning of the quantitative trait loci, *Hd1*, (*66*) *Hd3a* [see (*41*)], and *Hd6* (*67*) for flowering time in rice (known as heading date) has revealed that they encode proteins related to the *Arabidopsis* proteins, CO, FT, and CK2 alpha subunit [which regulates the *Arabidopsis* circadian clock (*68*)], respectively. *Hd1* alleles that cause decreased photoperiodic sensitivity have insertions or deletions that perturb CO function. How do the same components promote flowering in long days in *Arabidopsis* and in short days in rice? One difference is that rice CO/HD1 is required for the inhibition of flowering in long days (*66*). Therefore the distinction may lie in the output of the photoperiod pathway. With the identification of these components, the mechanism that distinguishes long day and short day induction should soon follow. CO has also been identified in the short day plant, morning glory [*Pharbitis nil* (Pn)] (*69*). As in *Arabidopsis*, Pn*CO* is regulated by photoperiod and exhibits a similar circadian rhythm of expression to *Arabidopsis CO.* The degree of conservation of *CO* between two plants that exhibit distinct photoperiod response is such that Pn*CO* can accelerate the late flowering of *Arabidopsis co* mutations (*69*). Not all flowering time gene orthologs are easy to identify. The *ID1* gene that encodes a zinc finger protein involved in regulating a leaf-generated signal required for the transition to flowering in maize (*70*) has not yet been identified in *Arabidopsis*.

Can differences in physiological characteristics between different species be explained by changing predominance of the flowering pathways? The vernalization requirement in *Arabidopsis* is conferred by the dominant activity of *FRI.* In cereals, such as winter wheat and barley, vernalization requirement is recessive (*71*), indicating the involvement of a different mechanism. If *FLC*-mediated repression is conserved in cereals, an autonomous pathway mutation might confer the vernalization requirement. However, vernalization in *Arabidopsis* does not act wholly through *FLC* (*8*) so there must be other as yet uncharacterized targets of the vernalization response. In cereals, these alternative targets may be key to the vernalization requirement.

There is still a lot to learn. The dissection of flowering time control, which combines environmental and endogenous signaling pathways, genetic and epigenetic regulation, and funda-

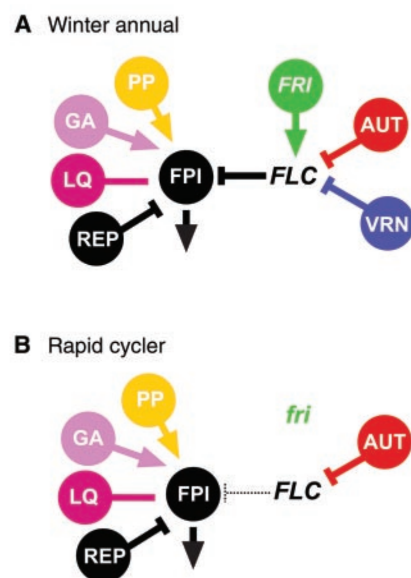

Fig. 4. Evolution of flowering time variants. Independent loss of function *FRI* mutations from winter annuals (**A**) account for the evolution of the majority of rapid-cycling *Arabidopsis* accessions (**B**). This removes the brake to activation of the floral pathway integrators (FPI), normally antagonized in winter annual accessions by vernalization (VRN).

mental and applied research will keep a large range of scientists busy for some time.

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