

## REVIEW

# The unfolding drama of flower development: recent results from genetic and molecular analyses

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There has been an explosion of information about flower development recently, largely because of genetic and molecular studies in *Arabidopsis thaliana* and *Antirrhinum majus*. A number of homeotic genes have been identified that regulate flower development, and models have been proposed for the specification of meristem and floral organ identities. Molecular cloning of many of these genes has allowed the testing of specific predictions of the models but also has led to modifications of a floral organ identity model. Furthermore, several of the floral genes contain a conserved region, the MADS box, which encodes a domain with striking sequence similarity with known transcription factors from human and yeast. Additional MADS box genes have been isolated from several plants; these genes are likely to play important regulatory roles during flower development. The genetic and molecular studies have uncovered many of the components of a complex network of regulatory proteins that directs flower development. Further characterization of these and other yet to be discovered components promises to contribute a great deal to our understanding of the mechanisms controlling flower development.

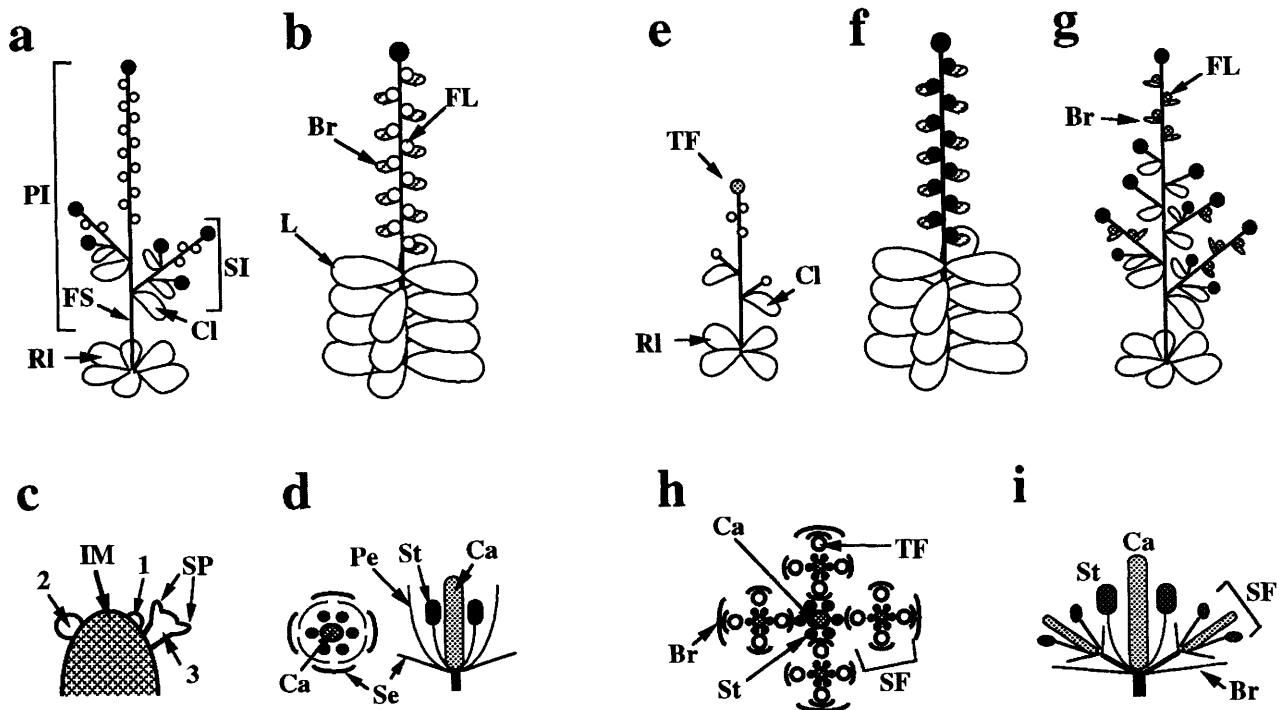
Flowering plants, like other land plants, have vegetative organs such as roots, stems, and leaves, which absorb nutrients and water from the soil, transport them to other parts of the plant, and synthesize organic compounds using the sun's energy. In addition, flowering plants produce elaborate reproductive structures, the flowers, which, following fertilization, become fruits and bear seeds. From the seasoned gardener to the casual observer, from the naturalist to the florist shopper, people have always been fascinated by the enormous variety of flowers, ranging from 2 mm to >10 cm in length, covering the whole visual spectrum with their colors, and differing in the arrangement of flowers and the symmetry within a flower. How do flowers develop? What genes regulate this complex process? In recent years, rapid advances have been made in addressing these questions, largely as a result of genetic and molecular studies in two distantly related flowering plants, *Arabidopsis thaliana*, a relative of cauliflower and cabbage, and the snapdragon, *Antirrhinum majus*.

Postembryonic plant development is repetitive, be-

cause of the reiterative nature of the morphogenesis initiated from the meristems, which are groups of undifferentiated progenitor cells. The meristem at the apex of the plant (or the tip of a stem) is called the apical meristem. While the cells at the very summit of the dome-shaped apical meristem divide and maintain the meristem, the cells at the periphery of the apical meristem divide to give rise to additional meristems (e.g., of branches) or organ primordia, which are groups of cells with specified fates and which develop into different organs, such as leaves. The cells just below the apical meristem divide and differentiate to form the stem itself. Many plants, such as trees, have a recognizable dominant stem (trunk), with the primary apical meristem, and additional branches, each with a meristem at the tip. Other plants lack an obvious dominant stem and a primary meristem, and have a bushy morphology. In *Arabidopsis*, the vegetative apical meristem produces leaves arranged in a spiral arrangement with very short distances between successive leaves, forming a rosette (Fig. 1a). In contrast, the *Antirrhinum* vegetative apical meristem produces pairs of leaves opposite to each other, and each pair is at right angle with the previous pair (Fig. 1b; Coen and Meyerowitz 1991).

Flower development requires several steps (Meyerowitz et al. 1991). The first step is floral induction, which establishes a reproductive meristem(s). The reproductive meristem is often called an inflorescence meristem because it gives rise to a series of flowers, called an inflorescence. The number of flowers in an inflorescence varies between species and ranges from several (determinate inflorescence) to indefinite (indeterminate inflorescence). Both *Arabidopsis* and *Antirrhinum* have indeterminate inflorescences (Fig. 1a,b). The second step is the formation of a floral meristem (Fig. 1c), which is homologous to a branch meristem, for a flower can be regarded as a very short stem with specialized organs. In some plants, floral induction results in the formation of a floral meristem directly, and a single flower develops at the end of a stem. In *Arabidopsis*, the primary inflorescence meristem gives rise to, in a spiral, first a small number of cauline leaf primordia (Fig. 1a), each with an adjacent secondary inflorescence meristem, and then a large (in-

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**Figure 1.** Schematic representation of wild-type (a–d) and mutant (e–i) *Arabidopsis* and *Antirrhinum* plants and flowers. (a) A wild-type *Arabidopsis* plant, showing rosette leaves (RL), floral stem (FS), primary inflorescence (PI), and secondary inflorescence (SI), which are subtended by cauline leaves (Cl). The leaves and flowers arise in a spiral arrangement. Flowers are represented by open circles, and inflorescences are represented by solid circles. (b) A wild-type *Antirrhinum* plant, showing leaves (L) and flowers (FL), subtended by bracts (Br). (c) The apex of a wild-type *Arabidopsis* inflorescence, with inflorescence meristem (IM), and floral primordia. The period from floral meristem initiation to floral bud opening has been divided into 12 stages on the basis of morphological landmarks (Smyth et al. 1990). The first three stages are as follows: (1) Floral meristem appears as a buttress on the flank of inflorescence meristem; (2) floral meristem becomes globular shaped; and (3) sepal primordia (SP) arise on the flank of the floral primordium. (d) Top (left) and side (right) views of a wild-type *Arabidopsis* flower, showing four whorls: four sepals (Se), four petals (Pe), six stamens (St), and an ovary with two united carpels (Ca). (e) An *Arabidopsis tfl1* plant, showing reduced number of rosette leaves, and flowers instead of secondary inflorescences are subtended by cauline leaves. At the apex, a terminal flower (TF) is formed. (f) An *Antirrhinum flo* plant. Flowers are converted to secondary inflorescences, which produce no flowers. The *squa* plants are similar, except that the secondary inflorescences do produce some flowers. (g) An *Arabidopsis lfy* plant. True inflorescences are shown as solid circles, and abnormal flowers with inflorescence properties are shown as hatched circles (FL). Note that the *lfy* plant has more secondary inflorescences than wild type, and that the abnormal flowers are subtended by bracts. Top (h) and side (i) views of an *ap1* flower: sepals are converted to bracts, and secondary flowers (SF) arise interior to the bracts, with tertiary flowers (TF) interior to the bracts of secondary flowers; petals are absent, whereas stamens and carpels are normal.

definite) number of floral meristems (Fig. 1a,c). In contrast, the *Antirrhinum* inflorescence meristem produces, also in a spiral, small leaf-like bracts, each with an adjacent floral meristem (Fig. 1b), but no secondary inflorescences. The third step is the formation of floral organ primordia, which are organized groups of cells occupying different positions within the floral meristem. After the organ primordia are formed, the identities of the organs are determined to specify the fate of cells within these organs. Finally, during floral organ development, specific programs are executed leading to organs with characteristic final forms and functions. *Arabidopsis* flowers have four concentric whorls (rings) of organs, and from the periphery to the center they are four green sepals (protective and most leaf-like), four white petals (in many plants, colorful and attractive to insects), six pollen-producing stamens (male), and an ovary (female) consisting

of two united carpels (Fig. 1d). Although *Antirrhinum* flowers also have the same four whorls of organs, the flowers have bilateral symmetry and are much larger than those of *Arabidopsis*. In addition, the petals of *Antirrhinum* flowers are fused in the lower half to form a tube.

Despite the apparent differences between *Arabidopsis* and *Antirrhinum*, flower development in these plants is regulated by remarkably similar genes (Schwarz-Sommer et al. 1990; Coen 1991, 1992; Coen and Meyerowitz 1991; Weigel and Meyerowitz 1993b). Many of the mutant phenotypes have been observed in plants that are evolutionarily divergent, suggesting that what is true for *Arabidopsis* and *Antirrhinum* is likely to be conserved in other plants even though a tremendous amount of variation exists among flowers of different plants (Meyerowitz et al. 1989). Furthermore, homologs of the *Ara*-

*bidopsis* and *Antirrhinum* floral genes have been identified in many other plants, including the monocot maize (e.g., Pnueli et al. 1991; Mandel et al. 1992a; Kempin et al. 1993; Schmidt et al. 1993; van der Krol et al. 1993). This review summarizes recent genetic studies in *Arabidopsis* and *Antirrhinum*, and emphasizes recent results from molecular analyses in these two plants, as well as some studies from a few other plants. These results indicate that a complex network of regulators controls the formation of the inflorescence meristem and its transition to the floral meristem, the initiation of floral organ primordia, and the floral organ identities. The first three sections present brief descriptions of mutant phenotypes. These are followed by discussions of genetic interactions based on double and triple mutant studies and on molecular analyses using cloned genes. Finally, the biochemical nature of many of the gene products and possible regulatory mechanisms is discussed. Because of limited space, morphological and physiological studies in other plants are not discussed here, nor are there detailed accounts of earlier genetic studies, for which the reader is referred to several excellent reviews (Meyerowitz et al. 1989, 1991; Schwarz-Sommer et al. 1990; Coen 1991; Coen and Meyerowitz 1991). Other recent reviews offer different perspectives and emphasis (Coen 1992; Coen and Carpenter 1992; Jack et al. 1993; Weigel and Meyerowitz 1993b).

### Prelude: floral induction

Floral induction is regulated by developmental and environmental factors (Bernier et al. 1993). In *Arabidopsis*, it seems that reproductive development is a default pathway and that normal vegetative growth occurs when the reproductive program is delayed as a result of inhibition. This inhibition is removed only when developmental and environmental signals are present, as indicated by genetic studies. The recessive mutant *emf* produces a single flower upon seed germination, without any vegetative growth (Sung et al. 1992), suggesting that *EMF* is required for the inhibition of reproductive growth. Mutations in another gene, *TFL1*, cause a reduction of the number of vegetative (rosette) leaves, and an earlier than normal appearance of inflorescence (Shannon and Meeks-Wagner 1991; Schultz and Haughn 1993). This suggests that the *TFL1* gene may enhance the inhibition of reproductive growth before the appropriate developmental stage, although this could be related to a negative role *TFL1* has in floral meristem initiation (Fig. 1e; also see below in Act 1).

Flower induction in *Arabidopsis* is influenced by the length of daylight and temperature (Bernier et al. 1993). Long days (14–16 hr light/8–10 hr dark) accelerate flowering as compared with short days (8–10 hr light/14–16 hr dark); furthermore, cold treatment promotes early flowering (Bernier et al. 1993). A group of mutants, known as late-flowering mutants, have been found to change the regulation of flowering by environmental conditions (Koornneef et al. 1991; Araki and Komeda 1993; Lee et al. 1993). Both long-day conditions and cold

reduce the delay of flowering in some, but not all, of the late flowering mutants. Biochemical studies (Burn et al. 1993) indicate that cold treatment causes demethylation of DNA and that the DNA demethylation may be involved in reducing the delay of flowering. It will be possible in the near future to learn the molecular mechanisms of the late flowering gene functions, for efforts have begun in earnest to isolate and characterize the late flowering genes at the molecular level (e.g., Putterill et al. 1993).

### Act 1: floral meristem initiation

The characterization of *Arabidopsis* and *Antirrhinum* mutants have identified several genes that control floral meristem initiation (Table 1). The phenotypes of several mutants (*leafy* and *apetala1* in *Arabidopsis*, and *floricaula* and *squamosa* in *Antirrhinum*; see below) suggest that the corresponding wild-type genes promote the transition from inflorescence to floral meristems (Coen et al. 1990; Irish and Sussex 1990; Schultz and Haughn 1991; Huala and Sussex 1992; Huijser et al. 1992; Mandel et al. 1992b; Weigel et al. 1992; Bowman et al. 1993). In the *Antirrhinum floricaula* (*flo*) mutants (Fig. 1f), floral meristems fail to form; secondary inflorescence meristems form instead. Similarly, in the *Arabidopsis leafy* (*lfy*) mutants (Fig. 1g), early flowers are replaced by secondary inflorescences. Although late *lfy* flowers do form, they are abnormal and subtended by bracts (not present in the wild type). These flowers resemble secondary inflorescences in several ways: (1) The outer organs resemble cauline leaves, with occasional secondary flowers; (2) the distance between whorls is extended; and (3) the organ arrangement is partially spiral. The *Arabidopsis AP-ETALA1* (*AP1*) and the *Antirrhinum SQUAMOSA* (*SQUA*) genes also act positively in the inflorescence-to-flower transition. The flowers of the *ap1-1* mutant (Fig. 1h,i) contain secondary flowers interior to the first whorl organs and tertiary flowers interior to the first whorl organs of the secondary flowers, making each primary flower a miniature inflorescence (although the arrangement is whorled instead of spiral). Likewise, *squa* mutants produce inflorescence-like shoots instead of flowers, indicating that the mutants are deficient in floral meristem initiation; however, these secondary shoots do eventually produce some flowers.

The *Antirrhinum FLO* and *SQUA*, and the *Arabidopsis LFY* and *AP1* genes, have been isolated (Coen et al. 1990; Huijser et al. 1992; Mandel et al. 1992b; Weigel et al. 1992). *FLO* and *LFY* encode homologous proteins with proline-rich and acidic regions, both characteristics of transcription factors. The idea that *LFY* is a transcriptional regulator is further supported by its localization to the nucleus (Weigel and Meyerowitz 1993a). The *AP1* and the *SQUA* genes were isolated independently and found homologous to each other; their gene products are members of a family with similarity to transcription factors (see below in The Players). All four genes are expressed in very early floral meristems, consistent with their roles in determining meristem identity (Coen et al.

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**Table 1.** *Arabidopsis* and *Antirrhinum* floral genes

Genes <sup>a</sup>		Gene products <sup>b</sup>	Single mutant phenotypes or expression patterns	References <sup>c</sup>
<i>Arabidopsis</i>	<i>Antirrhinum</i>			
<i>Genes regulating transition from vegetative to reproductive development</i>				
Late flowering genes	?	?	delayed flowering	1
EMF	?	?	flowering without vegetative growth	2
TFL1	?	?	early flowering	3
<i>Genes controlling floral meristem initiation and size</i>				
TFL1	?	?	inflorescence to floral meristems	3
?	CEN		terminal flower with radial symmetry	4
LFY	FLO	Transcription factor?	flowers to ( <i>lfy</i> , partial) inflorescences	4, 5
AP1	SQUA <sup>d</sup>	MADS domain	<i>ap1</i> , flowers interior of first whorl organs <i>squa</i> , inflorescence replacing flowers	6, 7
CAL	?	?	enhancement of <i>ap1</i> phenotype	7
CLV1	?	?	large meristem, more floral organs	8, 9
CLV2	?	?	more carpels	9
<i>Genes specifying floral organ identity</i>				
AP1	SQUA <sup>d</sup>	MADS domain	<i>ap1</i> , sepals to bracts, abnormal petals <i>squa</i> , abnormal organs in outer whorls	6, 7
AP2	?	?	sepals to carpels, petals to stamens	4, 10, 12
AG <sup>d</sup>	PLENA	MADS domain	stamens to petals, carpels to flowers	4, 10, 11
AP3	DEFA <sup>d</sup>	MADS domain	petals to sepals, stamens to carpels	4, 10, 13
PI	GLO <sup>d</sup>	MADS domain	similar to <i>ap3</i> and <i>defA</i>	4, 10, 13
?	SEP	?	similar to <i>defA</i>	4
SUP	?	?	more stamens, reduction of carpels	4, 14
<i>Genes controlling floral symmetry</i>				
—	CYC	?	bilateral to radial symmetry	4
<i>Genes isolated by sequence similarity to AG</i>				
AGL1		MADS domain	expressed in carpels	15
AGL2		MADS domain	expressed in flowers	15
AGL4		MADS domain	expressed in flowers	15
AGL5		MADS domain	expressed in flowers	15
AGL6		MADS domain	expressed in flowers	15

<sup>a</sup>Classification is based on single mutant phenotypes. The homologs are listed side by side.<sup>b</sup>The description of gene products is based on deduced amino acid sequences.<sup>c</sup>References: (1) Koornneef et al. (1991); Lee et al. (1993). (2) Sung et al. (1992). (3) Shannon and Meeks-Wagner (1991, 1993); Alvarez et al. (1992). (4) Carpenter and Coen (1990); Coen and Meyerowitz (1991). (5) Coen et al. (1990); Schultz and Haughn (1991); Huala and Sussex (1992); Weigel et al. (1992). (6) Irish and Sussex (1990); Huijser et al. (1992); Mandel et al. (1992b). (7) Bowman et al. (1993). (8) Clark et al. (1993). (9) Leyser and Furrer (1992). (10) Bowman et al. (1989, 1991b); Schwarz-Sommer et al. (1990). (11) Yanofsky et al. (1990); Bradley et al. (1993). (12) Kunst et al. (1989); Okamoto et al. (1993). (13) Sommer et al. (1990); Jack et al. (1992, 1993); Tröbner et al. (1992). (14) Schultz et al. (1991); Bowman et al. (1992). (15) Ma et al. (1991).<sup>d</sup>A number of homologs have been isolated (see text for references): AG, from *Brassica napus* (BAG1), maize (ZAG1), petunia (pMADS3) and tobacco (NAG1); AP3, from petunia (pMADS1); PI, from petunia (FBP1 and pMADS2), and tobacco (NTGLO). In addition, TM4 and TM6 from tomato share substantial sequence similarity with the *Arabidopsis* AP1 and AP3 (and *Antirrhinum* SQUA and DEFA) genes, respectively.

1990; Huijser et al. 1992; Mandel et al. 1992b; Weigel et al. 1992). Because *flo/lfy* and *squa/ap1* mutants reiterate an earlier developmental program (inflorescence instead of flower), they could be considered heterochronic mutants. However, the nature of plant development is such that spatial arrangements are often laid out in a temporal sequence; therefore, the same abnormal development could be regarded as both a spatial and a temporal conversion (Coen et al. 1990).

In contrast to the genes promoting floral meristem initiation, the *TFL1* gene inhibits floral meristem forma-

tion (Shannon and Meeks-Wagner 1991; Alvarez et al. 1992; Schultz and Haughn 1993; Shannon and Meeks-Wagner 1993). Apart from being early flowering, the *tfl1* mutants produce a determinate primary inflorescence with very few flowers and no secondary inflorescence (Fig. 1e), unlike the indeterminate wild-type inflorescence, which produces dozens of flowers as well as secondary and tertiary inflorescences. The *tfl1* mutant inflorescence terminates with an abnormal flower consisting of two to three incomplete flowers. It seems that in the *tfl1* mutants, the secondary inflorescence meristems



are converted to floral meristems and that the primary inflorescence meristem is converted to two or three closely spaced floral meristems.

## Act 2: organ primordia initiation and identity

Several *Arabidopsis* homeotic genes have been identified that affect the identity of floral organs, including *AP1*, *APETALA2* (*AP2*), *APETALA3* (*AP3*), *PISTILLATA* (*PI*), and *AGAMOUS* (*AG*) (Table 1). Each of these genes controls the identity of two adjacent whorls of floral organs. Both the *ap1* and *ap2* mutations affect the organ identity in the outer two whorls, with severity of the phenotype dependent on the particular *ap1* or *ap2* mutant alleles. The strong *ap1-1* mutant has a sepal-to-bract conversion in the first whorl, whereas weaker *ap1* mutants have abnormal petals. In plants with one of the most severe *ap2* alleles, the first and second whorl organs, if present, are converted from sepals and petals to carpels and stamens, respectively. Weaker alleles of *ap2* lead to conversion of sepals to leaves and petals to petaloid stamens. The *AP3* and *PI* genes are both required for correct second and third whorl organ types; *ap3* and *pi* mutants have conversion of petals to sepals and stamens to carpels. The *AG* gene is required for determining the identities of stamens and the carpels. In *ag* mutant flowers, the six stamens are converted to petals and the ovary is replaced by a second *ag* flower, such that the pattern of sepals, petals, and petals is repeated more than five times. The *ag* mutant phenotype indicates that *AG* function is also required for the maintenance of a determinate floral meristem. That the number of floral organs is altered in *ap2* and *ag* mutants indicates that these genes also function in regulating organ primordia initiation.

Mutations affecting organ identity have also been isolated in other plants (Meyerowitz et al. 1989), particularly in *A. majus* (Table 1). Many of the *Antirrhinum* mutations cause homeotic conversions similar to those found in *Arabidopsis*. The *deficiens* (*defA*) and *globosa* (*glo*) mutants have similar phenotypes to the *Arabidopsis ap3* and *pi* mutants, and so do mutants of another *Antirrhinum* gene, *SEPALOIDEA* (*SEP*). The *Antirrhinum plena* mutant is similar to the *Arabidopsis ag* mutant, with conversion of stamens to petals, and carpels to additional floral organs. In petunia, the *blind* mutant produces flowers with sepals exhibiting carpel features and conversion of petals (corolla) to staminoid organs (Tsuchimoto et al. 1993), similar to the flowers of weak *Arabidopsis ap2* mutants. Another petunia floral mutant, *green petal* (*gp*), has flowers with the petals converted to sepals (van der Krol et al. 1993).

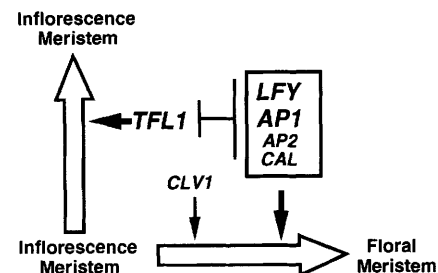
Other mutants have flowers with altered numbers of organs. For example, the *Arabidopsis superman* (*sup*) mutant flowers are normal in the three outer whorls but produce more whorl(s) of stamens at the expense of the ovary (Schultz et al. 1991; Bowman et al. 1992). Studies of *sup ap3* or *sup pi* double mutants suggest that *SUP* negatively regulates *AP3* and *PI* function in the fourth whorl. The *Arabidopsis clavata1* (*clv1*) and *clavata2* (*clv2*) mutant plants have ovaries consisting of more

than the normal two carpels (Koornneef 1987). Recent studies indicate that *clv1* mutants have a larger apical meristem and increased numbers of floral organs in all four whorls (Leyser and Furrer 1992; Clark et al. 1993). Finally, mutations in the *TOUSLED* (*TSL*) gene cause a reduction in the number of floral organs in all whorls, as well as abnormal leaf morphology (Roe et al. 1993).

## The dialogues: genetic interactions

### Interactions controlling floral meristem formation

Double mutant analyses indicate that the meristem identity genes of *Arabidopsis*, *LFY* and *AP1*, interact with each other to control floral meristem formation (Fig. 2). The *lfy ap1* double mutant has a more complete conversion of floral to inflorescence meristem than either single mutant, suggesting that these genes function in parallel pathways to promote floral meristem formation and that these pathways are partially redundant. Similar studies indicate that the *Antirrhinum FLO* and *SQUA* genes also act in parallel pathways (Coen 1992). This functional parallel is further supported by the observations that *LFY* (*FLO*) is expressed in the *ap1* (*squa*) mutant and that *SQUA* gene is expressed in the *flo* mutant (Huijser et al. 1992; Weigel et al. 1992). In addition, other genes contribute to the process of floral meristem initiation (Fig. 2). A variant allele of the *Arabidopsis* gene, *CAULIFLOWER* (*CAL*), was found to enhance the *ap1* mutant phenotype, although the *cal-1* allele alone has no phenotype, nor does the *cal-1* allele enhance the



**Figure 2.** Control of transition from inflorescence to floral meristem in *Arabidopsis*. The meristem identity genes *LFY* and *AP1* are two main players promoting floral meristem initiation, whereas *AP2* and *CAL* have little or no effect on meristem identity in the wild-type *LFY AP1* background. However, *cal* enhances the effect of *ap1*, and *ap2* enhances those of both *lfy* and *ap1*, on meristem identity. In addition, *AP1* and *CAL* together positively affect the expression of *LFY* and *AP1*. The box around these four genes indicates the positive genetic interactions and/or functional redundancy among these genes. *CLV1* also promotes the transition to floral meristem. *TFL1* promotes inflorescence meristem and antagonizes *LFY*, *AP1*, and *AP2*. Based on information from the following references, Alvarez et al. (1992); Huala and Sussex (1992); Weigel et al. (1992); Bowman et al. (1993); Clark et al. (1993); Okamuro et al. (1993); Schultz and Haughn (1993); Shannon and Meeks-Wagner (1993); and Weigel and Meyerowitz (1993c). (→) Positive interaction and (⊣) negative interaction.

phenotype of a strong *lfy* mutant (Bowman et al. 1993). In the *ap1* mutant background, *CAL* has been shown to positively affect the expression of both the *Arabidopsis* *LFY* and *AP1* genes. It is possible that in the wild type, the combination of both *LFY* and *AP1* activities is in excess of the minimal requirement (threshold) for floral meristem formation, and *CAL* is not necessary. In *ap1* mutants, the total activity for floral meristem is reduced to near the threshold, and further reduction due to a defect in *CAL* function manifests as a more severe phenotype than those of the *ap1* single mutants. Double mutant analyses also revealed that the organ identity gene *AP2* contributes to meristem identity. Although *ap2* single mutants show no defect in floral meristem formation, *ap2* mutations enhance the *ap1* or *lfy* mutant phenotypes, leading to a more complete conversion of floral to inflorescence meristems. One explanation is that *AP2* is required for floral meristem in the absence of *LFY* or *AP1* activities; this is consistent with the finding that *AP2* is also expressed at stages before floral organ formation. Finally, *clv1* mutations also enhance the phenotypes of *lfy* and *lfy ap1* mutants, indicating that *CLV1* is also involved in determining meristem identity. These double and triple mutant analyses indicate that although *LFY* and *AP1* are the major functions that promote floral meristem formation, *CAL*, *AP2*, and *CLV1* also contribute to this process.

Contrary to these positively acting genes, the *Arabidopsis* *TFL1* gene inhibits floral meristem development. Moreover, on the basis of double mutant studies it was proposed that *TFL1* antagonizes *LFY*, *AP1*, and *AP2* (Fig. 2). This is supported by the observation that the expression of *LFY* and *AP1* expands in a *tfl1* mutant to include the meristems occupying the positions of the wild-type inflorescence meristems (Weigel et al. 1992; Bowman et al. 1993; Gustafson-Brown et al. 1994). Although *ap1* mutations do not, *lfy* mutations partially suppress *tfl1* mutant phenotypes, especially under short-day conditions (Alvarez et al. 1992; Bowman et al. 1993; Schultz and Haughn 1993; Shannon and Meeks-Wagner 1993). Furthermore, combinations of *lfy* and *ap1*, or *lfy* and *ap2*, mutations clearly suppress *tfl1* meristem phenotypes (Schultz and Haughn 1993).

At least part of the function of the *Arabidopsis* meristem identity genes *LFY* and *AP1* is to regulate the expression of floral organ identity genes (Weigel and Meyerowitz 1993a), bridging these two stages of flower development. Analyses of the expression patterns of *AP3*, *PI*, or *AG* in *lfy* and *ap1* single or double mutants indicate that *LFY* and *AP1* synergistically activate the expression of *AP3* and *PI*, and regulate *AG* expression pattern (Weigel and Meyerowitz 1993a). These results are consistent with the finding that the *Arabidopsis* *LFY* and *AP1* genes are expressed in developing flowers during floral organ primordia formation, in addition to being expressed in earlier stages of floral meristems (Mandel et al. 1992b; Weigel et al. 1992). Likewise, the *Antirrhinum* *FLO* and *SQUA* genes are also expressed in early floral primordia at the time of organ primordia initiation (Coen et al. 1990; Huijser et al. 1992). On the basis of the tran-

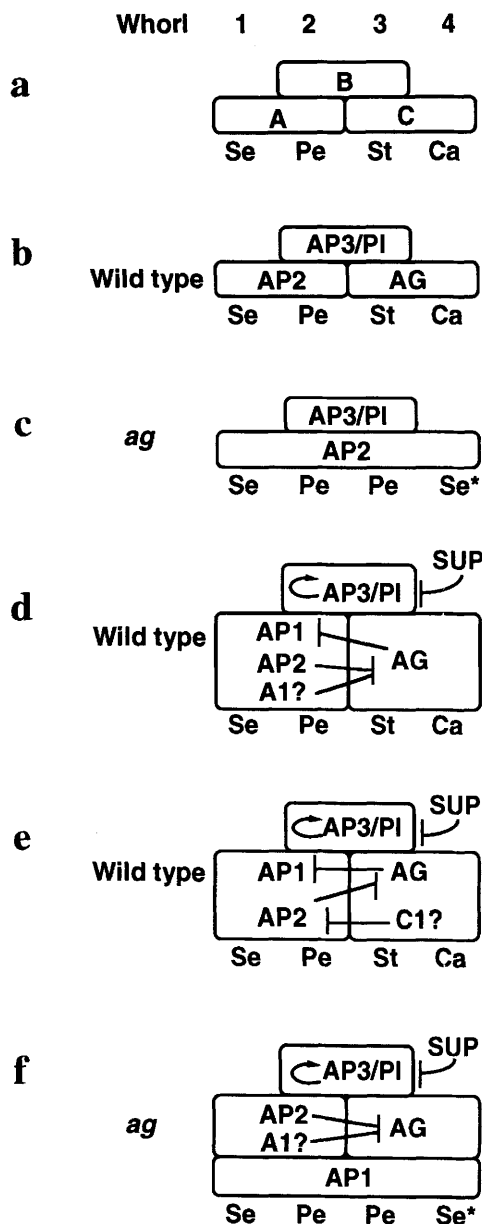
sient expression of *FLO* in whorls 1, 2, and 4, it was proposed that *FLO* activates some of the organ identity genes sequentially (Coen et al. 1990). It seems that the meristem identity genes function to set up the stage on which the floral homeotic genes play their roles in controlling the organ identities (see Fig. 3 and discussion below).

#### Models for the specification of floral organ identity

A model (the **ABC** model, Fig. 3a) for the determination of floral organ identity was proposed on the basis of genetic analyses in *Arabidopsis* and *Antirrhinum*. The *Arabidopsis* and *Antirrhinum* mutant phenotypes indicate that *AP2* is essential for the **A** function, that the *Arabidopsis* *AP3* and *PI* genes (*DEFA* and *GLO* from *Antirrhinum*) are components of the **B** function, and that the *Arabidopsis* *AG* gene (*PLENA* from *Antirrhinum*) is a necessary part of the **C** function, as shown in Fig. 3b. The proposed domains of gene action are supported by the expression patterns of several homeotic genes, including the *Arabidopsis* *AG* and *AP3*, and the *Antirrhinum* *DEFA*, *GLO*, and *PLENA* genes. An important aspect of this model is that the **A** and **C** functions antagonize each other, such that **A** inhibits **C** in whorls 1 and 2, and **C** inhibits **A** in whorls 3 and 4. This antagonism is supported by the fact that the expression of *AG* and its petunia homolog (*pMADS3*) expands outward to all floral whorls in the *Arabidopsis* *ap2* and the petunia *blind* mutant flowers, respectively. Moreover, ectopic expression of *AG* or the *AG* homologs from *Brassica*, petunia, and tobacco in the outer whorls of transgenic flowers results in *ap2*-like flowers, and a similar ectopic expression of the *PLENA* gene in *Antirrhinum* leads to the *ovulata* (*ap2*-like) mutant phenotype (Mandel et al. 1992a; Mizukami and Ma 1992; Bradley et al. 1993; Kempin et al. 1993; Tsuchimoto et al. 1993). The **A–C** antagonism also predicts that in the *ag* mutant, the **A** function would expand to whorls 3 and 4 and inhibit *AG* expression (Fig. 3b).

The **ABC** model is similar to an earlier model based on mutant analysis in *Antirrhinum*, which proposed that there are two functions (equivalent to **B** and **C** of the **ABC** model) but no equivalent to the **A** function (Schwarz-Sommer et al. 1990). This model can be reconciled with the **ABC** model because **A** and **C** are mutually exclusive and **A** is equivalent to the absence of **C**. Because the expression of the *Antirrhinum* **C** function gene *PLENA* has now been shown to be negatively regulated in whorls 1 and 2 (Bradley et al. 1993), the yet to be identified negative regulator may be an **A** function component in *Antirrhinum*. Other models for organ identity were also proposed in which the identity of an inner (later) whorl of organs was dependent on the organ identity of adjacent outer whorl(s) (Heslop-Harrison 1963; Green 1988). Because many mutants exist that show normal organs in some whorls and abnormal organs in the next whorl or vice versa, these sequential models are not consistent with the genetic results.

Although the simple **ABC** model for organ identity is



**Figure 3.** An illustration of the ABC floral organ identity model and revised models, using *Arabidopsis* as an example. According to the ABC model (Bowman et al. 1991b; Coen and Meyerowitz 1991; Meyerowitz et al. 1991), the wild-type floral organ identity is controlled by three functions, A, B, and C, which are localized to overlapping regions of the floral meristem (a). The floral organs are sepal (Se); petal (Pe); stamen (St); and carpel (Ca). The A function alone leads to sepals, whereas the combination of A and B functions dictates that petals are formed. The B and C functions together control the identity of stamen, and the C function alone results in the formation of carpels. In a wild-type *Arabidopsis* flower (b), AP2 and AG are representatives of the A and C functions, respectively, whereas AP3 and PI are both components of the B function. The domains of action for these genes correspond to their expression patterns (Drews et al. 1991; Jack et al. 1992; Schwarz-Sommer et al. 1992; Tröbner et al. 1992; Bradley et al. 1993), with the exception of AP2 (see below in revised models). In the *ag* mutant flower (c), the A function (AP2) expands to the inner two whorls, leading to the conversion of stamens and carpels to petals and sepals (with secondary flower), respectively. The domains of action of organ identity genes for a wild-type *Arabidopsis* flower according to two revised models (see text) are shown in d and e. (d) A revised model with a proposed component of function A (A1) needed to negatively regulate AG expression. In whorls 3 and 4, AP2 does not repress AG expression in the absence of A1. Furthermore, AG negatively regulates AP1 expression in whorls 3 and 4. In addition, AP3 and PI are negatively regulated in whorl 4 by SUP. AP2 is not placed in whorls 3 and 4 because AP2 does not seem to play a role in determining organ identity in these whorls, although its mRNA is present in these whorls. (e) An alternative revised model for organ identity, with a proposed component of function C (C1), that negatively regulates AP2 function (but not expression). In whorls 1 and 2, the absence of C1 allows AP2 to function as an organ identity gene and to repress AG expression. The other regulations are the same as in d. According to the revised model in (d), in the *ag* mutant flower (f), AG expression remains limited to whorls 3 and 4, because AP2 and A1 continue to function only in whorls 1 and 2. AP1 expression does expand to the inner whorls. The revised models are based on the information from the following references: AP2 expression (Okamuro et al. 1993); *ap1* phenotypes and expression (Irish and Sussex 1990; Mandel et al. 1992b; Bowman et al. 1993; Gustafson-Brown et al. 1994); AG expression in *ag* mutant (Gustafson-Brown et al. 1994); autoregulation of AP3 and PI (Jack et al. 1992); and regulation of AP3 and PI by SUP (Bowman et al. 1992; E.M. Meyerowitz, pers. comm.). (→) Positive interaction. (−) Negative interaction.

very attractive, it needs to be revised to account for more recent observations. First, more is now known than before about the A function and the antagonism between A and C functions. The phenotypes of *ap1* and *ap1 ap2* mutants indicate that AP1 is a component of the A function. In addition, AP1 is expressed only in the outer two whorls of the wild-type flowers but is also ectopically expressed in the inner whorls of *ag* mutant flowers, indicating that AG negatively regulates AP1 expression (Mandel et al. 1992b; Gustafson-Brown et al. 1994). Furthermore, AG expression pattern in the *ag-1* mutant flowers is the same as that in the wild-type flowers (Gustafson-Brown et al. 1994), indicating that the factor(s) regulating AG expression is not affected by the *ag-1* mutation. Finally, AP2 is expressed in all whorls (Okamuro et al. 1993) and it is needed to repress AG

expression in the outer two whorls; therefore, there may either be another factor (A1, Fig. 3d) in these whorls that is required for this repression, or an inhibitor (C1, Fig. 3e) of AP2 function (but not expression) in the inner two whorls. Because AP1 and AP2 are each essential components of the A function, the mutual antagonism between the A and C functions is accounted for by the inhibition of AG expression by AP2 (with the proposed moderation by A1 or C1) and the inhibition of AP1 expression by AG. The difference between the effects of *ap1* and *ap2* mutation on organ identity can be explained by the ectopic expression in the latter case of AG, which is required for stamen and carpel identities. Moreover, the phenotypes of 35S-AG transgenic flowers can be accounted for by the ectopic expression of AG and the inhibition of AP1 in the outer two whorls. On the other hand, in *ag* mu-



tants, the ectopic expression of *AP1* and the lack of *AG* function (but not *AG* expression) in the inner whorls result in the replacement of stamens and carpels by petals and sepals (Fig. 3f). A second aspect of the revisions involves the regulation of the **B** function genes. The analyses of expression of the *Arabidopsis* *AP3* gene in the *ap3* or *pi* mutant, and that of the *Antirrhinum* *DEFA* and *GLO* genes in *defA* or *glo* mutants, indicate that each gene pair regulates its own expression. *AP3* and *PI* are both required for persistent, although not the initial, expression of *AP3*, whereas *DEFA* and *GLO* are both needed for the elevated, but not low, levels of expression for each gene. In addition to the autoregulation, the *Arabidopsis* *AP3* and *PI* genes are regulated by *AP2* and *SUP*. The wild-type *AP2* function is required for a normal level of *AP3* expression at early stages and for any expression at later stages. The negative regulation of *AP3* and *PI* by *SUP* at the center of the flower (Figure 3d and e), as suggested from genetic studies, has been confirmed by the finding that expression of both *AP3* and *PI* expands toward the center in the *sup* mutant flower. Although the revised **ABC** models are probably still simplifications of a more complex reality, they contain a number of testable hypotheses and provide a framework for understanding the mechanisms that specify organ identities.

#### Other roles: possible late functions of the floral genes

Molecular analysis of floral genes not only supports predictions from genetic studies but also suggests functions of these genes other than specifying meristem or organ identity. The expression of the floral meristem identity genes, *FLO* from *Antirrhinum* and *LFY* from *Arabidopsis*, was observed in developing floral organs (Coen et al. 1990; Weigel et al. 1992), suggesting that *FLO* and *LFY* may have other functions in addition to specifying meristem identity. However, the nature of the potential late functions is not known. The floral organ identity genes, *AG*, *AP1*, and *AP3* from *Arabidopsis*, and *PLENA*, *SQUA*, *DEFA*, and *GLO* from *Antirrhinum*, are also expressed during later stages of floral organ development, after the organ types have been determined. In particular, *AG* is expressed in specific cell types in late stamens and gynoecium, as are the *AG* homologs from *Antirrhinum* (*PLENA*) and maize (*ZAG1*) (Bowman et al. 1991a; Bradley et al. 1993; Schmidt et al. 1993). Furthermore, ectopic expression of *AG* or its *Brassica* homolog (*BAG1*) leads to sterility in transgenic plants (Mandel et al. 1992a; Mizukami and Ma 1992). These results suggest that *AG* and its homologs are required for proper differentiation of specific cell types during late floral organ differentiation. Expression of *DEFA* is also found throughout organ development. Moreover, small sectors of as few as four petal cells have been observed in the second whorl sepals (converted from petals) of plants carrying a transposon insertion in *DEFA* (Coen and Meyerowitz 1991). These petal cells most likely result from the restoration of wild-type *DEFA* function after the excision of the transposon. The expression and somatic

reversion results of the *DEFA* gene suggest that it functions throughout organ development. Extended gene action for the *Arabidopsis* *AP3* gene has also been suggested by the analysis of a temperature-sensitive *ap3* mutant (Bowman et al. 1989).

#### The players: members of a conserved gene family

The sequences of many of the floral genes reveal that they are members of a conserved gene family. The amino-terminal region of the predicted *Arabidopsis* *AG* protein (Yanofsky et al. 1990) shares striking sequence similarity with the DNA-binding domains of the human serum response factor (SRF) and a regulator of yeast cell-type specific genes, MCM1 (Norman et al. 1988; Passmore et al. 1988), as well as a region of a yeast regulator of arginine metabolic genes, ARG80 (Dubois et al. 1987). The *Antirrhinum* *DEFA* gene also encodes a protein with a similarly conserved motif (Sommer et al. 1990). The conserved region found in these genes has been designated the MADS box (for MCM1, AG and ARG80, DEFA, and SRF; Schwarz-Sommer et al. 1990). The fact that *AG* and *DEFA* genes function in different pathways controlling flower development and still share a conserved MADS box, and the fact that the MADS box is an ancient motif, led to the proposal that other floral regulatory genes may also contain a MADS box (Ma et al. 1991). Several *Arabidopsis* and *Antirrhinum* floral homeotic genes have recently been shown to contain a MADS box (see Table 1). The petunia *DEFA* (*AP3*) homolog, *pMADS1*, was found to correspond to the floral homeotic gene *GP* (van der Krol et al. 1993). The *gp* mutant (a large deletion) has a petal-to-sepal conversion but nearly normal stamens, whereas *AP3* and *DEFA* are needed for petal and stamen formation. It is possible that in petunia, a gene functionally overlapping with *pMADS1* acts in the stamens; this gene may even be a MADS box gene similar to *pMADS1*, as petunia seems to have two genes very similar to the *Antirrhinum* *GLO* (see below). The phenotypic difference between *gp* and *defA* (or *ap3*) indicates that in different plants the **B** function genes may be functionally distinct (van der Krol et al. 1993).

The complexity of flower development suggests that other regulatory proteins are probably involved in addition to those identified by genetic analysis (Table 1). Using *AG* sequences as probes, six additional MADS box genes were isolated from *Arabidopsis* and designated *AGL1*–*AGL6*, for AG-Like (Ma et al. 1991). Five of these genes are flower specific, suggesting that, like *AG*, they encode regulators of flower development. In particular, *AGL1* is expressed in carpels. Five MADS box genes were isolated from tomato and designated *TM3*, *TM4*, *TM5*, *TM6*, and *TM8* (Pnueli et al. 1991). All but *TM3* are preferentially expressed in flowers. Among these, *TM6* and *TM4* are most similar in their sequences to *DEFA* and *SQUA* from *Antirrhinum*, respectively, and *TM5* may be a homolog of *AGL6* from *Arabidopsis*. In addition to *pMADS1* and *pMADS3*, other MADS box genes from petunia include *fbp1*, *fbp2*, *pMADS2*, and *pMADS4* (Ange-



nent et al. 1992; Tsuchimoto et al. 1993; van der Krol et al. 1993). All except *pMADS4* are expressed specifically in flowers. Furthermore, the expression of both *fbp1* and *pMADS2* is limited to the second and third whorls and is altered in the *gp* mutant, and the *fbp1* and *pMADS2* sequences are most similar to that of the *Antirrhinum* *GLO* gene (Angenent et al. 1992, 1993; van der Krol et al. 1993). MADS box genes have also been isolated from the monocot maize (Schmidt et al. 1993). In addition to the homolog of the *Arabidopsis* *AG* gene (*ZAG1*), there is another maize MADS box gene (*ZAG2*), which is most similar to the *Arabidopsis* *AGL5* gene in sequence and expression pattern. It is intriguing that *ZAG1* and *ZAG2* map very close to two loci known to affect flower development, *Polytypic ear* (*Pt*) and *Tassel seed4* (*Ts4*), respectively. The fact that several of the genetically defined floral homeotic genes in both *Arabidopsis* and *Antirrhinum* are MADS box genes, and that additional MADS box-containing genes from several plants are also flower specific, suggests that a family of MADS box genes function as regulators during flower development.

In addition to the MADS domain, the plant MADS domain proteins share a second conserved region. Although the sequences in this region are not as highly conserved as the MADS domain sequences, they show substantial similarity to a portion of the intermediate filament protein keratin; therefore, the region was designated the K domain and may potentially form amphipathic (coiled-coil) helices and possibly mediate protein-protein interaction (Ma et al. 1991; Pnueli et al. 1991). This is consistent with the finding that temperature-sensitive mutations in both the *Arabidopsis* *AP3* gene and the *Antirrhinum* *DEFA* gene are localized to this region and affect a lysine residue near either the carboxy-terminal (*ap3-1*) or the amino-terminal (*defA-101*) ends of the K domain (Jack et al. 1992; Schwarz-Sommer et al. 1992). Both of these lysines are highly conserved among the K domains, suggesting that they may play a structural or functional role shared by these proteins.

### Backstage: molecular mechanisms

The extensive in vivo and in vitro studies on SRF and MCM1 can provide useful hints about the mechanism of plant MADS box gene functions. SRF and MCM1 proteins have overlapping binding sequence specificities, with consensus target sequences containing a CArG box (CC(A/T)<sub>6</sub>GG; Pollock and Treisman 1990; Wynne and Treisman 1992). Containing the same type of conserved motif, the plant MADS domain proteins may also bind to similar sequences. In vitro experiments indicate that *AG* binds to sequences containing a CArG box (Mueller and Nordheim 1991; Huang et al. 1993; Shiraishi et al. 1993). Studies with the *Antirrhinum* *DEFA* and *GLO* proteins indicate that neither can bind DNA alone; however, together they bind as heterodimers to sequences with a CArG box (Schwarz-Sommer et al. 1992; Tröbner et al. 1992). Similarly, the *Arabidopsis* *AP3* and *PI* proteins interact in vitro (E.M. Meyerowitz, pers. comm.). These results suggest that plant MADS domain proteins are

probably sequence-specific DNA-binding proteins, as are SRF and MCM1. Furthermore, the regulatory functions of the floral homeotic genes indicate that the mutant phenotypes are probably attributable to the alteration in the transcription of genes normally controlled by the MADS domain proteins.

Many of the floral homeotic genes are expressed in more than one type of floral organs. For example, *AG* is expressed in stamens and carpels (Bowman et al. 1991a; Drews et al. 1991), whereas *AP3* is expressed in petals and stamens (Jack et al. 1992). Some of the morphological differences of the organs may be attributable to the activities of different sets of genes regulated in different organs by the same MADS domain regulator, perhaps through interactions with other factors, as is the case for MCM1. MCM1 is expressed in both the MAT $\alpha$  and MAT $\alpha$  haploid cells. However, different genes are expressed in these cell types because of the combined functions of MCM1 and other factors (Herskowitz 1990). In the MAT $\alpha$  cells, MCM1 alone activates the  $\alpha$ -specific genes. In the MAT $\alpha$  cells, MCM1 binds cooperatively with MAT $\alpha$ 1 to the promoters of  $\alpha$ -specific genes to activate them while the MCM1–MAT $\alpha$ 2 complex binds the upstream region of  $\alpha$ -specific genes to repress them. It is possible that plant MADS domain proteins interact with other factors through the K domain. The same MADS domain protein may interact with different accessory factors in different cells. For example, *AG* may regulate stamen and carpel development by cooperating with stamen- and carpel-specific factors.

### Conclusion

From the extensive genetic and molecular studies, it is clear that many regulatory proteins function in a complex network to control flower development. In this network, multiple genes/proteins interact with each other; the interaction could be either positive or negative, and at any level from transcription to protein-protein interaction. The parts of this network that operate at different developmental stages are connected in at least two ways. First, many of the genes, such as *TFL1* and *AP1*, are involved in more than one stage of flower development, suggesting that a single regulatory protein may interact with different factors, and/or control different genes, at different stages of development. Second, genes required at one stage can regulate genes that function at the next stage. This was clearly shown for the *Arabidopsis* floral meristem genes *LFY* and *AP1*, which regulate the expression of the organ identity genes *AP3*, *PI*, and *AG*. In addition, many of the regulatory genes identified thus far are members of the MADS box gene family, which includes several additional flower-specific MADS box genes. The fact that MADS domain proteins from mammals and yeast are known to interact with different proteins to differentially regulate transcription suggests a mechanism for the multifaceted functions of many of the floral genes. Although most of the regulatory genes isolated thus far seem to encode transcription factors, other types of proteins are likely to participate in the

network. Furthermore, some of the genes controlling flower development may also function during vegetative development. For instance, the *Arabidopsis* *TSL* gene is expressed in both floral and vegetative organs and encodes a protein with a domain similar to protein kinases; in addition, the *tsl* mutants have abnormal leaves and flowers, indicating that the wild-type gene function is required for normal leaf and floral development (Roe et al. 1993). The *Arabidopsis* *AP2* gene may be another example because it is also expressed in vegetative organs (Okamuro et al. 1993).

These studies also provide a large amount of new information supporting the idea advanced previously by Coen and Meyerowitz (1991) that similar genes operate in the two distantly related plants *Arabidopsis* and *Antirrhinum*. Several pairs of homologs have now been isolated that function in similar ways in these two plants. Furthermore, homologs of floral genes discovered in these two plants have now been isolated in many plants, including the monocot maize. These results and the observation that mutants similar to those in *Arabidopsis* and *Antirrhinum* have been found in many other plants indicate that much of the regulatory network is conserved in flowering plants.

How, then, can a conserved network of genes control the development of such diverse array of flowers? One possibility is that the homologs do not function in exactly the same way in each plant. This is the case for all of the pairs of homologs between *Arabidopsis* and *Antirrhinum*. For example, *FLO* and *LFY* are slightly different in that *flo* mutants show a complete conversion of flower to inflorescence, whereas *lfy* mutants show only partial conversions. Another example is the petunia *gp* mutant, which has a conversion of petals to sepals, but nearly normal stamens, while homologous mutations in *Arabidopsis* and *Antirrhinum* affect both petals and stamens. There are many possible mechanisms that could account for the divergence; for example, the homologs may interact with other factors or bind to target sites differently. In the case of the *gp* mutant, petunia may have a redundant gene function in stamens but not petals. Another way diversity can be achieved is by more dramatic changes: addition or elimination of a gene. The *Arabidopsis* *TFL1* and *Antirrhinum* *CEN* genes, which when eliminated lead to the formation of a terminal flower, may be examples of such changes. It is possible that in plants with terminal flowers, the equivalent of *TFL1* or *CEN* function is absent (Carpenter and Coen 1990). Another example is the *CYC* gene of *Antirrhinum*, which is required for the bilateral symmetry of the flower (Carpenter and Coen 1990). Therefore, it is likely that with variations on a conserved network of regulators, nature has created such an enormous amount of diversity in floral forms.

The results obtained thus far also raise many more questions and suggest possible ways to address these questions. How do the developmental and environmental signals regulate floral induction and the establishment of an inflorescence meristem? The cloning of the *EMF* and *TFL1* genes, as well as the late flowering genes,

will go a long way to uncover some of the mechanisms. What controls the floral meristem genes? Analysis of expression of the floral meristem genes in mutants affecting floral induction may provide some answers. In addition, molecular studies that identify factors that interact with the promoters of these genes can also be very powerful. How do the meristem genes and others regulate the floral homeotic genes? *AP1* and *SQUA* (MADS box) are likely to be transcription factors, and *FLO* and *LFY* may also be; it will be particularly interesting to learn whether they interact with other factors, and what are the direct target genes. What are the potential factors with which the homeotic gene products interact? And what target genes do the homeotic genes regulate? These questions go to the heart of homeotic gene functions and may be solved with a combination of genetic, molecular, and biochemical approaches.

In short, the fascinating story of flower development that we have learned so far is only the early part of an exciting drama. As it unfolds, new players will come onto the scene, and new secrets will be unlocked to provide us with further intriguing insights into the control of flower development.

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