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ARABIDOPSIS: A RICH HARVEST 10 YEARS AFTER COMPLETION OF THE GENOME SEQUENCE

The flowering of Arabidopsis flower development

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SUMMARY

Flowers come in a variety of colors, shapes and sizes. Despite this variety, flowers have a very stereotypical architecture, consisting of a series of sterile organs surrounding the reproductive structures. Arabidopsis, as the premier model system for molecular and genetic analyses of plant development, has provided a wealth of insights into how this architecture is specified. With the advent of the completion of the Arabidopsis genome sequence a decade ago, in combination with a rich variety of forward and reverse genetic strategies, many of the genes and regulatory pathways controlling flower initiation, patterning, growth and differentiation have been characterized. A central theme that has emerged from these studies is the complexity and abundance of both positive and negative feedback loops that operate to regulate different aspects of flower formation. Presumably, this considerable degree of feedback regulation serves to promote a robust and stable transition to flowering, even in the face of genetic or environmental perturbations. This review will summarize recent advances in defining the genes, the regulatory pathways, and their interactions, that underpin how the Arabidopsis flower is formed.

Keywords: Arabidopsis, flower, meristem.

INTRODUCTION

Plants grow through the continuous action of meristems. Meristems consist of a population of stem cells that undergo two antagonistic processes: the formation of derivatives that will go on to differentiate, and the renewal of the stem cell population. During vegetative development, the shoot apical meristem produces leaves and axillary buds on its flanks. Upon perceiving the appropriate environmental cues, the shoot apical meristem converts to a reproductively determined inflorescence meristem (Amasino, 2010, this issue). In Arabidopsis, the inflorescence meristem produces additional secondary inflorescence meristems, as well as floral meristems on its flanks, to give rise to the characteristic architecture of the mature plant.

A floral meristem differs from other meristems in a number of important ways. Notably, the floral meristem sequentially produces floral organs: the sepals, petals, stamens and carpels (Figure 1). These organs arise in concentric rings, or whorls (Steeves and Sussex, 1989; Smyth *et al.*, 1990). In Arabidopsis, four sepals arise in the outermost, or first, whorl; these leaflike organs enclose the flower bud as it develops. Four white petals arise in the second whorl, in positions that alternate with the sepals. Six stamens, which consist of a filament and an anther at the tip that produces the pollen, arise in the third whorl. The central fourth whorl produces the female reproductive structure, the gynoecium, which is composed of two fused carpels. The gynoecium contains the ovules, which, upon fertilization, will go on to produce the seed. Unlike vegetative shoot apical meristems that continue to produce leaves and axillary buds essentially indefinitely, the floral meristem is determinate, in that it is eventually consumed in the production of the flower, terminating its development.

In 1790, Goethe proposed that floral organs represent modified leaves (Goethe, 1790). This idea of a common underlying mechanism has been substantially reinforced by recent findings showing that the action of a floral meristem in forming floral organs has considerable similarities to that of a shoot apical meristem in producing leaves (Carles and Fletcher, 2003; Sablowski, 2007). Nonetheless, it is also clear that there are a number of gene products operating specifically during flower development. In many cases, these

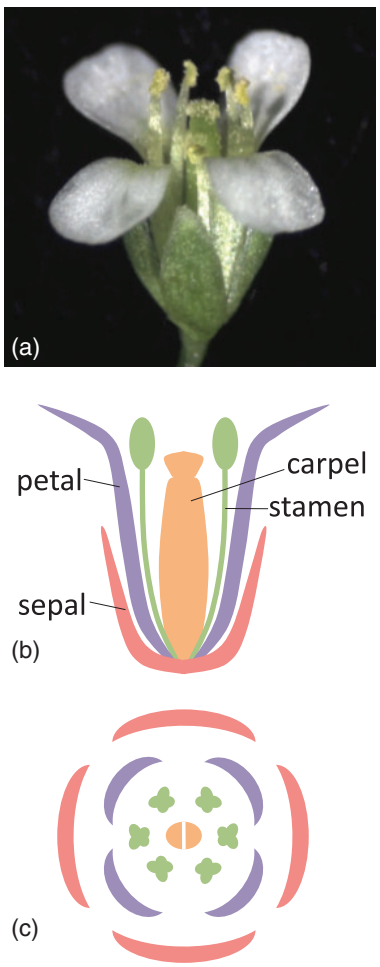

Figure 1. The Arabidopsis flower.
(a) Mature flower at anthesis.
(b) Cartoon of a lateral section through a mature flower, with organ types indicated.
(c) Floral diagram showing the relative placement of floral organs. Organ types are colored as in (b).

products interface with the 'ground-state' lateral-organ producing machinery and modify these processes to give rise to floral tissues. This review will focus on those pathways that appear to act specifically, or predominantly, during floral development to produce the unique organs and tissues of the flower.

ESTABLISHING THE FLORAL MERISTEM

The floral meristem emerges as a lateral outgrowth, or bulge, on the periphery of the inflorescence meristem. It is at this stage that some of the first markers of floral specific gene expression can be detected (Grandjean *et al.*, 2004; Reddy *et al.*, 2004; Heisler *et al.*, 2005). Once the floral meristem is established, it undergoes a stereotypical pattern of growth through a series of well-defined stages (Smyth *et al.*, 1990). Landmark stages include: stage 1, which corresponds to the first morphological appearance of an outgrowth on the flank of the inflorescence meristem; stage 3, when sepal primordia first appear; stage 5, when petal and stamen primordia become visibly apparent; and stage 13, when the bud opens and anthesis occurs.

The Arabidopsis floral meristem is, like other shoot apical meristems, composed of three clonally distinct cell layers. The outer L1 and subepidermal L2 are single-cell layers that maintain their layered organization through anticlinal cell divisions (Steeves and Sussex, 1989). The underlying L3 is composed of several cell layers that divide in all directions. Despite the relatively regular arrangement of oriented cell divisions, the occasional deviations from this regularity indicate that signaling among floral meristem cells is critical to produce a flower (Jenik and Irish, 2000; Reddy *et al.*, 2004; Kwiatkowska, 2006). Although relatively little is known of the mechanisms coordinating growth and differentiation of the floral meristem, the analyses of a number of genes and their interactions are beginning to shed light on some of these processes.

LEAFY (*LFY*) is a key player in the specification of floral meristem identity. Severe *LFY* mutations fail to initiate floral meristems and instead produce secondary inflorescence branches (Weigel *et al.*, 1992). Furthermore, ectopic expression of *LFY* induces precocious flower formation, indicating that *LFY* is also sufficient for specifying floral meristem identity (Weigel and Nilsson, 1995). *LFY* encodes a novel type of transcription factor, with homologs found throughout the plant kingdom (Maizel *et al.*, 2005; Hames *et al.*, 2008). In non-flowering plants, *LFY* appears to have a general role in regulating sporophyte development (Maizel *et al.*, 2005; Tanahashi *et al.*, 2005). In angiosperms, though, *LFY* appears to have acquired a new role in specifying floral meristem identity (Coen *et al.*, 1990; Souer *et al.*, 1998; Molinero-Rosales *et al.*, 1999; Bomblies *et al.*, 2003).

LFY is expressed at low levels in vegetative tissues and its expression is strongly upregulated in response to floral inductive signals, including photoperiodic signals mediated through the *FT* pathway as well as gibberellins (Hempel *et al.*, 1997; Blazquez *et al.*, 1998; Nilsson *et al.*, 1998; Wagner *et al.*, 1999; Blazquez and Weigel, 2000; Eriksson *et al.*, 2006; Achard *et al.*, 2007; Lee *et al.*, 2008). Because *LFY* responds to a variety of floral inductive signals and is central in eliciting a flowering response, it has been described as a floral pathway integrator (Simpson and Dean, 2002).

Plants mutant for *lfy* eventually do produce axillary meristems that possess some floral identity, due to the activity of *APETALA1* (*AP1*) (Huala and Sussex, 1992; Mandel *et al.*, 1992; Bowman *et al.*, 1993; Mandel and Yanofsky, 1995). Loss of function mutations in *AP1* show a partial conversion of floral meristems to a more inflorescence-like identity, and *lfy ap1* double mutants almost entirely lack flowers, indicating that these two genes together are largely

responsible for specifying the floral meristem (Irish and Sussex, 1990; Huala and Sussex, 1992; Bowman *et al.*, 1993; Shannon and Meeks-Wagner, 1993). *AP1* encodes a MADS box transcription factor (Mandel *et al.*, 1992), and a number of other MADS box genes also participate in promoting floral meristem identity. These include the *AP1* paralogs *CAULIFLOWER* (*CAL*) and *FRUITFULL* (*FUL*) (Bowman *et al.*, 1993; Kempin *et al.*, 1995; Ferrandiz *et al.*, 2000a), as well as *AGAMOUS-LIKE24* (*AGL24*), *SHORT VEGETATIVE PHASE* (*SVP*) and *SUPPRESSOR OF CONSTANS1* (*SOC1*) (Gregis *et al.*, 2008; Melzer *et al.*, 2008). The overlapping functions of these MADS box gene products presumably reflect redundancy in their action in regulating transcription of target genes required for flower development.

A variety of feedback loops govern the action of these genes in floral meristem specification (Figure 2). This serves to create a very robust and stable transition to flowering by both promoting a determinate floral meristem fate and repressing an indeterminate shoot fate. *TERMINAL FLOWER1* (*TFL1*) is necessary for indeterminate shoot fate, since *tfl1* mutants show conversion of inflorescence meristems to floral meristems (Bradley *et al.*, 1997; Ratcliffe *et al.*, 1998). *TFL1* has been proposed to act as a mobile shoot-promoting signal, potentially through developmentally regulated release from protein storage vacuoles (Conti and Bradley, 2007; Sohn *et al.*, 2007). One role of *AP1* and *LFY* is to repress *TFL1* and so suppress indeterminate fate (Weigel *et al.*, 1992; Liljegren *et al.*, 1999; Ratcliffe *et al.*, 1999). In turn, *TFL1* acts to repress *LFY* and *AP1* in inflorescence meristems (Ratcliffe *et al.*, 1998). This balance between *TFL1* and the floral meristem identity genes regulates overall shoot architecture, ensuring the formation of flowers at the appropriate place and time. Subtle shifts in this balance are probably responsible for variation in shoot architecture across flowering plant species (Prusinkiewicz *et al.*, 2007).

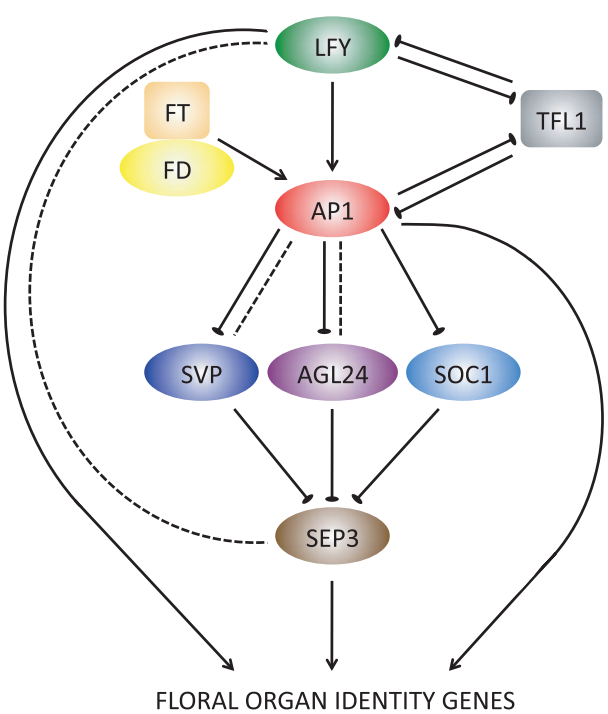

Figure 2. Genes involved in the establishment of the floral meristem.
A network of interactions governs the function of a variety of gene products, which culminates in the activation of the floral organ identity genes. Transcription factors are in ovals, other factors are in rectangles. Positive regulatory interactions are indicated by arrows and negative regulatory interactions by blunt-ended lines. Protein–protein interactions indicated by dotted lines.

LFY is initially expressed very early throughout the presumptive floral meristem, and its activity results in a cascade of transcriptional events controlling floral meristem formation (Weigel *et al.*, 1992; Simon *et al.*, 1996). *AP1* expression can be detected throughout the floral meristem well after the initial expression of *LFY* (Mandel *et al.*, 1992; Simon *et al.*, 1996; Hempel *et al.*, 1997; Wagner *et al.*, 1999). This reflects the fact that LFY directly activates the transcription of *AP1* (Mandel and Yanofsky, 1995; Wagner *et al.*, 1999). Even though *AP1* and *LFY* are expressed throughout the floral meristem, their gene products can act in a non-cell-autonomous fashion suggesting that their action in promoting a floral meristem is reinforced by cell-to-cell signaling (Sessions *et al.*, 2000; Wu *et al.*, 2003). Other factors also play a role in upregulating *AP1* expression in floral primordia. These factors include the direct activation of *AP1* by the photoperiodic responsive FT/FD complex (Wigge *et al.*, 2005). AP1 in turn represses the expression of *AGL24*, *SVP* and *SOC1* (Yu *et al.*, 2004a; Liu *et al.*, 2007, 2009). AGL24, SVP and SOC1 repress the expression of another MADS box gene, *SEPALLATA3* (*SEP3*), and so one consequence of *AP1* activation is to derepress *SEP3*. SEP3 can then physically interact with LFY to promote flower development through activation of floral organ identity genes, and through interactions with other MADS box proteins (Honma and Goto, 2001; Castillejo *et al.*, 2005; Immink *et al.*, 2009; Liu *et al.*, 2009). This cascade of regulation can control the precise timing of early events in the establishment of the floral meristem; subsequent downregulation of these genes promotes further differentiation of the floral meristem and production of floral organs.

AGAMOUS: THE LYNCHPIN OF DETERMINACY

AGAMOUS (*AG*) encodes a MADS box transcription factor, and is pivotal in promoting the determinate development of the floral meristem by limiting stem cell proliferation (Figure 3) (Bowman *et al.*, 1989; Yanofsky *et al.*, 1990). One of the main roles of LFY is to appropriately regulate *AG* expression. The relative timing of this regulation is important, as a precise balance is needed between the proliferative stem cell activity of the floral meristem during early phases

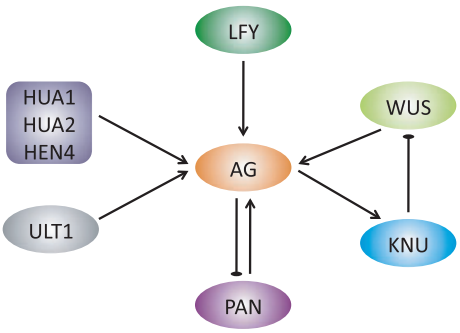

Figure 3. Genes involved in promoting a determinate floral meristem. Determinacy is controlled by a variety of regulatory inputs controlling *AG* expression and function. Notation as in Figure 2.

of floral organogenesis and its eventual termination to form the determinate flower.

During vegetative development, the continued proliferation of cells in the shoot apical meristem relies on the maintenance of stem cell activity. Maintenance of this stem cell population depends on the action of WUSCHEL (WUS), a homeodomain-containing transcription factor, which is expressed in the organizing center of the shoot apical meristem and is necessary and sufficient to maintain stem cell identity (Mayer *et al.*, 1998; Brand *et al.*, 2000; Schoof *et al.*, 2000). In floral meristems, WUS and LFY bind to adjacent sites in the *AG* regulatory region, promoting its upregulation (Busch *et al.*, 1999; Lenhard *et al.*, 2001; Lohmann *et al.*, 2001; Hong *et al.*, 2003). In turn, the activation of *AG* negatively feeds back on the expression of *WUS*, resulting in downregulated stem cell proliferation and promotion of determinacy. A number of lines of evidence suggest that AG-mediated downregulation of *WUS* is indirect (Sablowski, 2007), and at least one gene has been identified that may mediate this regulatory interaction. AG directly induces the expression of *KNUCKLES* (*KNU*), encoding a C2H2 zinc finger putative transcriptional repressor, which in turn is necessary for repression of *WUS* in the floral meristem (Payne *et al.*, 2004; Sun *et al.*, 2009). During normal floral development, *WUS* expression disappears by stage 6, and the temporal control of *WUS* downregulation appears to involve a progressive reduction in levels of the repressive histone H3 Lys 27 trimethylation at the *KNU* locus (Sun *et al.*, 2009). This could serve to regulate a timing mechanism that promotes the shift from proliferative to differentiative growth.

A number of other genes have been shown to participate in controlling determinacy by regulating *AG*. These include *PERIANTHIA* (*PAN*), initially identified on the basis of its extra floral organs mutant phenotype, which could reflect a subtle loss of floral determinacy (Running and Meyerowitz, 1996). *PAN* encodes a bZIP transcription factor that directly activates *AG*; AG in turn negatively regulates the expression of *PAN* in a feedback loop (Chuang *et al.*, 1999; Das *et al.*, 2009; Maier *et al.*, 2009). The *HUA1*, *HUA2* and *HEN4* gene products are also all required for floral determinacy and act to facilitate AG pre-mRNA processing (Chen and Meyerowitz, 1999; Cheng *et al.*, 2003). Determinacy is also controlled by the action of *ULTRAPETALA1* (*ULT1*), encoding a SAND-domain transcription factor that regulates *AG* expression (Carles *et al.*, 2005; Prunet *et al.*, 2008). It is not yet clear if all these pathways operate in parallel, or whether WUS mediates all of these inputs into regulation of *AG* expression. Together, though, these observations emphasize that there are several feedback loops that together modulate the precise balance between *AG* and *WUS* expression in controlling floral meristem determinacy.

THE ABCS OF ORGAN IDENTITY

Another role of the floral meristem identity genes is to activate the floral organ identity genes. Mutations in the floral organ identity genes result in homeotic transformations of one organ type into another. Analyses of these mutations led to the formulation of the now classic 'ABC' model of floral organ identity specification (Bowman *et al.*, 1991; Coen and Meyerowitz, 1991; Weigel and Meyerowitz, 1994). In this model, three classes of gene function, A, B and C, act in a combinatorial manner to uniquely specify each organ type in a specific spatial domain (Figure 4). A function specifies sepal identity in the first whorl, while A and B activities together specify petal identity in the second whorl. B plus C activity specifies stamens in the third whorl, while C activity in the fourth whorl specifies carpel identity. In addition, the A and C functions were proposed to negatively regulate each other's activity. Although this model was initially proposed based on genetic criteria, molecular analyses of the genes encoding the ABC functions have substantiated many of the tenets of this model.

AP1 and *APETALA2* (*AP2*) are both required for normal sepal and petal development, and are required for A function (Irish and Sussex, 1990; Bowman *et al.*, 1991, 1993). *APETALA3* (*AP3*) and *PISTILLATA* (*PI*) together confer B function, while *AG* is necessary for C function (Bowman *et al.*, 1991). In addition, four largely redundant *SEPALLATA* (*SEP1–4*) genes act in concert with the ABC genes to specify organ identity (Pelaz *et al.*, 2000; Ditta *et al.*, 2004). In fact, the combined ectopic expression of the SEP and ABC genes is sufficient to convert leaves into floral organs (Honma and Goto, 2001; Pelaz *et al.*, 2001). There is likely to be considerable overlap in the processes controlling floral meristem function and organ identity since *AP1*, *SEP3* and *AG* have all been shown to have additional roles in floral meristem establishment (see above). *AP1*, *AP3*, *PI*, *AG* and the *SEP* genes all encode MADS domain transcription factors, while *AP2* encodes a member of the AP2/EREBP family of transcription factors, implying that a transcriptional regulatory network is central to the specification of organ identity

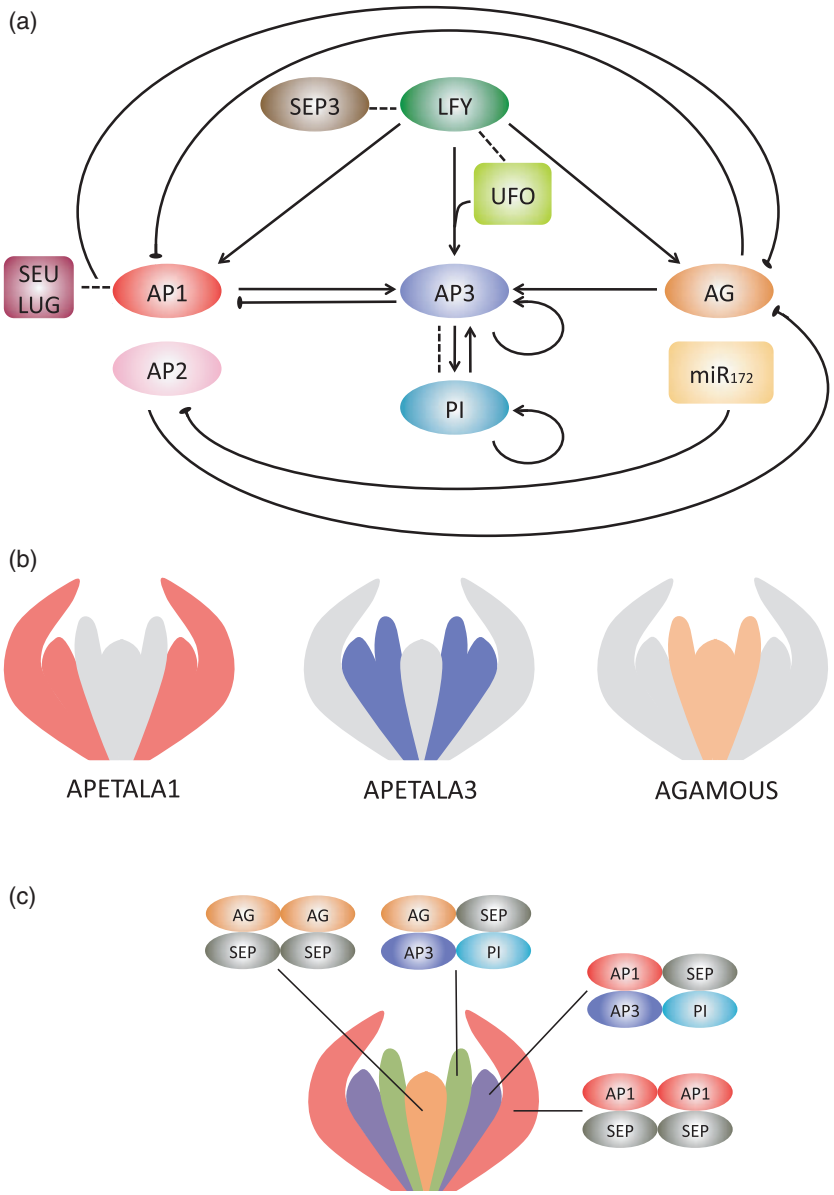

Figure 4. Genes involved in organ identity specification.
(a) Regulatory interactions important in the activation and maintenance of organ identity gene expression. Notation as in Figure 2.
(b) Cartoons of patterns of expression of three MADS box organ identity genes at stage 6 of flower development. At this stage, *APETALA1* (*AP1*) is expressed in the first and second whorls, *APETALA3* (*AP3*) is expressed in the second and third whorls and *AGAMOUS* (*AG*) is expressed in the third and fourth whorls.
(c) Distinct protein complexes can uniquely specify each organ type.

(Yanofsky *et al.*, 1990; Jack *et al.*, 1992; Mandel *et al.*, 1992; Goto and Meyerowitz, 1994; Jofuku *et al.*, 1994; Weigel, 1995; Pelaz *et al.*, 2000; Ditta *et al.*, 2004).

The roles of *AP1* and *AP2* as A function genes may be a relatively recent evolutionary acquisition as, in general, homologs of these genes in other species do not function in specifying sepal and petal identity (Zik and Irish, 2003a; Litt, 2007). Rather, such genes appear to have a common role in regulating meristem identity, suggesting that the role of *AP1* and *AP2* in Arabidopsis represents a novel modification of a more ancestral function that may have been associated with the origin of the flower itself.

The combinatorial action of the ABC genes depends on their expression in discrete regions of the developing flower (Figure 4). *AP1* is initially expressed throughout the floral meristem in response to *LFY* activity, and later its expression becomes restricted to the first and second whorls, consistent with its dual roles as a meristem identity and A function organ identity gene (Mandel *et al.*, 1992; Parcy *et al.*, 1998; Wagner *et al.*, 1999). This spatial localization depends on *AG* expression in the third and fourth whorls, which represses *AP1* in those regions (Gustafson-Brown *et al.*, 1994). It is not clear, however, how *AG* expression is restricted to the third and fourth whorls. Regulation by *WUS* during establishment of the floral meristem is not sufficient, as the domain of *WUS* expression in the center of the meristem is far smaller than that of *AG* (Mayer *et al.*, 1998). Genetic analyses indicate that the establishment of the third and fourth whorl domain of *AG* expression depends on *AP2* function (Bowman *et al.*, 1991; Drews *et al.*, 1991). Transcripts of *AP2* are found

throughout the floral meristem, although its function is restricted to the first and second whorls (Bowman *et al.*, 1991; Jofuku *et al.*, 1994). This occurs through the action of a microRNA, miR172, that acts to repress *AP2* function in the third and fourth whorls through a translational, as opposed to an RNA cleavage, mechanism (Aukerman and Sakai, 2003; Chen, 2004; Zhao *et al.*, 2007). Although initially expressed throughout the floral meristem, miR172 itself becomes localized to the inner two whorls; how this occurs is not yet known (Chen, 2004).

As an A function gene, *AP1* would be predicted to restrict *AG* expression to the third and fourth whorls; however, loss of *AP1* function does not result in ectopic *AG* expression (Weigel and Meyerowitz, 1993). AP1 does, however, form a protein complex with the LEUNIG (LUG) and SEUSS (SEU) transcriptional co-repressors that can bind to regulatory sequences of *AG*; this results in transcriptional repression of AG in the first and second whorls (Sridhar *et al.*, 2004, 2006; Gregis *et al.*, 2006). There is evidence that this co-repressor complex also includes the products of the *SEP3*, *SVP* and *AGL24* MADS box genes (Gregis *et al.*, 2006, 2009). *SEP3*, *SVP* and *AGL24* also mediate floral meristem identity (Figure 2), suggesting that multiple and distinct interactions between these MADS domain proteins coordinate both floral meristem and floral organ identity functions.

The specification of the B domain, in which petal and stamens arise, also depends on the activity of the floral meristem identity genes in concert with various feedback controls. Activation of *AP3* expression in petal and stamen primordia depends on the activity of *UNUSUAL FLORAL ORGANS (UFO)* in conjunction with *LFY* and *AP1* (Lee *et al.*, 1997; Ng and Yanofsky, 2001; Chae *et al.*, 2008). LFY, along with AP1, directly activates *AP3* transcription and this provides floral specificity (Hill *et al.*, 1998; Ng and Yanofsky, 2001; Lamb *et al.*, 2002). *UFO* is expressed in a variety of tissues, but in flowers its expression largely coincides with the B domain, providing regional specificity to *AP3* activation (Lee *et al.*, 1997; Long and Barton, 1998; Samach *et al.*, 1999). *UFO* encodes the F-box component of an SCF ubiquitin ligase, and its function in protein degradation is required to promote *AP3* expression (Chae *et al.*, 2008). *UFO* physically interacts with LFY, and so may act via degradation of proteins at the *AP3* promoter that in turn stimulates LFY activity (Chae *et al.*, 2008). SEP3 also acts as a LFY co-factor, not only in regulating *AP3*, but also *PI* and *AG* (Liu *et al.*, 2009).

Although *PI* is initially expressed more broadly than *AP3*, expression of *PI* and *AP3* in petal and stamen primordia becomes coincident through auto- and cross-regulatory interactions (Jack *et al.*, 1992, 1994; Goto and Meyerowitz, 1994). AP3 and PI bind to DNA as a heterodimer and the activities of both gene products are required to maintain their own and each other's expression (Jack *et al.*, 1992; Goto and Meyerowitz, 1994; Riechmann *et al.*, 1996). In the case of *AP3* these interactions appear to occur through direct binding of the AP3/PI heterodimer to *AP3* regulatory sequences (Hill *et al.*, 1998; Tilly *et al.*, 1998; Honma and Goto, 2000). Maintenance of *AP3* expression in petal and stamen primordia also depends on *AG* and *AP1* (Gomez-Mena *et al.*, 2005). Furthermore, the *AP3* gene product, in conjunction with *PI*, negatively regulates the expression of *AP1* early in flower development (Sundstrom *et al.*, 2006). Together, these positive and negative feedback controls operate to refine and maintain the domains of ABC gene expression.

Once expressed in specific spatial domains, these MADS box gene products probably act as part of larger protein complexes to specify distinct organ identities (Figure 4c). In most cases, these protein complexes consist of one or more ABC proteins in combination with a SEP protein (Fan *et al.*, 1997; Honma and Goto, 2001; Pelaz *et al.*, 2001; Favaro *et al.*, 2003; de Folter *et al.*, 2005; Sridhar *et al.*, 2006; Immink *et al.*, 2009). Since AP1 and the SEP proteins possess transcription activation domains while AG, PI and AP3 do not, it has been suggested that transcription of target gene promoters depends on the association of particular MADS box proteins so as to incorporate transactivation activity (Goto *et al.*, 2001; Honma and Goto, 2001; Jack, 2001; Theissen, 2001). Additionally, the formation of MADS protein complexes may facilitate transcription through stabilizing protein complex–DNA interactions or through cooperative binding to adjacent sites (Egea-Cortines *et al.*, 1999; Melzer *et al.*, 2009). The *SEP1*, *-2* and *-3* genes are expressed in the second, third and fourth whorls, while *SEP4* is expressed throughout the floral bud (Ma *et al.*, 1991; Flanagan and Ma, 1994; Savidge *et al.*, 1995; Ditta *et al.*, 2004). As such, the SEP proteins can act as general co-factors for the spatially limited ABC proteins in promoting transcription in different regions of the flower.

The combinatorial action of the organ identity gene products results in the specification of sepals, petals, stamens and carpels, yet how this occurs is still largely unknown. Temperature shift experiments and mosaic analyses have been used to suggest that the organ identity gene products are required throughout much of floral development (Bowman *et al.*, 1989; Carpenter and Coen, 1990). This implies that the organ identity gene products directly orchestrate the expression of different suites of genes at different times in development. This idea is borne out by the analyses of several targets of the MADS box organ identity genes. *SPOROCYTELESS*/*NOZZLE* (*SPL*/*NZZ*) is required during late stages of stamen development for microsporogenesis and consequent pollen formation (Schiefthaler *et al.*, 1999; Yang *et al.*, 1999). AG binds to the promoter of, and directly regulates the expression of, *SPL*/*NZZ* in the differentiating tissues of the stamen (Ito *et al.*, 2004). Similarly, AP3 and PI directly regulate the expression of *NAP* late in petal development during the transition from cell division

to cell expansion phases of organogenesis (Sablowski and Meyerowitz, 1998).

The organ identity genes also appear to control a number of phytohormone biosynthetic or response genes. For instance, AG regulates jasmonic acid production through directly regulating the expression of a jasmonic acid biosynthetic gene in late-stage stamens (Ito *et al.*, 2007). AG also directly regulates the expression of several genes implicated in gibberellin biosynthesis (Gomez-Mena *et al.*, 2005). Gibberellin signaling in turn upregulates the expression of *AP3*, *PI* and *AG*, as well as jasmonic acid biosynthesis, in a positive feedback loop to promote continued stamen development (Yu *et al.*, 2004b; Cheng *et al.*, 2009). Many other putative targets of the organ identity genes have been identified through whole genome-based approaches (Zik and Irish, 2003b; Wellmer *et al.*, 2004; Alves-Ferreira *et al.*, 2007; Peiffer *et al.*, 2008; Kaufmann *et al.*, 2009), and their characterization undoubtedly will lead to a greater understanding of the feedback loops and networks involved in multiple aspects of organ growth and differentiation.

SETTING THE BOUNDARIES

Floral organ formation also relies on the establishment of boundaries – boundaries between the floral meristem and the organ primordia to establish each whorl and boundaries within a whorl to define the individual organs. These boundaries are morphologically distinct regions; cells in the boundaries display lower rates of division and are smaller than cells in the surrounding regions (Breuil-Broyer *et al.*, 2004; Reddy *et al.*, 2004; Aida and Tasaka, 2006b). Such boundaries appear to be critical in isolating the distinct populations of cells that can then go on to form organ primordia (Aida and Tasaka, 2006b). A number of boundary genes have been defined that are essential for demarcating these domains and for organogenesis, as mutations in boundary genes can disrupt organ formation (Aida and Tasaka, 2006b; Rast and Simon, 2008). By specifying the boundary of an organ, these genes in effect define the size of the primordium and resulting organ.

Several genes have been identified that have roles in establishing or maintaining interwhorl boundaries. Since these interwhorl boundaries function in delimiting organ identity gene expression, alteration in the expression of organ identity genes is a readout of disruptions in boundary gene function. For instance, loss of function of *SUPERMAN* (*SUP*) results in extra stamens due to the ectopic expression of *AP3* and *PI* (Bowman *et al.*, 1992; Sakai *et al.*, 1995). *SUP* is expressed at the boundary between the third and fourth whorls, and appears to have a role in repressing growth in this region (Sakai *et al.*, 1995, 2000; Kater *et al.*, 2000; Nandi *et al.*, 2000). In turn, *AP3*, *PI* and *AG* are required for appropriate *SUP* expression at the third–fourth whorl boundary, implying that a feedback loop acts to maintain the correct demarcation of this boundary (Sakai *et al.*, 2000; Yun *et al.*, 2002). *SUP* encodes a single C2H2 zinc finger DNA-binding protein that has been shown to have a potent transcriptional repression domain required for its function (Dathan *et al.*, 2002; Hiratsu *et al.*, 2002, 2003, 2004). *RABBIT EARS* (*RBE*) also encodes a single C2H2 zinc finger protein that is closely related to *SUP,* and has similar roles in interwhorl boundary specification (Takeda *et al.*, 2004; Krizek *et al.*, 2006). *RBE*, however, acts to maintain the boundary between the second and third whorls. This occurs through the action of RBE in repressing *AG* expression in the second whorl (Krizek *et al.*, 2006).

Although it is clear that morphologically distinct interwhorl boundaries are established early in floral development and are associated with boundary-specific gene expression patterns, the extent to which establishing the domains of organ identity gene function is a prerequisite for establishing boundaries, or if the establishment of boundaries serves to define the domains of organ identity gene expression, remains unclear. Presumably, the maintenance of interwhorl boundaries depends on feedback between these different pathways. Furthermore, maintenance of these boundaries also depends on negative feedback regulation from genes expressed in the developing organ primordia themselves (Goldshmidt *et al.*, 2008; Xu *et al.*, 2008).

The *CUP-SHAPED COTYLEDON1*, *-2* and *-3* (*CUC1–3*) genes have a central role in specifying boundaries during both vegetative and floral development (Aida *et al.*, 1997, 1999; Takada *et al.*, 2001; Vroemen *et al.*, 2003; Aida and Tasaka, 2006a). These partially redundant NAC domain transcription factors are expressed at boundaries and are thought to inhibit cell growth in those regions. In flowers, the establishment of intrawhorl boundaries depends in part on the accurate regulation of the *CUC* genes through the action of a floral-specific microRNA, miR164c. *EARLY EXTRA PETALS1* (*EEP1*) encodes miR164c, and loss of function of *eep1* results in extra petals due to the failure to appropriately regulate *CUC* transcript accumulation at the boundaries between petal primordia (Baker *et al.*, 2005). Although miR164c is expressed in multiple tissues, it is the only member of the miR164 family that is expressed uniquely at the boundaries between petal primordia, thus conferring its flower-specific role (Laufs *et al.*, 2004; Baker *et al.*, 2005; Sieber *et al.*, 2007).

Regulating auxin accumulation is important for establishing boundaries during vegetative development, and this is also likely to be true in flower primordia (Heisler *et al.*, 2005; Rast and Simon, 2008). *PETAL LOSS* (*PTL*), encoding a trihelix transcription factor, is required to establish intrawhorl boundaries between sepal primordia and is expressed at the boundaries of these organs (Griffith *et al.*, 1999; Brewer *et al.*, 2004). *PTL* acts to suppress growth at intersepal boundary regions, since loss of *ptl* activity results in sepal fusions, while constitutive overexpression of *PTL*

results in a general inhibition of growth (Brewer *et al.*, 2004). *PTL* also positively regulates the expression of *RBE*, suggesting that *PTL* also participates in interwhorl boundary specification (Takeda *et al.*, 2004). The localized expression of *PTL* in boundary regions is regulated by *PINOID*, which regulates auxin transport in a number of tissues (Brewer *et al.*, 2004). This suggests that *PTL* is important in modulating the response to auxin in establishing or maintaining intrawhorl boundaries in a specific region of the flower. *PTL* appears to act independently of the *CUC* genes in boundary specification, suggesting that multiple independent pathways are important in establishing intrawhorl boundaries in the flower (Brewer *et al.*, 2004).

ORGAN GROWTH

The development of particular organ morphologies depends on appropriate regulation of size and shape. Specification of size and shape in turn depends on spatial and temporal control of both cell division and cell expansion. In flowers, each organ grows initially largely through cell proliferation, followed by a burst of directional cell expansion to sculpt the final form of the organ (Hill and Lord, 1989; Rolland-Lagan *et al.*, 2003; Dinneny *et al.*, 2004; Anastasiou and Lenhard, 2007). Cell-to-cell signaling is also important to coordinate growth across the developing organ (Jenik and Irish, 2000; Fulton *et al.*, 2009). Despite the unique attributes of floral tissues, surprisingly little is known of the molecular processes regulating floral organ growth. Quantitative trait locus analyses indicate that there are multiple loci that act specifically during Arabidopsis floral development to regulate floral organ size (Juenger *et al.*, 2005). This suggests, though, that any individual gene may have only minor effects on size control, precluding easy identification of such genes using genetic approaches. Nonetheless, a few genes have been identified that have roles in regulating growth in the flower.

Several genes have been identified that promote cell proliferation in floral organs. These include *AINTEGUMENTA* (*ANT*), encoding an AP2-domain family transcription factor, and its homologs, which act in part through negative regulation of *AG* (Elliott *et al.*, 1996; Klucher *et al.*, 1996; Krizek, 1999, 2009; Krizek *et al.*, 2000; Mizukami and Fischer, 2000). Plants mutant for *ant* show a reduction in organ size, and display ectopic *AG* expression that presumably disrupts *WUS*-dependent proliferative growth early during floral organogenesis. *JAGGED* (*JAG*) and *NUBBIN* (*NUB*), encoding partly redundant C2H2 zinc finger transcription factors, also promote cell proliferation but act predominantly in the distal regions of floral organs (Dinneny *et al.*, 2004, 2006; Ohno *et al.*, 2004). *KLUH*, encoding a cytochrome P450, promotes cell proliferation during early phases of organ growth (Zondlo and Irish, 1999; Anastasiou *et al.*, 2007). *KLUH* appears to be required for cell-to-cell signaling necessary for regulating organ growth, and it has been proposed that diluting out *KLUH* activity as cells divide can act as a size-sensing mechanism (Anastasiou *et al.*, 2007).

BIG BROTHER (*BB*), encoding an E3 ubiquitin ligase, appears to have the opposite effect, in that it is required to restrict floral organ growth by limiting the duration of cell proliferation (Disch *et al.*, 2006). Presumably BB targets one or more growth stimulators for degradation. These are unlikely to be ANT, JAG or KLUH as genetic evidence suggests that BB operates in a pathway independent of these gene products (Disch *et al.*, 2006; Anastasiou *et al.*, 2007).

Few genes have been identified that act specifically to regulate cell expansion during later phases of floral organ growth. One possible explanation for this is that the organ identity gene products differentially regulate ubiquitously acting factors controlling cell expansion to promote floral-organ specific growth. One example of this is the basic helix-loop-helix gene *BIG PETAL* (*BPE*) (Szecsi *et al.*, 2006). *BPE* produces two transcripts via alternative splicing, one that is ubiquitously expressed and the other that is expressed preferentially in differentiating petals; the production of the petal-specific transcript is positively regulated by *AP1*, *AP3*, *PI* and *SEP3* while being negatively regulated by *AG*. Presumably this regulation is indirect, with the organ identity gene products regulating components of the splicing machinery in a temporal- and organ-specific manner.

ORGAN AND CELL-TYPE DIFFERENTIATION

How does the information embodied in the action of the organ identity genes, boundary genes and genes involved in growth result in the differentiation of the unique tissues and cell types of the flower? The identification and characterization of the MADS box organ identity genes as well as floral genes involved in growth and patterning has paved the way for a number of recent investigations into elucidating how these differentiation processes are achieved.

Sepals

Sepals superficially resemble leaves, but they are smaller, lack stipules and possess highly elongated epidermal cells (Irish and Sussex, 1990). *SEP4* and *AP1* are both necessary for conferring these sepal-specific characteristics, reflecting their role as organ identity genes (Irish and Sussex, 1990; Ditta *et al.*, 2004). Apart from the action of these genes, though, little is known about how sepal-specific cell types are established. While whole genome approaches have identified a number of genes that appear to be expressed predominantly in sepals (Wellmer *et al.*, 2004; Ma *et al.*, 2005; Peiffer *et al.*, 2008), as of yet the processes controlled by such genes have not been investigated.

Petals

The processes controlling petal primordium initiation and growth are beginning to be elucidated (Irish, 2008), but only

a few genes involved in petal morphogenesis have been identified. These include *ROXY1*, encoding a glutaredoxin that presumably regulates the redox status of target proteins (Xing *et al.*, 2005). One such target appears to be PAN, since ROXY1 and PAN physically interact (Li *et al.*, 2009). As *PAN* is required for floral meristem determinacy, these observations suggest that post-translational controls also play an important role in feedback regulation necessary for floral organ formation.

Arabidopsis petals are quite distinctive. They are relatively large and spoon-shaped, and possess unusual conical epidermal cells on their adaxial surface. These cells give petals their sheen and, in insect pollinated species, can influence pollinator behavior (Noda *et al.*, 1994; Whitney *et al.*, 2009). Surprisingly, though, little is known as to how these, or other specialized petal cell types, arise. MYB domain transcription factors have been identified in *Antirrhinum* that control the formation or shape of these conical epidermal cells; homologs have been identified in Arabidopsis but no function has yet been ascribed to these genes (Baumann *et al.*, 2007).

Stamens

The stamens each consist of a four-lobed anther in which microsporogenesis occurs, and a filament that serves to transport nutrients to the anther (Goldberg *et al.*, 1993). The anther is composed of several cell types, including the epidermis, endothecium and tapetum that surround the microsporocyte, that are required for pollen development. A large number of genes expressed exclusively or predominantly in stamens have been identified through whole genome analyses (Zik and Irish, 2003b; Hennig *et al.*, 2004; Wellmer *et al.*, 2004; Ma, 2005; Nakayama *et al.*, 2005; Alves-Ferreira *et al.*, 2007; Wijeratne *et al.*, 2007). Also, a number of genes involved in stamen differentiation have been identified through screening for male sterile mutations (e.g. Sanders *et al.*, 1999). Many of the characterized stamen differentiation genes are required for either tapetum development and/or microsporogenesis (Feng and Dickinson, 2007). A number of these are also required for female reproductive development, indicating that there are some commonalities in these processes.

SPL/*NZZ*, which is transcriptionally activated by AG, is required for the formation of the endothecium and tapetum and for microsporogenesis (Schiefthaler *et al.*, 1999; Yang *et al.*, 1999; Ito *et al.*, 2004). *SPL*/*NZZ* expression, even in the absence of *AG* function, can still induce microsporogenesis, indicating that *SPL*/*NZZ* is required for specifying identity of a subset of the tissue types regulated by *AG* (Ito *et al.*, 2004). However, this induction of microsporogenesis is spatially limited to the distal-lateral regions of lateral organs, implying that the spatial domain of *SPL*/*NZZ* expression is regulated by AG-independent inputs. *SPL*/*NZZ* encodes a MADS-domain-related transcription factor, and regulates the expression of the glutaredoxin genes *ROXY1* and *ROXY2* (Xing and Zachgo, 2008). *ROXY1*, in addition to its role in petal morphogenesis, partially overlaps in function with *ROXY2* in regulating anther development (Xing and Zachgo, 2008). *ROXY1* and *-2* act in part through regulating the activation of *DYSFUNCTIONAL TAPETUM* (*DYT1*), a bHLH transcription factor that in turn is required for tapetum development (Zhang *et al.*, 2006). A number of other genes, including *EXCESS MICROSPOROCYTES1*/*EXTRA SPOROGENOUS CELLS* (*EMS1*/*EXS*) and *TAPETUM DETERMINANT1* (*TPD1*) have been identified that are also required for tapetum development and function to regulate the expression of *DYT1* (Canales *et al.*, 2002; Zhao *et al.*, 2002; Yang *et al.*, 2003). *EMS1*/*EXS* encodes a putative receptor kinase, while *TPD1* encodes a putative ligand, indicating that cell–cell signaling is an integral step in tapetum specification.

Carpels

Arabidopsis possesses two carpels that together form the gynoecium. The gynoecium consists of an ovary in which multiple seeds develop, a short style and is topped by a stigma. The gynoecium matures into the fruit, or silique, and a number of genes regulating the specification of different gynoecial cell types have been identified (Ferrandiz *et al.*, 1999; Ostergaard, 2009) (Figure 5). Several MADS box genes, including *AG*, *SHATTERPROOF1* and *-2 (SHP1*, *-2*) and *SEEDSTICK* (*STK*), have partially redundant roles in specifying carpel identity and probably function together in a transcriptional complex (Favaro *et al.*, 2003; Pinyopich

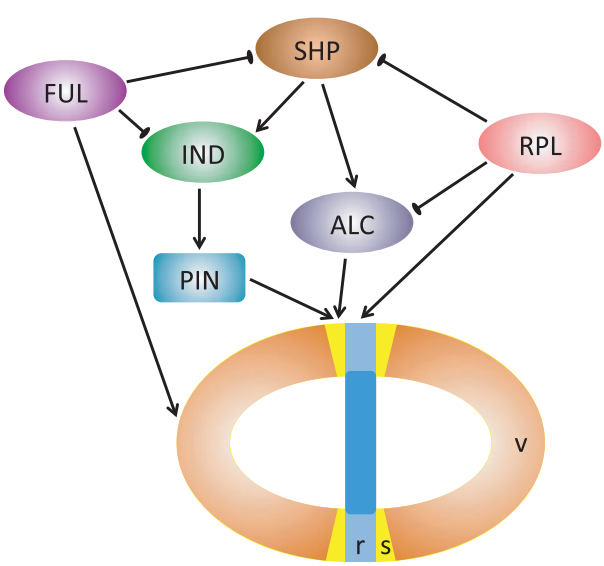

Figure 5. Genes involved in tissue specification in the gynoecium.
Cartoon diagram of a cross section of the gynoecium, with genes important in specifying the different tissue types indicated. At the valve margin, specialized cells that contribute to the separation layer differentiate and are necessary for seed pod shattering. Notation as in Figure 2. r = replum, v = valve, s = valve margin and separation layer.

et al., 2003). A variety of recent studies have illuminated some of the transcriptional cascades that then act to specify different gynoecial tissue types, as well as some of the roles for auxin in patterning both the radial and apical–basal axes of the gynoecium.

In addition to their role in promoting carpel identity, *SHP1* and *SHP2* are required for the differentiation of the dehiscence zone at the valve margins in the maturing fruit (Liljegren *et al.*, 2000). Plants doubly mutant for *shp1* and *shp2* fail to form lignified valve margin and separation layer cells that are necessary for pod shatter. In turn, SHP1 and SHP2 positively regulate the expression of two bHLH transcription factors, *INDEHISCENT* (*IND*) and *ALCATRAZ* (*ALC*), that are also required for normal differentiation of the valve margins (Rajani and Sundaresan, 2001; Liljegren *et al.*, 2004). The restriction of expression of *SHP1*, *SHP2*, *IND* and *ALC* to the valve margins is controlled by the MADS box transcription factor *FRUITFULL* (*FUL*), which is expressed in the valve (Ferrandiz *et al.*, 2000b; Liljegren *et al.*, 2004). Limiting *SHP1*, *SHP2* and *IND* expression to the valve margin also depends on the action of the homeodomain gene *REPLUMLESS* (*RPL*) which is required for replum development (Roeder *et al.*, 2003). At least part of the mechanism specifying the stripe of valve margin cells depends on the generation of an auxin minimum along these cells (Sorefan *et al.*, 2009). *IND* is required for the polar localization of PIN auxin transporters, and causes a localized depletion of auxin in the valve margin that in turn is necessary for the specification of this tissue (Sorefan *et al.*, 2009). Auxin presumably has a more general role in regulating carpel tissue differentiation, since *SPATULA* (*SPT*), which is required for the formation of the septum, stigma and transmitting tract, has been suggested to act as an inhibitor of auxin transport (Alvarez and Smyth, 1999; Nemhauser *et al.*, 2000; Heisler *et al.*, 2001; Balanza *et al.*, 2006). Furthermore, *HECATE1*, *-2* and *-3* (*HEC1–3*), three partly redundant bHLH genes whose products dimerize with that of *SPT* and presumably regulate the activity of the SPT protein, are also required for carpel tissue differentiation (Gremski *et al.*, 2007).

Auxin signaling is also important for the apical–basal patterning of the gynoecium, since a number of mutations affecting this process turn out to be lesions in genes required for auxin signaling or perception, while disruption of auxin synthesis or transport can result in aberrant gynoecium development (Sessions *et al.*, 1997; Nemhauser *et al.*, 2000; Cheng *et al.*, 2006). Based on these analyses, it has been proposed that a gradient of auxin action is necessary for gynoecium patterning, with high auxin concentrations being required for style and stigma development, and low levels permissive for specification of the base (Nemhauser *et al.*, 2000). *STYLISH1* and *-2* (*STY1*, *-2*) have partly redundant roles in specifying the style and stigma, and *STY1* has been shown to upregulate the expression of the auxin biosynthetic gene Y*UCCA4* in the apical portion of the gynoecium (Kuusk *et al.*, 2002; Sohlberg *et al.*, 2006). *STY1* also upregulates the expression of the *NGATHA* family of B3 transcription factors, which in turn act in a positive feedback loop to promote the expression of other auxin biosynthetic genes in the style (Alvarez *et al.*, 2009; Trigueros *et al.*, 2009).

THE NEXT DECADE

From the initial characterization of floral organ identity genes to the detailed view we now have of the diverse pathways orchestrating flower development, the past few decades of Arabidopsis research have indeed produced a rich harvest. It is now clear that not only are a number of feedback and cross-regulatory controls acting to specify different tissues and organs, but the relative timing of these events is critical for normal floral development to ensue. In the future, just as important as identifying new players in these pathways, we need to understand the details of when and where known gene products are acting at the cellular and subcellular levels. Given that so many of the key genes involved in regulating floral organogenesis encode transcription factors, elucidating the transcriptional cascades and associated gene regulatory networks controlled by such genes will be key. Ultimately, this will allow for a systems-level understanding of how all these components work together in forming the flower. The next decade of investigations into Arabidopsis flower development promises to be even more fruitful.

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