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Developmental and evolutionary diversity of plant MADS-domain factors: insights from recent studies

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Summary

Members of the MADS-box transcription factor family play essential roles in almost every developmental process in plants. Many MADS-box genes have conserved functions across the flowering plants, but some have acquired novel functions in specific species during evolution. The analyses of MADS-domain protein interactions and target genes have provided new insights into their molecular functions. Here, we review recent findings on MADS-box gene functions in *Arabidopsis* and discuss the evolutionary history and functional diversification of this gene family in plants. We also discuss possible mechanisms of action of MADS-domain proteins based on their interactions with chromatin-associated factors and other transcriptional regulators.

Key words: MADS-box genes, Plant development, Evolution, Transcriptional regulation

Introduction

MADS-domain transcription factors comprise one of the best-studied gene families in plants and members of this family play prominent roles in plant development. Two decades ago, the first MADS-box genes *AGAMOUS* (*AG*) from *Arabidopsis thaliana* (Yanofsky et al., 1990) and *DEFICIENS* (*DEF*) from *Antirrhinum majus* (Schwarz-Sommer et al., 1990) were discovered as regulators of floral organ identity. The sequence of the ~60 amino acid DNA-binding domains within these proteins showed striking similarities to that of the previously characterized proteins serum response factor (SRF) in *Homo sapiens* (Norman et al., 1988) and Minichromosome maintenance 1 (Mcm1) in *Saccharomyces cerevisiae* (Passmore et al., 1988). This shared and conserved domain was named the MADS domain (for MCM1, AG, DEF and SRF) and is present in all MADS-domain transcription factor family members (Schwarz-Sommer et al., 1990). Structural analysis of animal and yeast MADS domains showed that the N-terminal and central parts of the MADS domain make contacts with the DNA, while the C-terminal part of this domain contributes mainly to protein dimerization, resulting in a DNA-binding protein dimer consisting of two interacting MADS monomers (e.g. Pellegrini et al., 1995; Huang et al., 2000). Over the past 22 years, many MADS-box gene functions were uncovered in the model species *Arabidopsis thaliana* and in other flowering plants. Important model plant species for MADS-box gene research include snapdragon (*Antirrhinum majus*) (reviewed by Schwarz-Sommer et al., 2003), tomato (*Solanum lycopersicum*), petunia (*Petunia hybrida*) (Gerats and Vandenbussche, 2005), gerbera (*Gerbera hybrida*) (Teeri et al., 2006) and rice (*Oryza sativa*) (reviewed by Yoshida and Nagato, 2011).

Initially, MADS-box genes were found to be major players in floral organ specification, but more recent studies revealed functions for MADS-box genes in the morphogenesis of almost all organs and throughout the plant life cycle, from embryo to gametophyte development. The MADS-box gene family in higher plants is significantly larger than that found in animals or fungi, with more than 100 genes in representative flowering plant

Box 1. Glossary

Angiosperms. Flowering plants that produce: seeds from ovules contained in ovaries after double fertilization by pollen; and endosperm (a nutritive tissue) containing a seed surrounded by a fruit.

Apical meristem. A meristem located at the tip of a plant shoot (SAM) or root (RAM).

CArG box. The consensus MADS-domain binding motif with the DNA sequence: CC[A/T]$_6$GG.

Ecotype. A genetically distinct variety or population of a species that is adapted to a particular set of environmental conditions.

Floral meristem. A meristem that produces floral organs: sepals, petals, stamens and carpels.

Gymnosperms. Seed-bearing plants with ovules that are not contained in ovaries. Gymnosperms produce unenclosed ('naked') seeds.

Homeotic genes. Genes that control the transformation of one organ type into another.

Inflorescence meristem. A shoot meristem that produces flowers. In *Arabidopsis*, an example of a monopodial plant, inflorescence meristems (IMs) grow continuously and initiate flowers laterally. In tomato, a sympodial plant, IMs terminate in flowers and growth continues from new axillary IMs that repeat this process to generate compound inflorescences. In grasses, IMs produce lateral meristems with more specialized IM identities, reflecting the complex architecture of the grass inflorescence.

Meristem. A tissue of undifferentiated plant cells (analogous to stem cells) typically located at regions where growth takes place.

Neofunctionalization. The process by which a homologous gene develops a function that differs from that of the ancestral gene.

Orthologs. Homologous genes in different species that originated from a single ancestral gene through a speciation process. Owing to frequent gene duplication, which is often linked with polyploidization in plants, orthologs in a strict sense can only be found in very closely related species. A more correct, but less well-known, term would be 'orthogroup': the set of genes from extant species that descended from a single gene in the species' last common ancestor (Wapinski et al., 2007).

Paralogs. Homologous genes that originated from an ancestral gene through gene duplication.

Subfunctionalization. The process by which multiple functions of the ancestral gene are divided between homologous genes.

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genomes (De Bodt et al., 2005). This large family arose by a number of duplication events, which allowed divergence of functions of individual paralogs (see Glossary, Box 1).

In this review, we provide an overview of the developmental functions of MADS-box genes in flowering plants, with a main focus on *Arabidopsis*. We also summarize the roles of MADS-box genes in other plant species. Owing to the vast array of functions performed by MADS-box genes, and hence the large body of literature that is devoted to this field of research, a comprehensive review of all known studies of MADS-box genes would not be possible, but we hope that the examples discussed below illustrate different aspects of the evolution of MADS-box gene functions, their conserved roles, and their contribution to the origin of morphological novelties.

Type I and type II MADS-domain proteins

The MADS-box gene family can be divided into two lineages, type I and type II, based on their protein domain structure (Fig. 1). Genes from the type I lineage are a heterogeneous group, having only the ~180 bp DNA sequence encoding the MADS domain in common (De Bodt et al., 2003; Kofuji et al., 2003; Parenicová et al., 2003). They can be further classified into three subclasses: Mα, Mβ and Mγ (Fig. 1A). Type I genes were discovered only after the completion of the *Arabidopsis* genome sequence (The Arabidopsis Genome Initiative, 2000; Alvarez-Buylla et al., 2000). Although the type I MADS-box genes outnumber the type II genes, no gene functions were assigned to type I genes until relatively recently (reviewed by Masiero et al., 2011).

The type II lineage contains the well-studied floral homeotic genes (see Glossary, Box 1) as well as other genes involved in various developmental processes (e.g. embryogenesis, flowering time and fruit development). Plant type II MADS-domain proteins have a modular domain structure, which is referred to as the MIKC structure; they contain an N-terminally located DNA-binding MADS domain, followed by the I (intervening) and K (keratin-like) regions, which are essential for dimerization and higher-order complex formation, and finally a highly variable C-terminal domain, which may have roles in protein complex formation and transcriptional regulation (reviewed by Kaufmann et al., 2005a). Based on differences in their domain structure, MIKC-type MADS-box genes have been further classified into (canonical) MIKC^{C} and MIKC* types (Henschel et al., 2002) (Fig. 1B). The latter are characterized by an altered protein domain structure, possibly linked to the duplication of exons encoding a subregion of the K domain (Kwantes et al., 2012). Moreover, we can divide MIKC^{C}-type MADS-box genes into several distinctive subfamilies based on their phylogeny (Fig. 1B). Most subfamilies of MIKC^{C}-type genes appear to have originated in ancestral seed plants and have been named after their first identified founding members (Becker and Theissen, 2003). Proteins of the different subfamilies

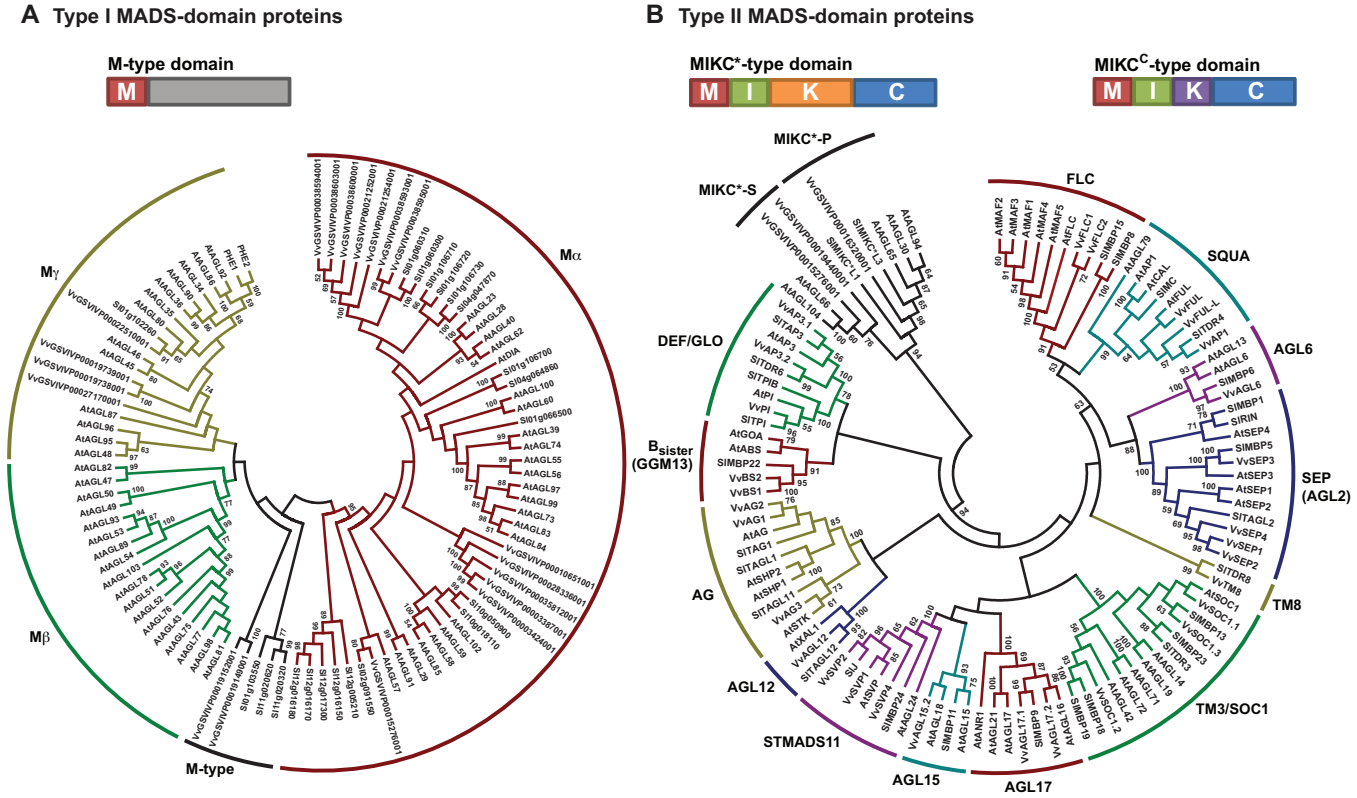


Fig. 1. Domain structure and classification of MADS-domain proteins. Phylogenetic analyses and the domain structure of selected representatives of (**A**) type I and (**B**) type II MADS-box transcription factors from thale cress (*Arabidopsis thaliana*, *At*), grape (*Vitis vinifera*, *Vv*) and tomato (*Solanum lycopersicum*, *Sl*). Trees were built after codon alignment by MUSCLE (Edgar, 2004) using the neighbor-joining method with a 1000 replicate bootstrap analysis and visualized in a topology-only mode. Phylogenetic analyses were conducted in MEGA5 (Tamura et al., 2011). Type I MADS-box transcription factors possess one conserved domain, the DNA-binding MADS domain (M, red), and a long, variable C-terminal domain (gray). Plant type II MADS-box transcription factors have four domains: the DNA-binding MADS, the intervening (I, green), the keratin-like (K, orange/purple) and the C-terminal (C, blue) domains. MIKC*-type proteins are usually longer than MIKC^{C}-type proteins, probably owing to a longer K domain (MIKC*, orange; MIKC^{C}, purple) (Kwantes et al., 2012).

are often characterized by distinct sequence motifs in their C-terminal domains, which further diversified during evolution by frameshift mutations (see Vandenbussche et al., 2003a). At least for some MIKC-type proteins, the C-terminal motifs appear to be dispensable for basic protein function (Piwarzyk et al., 2007; Benlloch et al., 2009).

Members of the different MIKC^C-type subfamilies often have related or even conserved functions in different flowering plant species. For example, the specification of stamens and carpels in the flower is exerted by genes of the AGAMOUS (AG) clade in different angiosperm species. In a similar fashion, members of the DEFICIENS (DEF) and GLOBOSA (GLO) subfamilies control stamen and petal identity, and members of the SQUAMOSA (SQUA) and SEPALLATA [SEP or AGAMOUS-LIKE 2 (AGL2)] have (partly) conserved roles in floral meristem (see Glossary, Box 1) and organ specification in various angiosperms. Members of other MIKC^C-type subfamilies, such as the TOMATO MADS-BOX 3 (TM3), FLOWERING LOCUS C (FLC) and SOLANUM TUBEROSUM MADS-BOX 11 (STMADS11) clades, act predominantly in floral transition. AGL12 and AGL17 subfamily members appear to act mostly in root development (although they also influence floral transition). Intriguingly, many MIKC^C-type genes act in more than one developmental process or developmental stage.

MADS-box gene functions in *Arabidopsis thaliana*

The functional characterization of *Arabidopsis thaliana* MADS-box genes started with their discovery in the early 1990s. To date, functions for nearly half of these genes have been described (Table 1). In addition to genetic studies, genome-wide expression and interaction studies have shed light on the potential roles of MADS-domain proteins in plant development. Below, we provide an overview of MADS-box gene functions in the *Arabidopsis thaliana* life cycle (summarized in Fig. 2), highlighting some of the recent studies and advances.

Gametophyte, embryo and seed development

The plant life cycle culminates in the generation of male and female haploid gametes (sperm cells and embryo sac, respectively) by meiosis. The gametes are then fused during the fertilization process to generate a diploid zygote. In *Arabidopsis* and many other flowering plant species a second sperm nucleus fuses with two nuclei of the central cell in the embryo sac to produce the extra-embryonic triploid endosperm. Embryonic development results in a developmentally arrested embryo in the mature seed in which the major body axis is established. As we highlight below, MADS-domain proteins are involved in several stages of gametophytic and embryonic development.

Genetic studies have revealed functions for several type I MADS-box genes in female gametogenesis and in seed development (Fig. 2 and Table 1) (reviewed by Masiero et al., 2011). For example, the Mγ protein AGL80 and the Mα protein DIANA (DIA; AGL61) form a functional protein dimer and control the differentiation of the central cell (Portereiko et al., 2006; Bemer et al., 2008; Steffen et al., 2008). *AGL80* is also expressed during endosperm development. *AGL62*, a close paralog of *DIA*, suppresses premature endosperm cellularization (Kang et al., 2008) and encodes a protein that can also interact with AGL80 (Kang et al., 2008), although the relevance of this interaction is not well understood. The overlapping mutant phenotypes and gene functions as well as interaction studies suggest that, similar to type II MADS-domain proteins, at least some type I proteins act together in heteromeric protein complexes. A large-scale yeast two-hybrid protein interaction screen revealed multiple interactions between type I MADS-domain proteins, mostly between members of different subclades (de Folter et al., 2005). A large-scale expression analysis showed that most (38 out of 61) type I MADS-box genes are active in the female gametophyte and seed development processes (Bemer et al., 2010), and some of them exhibit highly specific expression patterns in particular cells (Bemer et al., 2010; Wuest et al., 2010). However, for the majority of these genes no direct function has been attributed so far, probably owing to genetic redundancy.

Several type I MADS-box genes are epigenetically repressed by the action of a PRC2-type polycomb group (PcG) complex during seed formation and at other stages of plant development (Zhang et al., 2007; Dreni et al., 2011). Examples are *AGL23*, which is an Mα-type MADS-box gene that has a role in embryo sac development (Colombo et al., 2008), and *PHERES1* (*PHE1*; *AGL37*) (Köhler et al., 2003). *PHE1* provided one of the first examples of imprinting in plants: the expression of the maternal allele of *PHE1* is silenced by the PcG complex, whereas the paternal copy is active in embryo and endosperm, resulting in a parent-of-origin-dependent expression of *PHE1* in seeds (Köhler et al., 2005). Expression of *PHE1* is also regulated by DNA (de)methylation (Makarevich et al., 2008; Hsieh et al., 2009; Villar et al., 2009). The dual epigenetic regulation of *AGL36* provides another example of complex control of type I MADS-box gene expression in seed development (Shirzadi et al., 2011). The downregulation of *PHE1*, *PHE2*, *AGL35*, *AGL36*, *AGL40*, *AGL62* and *AGL90* coincides with the transition of endosperm from the syncytial to cellularized stage, and this appears to be crucial for endosperm differentiation (Kang et al., 2008; Walia et al., 2009). The dosage-sensitive PRC2-mediated repression of these type I genes contributes to postzygotic compatibility and reproductive isolation between species (Walia et al., 2009).

Whereas type I MADS-box genes predominantly regulate female gametophyte and seed development, MIKC*-type genes were found to control development of male gametophytes (pollen). Combinations of double and triple mutants of *agl65*, *agl66* and *agl104* MADS-box genes give rise to several pollen-affected phenotypes with disturbed viability, delayed germination and aberrant pollen tube growth (Verelst et al., 2007a; Adamczyk and Fernandez, 2009). Expression and interaction data confirmed that these MIKC*-type gene products form a protein interaction and regulatory network controlling pollen maturation (Verelst et al., 2007a; Adamczyk and Fernandez, 2009). Moreover, in-depth gene expression analysis in such double and triple mutants showed that these MIKC*-type MADS complexes regulate transcriptome dynamics during pollen development and revealed the extent of their functional redundancy (Verelst et al., 2007b). In summary, these findings highlight the importance of protein multimerization within the MADS-box family during gametophytic and embryo development.

Despite the fact that many MIKC^C-type MADS-box genes show detectable expression during embryo development (Lehti-Shiu et al., 2005), few roles have been attributed to them in this developmental process. One of the first MADS-box genes shown to play a potential role in embryogenesis was the MIKC^C-type gene *AGL15* (Heck et al., 1995; Perry et al., 1999). Although single *agl15* mutant plants do not show any obvious embryonic phenotype, overexpression of *AGL15* promotes the production of secondary embryos (Harding et al., 2003). The identification of AGL15 target genes revealed that it directly binds loci of B3-domain transcription factor genes, which are known regulators of embryogenesis (Zheng et al., 2009). In addition to this potential

Table 1. MADS-box gene functions in development of *Arabidopsis thaliana*

Gene	Symbol	Genomic locus	Phylogenetic group (subfamily)	Functions	References
AGAMOUS-LIKE 65, 66, 104	*AGL65, 66, 104*	At1g18750, At1g77980, At1g22130	MIKC*	Pollen maturation and tube growth	(Adamczyk and Fernandez, 2009)
AGAMOUS	*AG*	At4g18960	MIKC^C (AG)	Homeotic C-class gene; carpel and stamen specification	(Yanofsky et al., 1990)
SHATTERPROOF 1, 2	*SHP1, 2*	At3g58780, At2g42830	MIKC^C (AG)	Carpel, ovule and fruit development; dehiscence; periodic lateral root formation	(Liljegren et al., 2000; Moreno-Risueno et al., 2010)
SEEDSTICK	*STK*	At4g09960	MIKC^C (AG)	Carpel and ovule development; periodic lateral root formation	(Pinyopich et al., 2003; Moreno-Risueno et al., 2010)
XAANTAL1	*XAL1*	At1g71692	MIKC^C (AGL12)	Root development cell-cycle regulation; transition to flowering (activator)	(Tapia-Lopez et al., 2008)
AGAMOUS-LIKE 15	*AGL15*	At5g13790	MIKC^C (AGL15)	Embryogenesis*; transition to flowering (repressor) with AGL18; sepal and petal longevity*; fruit maturation*	(Heck et al., 1995; Fernandez et al., 2000; Harding et al., 2003)
AGAMOUS-LIKE 18	*AGL18*	At3g57390	MIKC^C (AGL15)	Transition to flowering (repressor) with AGL15	(Adamczyk et al., 2007)
AGAMOUS-LIKE 16	*AGL16*	At3g57230	MIKC^C (AGL17)	Number and distribution of stomata*	(Kutter et al., 2007)
AGAMOUS-LIKE 17	*AGL17*	At2g22630	MIKC^C (AGL17)	Transition to flowering (activator)*	(Han et al., 2008)
ARABIDOPSIS NITRATE REGULATED 1	*ANR1*	At2g14210	MIKC^C (AGL17)	Root development; nutrient response	(Zhang and Forde, 1998)
AGAMOUS-LIKE 6	*AGL6*	At2g45650	MIKC^C (AGL6)	Transition to flowering (activator); lateral organ development*	(Koo et al., 2010; Yoo et al., 2011)
ARABIDOPSIS BSISTER	*ABS*	At5g23260	MIKC^C (GGM13)	Seed pigmentation and endothelium development	(Nesi et al., 2002; Kaufmann et al., 2005b; de Folter et al., 2006)
GORDITA	*GOA*	At1g31140	MIKC^C (GGM13)	Fruit development	(Prasad et al., 2010)
APETALA3	*AP3*	At3g54340	MIKC^C (DEF/GLO)	Homeotic B-class gene; petal and stamen specification	(Jack et al., 1992)
PISTILLATA	*PI*	At5g20240	MIKC^C (DEF/GLO)	Homeotic B-class gene; petal and stamen specification	(Goto and Meyerowitz, 1994)
FLOWERING LOCUS C	*FLC*	At5g10140	MIKC^C (FLC)	Transition to flowering (repressor); germination*; juvenile-to-adult transition*; initiation of flowering*; flower organ development*	(Michaels and Amasino, 1999; Chiang et al., 2009; Deng et al., 2011)
MADS AFFECTING FLOWERING 1-4	*MAF1-4*	At1g77080, At5g65050, At5g65060, At5g65070	MIKC^C (FLC)	Transition to flowering (repressors)*	(Ratcliffe et al., 2001; Ratcliffe et al., 2003)
MADS AFFECTING FLOWERING 5	*MAF5*	At5g65080	MIKC^C (FLC)	Transition to flowering (activator)*	(Ratcliffe et al., 2003)
SEPALLATA1-4	*SEP1-4*	At5g15800, At2g03710, At1g24260, At3g02310	MIKC^C (AGL2)	Homeotic E-class genes; sepal, petal, stamen and carpel specification	(Mandel and Yanofsky, 1998; Pelaz et al., 2000; Ditta et al., 2004)
AGAMOUS-LIKE 19	*AGL19*	At4g22950	MIKC^C (TM3/SOC1)	Transition to flowering (activator)	(Schonrock et al., 2006)
AGAMOUS-LIKE 42 (*FOREVER YOUNG FLOWER*)	*AGL42* (*FYF*)	At5g62165	MIKC^C (TM3/SOC1)	Transition to flowering (activator); flower organ senescence and abscission*; root development*	(Nawy et al., 2005; Chen et al., 2011; Dorca-Fornell et al., 2011)
AGAMOUS-LIKE 71, 72	*AGL71, 72*	At5g51870, At5g51860	MIKC^C (TM3/SOC1)	Transition to flowering (activators) with AGL42	(Dorca-Fornell et al., 2011)
SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1	*SOC1*	At2g45660	MIKC^C (TM3/SOC1)	Transition to flowering (activator); periodic lateral root formation	(Lee et al., 2000; Moreno-Risueno et al., 2010)
APETALA1	*AP1*	At1g69120	MIKC^C (SQUA)	Meristem identity specification; homeotic A-class gene	(Mandel et al., 1992; Weigel et al., 1992; Ferrandiz et al., 2000b)
CAULIFLOWER	*CAL*	At1g26310	MIKC^C (SQUA)	Meristem identity specification	(Kempin et al., 1995; Ferrandiz et al., 2000b)
FRUITFULL	*FUL*	At5g60910	MIKC^C (SQUA)	Meristem identity specification; annual life cycle regulator, with SOC1; fruit development; cauline leaf growth	(Gu et al., 1998; Ferrandiz et al., 2000b; Ferrandiz et al., 2000a; Melzer et al., 2008)

Table 1. Continued

Gene	Symbol	Genomic locus	Phylogenetic group (subfamily)	Functions	References
AGAMOUS-LIKE 24	*AGL24*	At4g24540	MIKC^C (STMADS11)	Transition to flowering (activator)	(Michaels et al., 2003)
SHORT VEGETATIVE PHASE	*SVP*	At2g22540	MIKC^C (STMADS11)	Transition to flowering (repressor)	(Hartmann et al., 2000)
AGAMOUS-LIKE 23	*AGL23*	At1g65360	Mα	Embryo sac development	(Colombo et al., 2008)
AGAMOUS-LIKE 28	*AGL28*	At1g01530	Mα	Transition to flowering (activator)*	(Yoo et al., 2006)
DIANA (*AGAMOUS-LIKE 61*)	*DIA* (*AGL61*)	At2g24840	Mα	Central cell and endosperm development	(Bemer et al., 2008; Steffen et al., 2008)
AGAMOUS-LIKE 62	*AGL62*	At5g60440	Mα	Central cell development	(Kang et al., 2008)
AGAMOUS-LIKE 80	*AGL80*	At5g48670	Mγ	Central cell and endosperm development	(Portereiko et al., 2006)
PHERES1 (*AGAMOUS-LIKE 37*)	*PHE1* (*AGL37*)	At1g65330	Mγ	Seed development*	(Kohler et al., 2003; Kohler et al., 2005)

Subfamily names are according to Becker and Theissen (Becker and Theissen, 2003).
*Function that is inferred based on other than mutant phenotype analysis.

role in embryo development, *AGL15* represses floral transition, together with its close paralog *AGL18* (Adamczyk et al., 2007; Zheng et al., 2009).

Phase transitions in sporophytic development

In *Arabidopsis* and other plant species, major developmental transitions occur during postembryonic growth: the change from the juvenile to the vegetative phase, and later to the reproductive phase. The juvenile-to-adult transition is characterized mainly by changes in the morphology and epidermal patterning of leaves in *Arabidopsis*. The vegetative-to-reproductive transition results in the conversion of the vegetative apical meristem (see Glossary, Box 1) into an inflorescence meristem (IM; see Glossary, Box 1), which then produces flowers and cauline leaves. Developmental transitions are regulated by external and internal cues, such as light, plant age and temperature (Blázquez, 2000; Poethig, 2003). The different signaling cascades that respond to these cues are integrated by transcriptional master regulators, many of which are MIKC^C-type MADS-box transcription factors. These factors can act as repressors or activators of the transition, and integrate the input from temperature, day-length, autonomous and hormonal pathways.

An important repressor of the floral transition is *FLC*, the expression of which is controlled by vernalization (Michaels and Amasino, 1999). During prolonged cold exposure, *FLC* expression is downregulated by epigenetic chromatin regulators and possibly by long non-coding RNAs, allowing the plant to flower in spring in winter-annual accessions of *Arabidopsis* (reviewed by Kim and Sung, 2012). FLC interacts with another MIKC^C-type floral repressor, SHORT VEGETATIVE PHASE (SVP) (Li et al., 2008). FLC and SVP repress the expression of the mobile floral inducer ('florigen') *FLOWERING LOCUS T* (*FT*) and other genes that initiate floral transition, in a partly tissue-specific fashion (Searle et al., 2006; Li et al., 2008; Jang et al., 2009). Recently, data from chromatin immunoprecipitation followed by hybridization to tiling arrays (ChIP-CHIP) revealed that SVP also directly activates the expression of other flowering repressors, including members of the APETALA2 (AP2) transcription factor family (Tao et al., 2012), which in turn also repress *FT*. A similar genome-wide target gene identification approach indicated that *FLC* is involved in developmental processes beyond floral repression, including the juvenile-to-adult transition and floral organ development (Deng et al., 2011). *FLC* also has a role in temperature-dependent seed germination (Chiang et al., 2009).

One major target of repression by FLC is the MIKC^C-type transcription factor *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1* (*SOC1*), which is an activator of floral transition at the shoot apex. *SOC1* integrates external (e.g. light) and internal signals (Lee et al., 2000; Samach et al., 2000; Seo et al., 2009) and acts in a positive-feedback loop with *AGL24* (Liu et al., 2008), yet another important MIKC^C-type factor that positively regulates flowering in *Arabidopsis* (Michaels et al., 2003). SOC1 and AGL24 appear to work in a larger molecular complex and transmit the flowering signals onto *LEAFY* (*LFY*) (Lee et al., 2008), which is a non-MADS regulator of floral meristem identity that links floral induction with flower development (Weigel et al., 1992). Additionally, SOC1 represses the precocious expression of floral homeotic B-, C- and E-class genes (see Box 2) in IMs and early floral meristems in a redundant manner with AGL24 and SVP, respectively (Gregis et al., 2009; Liu et al., 2009; Torti et al., 2012). *SOC1* also interacts with *FRUITFULL* (*FUL*) and together they play a role in establishing the annual life habit of *Arabidopsis* (Melzer et al., 2008). Recently, it was revealed that the floral activator SOC1 and the floral repressor SVP act in an opposing fashion on a partially overlapping set of direct target genes during floral transition (Tao et al., 2012).

A number of other MIKC^C-type genes, for example other TM3 clade members in addition to *SOC1* (Table 1) (Dorca-Fornell et al., 2011), have been shown to regulate floral transition in *Arabidopsis*. We conclude that flowering time is determined by the interplay between multiple MADS-box genes, whereby master regulators such as the flowering repressor *FLC* and the flowering activator *SOC1* act in concert with other non-MADS key regulators such as the *FT-FD* complex and *LFY* to integrate and process external and internal flowering signals (reviewed by Posé et al., 2012).

Flower and fruit development

The floral transition results in the formation of IMs, which generate floral meristems at their flanks that in turn produce floral organs (sepals, petals, stamens and carpels). Meristems are specified by the action of meristem identity genes, which interact in complex regulatory networks with multiple feedback and feedforward loops (Kaufmann et al., 2010a). Whereas *SOC1* and *AGL24* have been referred to as IM identity genes, the partially redundantly acting MIKC^C-type genes *AP1* and *CAULIFLOWER* (*CAL*) specify floral meristem identity (Kempin et al., 1995). It has been shown that

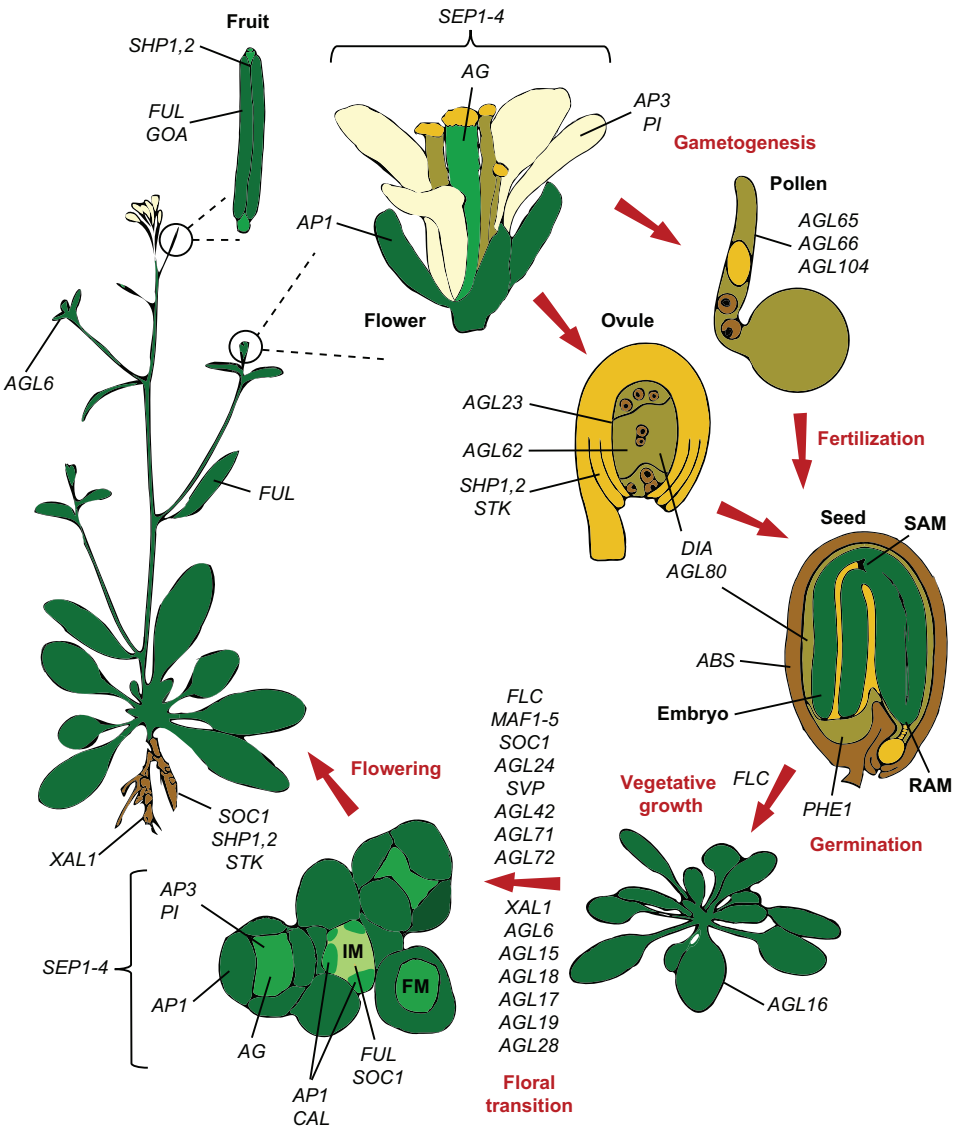
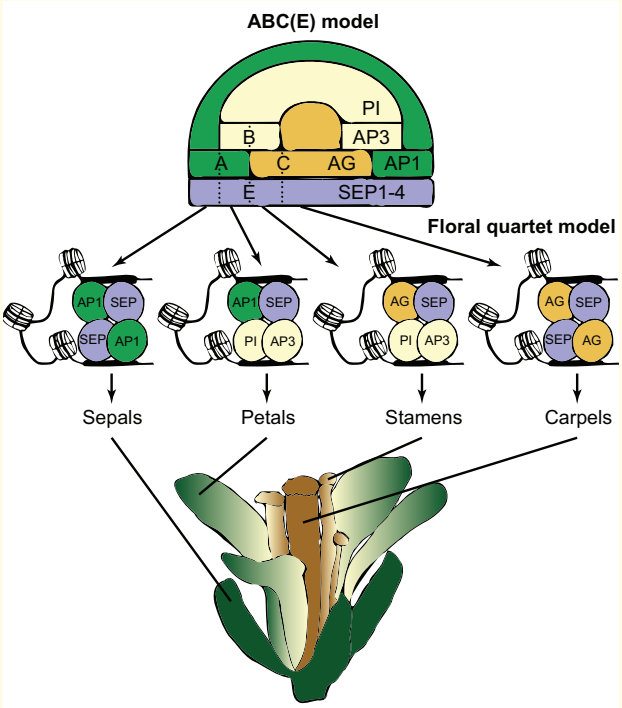


Fig. 2. Functions of MADS-box genes throughout the life cycle of *Arabidopsis thaliana*. *Arabidopsis* progresses through several major phase changes during its life cycle and MADS-box genes play distinct roles in the various developmental phases and transitions. Reproductive development starts with the generation of male and female haploid gametes (gametogenesis) and, after double fertilization, this results in a developmentally arrested embryo that possesses a root apical meristem (RAM) and a shoot apical meristem (SAM), enclosed within a seed. Under favorable conditions, seeds germinate and young plants go through the vegetative phase of development in which leaves are formed and plants gain size and mass. Finally, the plant is ready to flower and the floral transition stage results in the conversion of vegetative meristems into inflorescence meristems (IMs) and floral meristems (FMs) that produce floral organs. Subsequently, gametes are formed within the inner flower organs, thus completing the cycle. The MADS-box genes that are involved in each of the various stages of development are indicated.

most of the early AP1 target genes are downregulated by AP1, suggesting that this protein acts mainly as a transcriptional repressor during floral meristem initiation (Kaufmann et al., 2010b). During the early stages of flower development, AP1 can interact with SVP and this complex may initially repress homeotic gene activity in early floral meristems (Gregis et al., 2009). In addition, AP1 activates (together with LFY) the expression of (other) floral homeotic genes and other genes involved in floral patterning, at least at later developmental stages (Ng and Yanofsky, 2001; Kaufmann et al., 2010b; Winter et al., 2011).

The identities of different types of floral organs (sepals, petals, stamens and carpels) are specified by homeotic genes, nearly all of which encode MIKC^{C}-type proteins. Fundamental models have been proposed to explain the genetic and molecular interactions of these floral master regulators (see Box 2). Homeotic genes were classified into functional classes A to E based on their characteristic mutant phenotypes (Coen and Meyerowitz, 1991; Colombo et al., 1995; Theissen, 2001). The homeotic A-function has received critical attention in recent years. The A-class gene *APETALA1* (*AP1*) has recently been proposed to have a more general role in establishing floral meristem fate, which more accurately explains the phenotype of most *ap1* mutant alleles in *Arabidopsis* and those of orthologous genes in other plant species (Causier et al., 2010). It has also been proposed that the second traditional 'A-class' gene *AP2*, the only non-MADS-box transcription factor in the ABCDE model, acts as a cadastral gene, which becomes restricted in its expression by microRNA172; the miR172/AP2 module coordinates the specification of perianth versus reproductive organs (Wollmann et al., 2010). The E-class proteins, which comprise the four largely redundantly acting SEP subfamily members, have a special role as mediators of higher-order complex formation among floral MADS-domain proteins (Honma and Goto, 2001). Homeotic MADS-box genes are initially expressed in a patterned fashion in floral meristems and maintain expression during floral organ differentiation (Urbanus et al., 2009) (for a review, see Krizek and Fletcher, 2005). They control the expression of many other genes at different stages, a number of them directly (reviewed by Ito, 2011). The D-class genes *SHATTERPROOF 1* and *2* (*SHP1,2*) and *SEEDSTICK* (*STK*) specify ovule identity and differentiation (Favaro et al., 2003; Pinyopich et al., 2003; Matias-Hernandez et al., 2010). D-class proteins interact in larger complexes with E-class proteins and the homeobox transcription factor BELL1 (Favaro et al., 2003; Brambilla et al., 2007).

Box 2. ABC and floral quartet models of floral organ specification



As for the majority of angiosperm flowers, the *Arabidopsis thaliana* flower is structured into four concentric whorls of floral organs. The four organ types are sepals (outermost whorl, whorl 1), petals (whorl 2), stamens (whorl 3) and carpels (whorl 4) (Haughn and Somerville, 1988). In the classic ABC model, which is based on homeotic mutant phenotypes in *Arabidopsis thaliana* and *Antirrhinum majus*, three classes of genes (A, B and C) are essential to guide the specification and formation of floral organs (Coen and Meyerowitz, 1991; see also Haughn and Somerville, 1988): A-class genes specify sepal identity, A-class and B-class genes together determine petals, B-class genes and the C-class gene specify stamens, and the C-class gene determines carpel identity. In *Arabidopsis*, the A-class genes are *APETALA1* (*AP1*) and *AP2*, B-class genes are *APETALA3* (*AP3*) and *PISTILLATA* (*PI*), and the C-class gene is *AGAMOUS* (*AG*). Based on the overexpression phenotypes of the AG clade gene *FLORAL BINDING PROTEIN 11* (*FBP11*) in petunia, an additional homeotic gene class, the D class, was proposed to specify ovule identity (Colombo et al., 1995), and, in *Arabidopsis*, ovule identity is specified by the related AG subfamily member *SEEDSTICK* (*STK*) together with *SHATTERPROOF 1* and *2* (*SHP1,2*) (Pinyopich et al., 2003). Identification of the redundantly functioning SEPALLATA genes (*SEP1-4*), which are essential for the development of all flower whorls (Pelaz et al., 2000; Ditta et al., 2004), led to the extension of the ABC model to include these E-class genes (Theissen, 2001). The homeotic A-function has been under debate in recent years (see text).

Except for *AP2*, all floral homeotic genes encode MADS-domain transcription factors. In line with the observed combinatorial higher-order complex formation of MADS-domain proteins (Honma and Goto, 2001), the floral quartet model was postulated to explain the molecular mechanism of action underlying ABCDE protein function in floral organ specification (Theissen, 2001; Theissen and Saedler, 2001). The organ-specific combinatorial quaternary MADS-domain protein complexes are proposed to control differentiation and outgrowth of the distinct floral organs in the four concentric whorls.

Fruit differentiation is controlled by the antagonistically acting *SHP1,2* and *FUL* genes, which are expressed in the valve margins and in the valves, respectively (Ferrándiz et al., 2000a; Colombo et al., 2010). The B_{sister} clade gene *GORDITA* (*GOA*), which has a divergent protein sequence, regulates fruit size in *Arabidopsis* by repressing cell expansion (Prasad et al., 2010). A close paralog of *GOA*, the more conserved B_{sister} gene *ARABIDOPSIS BSISTER* (*ABS*; *TT16*), controls endothelium development and (thereby) seed maturation (Nesi et al., 2002; Kaufmann et al., 2005b; de Folter et al., 2006; Mizzotti et al., 2012). The interaction of ABS with AG clade proteins is mediated by SEP proteins, suggesting roles for tetrameric MIKC^C-type protein complexes in processes beyond floral organ specification (Kaufmann et al., 2005b; Mizzotti et al., 2012).

Root and leaf morphogenesis

Although MIKC^C-type MADS-box genes are best known for their roles in floral transition and flower development, several of them have additional or specific functions during root morphogenesis. The AGL17 clade gene *ARABIDOPSIS NITRATE REGULATED 1* (*ANR1*) has a function in nutrient response in roots and controls lateral root elongation in response to nitrate (Zhang and Forde, 1998; Gan et al., 2005). Other members of the AGL17 clade (e.g. *AGL16*, *AGL17* and *AGL21*) are also expressed predominantly in roots (Burgeff et al., 2002). *AGL16* and *AGL21* are regulated by nitrogen, similar to *ANR1*, and AGL21 has recently been shown to interact with an endosome-associated protein that promotes intercellular movement (Gan et al., 2005; Koizumi et al., 2011). Besides its potential role in root morphogenesis, *AGL17* also affects floral transition (Han et al., 2008).

XAANTAL1 (*XAL1*; *AGL12*) controls auxin-dependent cell-cycle regulation affecting root growth and also affects flowering time (Tapia-López et al., 2008). *SOC1*, as well as the AG clade genes *SHP1,2* and *STK*, which have well-described roles in reproductive transition and carpel development, have recently been shown to act in periodic lateral root formation (Moreno-Risueno et al., 2010). Other TM3/SOC1 clade genes that control floral transition in the shoot are also expressed in the root (Nawy et al., 2005), but the biological relevance of this is not yet known.

As with their functions in roots, the roles of MADS-box genes in leaf development are largely unexplored. One example of a functionally characterized gene is the microRNA-regulated *AGL16*, which controls stomata initiation in leaves and other organs (Kutter et al., 2007). More studies are needed, however, to unveil whether other MADS-box genes that are expressed in leaves play roles in leaf morphogenesis.

Examples of MIKC^C-type MADS-box gene functions in other plant species

The key functions of MIKC^C-type MADS-box transcription factors in a variety of developmental processes in plants suggest possible roles in the evolution of morphologies, life history strategies and reproductive mechanisms (see Table 2 for examples). MIKC^C-type genes are thus major research targets in evolutionary developmental biology (evo-devo) studies, as well as in crop plant biotechnology and domestication research. The availability of transcriptome datasets and/or genome sequences led to a more comprehensive identification and characterization of specific MIKC^C-type genes in different plant species, such as tomato (Hileman et al., 2006) and grapevine (*Vitis vinifera*) (Díaz-Riquelme et al., 2009), or of MADS-box genes in general in species such as rice (Arora et al., 2007), poplar (*Populus*

Table 2. Evolution of MIKC^C-type MADS-box gene functions in flowering plants

Subfamily	Functions in *Arabidopsis*	(Additional) functions in other plant lineages	References
AG	Floral homeotic C and D functions	Lineage-specific subfunctionalization of the homeotic C function; fruit development, e.g. tomato versus *Arabidopsis*	(Causier et al., 2005; Airoldi et al., 2010)
AP3, PI	Floral homeotic B function	Tepal diversification in orchids; variable roles in specification of petaloid organs	(Mondragon-Palomino and Theissen, 2008; Chang et al., 2010)
STMADS11	Control of floral transition; repression of precocious homeotic gene expression	Inflated calyx syndrome in *Physalis*; floral bud dormancy in *Prunus*; repression of prophyll development in *Antirrhinum*; flower abscission zone development in tomato	(Mao et al., 2000; Masiero et al., 2004; He and Saedler, 2005; Li et al., 2009)
AGL2	Floral homeotic E function	Inflorescence meristem determinacy in *Gerbera*; tomato fruit ripening	(Vrebalov et al., 2002; Uimari et al., 2004)
SQUA	Floral meristem and organ identity specification; floral transition; fruit development	Potato axillary bud formation; potential role in *Vitis* tendril development; variable roles in fruit development, sepal size and floral abscission in tomato; variable roles in floral transition	(Rosin et al., 2003; Calonje et al., 2004; Nakano et al., 2012)
FLC	Repressor of floral transition; seed germination	Potential role in floral bud dormancy; perennial life history in *Arabis alpina*	(Du et al., 2008; Wang et al., 2009; Zhang et al., 2009)

This table exemplifies MIKC^C-type gene subfamilies for which gene functions have been studied in different angiosperm species. Subfamily names are according to Becker and Theissen (Becker and Theissen, 2003).

trichocarpa) (Leseberg et al., 2006) and cucumber (*Cucumis sativus*) (Hu and Liu, 2012). Because of the tremendous amount of research carried out on MIKC^C-type genes in various species, we highlight here only some of the recent findings. We focus on examples where the function or regulation of MIKC^C-type genes deviates from their orthologs in *Arabidopsis* and might thus have an impact on evolution.

Flower development

A major model system in evo-devo research is the angiosperm (see Glossary, Box 1) flower. While the basic types of floral organs are largely conserved, the number and morphology of floral organs are highly diverse, reflecting diversity in reproductive strategies (Soltis et al., 2002). Next to *Arabidopsis*, the roles of MIKC^C-type genes in flower development have been extensively studied in eudicot species such as snapdragon, petunia and tomato, as well as in monocots such as rice and the orchid *Phalaenopsis*. Among the upcoming model species are pea (*Medicago sativa*) (Hecht et al., 2005) and basal eudicots such as California poppy (*Eschscholzia californica*) (Zahn et al., 2010). The ability to analyze gene functions in a plant species depends on the availability of tools, such as the ability to transform the plant or amenability for virus-induced gene silencing (VIGS) (Becker and Lange, 2010), and of genome and/or transcriptome resources.

Some of the core functions of MIKC^C-type genes (e.g. in floral organ identity specification) appear to be largely conserved across flowering plants. For example, the mutant phenotypes of B-, C-, D- and E-class homeotic genes in grasses such as rice and maize (*Zea mays*) revealed basic conservation of the (A)BCE model, although it is not always readily apparent based on single-mutant phenotypes owing to the presence of multiple, largely functionally redundant paralogs, for example of C-class genes in rice (e.g. Dreni et al., 2011) [for a detailed review on floral MIKC^C-type genes in grasses see Ciaffi et al. (Ciaffi et al., 2011)]. The A class is the most debated and apparently least evolutionarily conserved homeotic function (Causier et al, 2010). Recent analysis of the function of SQUA subfamily genes from basal eudicots suggests that the 'A-function' evolved via subfunctionalization after gene duplication(s) at the base of core eudicots from a more broad action of SQUA subfamily members in floral meristem specification, floral organ specification and fruit development [see Pabón-Mora et al. (Pabón-Mora et al., 2012) and references therein]. Interestingly, the E function appears to be exerted not only by genes from the SEP subfamily, but also by the closely related AGL6 subfamily, at least in some flowering plant species such as petunia (Vandenbussche et al., 2003b; Rijpkema et al., 2009), rice (Ohmori et al., 2009; Cui et al., 2010; Gao et al., 2010; Li et al., 2011) and maize (Thompson et al., 2009). This provides an indication that partial functional redundancy of members from different subfamilies might have persisted over long evolutionary time-scales. Future research needs to reveal how this apparent redundancy is reflected in the molecular action of the different genes.

Independent MIKC^C-type gene duplication events in the different flowering plant lineages can be associated with the lineage-specific subfunctionalization (see Glossary, Box 1) or, to a lesser extent, neofunctionalization (see Glossary, Box 1), of individual paralogs. The process of plant lineage-specific subfunctionalization after gene duplication is also exemplified by the functionally equivalent paralogous homeotic C-function genes *AG* from *Arabidopsis* and *PLENA* (*PLE*) from *Antirrhinum* (Bradley et al., 1993). Their respective orthologs (see Glossary, Box 1), *FARINELLI* (*FAR*) in *Antirrhinum* (Davies et al., 1999) and *SHP1,2* in *Arabidopsis* (Liljegren et al., 2000), have undergone independent subfunctionalization (Causier et al., 2005; Airoldi et al., 2010). Plant lineage-specific functional diversification of AG clade genes is also reflected in the evolution of their cis-regulatory regions (Causier et al., 2009; Moyroud et al., 2011).

A crucial aspect in the patterning of the floral meristem and the ABC model is the restriction of C-class expression to the inner two floral whorls in the floral meristem and during organ development. Many factors regulating *AG* expression in *Arabidopsis* at the transcriptional level have been characterized (reviewed by Kaufmann et al., 2010a). It was shown that C-class repression in the outer whorls is mediated by mechanisms that differ somewhat in different eudicot species: in *Arabidopsis*, *AG* expression is, among others, regulated by the miRNA172/AP2 module, whereas in *Petunia* and *Antirrhinum* an miRNA169/NF-YA module has a primary role in restricting the expression of the C-class genes *pMADS3* and *PLE*, respectively, to the inner floral whorls (Cartolano et al., 2007). In contrast to *Arabidopsis* miR172,

miR169 (which is encoded by the *BLIND* locus in *Petunia* and *FISTULATA* in *Antirrhinum*) has a repressive role in C-gene regulation, repressing the activity of NF-YA genes that in turn activate C-class gene expression. A broad expression of miR169 is thought to translate into a threshold activation of C-class gene expression that induces positive autoregulatory feedback. Conserved DNA-binding sites for NF-YA factors are also found in the *Arabidopsis AG* regulatory intron, although the role of NF-YA genes in regulating *AG* expression is still not well understood (Hong et al., 2003).

Regulatory and protein-protein interactions of homeotic MADS-domain factors have also undergone changes during evolution. For example, the class-B floral homeotic genes encode closely related DEF-like and GLO-like MADS-domain transcription factors, which originated by a gene duplication event prior to the origin of angiosperms (reviewed by Becker and Theissen, 2003). DEF- and GLO-like proteins bind to DNA only as heterodimers in a number of flowering plant species (especially core eudicots), but not as homodimers. Heterodimerization is therefore also required for a positive autoregulatory loop that is important for class-B homeotic gene function. The finding that these proteins have the ability to homodimerize in some flowering plant species and in gymnosperms led to the hypothesis that obligate heterodimerization of DEF- and GLO-like proteins arose from homodimerization (several times independently) during flowering plant evolution (Winter et al., 2002), probably owing to a selective advantage (Lenser et al., 2009). Autoregulatory circuits of B-class proteins also partially diverged following more recent gene duplication events and differential gene loss (Lee and Irish, 2011), for example in Solanaceae (Rijpkema et al., 2006; Geuten and Irish, 2010) and the basal eudicot opium poppy (*Papaver somniferum*) (Drea et al., 2007).

Changes in homeotic gene expression in the different floral whorls have suggested a role for homeosis in the evolution of flower morphologies (reviewed by Hintz et al., 2006). Heterotopic expression of B-class genes in first whorl floral organs has been implicated in the formation of petaloid tepals instead of sepals in tulips (Kanno et al., 2003), as proposed in the 'shifting boundaries' model (Van Tunen and Angenent, 1993). B-class gene duplications followed by functional divergence have also been implicated in the formation of different tepal types in orchids (e.g. Chang et al., 2010; Mondragón-Palomino and Theissen, 2011). However, the evolution of petal-like sepals may not always involve shifts in B-class gene expression (Landis et al., 2012). In basal angiosperms, B-class genes in particular show broader expression in floral whorls compared with more derived flowering plant lineages (Kim et al., 2005), which has been suggested to be linked with the gradual morphological intergradations often observed between adjacent floral organs in basal angiosperms [see the 'fading boundaries' model (Buzgo et al., 2004)]. It should be noted that it will be important in the future to complement comparative gene expression studies in evo-devo research with analysis of mutants of the respective genes in the species studied because we know, for example from *Arabidopsis*, that mRNA expression does not always reflect protein expression/function in certain organs or tissues; for instance, the B-class factor *AP3* is post-transcriptionally regulated (Jack et al., 1994).

Because of their role in the specification of male and female reproductive organs, B- and C-class MADS-box genes have also been implicated in the evolution of unisexual flowers. Although the mechanisms underlying sex determination in dioecious plants are highly variable, in some species, such as *Thalictrum dioicum* and *Spinacia oleracea*, sex determination evolved by changes in the regulation of B- and C-class gene expression (Di Stilio et al., 2005; Sather et al., 2010) (for a review, see Diggle et al., 2011). Also, the presence of B-class gene loci on X chromosomes in *Silene* species suggests a role in the evolution of unisexual flowers (Cegan et al., 2010).

Inflorescence architecture and transfer of functions

Changes in plant morphologies have been linked to the heterotopic expression of normally vegetatively expressed MIKC^{C}-type genes in flowers, or of floral homeotic MIKC^{C}-type genes outside the flower. For example, the study of petaloid bracts in the dove tree (*Davidia involucrata*) shows that petal identity can be partially transferred to organs outside the flower, such as bracts surrounding a contracted inflorescence with reduced flowers (Vekemans et al., 2012). In *Gerbera*, the *SEP1* ortholog *GERBERA REGULATOR OF CAPITULUM DEVELOPMENT 2* (*GRCD2*) functions in inflorescence determinacy (Uimari et al., 2004) and controls inflorescence architecture (Teeri et al., 2006). SEP subfamily members also control the development of grass-specific spikelet meristems and thereby inflorescence development in grasses (Malcomber and Kellogg, 2004; Cui et al., 2010; Gao et al., 2010; Kobayashi et al., 2010). Another example of an MIKC^{C}-type factor with a role in controlling inflorescence architecture is the *VEG1* gene, which is an *AGL79*-like gene (SQUA subfamily) that controls secondary IM identity to generate a compound inflorescence in pea (Berbel et al., 2012).

Whereas some floral MADS-box genes have adapted novel roles outside the flower, others have frequently been recruited in evolution to functions in floral organ development. *INCOMPOSITA* (*INCO*), a member of the STMADS11 subfamily, whose members in *Arabidopsis* mostly control floral transition, represses the development of prophylls (extra flower organs) and therefore regulates floral architecture in *Antirrhinum* (Masiero et al., 2004). *MPF2*, another member of the STMADS11 subfamily in *Physalis floridana* (Solanaceae), has been shown to control the inflated-calyx syndrome, which is a morphological novelty in which sepals resume growth after pollination in order to protect the mature fruit (He and Saedler, 2005; He and Saedler, 2007). Furthermore, gene duplication of *MPF2*-like genes followed by functional diversification at the regulatory and protein levels can be linked to the complex evolution of sepal morphologies in Solanaceae (Khan et al., 2009).

Fruit development

Beyond their roles in floral organ specification, MIKC^{C}-type genes have also been recruited to control the development of various fruit morphologies and seed dispersal mechanisms in flowering plants, and therefore have also likely played a role during crop plant domestication. For example, *SHP1,2* (from the AG subfamily) in *Arabidopsis* specify the replum in the silique. By contrast, their tomato ortholog *TAGL1* controls fleshy fruit expansion and the ripening process (Itkin et al., 2009; Vrebalov et al., 2009; Giménez et al., 2010).

Remarkably, members of the same subfamilies have been recruited to function in very different fruit types, for example in *Arabidopsis* (silique), *Solanum* and *Vaccinium* ('berry'), *Fragaria* (strawberry, which is botanically not a berry and is derived from the receptacle of the flower) and *Malus* (apple, a 'pume') (e.g. Cevik et al., 2010; Jaakola et al., 2010; Seymour et al., 2011). The strawberry *SEP1,2* ortholog *FaMADS9* (Vrebalov et al., 2002) has an important function in receptacle (and thereby fruit) development, and it also controls ripening programs during later stages of development (Seymour et al., 2011). Besides its role in

flower development, the tomato *SEP1,2* ortholog *TM29* also functions in fruit development, as its downregulation results in the generation of parthenocarpic fruits (Ampomah-Dwamena et al., 2002). However, *TM29* is not reported to affect fruit ripening. By contrast, the tomato *SEP4* ortholog *RIPENING INHIBITOR* (*RIN*) is a key regulator of fruit ripening and controls climacteric respiration and ethylene biosynthesis (e.g. Vrebalov et al., 2002; Fujisawa et al., 2011; Martel et al., 2011).

The tomato *AP1* ortholog *MACROCALYX* (*MC*) (SQUA subfamily), a regulator of sepal size and inflorescence determinacy (Vrebalov et al., 2002), controls development of the pedicel abscission zone and thereby seed dispersal. The MC protein interacts with JOINTLESS (J), a member of the STMADS11 subfamily and a regulator of fruit abscission, to form a functionally active transcription factor complex (Nakano et al., 2012). The multiple roles of SQUA subfamily members in floral transition, axillary meristem growth, perianth identity and fruit development are already evident in the basal eudicot species California poppy and opium poppy (Pabón-Mora et al., 2012).

Transition to flowering

The evolution of MADS-box gene subfamilies that control the vegetative-to-floral transition appears to be highly dynamic and linked to the enormous complexity of life history strategies in flowering plants ranging from ephemeral annuals to long-lived trees. An example is the STMADS11 subfamily, whose members evolved novel functions in reproductive transition alongside acquiring roles in flower and fruit development. An example is the series of tandem duplications in peach (*Prunus persica*) that led to six DORMANCY-ASSOCIATED MADS-BOX (DAM) genes that are associated with floral bud dormancy, and thereby seasonal flowering, in this species (Jiménez et al., 2009; Li et al., 2009). Also, *BpMADS4*, a member of the SQUA subfamily and ortholog of the uncharacterized *Arabidopsis AGL79*, has a role in the initiation of inflorescence development and the transition from vegetative to reproductive development in the silver birch tree (*Betula pendula*) (Elo et al., 2007).

Another subfamily of MIKC^C-type genes with a highly dynamic evolution is the FLC subfamily. *FLC*-like genes have been mainly identified as vernalization-controlled floral repressors in *Arabidopsis*, *Brassica* and sugar beet (*Beta vulgaris*) (Michaels and Amasino, 1999; Tadege et al., 2001; Schranz et al., 2002; Reeves et al., 2007). Natural variation in *FLC* gene activity is associated with flowering time variation and differential vernalization response among ecotypes (see Glossary, Box 1) of *Arabidopsis* and related species (Schranz et al., 2002; Nah and Chen, 2010; Salomé et al., 2011). Evolutionarily diverged regulation of *FLC* orthologs has been linked with the perennial life habit, such as *PERPETUAL FLOWERING 1* (*PEP1*) in *Arabis alpina* (Wang et al., 2009), and has also been observed in species with floral bud dormancy, for example *PtFLC* in trifoliate orange (*Poncirus trifoliate*) (Zhang et al., 2009) and *TrMADS3* in Rosaceae (*Taihangia rupestris*) (Du et al., 2008).

The origin and early evolution of major plant MADS-box gene lineages

Type I and type II MADS-box genes have been identified in all major land plant lineages, from bryophytes to flowering plants (Gramzow and Theissen, 2010). Importantly, the number and functional diversity of MADS-box genes increased considerably during land plant evolution and is linked to the elaboration of plant body plans and life history strategies (Becker and Theissen, 2003; Kaufmann et al., 2005a; Kramer and Hall, 2005).

Land plants evolved from multicellular charophycean algae ~500 million years ago. The colonization of land was associated with the elaboration of the sporophytic (diploid) phase in the plant life cycle. MIKC-type MADS-box genes are found in land plants and charophycean algae, but not in other, more primitive, algae (Tanabe et al., 2005). Expression studies in charophycean algae suggest an ancestral role for MIKC-type MADS-box genes in haploid reproductive cell differentiation in the gametophytic phase (Tanabe et al., 2005). Prior to the origin of the most primitive extant lineages of land plants, the bryophytes, a gene duplication event led to the origin of MIKC^C-type and MIKC*-type genes (Henschel et al., 2002). In the moss *Physcomitrella patens*, MIKC^C-type genes function in the gametophyte as well as in specific tissues of the sporophyte, whereas MIKC*-type genes are specifically expressed in the gametophyte (Singer et al., 2007; Kwantes et al., 2012). This gametophytic expression appears to be highly conserved across land plant evolution and might reflect an ancestral, conserved role of MIKC*-type genes in gametophyte development (Verelst et al., 2007a; Zobell et al., 2010; Kwantes et al., 2012).

MIKC^C-type MADS-box genes: the key to the origin of seeds and flowers?

The enigmatic origin and success of seed plants and, more recently, of flowering plants (angiosperms), is one of the biggest evolutionary mysteries. Seed plants now constitute more than 90% of all land plant species, and by far the greatest diversity is seen in angiosperms, which comprise 250,000-400,000 species. Key to the success of seed plants was a major elaboration of reproductive organ morphologies, most markedly the origin of the seed and, in angiosperms, the origin of the bisexual flower. In addition, the elaboration of floral transition and plant architecture can be considered as major evolutionary innovations.

Extant seed plants, which comprise flowering plants and gymnosperms (see Glossary, Box 1), evolved from a most recent common ancestor ~300 million years ago. Many subfamilies of MIKC^C-type genes appear to have originated in ancestral seed plants (Becker and Theissen, 2003), and gene expression analyses suggest that basic functions of some subfamilies might be conserved between angiosperms and gymnosperms. Examples are the homeotic AG (C/D class) and DEF/GLO (B class) subfamilies, as well as the B_{sister} subfamily (e.g. Tandre et al., 1995; Becker et al., 2002) (for a review, see Becker and Theissen, 2003). Their important functions and conserved expression suggest roles in the origin and evolution of seed plant reproductive structures.

The seed represents a special type of heterospory in which the female gametophyte is protected by integuments that, after fertilization, allow the developing embryo to be retained and nourished on the mother plant. Interestingly, whereas B genes show conserved expression in male reproductive organs (and angiosperm petals), B_{sister} genes exhibit conserved expression in the evolutionarily most conserved parts of the ovule (Becker et al., 2002). The contrasting expression of B and B_{sister} genes has led to the hypothesis that the origin of these subfamilies played an important role in the evolution of male and female reproductive structures in seed plants (Becker et al., 2002). B_{sister} genes control endothelium formation as well as later aspects of seed development in *Arabidopsis* (Nesi et al., 2002; Mizzotti et al., 2012), *Petunia* (de Folter et al., 2006) and rice (Yin and Xue, 2012), supporting a role for this subfamily in the evolution of the seed.

Another major innovation in seed plant evolution was the origin of the angiosperm flower, as characterized by synorganization of female and male reproductive organs (Bateman et al., 2006). Given

their important role in floral meristem formation, the SQUA and SEP subfamilies, which are only found in flowering plants (Becker and Theissen, 2003), could be key to the origin of flowers. In addition, concerted gene duplications linked to rounds of whole-genome duplications in different MIKC^C-type subfamilies prior to the origin of extant flowering plants, and at the base of core eudicots, might have contributed to the evolution of the floral bauplan (see Zahn et al., 2005; Shan et al., 2009). Genome sequences from extant gymnosperms are likely to reveal the full complement of MIKC^C-type genes outside flowering plants in the near future, and thereby shed light on the origin and early diversification of these genes in seed plant evolution.

Molecular mechanisms of action of MADS-domain proteins

Despite the wealth of information about the biological functions of plant MADS-domain proteins from genetic studies, we still do not fully understand their molecular mode of action. In the early 1990s it was shown that, in analogy with mammalian MADS-domain proteins, plant MADS proteins bind their consensus DNA binding site (the CArG box; see Glossary, Box 1) as dimers (Schwarz-Sommer et al., 1992). Around this time, the yeast two-hybrid system was introduced as a method with which to study protein-protein interactions and, a few years later, evidence was provided for multiple interactions between *Antirrhinum* floral homeotic MIKC^C-type MADS-domain proteins (Davies et al., 1996). These initial studies were followed by large-scale MADS-domain protein interaction screenings in a variety of species, which provided information about MADS-domain protein dimerization potential (Immink et al., 2003; de Folter et al., 2005; Leseberg et al., 2008; Liu et al., 2010; Ruokolainen et al., 2010).

The next breakthrough in our understanding of MADS-domain protein function came from the finding that MIKC^C-type proteins can assemble into higher-order complexes (Egea-Cortines et al., 1999; Honma and Goto, 2001), which led to the postulation of the 'floral quartet' model (see Box 2). According to this model, a tetrameric protein complex consisting of two dimers binds to a target DNA sequence containing two CArG boxes and thereby generates a DNA loop between the two binding sites (Theissen, 2001; Theissen and Saedler, 2001). Although the presence of two CArG boxes may provide stability through cooperative DNA binding, heterotetrameric homeotic protein complexes can also bind to DNA sequences containing only one CArG box, which may or may not contain additional 'weak affinity' binding sites (Smaczniak et al., 2012; Melzer and Theissen, 2009). Members of the SEP subfamily play an important role as mediators of higher-order complex formation (Immink et al., 2009), but at least some proteins from other subfamilies can also mediate higher-order complex formation (Egea-Cortines et al., 1999; Ciannamea et al., 2006). The K domain in particular plays a role in the formation of higher-order complexes of MIKC^C-type proteins (Egea-Cortines et al., 1999; Honma and Goto, 2001; Yang and Jack, 2004; Melzer and Theissen, 2009), and in some cases it also contributes to heterodimerization (Yang et al., 2003). The K domain probably forms three amphipathic α-helices that may assemble into coiled-coil structures (reviewed by Kaufmann et al., 2005a). Large-scale yeast-based screenings showed that various *Arabidopsis*, tomato and *Gerbera* MIKC^C-type MADS-domain proteins have the capacity to multimerize (Leseberg et al., 2008; Immink et al., 2009; Ruokolainen et al., 2010), and ternary complexes consisting of type I proteins could also be identified (Immink et al., 2009). Floral homeotic B- and C-class MADS-domain proteins from the gymnosperm *Gnetum gnemon* also have the ability to form higher-order protein complexes (Wang, Y.-Q. et al., 2010), suggesting that the requirement for angiosperm-specific SEP proteins in mediating higher-order complex formation among floral homeotic proteins is a derived state that evolved due to differential loss of the ability of B+C class proteins to multimerize. Multimerization expands the number of potential and unique MADS protein transcription factor units and might be a key molecular mechanism for providing DNA-binding specificity. The latter hypothesis is supported by in vitro binding assays that show stabilized binding of DNA sequences containing two CArG-box elements by quaternary MADS-domain protein complexes (Egea-Cortines et al., 1999; Melzer and Theissen, 2009; Smaczniak et al., 2012).

Recent technological progress, such as sensitive mass spectrometry analysis, has allowed the isolation of MADS-domain protein complexes from plant tissues. A recent pioneering study (Smaczniak et al., 2012) unveiled the composition of homeotic protein complexes on which the floral quartet model is based. In addition to the expected identification of MADS-domain protein interaction partners, co-repressors, chromatin remodeling factors and transcription factors from other families were identified as interaction partners. The identification of transcription factors from other families in the isolated complexes points to a role for these transcription factor interactions in target gene selection. Previously, evidence was provided for the assembly of MADS protein complexes that include the SEUSS and LEUNIG transcriptional co-repressors (Sridhar et al., 2006). Physical interactions had also been reported between SVP, SOC1 and AGL24 with chromatin-associated factors that mediate gene repression. These factors include the polycomb PRC1 analog TERMINAL FLOWER 2 [TFL2; LIKE HETEROCHROMATIN PROTEIN 1 (LHP1)] and the SIN3 histone deacetylase complex component SAP18 (Liu et al., 2009), and the interactions with these factors are proposed to play a role in compacting the chromatin at bound loci and thereby in transcriptional repression. These interactions presumably prevent premature activation of floral homeotic genes in inflorescence and early floral meristems (Liu et al., 2009). This repression might be overcome by interactions of AP1 and other floral homeotic proteins and chromatin remodelers. This hypothesis (Fig. 3) is exemplified by the finding that SEP3 physically interacts with the SWI2/SNF2 ATPases BRAHMA (BRM) and SPLAYED (SYD), providing complexes that overcome polycomb-mediated repression of *AP3* and *AG* during early floral meristem development (Smaczniak et al., 2012; Wu et al., 2012). The direct activation of the C2H2-type zinc-finger gene *KNUCKLES* (*KNU*) by AG has also been shown to be associated with release from repressive H3K27me3 chromatin states, and therefore provides another example of interplay between MADS-box transcription factors and epigenetic regulators (Sun et al., 2009). In fact, a number of MIKC^C-type MADS-box genes are targets of polycomb-mediated repression, as indicated by the deposition of repressive H3K27me3 marks and ectopic activation in polycomb mutants (Goodrich et al., 1997; Turck et al., 2007; Zhang et al., 2007). This suggests that overcoming or enforcing repressive chromatin states might be an important mode of action in regulatory networks that are formed by MIKC^C-type proteins during developmental transitions.

A combination of genome-wide expression analysis and ChIP followed by deep sequencing (ChIP-Seq) or hybridization to microarrays (ChIP-CHIP) has revealed genes, and hence biological processes, that are directly controlled by MADS-domain transcription factors. These experiments showed that the MIKC^C-type proteins bind hundreds to thousands of loci. Analysis of the

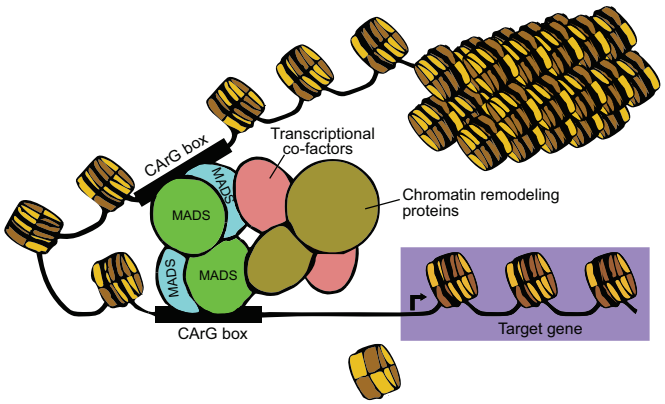


Fig. 3. Model for the action of MADS-domain protein complexes. Shown is a model of MADS-domain protein complex formation and a hypothesized mechanism of regulatory action. In this model, MADS-domain proteins (green and blue) form quaternary complexes according to the 'floral quartet' model and interact with two DNA binding sites (CArG boxes; black) in close proximity, resulting in DNA looping. Subsequently, MADS-domain proteins recruit transcriptional co-factors (pink), which mediate transcriptional regulation and may influence target gene specificity, as well as chromatin remodeling proteins (brown), which relax the chromatin structure at the target gene transcription start site allowing for the initiation of transcription. Depending on the selection of transcriptional co-factors and chromatin remodeling factors, the complex may also play a role as a transcriptional repressor.

target gene sets for the floral repressor FLC (Deng et al., 2011) and the homeotic proteins SEP3 and AP1 (Kaufmann et al., 2009; Kaufmann et al., 2010b) revealed a large number of genes involved in transcriptional and cellular signaling, for example hormonal regulation. Among the FLC targets, various genes involved in abscisic acid (ABA) signaling were identified, which could be related to the role of FLC in temperature-dependent germination (Chiang et al., 2009). Among the potential direct SEP3 target genes, auxin-response genes could be related to the role of SEP3 in floral organ outgrowth and morphogenesis (Kaufmann et al., 2009). The current data suggest that floral homeotic MADS-domain proteins directly regulate the expression of a variety of genes that are important for the growth, shape and structure of different organs, indicating that floral MADS-domain proteins not only specify organ identity at the onset of organ primordia initiation, but are also involved in subsequent differentiation processes (reviewed by Ito, 2011; Dornelas et al., 2011).

The data also reveal complex regulatory interactions among MADS family members and the existence of a large number of positive and negative (auto)regulatory loops. Negative-feedback loops are required for developmental phase switches and have been hypothesized to be important for MADS-box gene function during the transition from vegetative to reproductive growth (Yu et al., 2004; de Folter et al., 2005), while feedforward loops are important for robust and balanced expression of target genes. The non-MADS transcription factor LFY is, for example, involved in activation of the MADS-box gene *SEP3*, and, in turn, both LFY and SEP3 are essential for the activation of the MADS-box genes *PI*, *AP3* and *AG* (reviewed by Wagner, 2009). Positive (auto)regulatory loops involving two partners, for example, can facilitate stable upregulation and maintenance of gene expression, as is the case for the B-type MADS-box genes (Schwarz-Sommer et al., 1992; Lenser et al., 2009) and for *AGL24* and *SOC1* (Liu et al., 2008).

The spatiotemporal activity of MADS-domain proteins is not only regulated at the transcriptional level, and a few examples of post-translational modifications affecting MADS-domain protein function have been described. Wang and colleagues (Wang, Y. et al., 2010) demonstrated the phosphorylation-dependent prolyl cis/trans isomerization of AGL24 and SOC1, and showed that this modification affects the stability of AGL24 in the nucleus. Furthermore, the transport of (at least some) MADS proteins from the cytoplasm to the nucleus appears to be regulated (see also He and Saedler, 2007) and for some type II and type I MADS-domain proteins dimerization was shown to be essential for translocation to the nucleus (e.g. McGonigle et al., 1996; Bemer et al., 2008). Additionally, intercellular transport could be demonstrated for a few selected MADS-domain proteins from different species (Perbal et al., 1996; Sieburth et al., 1998; Urbanus et al., 2010), providing an additional mechanism for spatial control of their activity.

Conclusions

In the past 20 years, a tremendous knowledge of plant MADS-domain transcription factors has been generated. We have also obtained a better understanding of previously overlooked lineages of MADS-box genes, such as the type I and MIKC*-type genes. MADS-box genes have been shown to play roles in a variety of developmental processes and a surprising number of them have more than one function in seemingly unrelated processes. Future research should address the issue of how such apparently different functions of the same MADS-box gene, for example in the shoot and in the root, relate to each other. This could also help us to understand the evolutionary mechanisms by which MADS-box genes are recruited to new functions in other species.

Functional redundancy might have hampered the assignment of functions to some genes, but we also need a better understanding of what 'redundancy' really means, for example by characterizing molecular phenotypes and analyzing natural variation in gene regulatory networks in more depth. This holds for the exploration of type I as well as for type II genes. The recent finding that AG clade MIKC^{C}-type genes have a role in lateral root initiation in addition to their well-known function in reproductive development also emphasizes that we might need to employ more systematic and comprehensive approaches in the characterization of mutant phenotypes. MIKC^{C}-type genes, in particular, are involved in evolutionarily highly dynamic developmental processes, such as control of flowering time. Analyzing the natural variation in regulatory networks formed by MIKC^{C}-type genes is therefore likely to provide new insights into the dynamics and significance of specific regulatory interactions, and this approach might unveil gene functions that are not obvious from the analysis of only one specific ecotype. A classic example in this respect is the finding that *FLC* is dependent on the *FRIGIDA* locus, of which different alleles are present in the ecotypes with strongly varying flowering times (Johanson et al., 2000).

Although recent studies have revealed functions of some type I and MIKC*-type genes, most remain to be characterized, especially in species other than *Arabidopsis*. The current data suggest that these genes are important regulators of gametophytic and embryo development in plants. Therefore, understanding the evolution of these MADS-box gene functions might also help us to gain more insight into essential aspects of plant reproductive processes.

Recent results have also provided insights into the molecular mechanisms by which plant MADS-domain transcription factors recognize and control the expression of their target genes. MIKC-type proteins, and possibly also type I MADS-domain proteins, form complex protein interaction networks. But how do MADS-domain proteins obtain their functional specificity? The first genome-wide DNA-binding studies of MADS-domain proteins (Kaufmann et al., 2009; Zheng et al., 2009; Kaufmann et al., 2010b; Deng et al., 2011) revealed a large number of binding sites and potential direct target genes. Even proteins that act at different developmental stages show at least some overlap in DNA binding sites. This could indicate that these factors control overlapping sets of target genes and achieve their regulatory specificity by whether they activate or repress expression. Target gene activity would then be controlled by different MADS-domain factors that compete for common binding sites. It is also conceivable that common target genes might be responsible for general cellular processes, whereas the distinct target genes might be specific for a particular biological or developmental process. Understanding the specificity of target gene regulation by MADS-domain proteins will be a challenge for future research. The consequences of DNA binding for spatial promoter organization, including the formation of DNA loops, also need to be considered here.

MADS-domain proteins form complex intrafamily interaction and regulatory networks. MADS-box gene expression appears to be regulated at many levels: transcriptionally, post-transcriptionally and post-translationally (e.g. protein localization). Advanced proteomics and in vivo imaging approaches can be used to systematically study the regulation of MADS-box transcription factor activities in planta. In addition, the modeling of MADS-box regulatory networks can provide novel insights (Espinosa-Soto et al., 2004; van Mourik et al., 2010), but will require more quantitative in vivo data in the future.

Finally, a number of studies have shown that many MADS-box genes have roles in more than one organ or developmental stage. How can the same factor have different functions in different developmental contexts? And how can apparently conserved proteins control diverse organ morphologies, such as flower development? In order to address these questions, we need to understand the developmental and evolutionary dynamics of regulatory networks formed by MADS-domain transcription factors. This will provide insight into the recruitment of MADS-domain proteins during the origin of morphological innovations and, thereby, help us to understand the morphological diversity of flowering plants.

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Competing interests statement

The authors declare no competing financial interests.

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