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REVIEW

Leaf development and morphogenesis

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ABSTRACT

The development of plant leaves follows a common basic program that is flexible and is adjusted according to species, developmental stage and environmental circumstances. Leaves initiate from the flanks of the shoot apical meristem and develop into flat structures of variable sizes and forms. This process is regulated by plant hormones, transcriptional regulators and mechanical properties of the tissue. Here, we review recent advances in the understanding of how these factors modulate leaf development to yield a substantial diversity of leaf forms. We discuss these issues in the context of leaf initiation, the balance between morphogenesis and differentiation, and patterning of the leaf margin.

KEY WORDS: Flexibility, Leaf, Morphogenesis, Plant hormones, Transcription

Introduction

Leaf development exemplifies the dynamic nature and flexibility of plant development in response to internal and external cues. Just as two plants – even if genetically identical – do not look the same, two leaves on the same plant are different, and the final shape of a leaf is not predetermined when it starts to form. Leaves evolved from lateral branches following the acquisition of determinate growth and a flat structure (Floyd and Bowman, 2010; Kaplan, 2001; Sarojam et al., 2010; Zimmerman, 1952). Leaves can be divided into two basic forms: simple and compound (Fig. 1; see Glossary, Box 1). A simple leaf has an entire, continuous lamina, whereas a compound leaf is composed of multiple subunits termed leaflets, each resembling a simple leaf. On a developmental timescale, simple leaves differentiate and flatten relatively fast, whereas compound leaves are in some ways intermediate forms between lateral branches and simple leaves.

Leaves develop from the shoot apical meristem (SAM), which contains different functional regions, including a central zone (CZ) that houses pluripotent cells, and a peripheral zone (PZ) from which lateral organs are formed (Fig. 2A) (Barton, 2010). General leaf development is exemplified in Fig. 2 by the tomato shoot. Leaves initiate at the flanks of the SAM in a process involving the determination of several axes of symmetry: proximo-distal, adaxial-abaxial and medio-lateral (Fig. 2C). In compound leaves, leaflets initiate at the leaf margin in a similar fashion. Following initiation (see Glossary, Box 1), the lamina expands and the basic leaf form is determined during the process of primary morphogenesis (see Glossary, Box 1). Finally, the leaf grows and its cells undergo cell-fate determination and differentiation during secondary morphogenesis (see Glossary, Box 1; Fig. 2B). During its development, the different layers of the leaf, its vasculature and specialized epidermal cells, such as trichomes and stomata guard cells, undergo differentiation. Leaf margins are also patterned concomitantly with morphogenesis and differentiation (see Glossary, Box 1).

The extensive variability of plant leaf forms in nature results from a corresponding variability in leaf ontogeny. This variability is generated by flexible tuning of partially common players in leaf developmental pathways, and combinatorial as well as spatio-temporal variability allows for an almost infinite number of outcomes. Recent advances in the field have revealed new interactions between hormones and transcription factors during leaf development, and have also started to uncover the role of mechanical forces in leaf initiation. Here, we discuss these recent advances in the context of individual developmental stages and the simple-to-complex leaf continuum. We also touch briefly on environmental factors that can impact leaf development (see Box 2), and on recently developed quantitative approaches (see Box 3), which can serve to further characterize and understand leaf development. We chose not to discuss adaxial-abaxial, vascular, trichome or stomatal patterning, as several recent reviews have discussed these topics (Grebe, 2012; Kidner and Timmermans, 2010; Lau and Bergmann, 2012; Nakata and Okada, 2013; Sack and Scoffoni, 2013).

Leaf initiation

During initiation, a distinct domain within the SAM, which is separated from the rest of the SAM by a boundary domain, is specified (Aida and Tasaka, 2006; Žádníková and Simon, 2014). According to the Hofmeister principle, leaf initiation occurs at the point most distant from existing primordia, leading to the hypothesis that existing primordia generate an inhibition field (Braybrook and Kuhlemeier, 2010; Snow and Snow, 1932). As we discuss below, the specification of organ initiation involves a complex network of genetic, hormonal and mechanical factors (Fig. 3).

The role of auxin during leaf initiation

The plant hormone auxin has emerged as a central regulator of organ initiation. Points of auxin response maxima are observed prior to organ initiation. These are generated by auxin biosynthesis in the SAM and by directional auxin transport facilitated by the PIN-FORMED1 (PIN1) auxin transporter (Benková et al., 2003; Cheng et al., 2007; Heisler et al., 2005; Pinon et al., 2013; Reinhardt et al., 2003). Accordingly, inhibition of polar auxin transport or a mutation in *PIN1* inhibits organ initiation, whereas auxin application in the PZ of meristems is sufficient to induce organ initiation. Mutations in auxin biosynthesis genes from the YUCCA family also inhibit organ initiation. Auxin gradients and/or flow are thought to direct PIN1 polarization in a positive-feedback loop, and auxin depletion by developing primordia is thought to comprise at least part of the hypothesized inhibitory field (Braybrook and Kuhlemeier, 2010).

The response to auxin is mediated by transcription factors known as auxin response factors (ARFs). Mutations in the *Arabidopsis* ARF gene *MONOPTEROS* (*MP*) lead to a wide variety of aberrant phenotypes, including reduced flower initiation. MP might therefore mediate the activity of auxin in organ initiation (Hardtke

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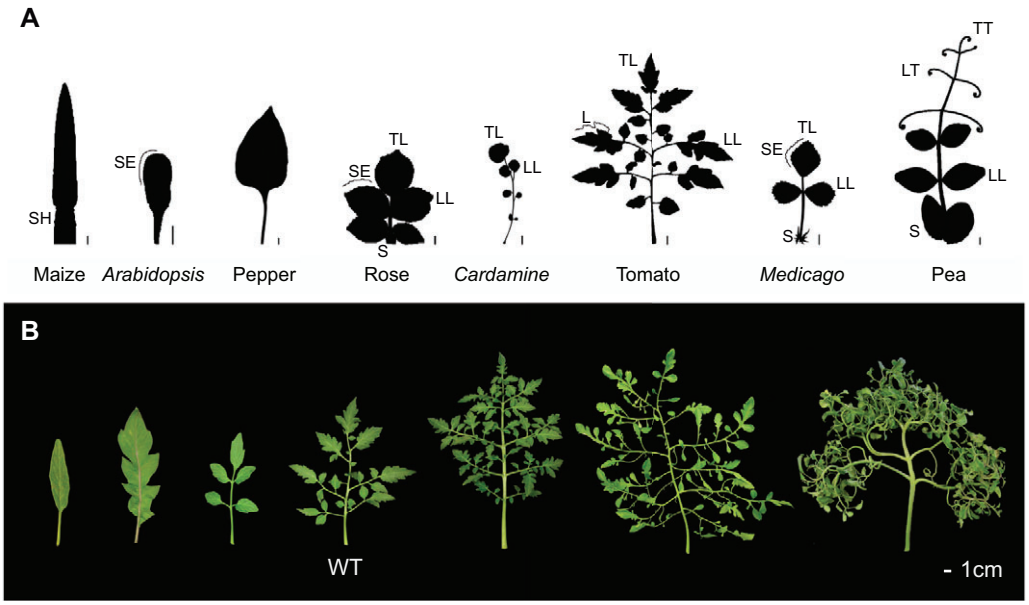

Fig. 1. Variety in plant leaves. (A) Simple and compound leaves found in nature. Left to right: the simple leaves of maize, *Arabidopsis* and pepper, and the compound leaves of rose, *Cardamine*, tomato, *Medicago* and pea. SH, sheath; S, stipule; SE, serration; L, lobe; LL, lateral leaflet; TL, terminal leaflet; LT, lateral tendril; TT, terminal tendril. Scale bars: 1 cm. (B) Variability of tomato leaf form. Presented are various mutants with an altered leaf form, causing simplification (to the left of the wild-type leaf, indicated by WT) and elaboration (to the right of the WT leaf), demonstrating the scope of the 'simple-to-complex' leaf continuum in tomato. Scale bar: 1 cm.

and Berleth, 1998; Yamaguchi et al., 2013). However, it should be noted that much of the research to date on organ initiation in *Arabidopsis* has involved inflorescence meristems, which form flower meristems rather than leaf primordia. Flower meristems in *Arabidopsis* are derivatives of axillary meristems that form in the axils of cryptic bracts, which are miniature underdeveloped leaves (Long and Barton, 1998). Leaf and flower initiation are thus different processes and their regulation might, at least in part, involve different factors. This is exemplified by *Arabidopsis pin1* mutants: in *pin1* inflorescences, flower initiation is completely abolished, whereas leaf initiation is only partially compromised in *pin1* vegetative meristems, as well as when multiple *PIN* genes are mutated (Guenot et al., 2012; Okada et al., 1991).

Leaf initiation is closely correlated with the initiation of the midvein, a vascular strand in the middle of the leaf. The midvein initiates from the auxin maxima at the leaf initiation site and gradually connects to the existing vasculature (Scarpella et al., 2006). A strand of high auxin concentration marks the midvein initiation site and is correlated with a switch in PIN1 polarization, from polarization towards the convergence point in the outermost cell layer (L1) to basal localization towards the future midvein. This was hypothesized to be accompanied by a switch from auxin transport towards the highest auxin concentration to transport in the direction of auxin flow (Bayer et al., 2009). Distinct regulators of PIN1 localization were shown to be involved in these different phases – whereas the localization towards the convergence point is regulated in part by the serine/threonine kinase PINOID (Friml et al., 2004), which phosphorylates PIN1 (Huang et al., 2010), the switch to basal polarization is regulated by the MAB4 gene family (Cheng et al., 2008; Furutani et al., 2014). In angiosperm species other than the Brassicaceae, leaf initiation and vascular formation were suggested to be regulated by distinct members of the PIN family (O'Connor et al., 2014).

Box 1. Glossary

Compound leaf. A leaf that is composed of separate subunits that are separated by a bladeless region.
Differentiation. Acquisition of a specialized form and function.
Initiation. The formation of a leaf primordium at the flanks of the shoot apical meristem.
Leaf maturation. The gradual process of the acquisition of leaf shape and size, from leaf initiation to a mature functional leaf to senescence.
Primary morphogenesis. The establishment of the basic form of the leaf during the early stages of leaf development. Primary morphogenesis includes the initiation of the lamina, the specification of the distinct domains of the lamina – the midrib, the petiole and the leaf base – and the formation of marginal structures, such as leaflets, lobes and serrations.
Secondary morphogenesis. The formation of the mature leaf shape. During this stage, most of the leaf expansion occurs, specific tissues complete their differentiation and the leaf shape might change through differential growth. The final leaf shape is determined by events happening during the entire process of leaf development.
Simple leaf. A leaf with a single undivided blade.

The balance between auxin and cytokinin

In addition to auxin, leaf initiation involves the plant hormone cytokinin, which plays an important role in SAM maintenance (Gordon et al., 2009; Kurakawa et al., 2007; Werner et al., 2003). As we discuss below, the specification of leaf initiation involves a delicate balance and complex feedback relationship between auxin and cytokinin.

Recently, light has been shown to be essential for leaf initiation in tomato, and this effect is mediated by both auxin and cytokinin (Yoshida et al., 2011). In maize, the response regulator (RR) protein ABPHYL1 (ABPH1) is expressed at the site of future leaf initiation together with PIN1, and both are induced by cytokinin (Lee et al., 2009). ABPH1 regulates SAM size and phyllotaxis, and belongs to a family of two-component RRs that are rapidly induced by cytokinin and are thought to act as negative regulators of the cytokinin response (Giulini et al., 2004; Kieber and Schaller, 2014). ABPH1 positively regulates organ initiation, perhaps by inhibiting the cytokinin response. In *Arabidopsis*, the RRs ARR7 and ARR15 are negatively regulated by MP, and mutants with elevated cytokinin levels suppress the flower initiation defect of *mp* mutants. This led to the hypothesis that auxin and cytokinin act synergistically in organ initiation in the *Arabidopsis* SAM, in contrast to their antagonistic action in the root (Vidaurre et al., 2007; Zhao et al., 2010). Thus, RRs are involved in balancing SAM size and organ initiation in both maize vegetative meristems and *Arabidopsis* inflorescences, but have opposing interactions with

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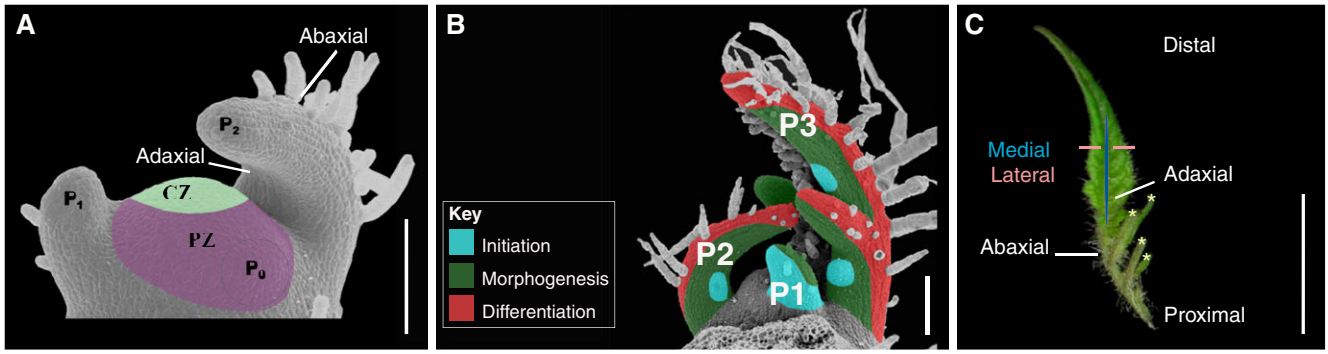

Fig. 2. The stages of leaf development. (A) Scanning electron microscope (SEM) image of the shoot apical meristem (SAM) of a typical tomato shoot, showing the central zone (CZ) that houses pluripotent cells, and the peripheral zone (PZ), from which lateral organs/primordia (P_1, P_2 and P_3) initiate. The adaxial and abaxial sides of the leaf are indicated on the P_2 leaf primordium. Scale bar: 100 µm. (B) Schematic representation of the stages of leaf development, illustrated on an SEM image of a wild-type tomato shoot. The SAM and the three youngest leaf primordia (P_1, P_2 and P_3) are shown. Zones of initiation are indicated in blue, zones of morphogenesis are indicated in green and zones of differentiation are indicated in red. Scale bar: 100 µm. (C) Axes of symmetry presented on a newly expanded (P_7) tomato leaf. Lateral leaflets are indicated by yellow asterisks. Scale bar: 1 cm.

auxin in these two tissues. More recently, AHP6, another negative regulator of cytokinin signaling, was shown to regulate flower initiation downstream of auxin in a non-autonomous manner (Besnard et al., 2014). Together, these studies suggest that a fine coordination of local auxin and cytokinin responses regulates and stabilizes leaf initiation. However, whereas auxin is clearly a positive regulator of organ initiation, the exact effect of the cytokinin response on initiation is more complex, and its role appears to be dependent on species and developmental context. Furthermore, relative rather than absolute levels of cytokinin signaling, as well as the ratio between cytokinin and auxin and the tuning of hormone sensitivities, probably play a role.

Genes that regulate initiation

Specification of the organ initiation domain is also accompanied by differential expression of genes that regulate the balance between meristematic and initiation fates. For example, class I KNOTTED-LIKE HOMEOBOX (KNOXI) transcription factors, which promote SAM function, are expressed in the CZ of the SAM and are downregulated at the site of organ initiation (Hay and Tsiantis, 2010). KNOXI expression is downregulated at the site of leaf initiation by ARP [ASYMMETRIC LEAVES1 (AS1), ROUGH SHEATH2 (RS2), PHANTASTICA] transcription factors, together with the LBD protein AS2 and the chromatin remodeling factor HIRA, promoting specification of the organ initiation domain (Barkoulas et al., 2007). Several recent studies have established a role for chromatin remodeling factors in the repression of KNOXI genes by AS1-AS2 in *Arabidopsis*. For example, AS1 interacts with the histone deacetylase HDA6, and several KNOXI genes show increased acetylation in *hda6* mutants (Luo et al., 2012). In addition, the AS1-AS2 complex has recently been shown to recruit POLYCOMB-REPRESSIVE COMPLEX 2 (PRC2), a complex involved in chromatin structure modification, to the promoters of two KNOXI genes, possibly enabling their stable repression at later stages of leaf development (Lodha et al., 2013). The expression of KNOXI genes is also regulated by BLADE ON PETIOLE (BOP) (Ha et al., 2007; Ichihashi et al., 2014), JAGGED LATERAL ORGANS (JLO) (Rast and Simon, 2012) and auxin (Hay et al., 2006). KNOXI proteins, in turn, feedback to regulate the auxin response (Bolduc et al., 2012; Scanlon et al., 2002; Tsiantis et al., 1999). KNOXI proteins also regulate the balance between cytokinin, which promotes meristematic fate, and gibberellic acid (GA), which promotes differentiation (Hay et al., 2002; Jasinski et al., 2005; Scofield et al., 2013; Yanai et al., 2005). Thus, KNOXI proteins coordinate the activity of several plant hormones during the specification of the distinct domains in the SAM, enabling the balance between continuous SAM function and organ initiation.

Additional early markers of the leaf initiation domain include genes encoding transcription factors from the AINTEGUMENTA (ANT)-like (AIL)/PLT family, and genes from the YABBY (YAB) family of HMG-like proteins. AIL/PLT genes have been shown to promote organ initiation and growth in *Arabidopsis* (Horstman et al., 2014; Krizek, 2009) and to partially mediate the effect of MP on organ initiation (Yamaguchi et al., 2013). Recently, some AIL/PLT genes were suggested to affect phyllotaxis by promoting auxin biosynthesis in the CZ of the SAM (Pinon et al., 2013). Phenotypes resulting from mutations and overexpression of YABBY genes suggest that they are involved in the specification of organ fate and the suppression of meristem fate, in addition to their role in leaf polarity (Kumaran et al., 2002; Sarojam et al., 2010). The role of

Box 2. Effects of the environment on leaf shape

Plants are able to change quickly in response to environmental cues, and leaf shape exemplifies this principle well. Although certain parameters are relatively fixed within the developmental program, extensive variation in leaf shape exists, based on different environmental conditions. This variation can be more apparent in compound leaf species. For example, low light intensity can promote elongation of the leaf petiole while inhibiting expansion of the leaf blade. This is part of the 'shade avoidance syndrome'. The effects of light intensity on leaf shape can involve both cell expansion and cell replication (Kozuka et al., 2005; Tsukaya, 2005). In a recent study conducted in several wild tomato species, leaf size was found to correlate with foliar shade measures, whereas leaf size and serration were also found to correlate in a species-dependent fashion with temperature and precipitation (Chitwood et al., 2012). Limited water or other resources can also cause reductions in leaf size in stressful environments (Royer et al., 2005; Sack et al., 2003), and in *Arabidopsis* these responses are at least in part executed by ethylene response factors and gibberellin catabolism (Dubois et al., 2013). Reduced gibberellin activity can promote drought tolerance in tomato (Nir et al., 2014). Interestingly, more pronounced effects were observed in simple leaves than in compound leaves in this case (Gurevitch and Schuepp, 1990). Salinity can also affect leaf development. Achard et al. (2006) showed that the abscisic acid and ethylene pathways regulate root and shoot development through DELLA, and demonstrated that salt-induced signaling pathways enhance the growth-repressing effects of DELLAs, in part through reducing the levels of bioactive gibberellins.

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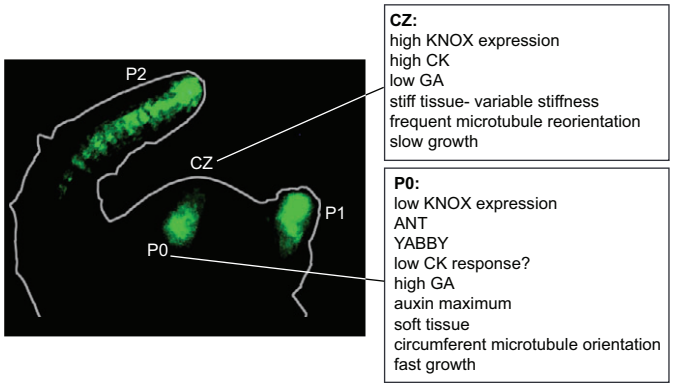

Fig. 3. Leaf initiation. Stereoscope image of a tomato shoot apical meristem (SAM) expressing VENUS (green) driven by the auxin-responsive DR5 promoter. P0 denotes the site of initiation of the next primordium, which is clearly marked by an auxin-response maximum. Factors known to be involved in leaf initiation are listed, highlighting those that are involved in promoting initiation in P0 (bottom) and those that are involved in the central zone (CZ) in promoting the maintenance of meristematic identity, thus repressing initiation (top).

these gene families – as well as that of other early markers of leaf initiation – during the specification of leaf initiation is still not completely understood.

The mechanics of leaf initiation

Accumulating evidence points to the potential role of mechanics in the regulation of leaf positioning and initiation, either as a signal or via differential tissue properties (Robinson et al., 2013). Tissue and cell geometry, mechanical stresses, cellulose and microtubule orientation and growth directions have long been proposed to be involved in morphogenesis, both in plants and animals (Green, 1980; Thompson, 1942). Using atomic force microscopy (AFM), cell walls in the CZ were found to be stiffer and their stiffness more variable than that of cell walls in the PZ (Milani et al., 2011). In agreement, using osmotic manipulations, the CZ and the PZ were shown to differ in their mechanical properties, and these differences correlated with increased growth in the PZ (Kierzkowski et al., 2012). Mechanical forces were also shown to affect microtubule orientation (Hamant et al., 2008). This effect is mediated by the microtubule-severing protein KATANIN that promotes growth variability between neighboring cells (Uyttewaal et al., 2012). Thus, correlated mechanical properties, growth directions and microtubule orientation characterize the CZ, PZ and the boundary region between them.

What is the relationship between auxin and mechanical forces in leaf initiation and growth? Organ initiation involves loosening of the cell wall by cell-wall modifiers, such as expansins and pectin methylesterases (PMEs) (Fleming et al., 1997; Peaucelle et al., 2011). Auxin induces these factors, and they thus partially mediate the effect of auxin on organ initiation (Braybrook and Peaucelle, 2013). Additionally, mechanical forces as well as the cell wall were shown to affect the levels and polar distribution of PIN1 within the cell (Feraru et al., 2011; Heisler et al., 2010; Nakayama et al., 2012). However, mechanical stress appears to affect microtubule orientation and PIN1 polarization in parallel, as disruption of microtubule polymerization did not affect organ initiation in the short term (Hamant et al., 2008; Heisler et al., 2010). Together, these studies point to a scenario in which organ initiation is instructed in part by the geometry of the SAM and differential mechanical properties of distinct regions within the SAM. These properties affect the growth properties of the tissue as well as auxin distribution. Auxin, in turn, induces changes in cell wall properties and also interacts with transcription factors and additional hormones to specify leaf initiation and growth.

Box 3. Quantitative analyses of leaf development

A number of studies have developed methods that allow for the quantitative analysis of leaf shape and patterning:

- Lee et al. (2006) used optical projection tomography (OPT) to capture three-dimensional data from plant specimens.
- Bensmihen et al. (2008) applied a quantitative approach to leaf shape mutants, generating 'low-dimensional' spaces that capture key variations in leaf shape and size.
- Kuchen et al. (2012) modeled leaf patterning by differential regulation of growth rate and orientation along the leaf axes, which responds to tissue deformation. The model is consistent with Arabidopsis leaf shape and can be modulated to generate a variety of leaf forms.
- Chitwood et al. (2013) used detailed phenotyping and genotyping to identify more than 1000 quantitative trait loci (QTLs) affecting tomato leaf shape, and identified new correlations between leaf shape and other traits, such as sugar content in the fruit.
- Rolland-Lagan et al. (2014) quantified tissue deformation and surface shape changes during leaf development.
- Armon et al. (2014) quantified the waviness and lobiness of leaves and suggested that leaf waviness is associated with normal curvature along the margins, whereas lobiness is associated with geodesic curvature.
- Vlad et al. (2014) quantified growth and serration of the leaf margin using time-lapse imaging data.
- Atomic force microscopy (AFM) was used to quantify mechanical properties of different regions in the SAM (Braybrook and Peaucelle, 2013; Milani et al., 2011; Peaucelle et al., 2011).

The balance between morphogenesis and differentiation

Following initiation, the leaf primordia undergoes growth, morphogenesis and differentiation in a highly flexible process that ultimately gives rise to the final leaf shape. This flexibility is manifested in a continuum of leaf shapes, ranging from very simple to highly complex (Figs 1 and 4). The flexibility of leaf development is achieved by modulating the overall rate of leaf maturation (see Glossary, Box 1) and the balance between morphogenesis and differentiation, as well as specific patterning events. What are the factors that affect this balance and how are they utilized by different species along this continuum?

The regulation of lamina initiation and growth

One of the first events during primary morphogenesis is the initiation and growth of a lamina, leading to the formation of a flat rather than a radial structure. Lamina initiation and growth are thought to require the juxtaposition of abaxial and adaxial tissues (Waites and Hudson, 1995), and a number of genes have been implicated in this process. YABBY and AIL/PLT genes, for example, have been linked to the promotion of lamina outgrowth and expansion in *Arabidopsis*, maize and rice (Dai et al., 2007; Elliott et al., 1996; Juarez et al., 2004; Mizukami and Fischer, 2000; Sarojam et al., 2010). In addition, JAGGED (JAG) and its paralog NUBBIN (NUB) are redundant, positive regulators of leaf blade growth in *Arabidopsis* (Dinneny et al., 2006; Ohno et al., 2004). Accordingly, *jag nub* double mutants have a reduced leaf blade area, and combined *jag-1/fil/yab3* mutations result in a severe loss of blade development. Recently, JAG was shown to directly repress

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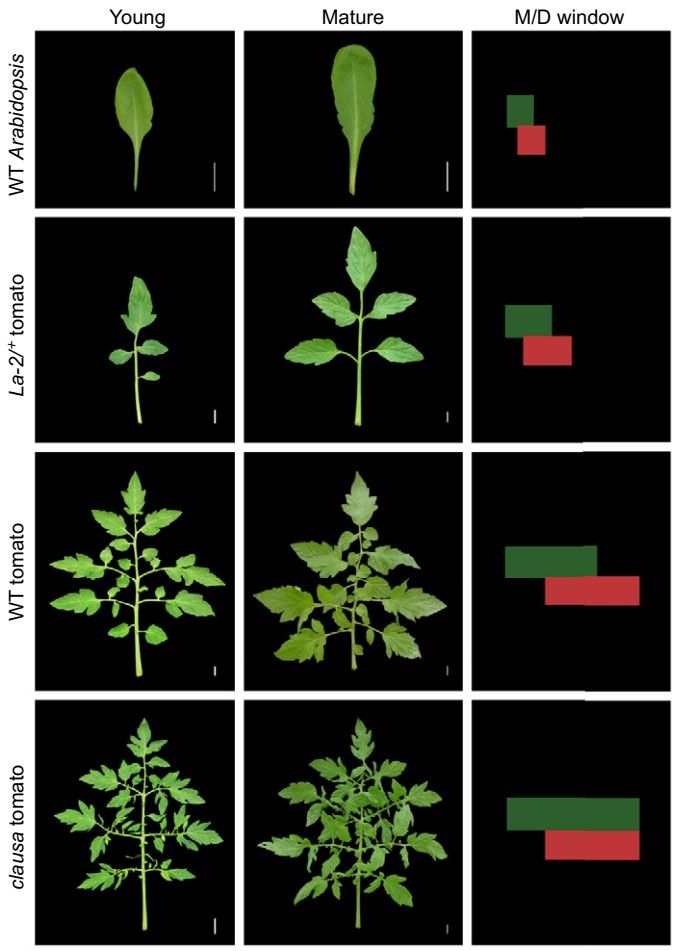

Fig. 4. Generating leaf diversity. The balance between morphogenesis and differentiation modulates leaf diversity, as illustrated by the different length of the leaf morphogenetic window in *A. thaliana* and in three tomato genotypes (all in an M82 background). The fifth leaf is depicted in all images (for both tomato and *Arabidopsis*). For tomato, young leaves were photographed 45 days after seeding and mature leaves were photographed 70 days after seeding. For *Arabidopsis*, young leaves were photographed 30 days after seeding and mature leaves were photographed 60 days after seeding. Tomato plants were grown in a net house. *Arabidopsis* plants (ecotype Columbia) were grown under an 8:16 h light:dark regimen. All images were captured using a Nikon D5200 digital camera. Scale bars: 1 cm. The relative lengths of the developmental stages within the morphogenesis/differentiation (M/D) window (with green representing morphogenesis and red representing differentiation) are presented to the right of each genotype. A longer morphogenetic window can result in a more complex leaf, as is evident in the *clausa* mutant, whereas a shorter morphogenesis stage results in a simplified leaf form, as in the case of the *Arabidopsis* simple leaf and the tomato *La-2*$^{+}$ mutant.

meristematic and cell cycle genes, thus promoting differentiation (Schiessl et al., 2014). WOX transcription factors have also been linked to the promotion of blade outgrowth in several species. For example, the *Nicotiana sylvestris* WOX gene mutant *lam1* has vestigial lamina-less leaves that lack mesophyll differentiation (Ishiwata et al., 2013; Lin et al., 2013; Zhang et al., 2014). It therefore appears that an overlapping set of genes is involved in lamina initiation and expansion and in leaf initiation, and that these processes require repression of meristematic fate. It remains to be seen how the activities of these different regulators of lamina initiation and growth are coordinated.

Lamina growth also requires coordination between the epidermis and the mesophyll layers, and it was recently shown that the transcriptional co-activator ANGUSTIFOLIA3 (AN3) is produced only in mesophyll cells but moves into the epidermis to promote growth in both layers (Kawade et al., 2013). AN3 was subsequently shown to modulate transcription through interaction with chromatin-remodeling factors (Vercruyssen et al., 2014).

Several genes involved in basic cellular functions have also been shown to influence leaf lamina growth. In *Arabidopsis*, ribosomal protein mutants have pointed leaves with more prominent marginal serrations, possibly due to a decrease in the relative cellular growth rate (Horiguchi et al., 2012; Pinon et al., 2008; Szakonyi and Byrne, 2011). Furthermore, the E3 ubiquitin-ligase BIG BROTHER (BB) can repress plant organ growth, probably by marking cellular proteins for degradation (Disch et al., 2006). Recently, poly(A) polymerases (PAPS) have been shown to influence leaf size and shape, probably by affecting the expression of specific subsets of relevant genes (Vi et al., 2013). In *Cardamine hirsuta*, the ribosome-associated protein SIMPLE LEAF3 also affects leaf growth and leaflet development (Kougioumoutzi et al., 2013). It is still unclear whether the effect of these genes on leaf development reflects a general effect on growth or whether they have specific roles in leaf patterning, which might reflect specific targets.

Role and maintenance of the marginal blastozone

Leaf growth is mostly determinate. However, transient indeterminate growth is maintained in specific regions of the leaf. These include a growing region at the leaf base or the leaf tip, depending on the species (Tsukaya, 2014), and regions in the leaf margin that possess organogenic potential, known as marginal blastozones (MBs) (Hagemann and Gleissberg, 1996). The MB is responsible for lamina initiation and the organogenesis of marginal structures. Classic and recent research has shown that compound leaf development requires prolonged activity of the MB during primary morphogenesis. Genetic and hormonal factors that regulate MB activity were shown to partially overlap with those regulating SAM activity, in accordance with the evolutionary origin of a leaf as a modified shoot (Brand et al., 2007; Floyd and Bowman, 2010). The temporal and spatial length of the MB activity determines the extent of the indeterminate phase in leaf growth and the consequent level of leaf complexity (Hagemann and Gleissberg, 1996) (Fig. 4).

Antagonistic transcription factors affect the balance between morphogenesis and differentiation

As discussed above, the transient indeterminate state of leaf development is characterized by the maintenance of a developmental window of morphogenetic activity at the MB, which underlies much of the variability in leaf shape. The extent of this morphogenesis window is determined by antagonistic activities that delay or promote differentiation. Differentiation itself is a gradual process, and in many species cell differentiation and expansion progress from the leaf tip towards the base in a moving 'cell cycle arrest front' (Donnelly et al., 1999; Nath et al., 2003; Poethig and Sussex, 1985). Recent studies in *Arabidopsis* suggest that progression of the arrest front is not completely gradual and goes through two rather sharp transitions that correlate with the onset of photosynthesis (Andriankaja et al., 2012; Kazama et al., 2010).

CIN-TCP transcription factors affect leaf shape by promoting differentiation. In *Antirrhinum*, CIN promotes tissue differentiation and growth arrest of the leaf lamina, pulling the developmental program towards secondary morphogenesis (Nath et al., 2003). In *Arabidopsis*, upon lamina initiation, sequential TCP activities promote the transition from primary morphogenesis into the cell expansion and secondary morphogenesis phase (Efroni et al.,

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2008). A subset of CIN-TCPs, including LANCEOLATE (LA) from tomato, is negatively regulated by the microRNA miR319. In the tomato semi-dominant gain-of-function mutant *La*, a mutation in the miR319-binding site leads to precocious *LA* expression, resulting in precocious differentiation and small, simplified leaves (Dengler, 1984; Mathan and Jenkins, 1962; Ori et al., 2007; Shleizer-Burko et al., 2011; Stettler, 1964). Concurrently, premature expression of the miR319-insensitive *TCP4* in *Arabidopsis* plants causes early onset of maturation, resulting in a range of leaf patterning defects (Efroni et al., 2008; Palatnik et al., 2003). By contrast, downregulation of CIN-TCP genes by overexpression of miR319 results in a substantial delay in leaf maturation and prolonged indeterminate growth in the leaf margin (Efroni et al., 2008; Koyama et al., 2007; Ori et al., 2007; Shleizer-Burko et al., 2011). It would thus seem that maintenance of the morphogenic window is dependent on low TCP activity during the early stages of leaf development.

We have recently reported that tomato APETALA1/FRUITFULL (AP1/FUL) MADS box genes are involved in tomato leaf development and are repressed by LA. The suppression of the activity of FUL-like genes results in reduced leaf complexity and in a partial suppression of the phenotype caused by miR319 overexpression. Overexpression of one of the genes from this family suppressed the *La* gain-of-function phenotype (Burko et al., 2013). This suggests that AP1/FUL proteins promote the morphogenetic activity of the tomato leaf margin, in agreement with accumulating evidence pointing to a role for FUL-like genes in leaf development in *Arabidopsis*, poppy, pea and *Aquilegia* (Ferrandiz et al., 2000; Pabon-Mora et al., 2012, 2013; Teper-Bamnolker and Samach, 2005).

As mentioned above, KNOXI proteins are involved in SAM maintenance. However, studies have shown that KNOXI proteins also play important roles in maintaining the transient morphogenetic window during early leaf development in some species. In species with simple leaves, *KNOXI* overexpression can lead to variable phenotypes, which include knot-like structures on the leaves, curled or lobed leaves and ectopic meristems on leaves (Hay and Tsiantis, 2010). In maize, the KNOXI protein KNOTTED-1 (KN1) is expressed in proximal regions of leaf primordia, and misexpression of *KN1* leads to the displacement of proximal tissues to more distal locations, suggesting that KN1 normally participates in the establishment of proximal/distal polarity (Bolduc et al., 2012; Ramirez et al., 2009). In many plants with compound leaves, *KNOXI* expression is restored in developing leaf primordia (Bharathan et al., 2002) pursuant to their emergence from the SAM, and downregulation of KNOXI activity results in accelerated leaf maturation and decreased leaf complexity (Hay and Tsiantis, 2006; Shani et al., 2009). *Arabidopsis* leaves have been proposed to have derived from a more complex-leaved ancestor through loss of *KNOXI* (STM) expression (Piazza et al., 2010). In general, it would seem that upregulation of KNOXI genes serves to delay leaf differentiation and increase leaf complexity (Hareven et al., 1996; Janssen et al., 1998). Overexpression and silencing experiments showed that the effects of KNOX genes on leaf morphogenesis depend mostly on their timing of expression and the tissue/locale of expression, rather than their actual expression levels, particularly in compound leaves (Shani et al., 2009).

Several factors have been reported to regulate *KNOXI* expression in leaves. In tomato, the recessive *clausa* (*clau*) and *tripinnate* (*tp*) mutants (Clayberg et al., 1966) exhibit leaves of increased complexity and have increased *KNOXI* expression (Avivi et al., 2000; Harrison et al., 2005; Hay and Tsiantis, 2010; Jasinski et al., 2007). BEL-LIKE HOMEODOMAIN (BELL) proteins also regulate KNOX1 activity (Smith et al., 2002). In tomato, the BELL protein BIPINNATE (BIP) was shown to interact with the KNOXI protein TKN2/LeT6, and the *bip* mutant is characterized by a more compound leaf than the wild type. The BIP-KNOXI interaction might therefore repress KNOXI activity (Kimura et al., 2008; Stubbe, 1959).

Several additional factors were shown to affect the rate of maturation and consequently the level of complexity of tomato leaves. The TRIFOLIATE (TF) protein, which is a MYB transcription factor related to the *A. thaliana* LATERAL ORGAN FUSION1 (LOF1) protein, is required for the maintenance of morphogenetic potential during leaf development in tomato (Naz et al., 2013). *tf* mutants have simplified leaves that lack lobing and serrations. TF also regulates leaflet and axillary meristem initiation. The ratio between SINGLE FLOWER TRUSS (SFT), the tomato FT homolog, and SELF-PRUNING (SP), which both affect the induction of flowering, was also shown to be involved in general plant growth regulation and determination, including the control of leaf shape. In the leaf, a high SFT/FT ratio promotes maturation, leading to a simplified leaf form. This effect is enhanced in conjunction with the *trifoliate* (*tf*) mutant and is suppressed by miR319 overexpression (Burko et al., 2013; Shalit et al., 2009).

Morphogenesis in pea and *Medicago truncatula* leaves is regulated at least partially by different factors compared with tomato and *C. hirsuta*. In pea, the *UNIFOLIATA* (*UNI*) gene, the ortholog of *Arabidopsis LEAFY* (*LFY*) (Hofer et al., 1997), is important in MB maintenance. UNI is expressed in the leaf blastozone during initiation and is downregulated during leaf maturation. Correspondingly, *uni* mutant leaves, as well as leaves of the *M. truncatula uni* ortholog *SINGLE LEAFLET* (*SGL*) mutant, have reduced complexity (Gourlay et al., 2000; Wang et al., 2008). In addition, prolonged *UNI* expression leads to increased blastozone activity in the complex leaves of *afila* (*af*), *cochleata* (*coch*) and *afila tendril-less* (*af tl*) mutant plants (Champagne et al., 2007; DeMason et al., 2013; DeMason and Chetty, 2011; Gourlay et al., 2000; Hofer et al., 2001).

Cumulatively, these studies show that a window of morphogenetic activity is defined by the antagonistic activity of transcription factors that promote differentiation and those that repress it. The specific factors can differ among species, and leaf diversity results in part from tuning the timing of the activity of these factors.

Hormones affecting the balance between morphogenesis and differentiation

The rate of leaf maturation is also regulated by several plant hormones, many of which interact with the transcription factors discussed above. For example, GA was found to regulate cell proliferation and expansion rate in *Arabidopsis* leaves (Achard et al., 2009). Not surprisingly, GA negatively regulates leaf complexity in tomato. Upon increased GA levels or response, only primary leaflets with smooth margins are formed and the leaves mature faster than wild-type leaves do (Bassel et al., 2008; Chandra-Shekhar and Sawhney, 1991; Fleishon et al., 2011; Gray, 1957; Hay et al., 2002; Jasinski et al., 2008; Jones, 1987; Van Tuinen et al., 1999). Similarly, *solanifolia* (*sf*) mutants produce primary and intercalary leaflets only, with smooth margins, possibly due to elevated GA levels (Chandra-Shekhar and Sawhney, 1991). These findings suggest that GA promotes leaf maturation. However, in some species GA has the opposite effect of inducing more compound leaves (DeMason and Chetty, 2011; Robbins, 1957; Rogler and Hackett, 1975). For example, in pea, GA and auxin positively promote leaf dissection during leaf morphogenesis by

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prolonging the temporal window during which acropetally initiated leaflets are produced. (DeMason and Chetty, 2011). KNOXI and TCP proteins have also been linked to GA dynamics. KNOXI proteins negatively affect GA levels by repressing the GA biosynthesis gene *GA20ox* and activating the GA inactivation gene *GA2ox*. These effects on GA homeostasis mediate the function of KNOXI in tuning the SAM-leaf boundary and in modulating compound leaf development in *Arabidopsis*, maize, tobacco and tomato (Bolduc and Hake, 2009; Hay et al., 2002; Jasinski et al., 2005; Sakamoto et al., 2001). By contrast, the TCP protein LA positively affects GA homeostasis in tomato (Yanai et al., 2011). Modulation of GA homeostasis therefore appears to be a common mechanism by which different transcription factors tune the rate of maturation and differentiation.

Cytokinin was also shown to affect the balance between morphogenesis and differentiation in leaf development. Increased cytokinin degradation in *Arabidopsis* leaf primordia accelerated cell expansion and early termination of cell proliferation, demonstrating that cytokinin delays the onset of cell differentiation (Holst et al., 2011; Werner et al., 2001). Interestingly, lettuce (*Lactuca sativa*) leaves that overexpress the *Arabidopsis* KNOXI gene *BP* acquire characteristics of indeterminate growth, which is associated with the accumulation of specific types of cytokinins (Frugis et al., 2001). Cytokinin was also shown to be involved in the maintenance of prolonged morphogenetic activity in the tomato leaf margin (Shani et al., 2010). Genetic and molecular analysis indicated that cytokinin acts downstream of KNOXI activity in delaying leaf maturation. Conversely, promotion of leaf maturation by CIN-TCPs in *Arabidopsis* is mediated by reducing leaf sensitivity to cytokinin. TCP4 was shown to interact with the chromatin remodeler BRAHMA to directly activate the expression of *ARR16*, which encodes an inhibitor of cytokinin responses (Efroni et al., 2013). Interestingly, the class I TCPs TCP14 and TCP15, which are thought to act antagonistically with class II TCPs, positively regulate cytokinin response (Steiner et al., 2012). Thus, the antagonistic effect of KNOXI and TCP transcription factors on leaf maturation converges on the regulation of the GA/cytokinin homeostasis. It is interesting to see whether other factors affecting the rate of leaf maturation also affect this homeostasis. GA and cytokinin were also shown to antagonize the response of each other during tomato leaf development (Fleishon et al., 2011). Leaves of some species, including tomato, maintain morphogenetic activity after leaf expansion, leading to further variability in leaf shape, as seen in the *cla* mutant (Fig. 4). Interestingly, GA and cytokinin were both shown to modulate this late morphogenetic activity in tomato (Shani et al., 2010; Yanai et al., 2011). Cumulatively, these studies suggest that the flexibility of leaf shape is achieved by tuning the balance between hormones that promote indeterminate state, such as cytokinin, and hormones that promote differentiation, such as GA.

Controlling leaf size

Leaf size is largely dependent on the plant species, but is variable to a certain extent and is also tuned by environmental factors (Box 2). Recent studies have shown that leaf size and the rate of leaf maturation are regulated by partially overlapping pathways, including those involving CIN-TCPs, ARP/AS2 and hormone dynamics. However, leaf size is not always correlated with leaf complexity or with the number of cells, pointing to partially independent regulation of these three processes (Efroni et al., 2010; Kaplan, 1992; Shleizer-Burko et al., 2011). The issue of leaf size has been the recent focus of several reviews to which we refer the reader (Hepworth and Lenhard, 2014; Powell and Lenhard, 2012).

Marginal patterning in simple and compound leaves

Marginal patterning, which occurs during both primary and secondary morphogenesis, involves the formation of serrations, lobes and leaflets at the leaf margin (Fig. 1), and flexibility in these patterning events further expands the variability in leaf form. The formation of marginal structures results from differential growth in adjacent regions and can be caused by a local restriction or promotion of growth (Kawamura et al., 2010; Malinowski et al., 2011; Vlad et al., 2014). As we discuss below, marginal patterning in simple and compound leaves involves partially overlapping mechanisms, many of which involve auxin signaling.

The interaction between auxin and *NO APICAL MERISTEM* (*NAM*)/*CUP-SHAPED COTYLEDON* (CUC) transcription factors is involved in marginal patterning in both simple and compound leaves. NAM/CUC transcription factors regulate many developmental processes, including boundary specification (Aida and Tasaka, 2006; Žádníková and Simon, 2014). In simple *Arabidopsis* leaves, they promote leaf serrations (Hasson et al., 2011; Nikovics et al., 2006), and in compound leaves they promote leaflet specification and separation (Brand et al., 2007). The expression of *NAM/CUC* mRNA marks the boundary between the leaf margin and the future leaflet in an array of species with compound leaves, and NAM/CUC silencing leads to leaf simplification (Berger et al., 2009; Blein et al., 2008; Cheng et al., 2012). A subset of *CUC* genes are negatively regulated by miR164. In tomato, the transgenic expression of a miR164-insensitive form of the NAM/CUC gene *GOBLET* (*GOB*) leads to ectopic initiation events in the leaflet margins, which later fuse to produce a final leaf form that is relatively simple and deeply lobed. Thus, both reduced and expanded expression domains of *GOB* lead to leaflet fusion (Berger et al., 2009), suggesting that distinct and sufficiently distant domains of *GOB* expression are essential for leaflet separation. NAM/CUC genes are therefore conserved modulators of the positioning and separation of marginal structures. In tomato, the *Potato-leaf* (*C*) gene, an ortholog of the *Arabidopsis* branching regulator *REGULATOR OF AXILLARY MERISTEMS1* (*RAX1*), also regulates leaf complexity; *c* mutants show reduced leaf complexity compared with the wild type, and smooth leaf blade margins. Interestingly, combining the *c* and the *gob* mutations results in the elimination of leaflet initiation, suggesting that they act partially redundantly in marginal patterning (Busch et al., 2011).

Auxin was also shown to be involved in leaf serration (Bilsborough et al., 2011; Hay et al., 2006) and in the initiation and separation of leaflets and lobes from the margin of compound leaf primordia, similar to its role in leaf initiation from the flanks of the SAM. In compound leaves, inhibition of auxin transport or activity resulted in the development of simplified leaves. Furthermore, PIN1 subcellular localization was found to converge at sites pre-marking leaflet initiation, leading to peaks in expression of the auxin-response sensor DR5, whereas external auxin application led to ectopic lamina growth and/or leaflet initiation (Al-Hammadi et al., 2003; Avasarala et al., 1996; Barkoulas et al., 2008; Ben-Gera et al., 2012; DeMason and Polowick, 2009; Koenig et al., 2009). These observations indicate that discrete auxin maxima promote leaflet initiation and growth. Interestingly, in *M. truncatula*, leaves of the *MtPIN10/SLM1* (the *Medicago PIN1* ortholog) mutant exhibit increased complexity and decreased marginal patterning, suggesting a more complex effect of auxin on leaf patterning in *Medicago*. However, the increased complexity might result from fusion of several leaves (Peng and Chen, 2011; Zhou et al., 2011).

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A role for auxin in margin patterning has also been implied based on studies of the tomato *ENTIRE* (E, *SlIAA9*) gene, which encodes a protein from the Aux/IAA family of auxin response repressors (Berger et al., 2009; Wang et al., 2005; Zhang et al., 2007). Leaves of the tomato mutant *e* are much simpler than wild-type leaves (Dengler, 1984; Rick and Butler, 1956), and *e* leaf primordia initiate leaflets, but these fuse during the formation of the final *e* leaf form (Ben-Gera et al., 2012; Dengler, 1984; Koenig et al., 2009). In *e* leaf primordia, the expression of the *PIN1:PIN1-GFP* reporter is upregulated and the expression of the auxin response sensor DR5 expands to the entire leaf margin (Ben-Gera et al., 2012; Koenig et al., 2009). These observations suggest that E restricts lamina growth between developing leaflets by inhibiting auxin response. Together, these studies demonstrate that auxin promotes the formation and growth of diverse marginal structures.

How do NAM/CUC proteins and auxin interact in marginal patterning? Combining computational modeling and genetic approaches, it was proposed that, in *Arabidopsis*, CUC2 promotes PIN1 localization, and auxin in turn represses CUC2 expression, leading to regular patterns of leaf serrations (Bilsborough et al., 2011). Whereas in *Arabidopsis* auxin is thought to regulate *NAM/CUC* expression in both the SAM and the leaf (Aida and Tasaka, 2006; Bilsborough et al., 2011; Furutani et al., 2004; Heisler et al., 2005; Vernoux et al., 2000), auxin in tomato affects *GOB* expression in apices but not in leaf primordia. Furthermore, the auxin response appears to act downstream of GOB in tomato leaf development, and it seems to be affected by both GOB and E (Ben-Gera et al., 2012). Combining the *gob* and *e* mutations led to the complete elimination of leaflet initiation, suggesting that these factors also act via independent pathways (Ben-Gera et al., 2012). These studies show that the interaction between NAM/CUCs and auxin patterns margins in both simple *Arabidopsis* and compound tomato leaves, but the details of this interaction are tuned to pattern diverse leaf forms. The tomato LYRATE (LYR) gene, an ortholog of *JAG*, was shown to promote organ growth at the leaf margin, similar to the role of JAG in promoting growth of the main leaf lamina in *Arabidopsis*. Leaves of the *lyr* mutant have more leaflets in comparison to the wild type, and LYR overexpression leads to leaflet fusion (Clayberg et al., 1966; David-Schwartz et al., 2009). LYR possibly affects auxin response or distribution (David-Schwartz et al., 2009), and it will be interesting to see how it interacts with NAM/CUC genes in marginal patterning. Interestingly, CUC genes, *AS1* and auxin responsive genes were identified as targets of CIN-TCPs in *Arabidopsis* (Koyama et al., 2007). Combining downregulation of CIN-TCPs and upregulation of CUCs and STIMPY/WOX9 genes led to substantially increased margin elaboration in *Arabidopsis*, giving rise to a leaf shape that resembles a compound leaf (Blein et al., 2013). These studies show that common genes can affect both leaf maturation and marginal patterning.

Recent work has identified the REDUCED COMPLEXITY (RCO) homeodomain protein as necessary for leaflet development (Vlad et al., 2014). RCO is present in *C. hirsuta* and has evolved via duplication in the Brassicaceae family, but was lost in *Arabidopsis*, thus contributing to leaf simplification. RCO is thought to promote compound-leaf development by inhibiting growth between leaflets, but it does not affect auxin response distribution (Vlad et al., 2014). Another recent work compared the level of leaf dissection in various species of the genus *Capsella* and found that diversification in the RCO paralogs can account for naturally occurring leaf-shape variation in this Brassicaceae family. RCO expression can be temperature responsive in some cases, which is possibly involved in the plasticity of leaf shape under different temperatures (Sicard et al., 2014). In both *Capsella* and *C. hirsuta*, differential expression rather than protein function is thought to account for the evolution of the function in leaf complexity. It will be interesting to see how RCO interacts with other regulators of marginal patterning.

In addition to the genes and hormones discussed above, components of the trans-acting short interference RNA (tasiRNA) pathway are involved in leaf marginal patterning. Mutations in several genes in the tomato tasiRNA pathway, which are negative regulators of ARF2, 3 and 4, were shown to underlie the tomato '*wiry*' syndrome of very narrow leaves with reduced complexity (Lesley and Lesley, 1928; Yifhar et al., 2012). Interestingly, compromised tasiRNA pathway activity in *M. truncatula* led to a milder phenotype of increased leaf lobing with no effect on the number of leaflets (Zhou et al., 2013), whereas leaf development in *Arabidopsis* was unaffected (Hunter et al., 2006). Thus, whereas some mechanisms of marginal patterning are conserved among species, others differ substantially.

In summary, marginal patterning depends on the flexible positioning of regions in which lamina growth occurs and regions in which growth is inhibited. An indefinite number of leaf margin forms is achieved by tuning the interactions between plant hormones, transcription factors and growth regulators.

Conclusions

Leaf development as a whole can be viewed as sequential developmental programs that are executed by different combinations of factors. Different developmental stages within a given program are often controlled by overlapping sets of factors or 'tools', thus comprising the 'toolbox' of leaf development. Particular examples of such tools that are involved in different stages of the same developmental program are discussed above. For instance, the involvement of YABBY family genes in several different stages and aspects of leaf development, together with their existence in seed plants only, has led to the notion that YABBY genes are integral to the ancestral specification of a leaf with determinate growth as opposed to a shoot from which a leaf is thought to have evolved (Sarojam et al., 2010). Indeed, although for the purpose of clarity we have divided the analysis of leaf development into initiation, morphogenetic balance and marginal patterning, this division can be misleading, as many of the factors involved in fact affect several stages. For example, in addition to their role in leaflet initiation and separation, GOB, auxin and possibly ENTIRE/AUXIAA9 also affect the rate of leaf maturation (Berger et al., 2009).

In connection with compound leaves, we have also highlighted the increased importance of repurposing tools to serve different functions or perhaps similar functions in different developmental contexts. Indeed, *C. hirsuta*, pea, *Medicago* and tomato all possess compound leaves, and all employ some – but not all – of the same tools to execute their developmental programs. The resulting variation between different 'compound leaves' thus results both from the developmental program itself and from the length of the morphogenetic window within the developmental program of each discrete species. Differences – or commonalities – in the executive functions of each tool are context dependent and cannot on their own account for the immense variation between compound leaves found in nature. Together, a deeper understanding of the specific 'tools' used by plants during leaf development and their activities in different species will be invaluable in the elucidation of leaf development as a whole.

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