Review Article

REVIEW ON THE ROOT, STEM AND LEAF INITIATIONS IN PLANTS

Abstract

The root and shoot apical meristem serve as sources of pluripotent cells and provide new cells for repetitive organ initiation, they are the major meristematic regions on which plant development take place. New meristems are incessantly formed as plants produce new branches or lateral roots thus making the understanding of meristem function central to how plants can establish different growth types, ranging from tiny herbs to huge trees. The sizes and numbers of meristems that are initiated during advanced development control the size and number of fruits and the generation of seeds. The development of a lateral root from a limited number of cells requires compactly coordinated asymmetric cell divisions to generate cell diversity and tissue patterns which characteristically involves the specification of founder cells, followed by a number of cellular changes until the cells divide and give rise to unequally sized daughter cells. Leaf development exemplifies the dynamic nature and flexibility of plant development in response to internal and external cues which is evidenced in the fact that 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, thus the specification of organ initiation involves a complex network of genetic, hormonal and mechanical factors which has been discussed in this review.

Keywords: Initiation, Meristem, pluripotent, hormones.

INTRODUCTION

Plant development depends on the activity of two main meristems; the root meristem and the shoot apical meristem, which serve as a source of pluripotent stem cells and provide new cells for repetitive organ initiation [1]. Thus, plant meristems are the stem cell niches that allow stem cells to remain undifferentiated and to proliferate. Meristems are dynamic structures that can be generated de-novo, for example during flower formation [2]. New meristems are continuously formed in the process of production of new branches and lateral roots in plants. Understanding meristem function is therefore central to how plants can establish different growth types. The quantity of meristems initiated during advanced development play a determining role in the size and number of fruits and seeds [2].

The formation of a plant root system takes place post-embryonically and relies on de novo formation of organs [2]. Typically, lateral root organs are initiated close to the root tip and emerge in the differentiation zone. Over the past few years, knowledge about the regulatory mechanisms behind many aspects of lateral root formation has increased considerably [3, 4]. The development of a lateral root from a limited number of cells requires tightly coordinated asymmetric cell divisions to generate cell diversity and tissue patterns. This characteristically involves the specification of founder cells, followed by a number of cellular changes until the cells divide and give rise to unequally sized daughter cells [5].

The development of plant leaves follows a common basic program that is flexible and is adjusted according to species, developmental stage and environmental circumstances [6]. Leaves initiate from the flanks of the shoot apical meristem and develop into flat structures of variable sizes and forms [6]. This process is regulated by plant hormones, transcriptional regulators and mechanical properties of the tissue [6].

ROOTS DEVELOPMENT IN PLANTS

Roots serve a multitude of functions such as anchorage, as the conduit to supply both nutrients and water to the plant from the soil, a location for the synthesis and exchange of various plant hormones, and storage organs of plant resources [7, 8]. Plant roots grow in a highly heterogeneous environment such as the soil and possess an ability to react to this heterogeneity and modify the form of their root system as a consequence. This is a "phenotypic plasticity" which is influenced by a genetic program and environmental factors and the ultimate configuration of the root system. To understand the morphogenesis of roots it is necessary to define the organization of the root meristem and attempt to determine the fate map of cells emerging from the root meristem [9]. Primary root growth occurs from the root apical meristem (RAM) and is dependent on a stem cell niche or microenvironment being established giving rise to the quiescent Centre (QC) [9, 10]. The RAMs are maintained by retaining a stem cell reservoir and a pool of undifferentiated initial cells [7].

ROOT MORPHOGENESIS

The Root Apex

Many of the important unanswered questions in root development involve events that occur at the root apex. For example, little is known about the nature of the stem cells, how cell files are established, how cell numbers and vascular patterning are determined, what controls the organization and size of the meristem, how root hair initials are formed, how cell expansion is regulated, and, perhaps most important, what controls the cell cycle and the planes of cell division [8] Many of these are general questions that apply equally well to morphogenesis in other parts of the plant. However, severa1 aspects of root morphogenesis serve to simplify the study of these basic questions. First, the root apical meristem is easily accessible (not enclosed the way the shoot apical meristem is), essentially transparent (due to a lack of pigment), and lacks branching primordia. Second, the root as a whole is a simple organ that displays a radial symmetry in the externa1 layers of cells. Third, root morphogenesis normally occurs in a reiterative and uniform fashion, without any major change in the organization of the root apex. Thus, all stages of root development are apparent at all times, and there is nothing analogous to the vegetative to floral conversion that occurs in shoot meristems. Fourth, roots have relatively few differentiated cell types. Finally, the various developmental processes are largely confined to classically defined "zones" along the length of the root, as indicated in Figure 1. These include the meristematic zone (site of cell divisions), elongation zone (cell expansion), and specialization zone (cell differentiation). Although this zona1 classification is probably too simplistic (there is overlap in the cellular processes occurring in the various zones), it nonetheless serves to emphasize the spatial separation of these processes in cell files of roots [8].

To fully understand the morphogenesis of roots, it is necessary to define the organization of the root meristem and determine the fate of cells that emerge from the meristem. One of the most

revealing analyses of this type was performed on the root of the water fern *Azolla* [8, 10]. The precise placement and timing of each cell division were determined and mapped, providing a complete cellular fate map of the root. In higher plants, the characterization of multicellular root meristems led to the discovery of a unique set of cells, the quiescent center, which is located at the center of the root apex but undergoes relatively infrequent cell divisions [11]. The precise function of the cells of the quiescent center and their relationship to the rest of the meristem still need to be defined.

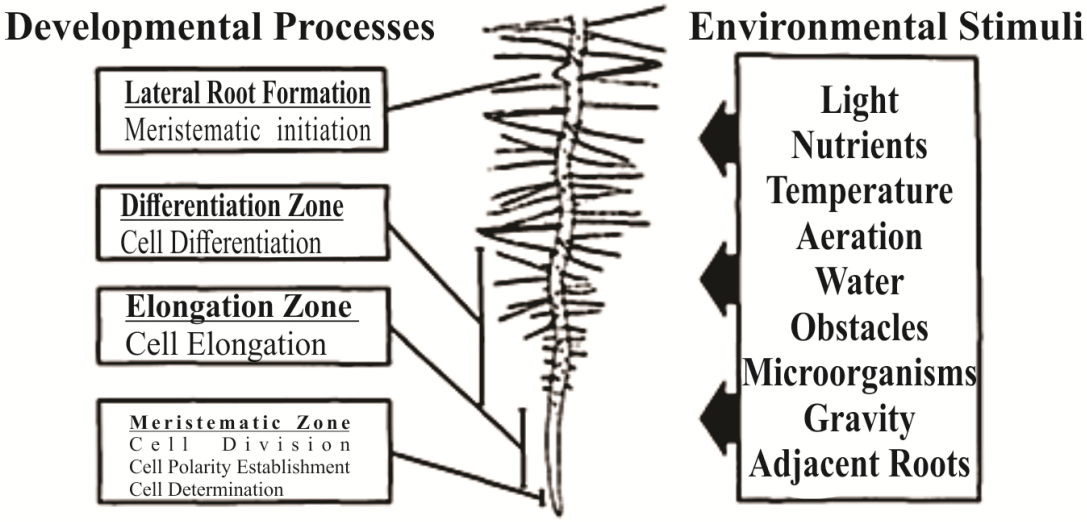

Figure 1. Schematic Outline of Interna1 Processes and Externa1 Factors That Control Root Development [8].

The classically defined zones of cellular activities are indicated, as are the environmental stimuli that influence root morphogenesis.

Lateral Roots

Branching in roots differs from branching in stems. Lateral roots do not develop directly from cells in the apical meristem but rather develop from differentiated cells in a special layer (the pericycle) located just below the endodermal layer. Evidence that this process involves redifferentiation comes from an analysis of the expression pattern of the enzyme hyoscyamine 6-@-hydroxylase, which is localized to pericycle cells. Upon induction of lateral roots, expression of the enzyme decreases dramatically [13]. Not all pericycle cells have an equal probability of giving rise -to lateral root primordia; lateral roots are not usually initiated near the root tip (suggesting the presence of an inhibitor diffusing from the tip) and normally are formed from pericycle cells opposite to the xylem elements [14].

The formation of lateral roots is a particularly intriguing aspect of root development because it represents the initiation of a new meristem and may provide clues as to how the primary root meristem arises during embryogenesis [15]. However, important questions regarding lateral root development remain unanswered. The initiation of lateral roots must involve some sort of signal that is perceived by pericycle cells. A single cell may be activated that then recruits others; alternatively, multiple cells may simultaneously perceive the signal. Once the meristem is

formed, it must elaborate a root that somehow forces its way through the existing cortex and epidermal tissue and emerges into the externa1 environment. It should be possible to address these issues by identifying genes specifically expressed in these cells and by isolating mutants blocked at different stages of lateral root development [15].

Plant Hormones

All aspects of root development are profoundly affected by plant hormones, with the strongest effects attributed to auxin, cytokinins, and ethylene [16, 17]. Because of the difficulty in interpreting the effect of exogenously applied hormones on interna1 hormone ratios, there is considerable controversy in the literature as to the relative importance of various growth regulators on root development [17]. Alternative approaches, such as the analysis of transgenic plants in which hormone ratios have been modified in vivo by expression of hormone biosynthetic enzymes [17, 18, 19] and the characterization of mutants with reduced hormone biosynthesis or altered sensitivity [20], may help resolve many of the outstanding questions.

Environmental influences

Although root morphology is guided by a genetic program, the ultimate configuration of a root system under natural conditions is largely determined by environmental factors. The effects of gravity on root growth have been explored most extensively; roots generally respond in a positive fashion to gravity, with the root cap cells playing a major role in perception [21].

Roots also respond to chemical gradients; they proliferate in regions of the soil that contain high concentrations of certain ions, such as nitrate or phosphate [22, 23]. In addition, root growth can be influenced by the soil moisture content, with roots penetrating deeper when soil moisture is low [24] and developing air spaces (aerenchyma) when the soil is waterlogged [25]. Although roots usually grow in a subterranean environment, light has been shown to affect root extension, gravitropism, and lateral root production in some species [26, 27, 28].

Furthermore, the growth of roots can be influenced by temperature gradients [29, 30], mechanical impedance [31], aeration [32, and the roots of adjacent plants [33]. The morphological plasticity of roots represents one of the most interesting aspects of root development, and there is a clear need for further exploration of the manner in which external stimuli affect the root's developmental program.

LEAF DEVELOPMENT

Leaf development demonstrates 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 [6]. Leaves evolved from lateral branches following the acquisition of determinate growth and a flat structure [34, 35, 36, 37]. Leaves can be divided into two basic forms: simple and compound. A simple leaf has an entire, continuous lamina, whereas a compound leaf is composed of multiple subunits termed leaflets, each resembling a simple leaf [36]. 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 [37].

LEAF INITIATION

During initiation, a distinct domain within the shoot apical meristem (SAM), which is separated from the rest of the SAM by a boundary domain, is specified [38, 39]. 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 [40, 41]. The specification of organ initiation involves a complex network of genetic, hormonal and mechanical factors.

THE MECHANICS OF LEAF INITIATION

Accumulating evidences point to the potential role of mechanics in the regulation of leaf positioning and initiation, either as a signal or via differential tissue properties [42]. 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 [43]. Using atomic force microscopy (AFM), cell walls in the Central Zone were found to be stiffer and their stiffness more variable than that of cell walls in the Peripheral Zone [44]. In agreement, using osmotic manipulations, the Central Zone and the Peripheral Zone were shown to differ in their mechanical properties, and these differences correlated with increased growth in the Peripheral Zone [45]. Mechanical forces were also shown to affect microtubule orientation [45]. This effect is mediated by the microtubule-severing protein KATANIN that promotes growth variability between neighboring cells [47]. Thus, correlated mechanical properties, growth directions and microtubule orientation characterize the Central Zone, Peripheral Zone and the boundary region between them.

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) [48, 49]. Auxin induces these factors, and they thus partially mediate the effect of auxin on organ initiation [50]. Additionally, mechanical forces as well as the cell wall were shown to affect the levels and polar distribution of PIN1 within the cell [51, 52, 53]. 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 [46, 51]. Together, these studies point to a scenario in which organ initiation is instructed in part by the geometry of the Shoot Apical Meristem and differential mechanical properties of distinct regions within the Shoot Apical Meristem. 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.

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 Shoot Apical Meristem function, are expressed in the Central Zone of the Shoot Apical Meristem and are down regulated at the site of organ initiation [54]. KNOXI expression is down regulated 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 [55]. 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 [54]. 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 [57]. The expression of KNOXI genes is also regulated by BLADE ON PETIOLE (BOP) [58, 59], JAGGED LATERAL ORGANS (JLO) [60] and auxin [61]. KNOXI proteins, in turn, feedback to regulate the auxin response [62, 63, 64]. KNOXI proteins also regulate the balance between cytokinin, which promotes meristematic fate, and gibberellic acid (GA), which promotes differentiation [65, 66, 67, 68]. Thus, KNOXI proteins coordinate the activity of several plant hormones during the specification of the distinct domains in the Shoot Apical Meristem, enabling the balance between continuous Shoot Apical Meristem 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* [69, 70] and to partially mediate the effect of MP on organ initiation [71]. Recently, some AIL/PLT genes were suggested to affect phyllotaxis by promoting auxin biosynthesis in the Central Zone of the Shoot Apical Meristem [72]. 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 [73, 36].

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 [36]. The flexibility of leaf development is achieved by modulating the overall rate of leaf maturation and the balance between morphogenesis and differentiation, as well as specific patterning events [74].

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 [75], 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 [76, 77, 78, 36]. In addition, JAGGED (JAG) and its paralog NUBBIN (NUB) are redundant, positive regulators of leaf blade growth in *Arabidopsis* [79, 80]. 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 meristematic and cell cycle

genes, thus promoting differentiation [81]. 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 [82, 83, 84]. 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 [85]. AN3 was subsequently shown to modulate transcription through interaction with chromatin-remodeling factors [86].

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 [87, 88, 89]. Furthermore, the E3 ubiquitin-ligase BIG BROTHER (BB) can repress plant organ growth, probably by marking cellular proteins for degradation [90]. 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 [91]. In *Cardamine hirsuta*, the ribosome-associated protein SIMPLE LEAF3 also affects leaf growth and leaflet development [92]

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 [93], and regions in the leaf margin that possess organogenic potential, known as marginal blastozones (MBs) [94]. The marginal blastozone 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 marginal blastozone during primary morphogenesis. Genetic and hormonal factors that regulate marginal blastozone activity were shown to partially overlap with those regulating SAM activity, in accordance with the evolutionary origin of a leaf as a modified shoot [95, 34]. The temporal and spatial length of the marginal blastozone activity determines the extent of the indeterminate phase in leaf growth and the consequent level of leaf complexity [94].

HORMONES THAT AFFECT THE BALANCE BETWEEN MORPHOGENESIS AND DIFFERENTIATION IN LEAF

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 [96]. 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 [97, 98, 99, 100]. Similarly, *Nicotiana solanifolia* mutants produce primary and intercalary leaflets only,

with smooth margins, possibly due to elevated GA levels [97]. These findings suggest that GA promotes leaf maturation. However, in some species GA has the opposite effect of inducing more compound leaves [101, 102, 103]. For example, in pea, GA and auxin positively promote leaf dissection during leaf morphogenesis by prolonging the temporal window during which acropetally initiated leaflets are produced [103]. 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 [104, 105]. By contrast, the TCP protein LA positively affects GA homeostasis in tomato [106]. 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 [107, 108]. 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 [109]. Cytokinin was also shown to be involved in the maintenance of prolonged morphogenetic activity in the tomato leaf margin [110]. 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 [111]. Interestingly, the class I TCPs TCP14 and TCP15, which are thought to act antagonistically with class II TCPs, positively regulate cytokinin response [112]. 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 [99]. 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. Interestingly, GA and cytokinin were both shown to modulate this late morphogenetic activity in tomato [110, 106]. 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.

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 Shoot Apical Meristem and by directional auxin transport facilitated by the PIN-FORMED1 (PIN1) auxin transporter [113, 114, 115, 116]. Accordingly, inhibition of polar auxin transport or a mutation in *PIN1* inhibits organ initiation, whereas auxin application in the Peripheral Zone of meristems is sufficient to induce organ initiation. Mutations in auxin biosynthesis genes from the YUCCA family also inhibit organ initiation [113]. 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 [40].

The response to auxin is mediated by transcription factors known as auxin response factors (ARFs). Mutations in the plant 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 [117, 71]. 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 [118]. 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 [119, 120].

Leaf initiation is closely correlated with the initiation of the midvein, a vascular strand in the middle of the leaf. The mid vein initiates from the auxin maxima at the leaf initiation site and gradually connects to the existing vasculature [121]. 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 [121]. 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 [122], which phosphorylates PIN1 [123], the switch to basal polarization is regulated by the MAB4 gene family [124, 125]. In angiosperm species other than the Brassicaceae, leaf initiation and vascular formation were suggested to be regulated by distinct members of the PIN family [126].

THE BALANCE BETWEEN AUXIN AND CYTOKININ

In addition to auxin, leaf initiation involves the plant hormone cytokinin, which plays an important role in Shoot Apical Meristem maintenance [127, 128, 129]. 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 [130]. 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 [131]. ABPH1 regulates Shoot Apical Meristem 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 [132]. 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 [133, 134]. Thus, RRs are involved in balancing Shoot Apical Meristem size and organ initiation in both maize vegetative meristems and *Arabidopsis* inflorescences, but have opposing interactions with 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 [135]. 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.

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 factor [136]. 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 [135, 136]. The issue of leaf size has been the recent focus of several reviews to which we refer the reader [137].

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, 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 [138, 139, 140]. 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 [38]. In simple *Arabidopsis* leaves, they promote leaf serrations [141], and in compound leaves they promote leaflet specification and separation [95]. 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 [142, 143, 144]. 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 [143], 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 [145].

Auxin was also shown to be involved in leaf serration [141, 61] 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 [146, 147, 148, 149, 150, 151]. 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 [152, 153].

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 [143,154]. Leaves of the tomato mutant *e* are much simpler than wild-type leaves [155] and *e* leaf primordia initiate leaflets, but these fuse during the formation of the final *e* leaf form [149, 155, 151]. 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 [149, 151]. 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.

Looking at the interaction of NAM/CUC proteins and auxin 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 [141]. Whereas in *Arabidopsis* auxin is thought to regulate *NAM/CUC* expression in both the SAM and the leaf [38, 141, 156, 114, 157], 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 [149]. Combining the *gob* and *e* mutations led to the complete elimination of leaflet initiation, suggesting that these factors also act via independent pathways [149]. 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 [158, 159]. LYR possibly affects auxin response or distribution [159], 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* [160]. Combining downregulation of CIN-TCPs and up regulation 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 [161]. 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 [140]. 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 [140]. 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 [162]. 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 [163]. 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 [164], whereas leaf development in *Arabidopsis* was unaffected [165. 166]. 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.

CONCLUSION

In conclusion, it is now clear that lateral root initiation comes about through the sequential activities of independent and ⁄ or overlapping auxin response modules. While various developmental systems have proved to be useful in understanding aspects of asymmetric cell division [5], lateral root initiation occurs deep within the primary root, hampering analysis of what controls the polarity of the pericycle cells that will undergo this division, the coordination of the simultaneous nuclear migration, and the determination of the position of the division plane. However, with the improved imaging technology and the availability of new markers, elucidating these aspects of lateral root initiation and identifying the key players involved in these processes is possible. However, 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 [36]. 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 [143].

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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