Review

New clues to organ size control in plants

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Abstract

Plant growth has unparalleled importance for human civilization, yet we are only starting to gain an understanding of its mechanisms. The growth rate and final size of plant organs is determined by both genetic constraints and environmental factors. Regulatory inputs act at two control points: on proliferation; and on the transition between proliferation and differentiation. Cell-autonomous and short-range growth signals act within meristematic domains, whereas diffusible signals from differentiated parts to proliferating cells provide measures of geometry and size and channel environmental inputs.

There is large variability in sizes and morphologies in the plant kingdom, but within species there are well defined shape and size constraints that are only modified within certain limits by environmental factors. What are the mechanisms that regulate the attainment of the final sizes and shapes of plant organs? Is size set by the growth and proliferation potential of individual cells or determined globally at the organ level? How is growth coordinated among the different parts of organs and the whole plant? We are starting to gain some understanding of these basic questions through genetic screens for mutants, genetic variation in natural populations, imaging technologies, and genome-based molecular profiling studies.

The growth of a plant is limited to meristematic regions. These contain self-renewing stem cells that produce proliferating cells whose progeny are laid down in a correct spatial orientation, glued together through their cell walls to give files of cells that make up the plant tissues. As cells are pushed out from the meristem they stop dividing and become incorporated into organs, leading to the extension of stems and branches [1,2], the production of leaves [3,4] and flowers and the elongation and branching of roots. This growth process can be subdivided into two phases: the proliferative first phase is driven through the increase in cell mass by the synthesis of macromolecular cell constituents, coupled with cell division. After cells exit cell proliferation in the second phase, growth continues by cell expansion, largely achieved through a turgor-driven water uptake and concomitant loosening of the cell wall. In many plants and certain cell types, DNA endoreduplication (DNA replication without cell division) accompanies the cell-enlargement and cell-differentiation programs.

Although generally sequential, division and differentiation can partly overlap. For example, in shoot apices, live-cell imaging has shown that distinct rates and orientation of cell division accompany the differentiation of separate regions during the earliest stages of flower development [5]. In the case of the root epidermis, cells that eventually develop into root hairs (trichoblasts) continue dividing after their epidermal neighbors have stopped. Interaction among chromatin remodeling, the cell cycle, and differentiation factors is central for the determination of trichoblast cell fate [6].

Environmental and intrinsic inputs, called 'organ size control points', can either act on the first phase of growth to increase or decrease cell growth and proliferation capacity, or on determination of the timing at which cells exit from proliferative growth into cell differentiation and expansion (Figure 1). The first control point is frequently used when organ growth is initiated, for example, from dormant seeds, buds and meristems, or during lateral root outgrowth. One recent area of progress in our understanding of elementary

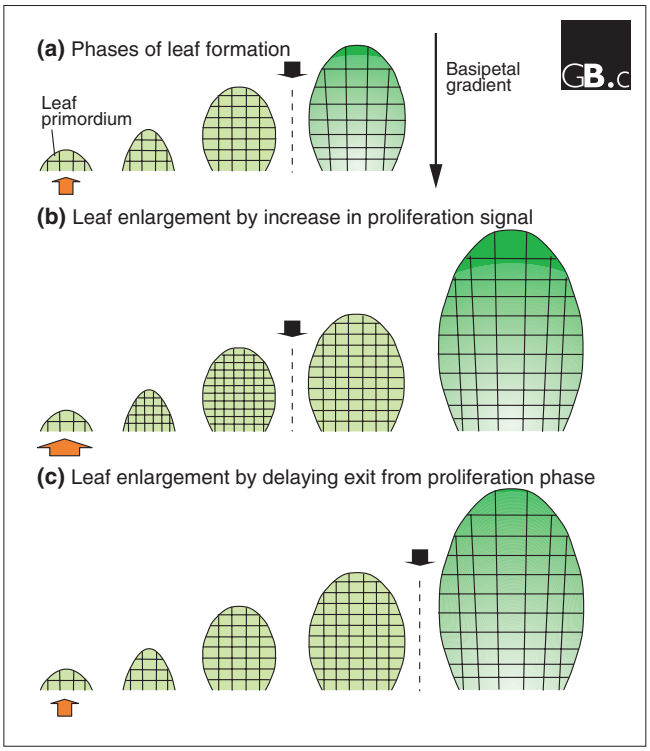

Figure 1
Mechanisms for organ size control. **(a)** Organ formation, exemplified here by leaf development, consists of two stages. The first phase is underpinned by cell proliferation, characterized by intense macromolecular/cytoplasmic synthesis and rapid cell division. The second phase is characterized by cell expansion and differentiation. Differentiation takes place along a basipetal gradient (that is, from leaf tip to leaf base), as indicated here by the gradient in cell size and cell greening. The red arrow summarizes the proliferative inputs, and the black arrow the arrest of proliferation and initiation of differentiation. **(b,c)** The two principal mechanisms for controlling organ size. Enlargement of organs can be produced by either (b) increasing proliferation signals or (c) delaying the transition between proliferation and differentiation. In both cases the number of cells available for organ formation at the end of the proliferative phase is increased, but the underlying mechanisms are different.

growth processes that drive the first phase of organ growth has been the application of genome-wide gene expression time-course analysis to growth phenomena under the control of exogenous signals [7-11], and to cultured cells synchronized for cell-cycle progression and proliferation [12].

These studies have identified common sets of genes that underlie cell proliferation and organ growth, as well as identifying organ-specific differences. For example, during germination and lateral root emergence, the G1 to S cell-cycle control point is used [7,8], whereas in the dark, the shoot apex is arrested at G1 and G2 but is rapidly released from both these arrest points upon transfer of seedlings to the light [9]. On the other hand, in an already active meristem, growth is mostly regulated by altering the timing at which cells exit proliferation, a key determinant for the number of cells produced in the meristem. Understanding organ size control thus requires teasing apart the individual components of growth, understanding the biology of the meristem, and understanding the mechanisms of proliferative growth arrest in organs. Here we will briefly review our current understanding in these areas.

Plant hormones set up domains of cell proliferation and differentiation within meristems

Central to the function of a meristem is keeping the balance between cell proliferation and the incorporation of newly produced cells into organs through cellular differentiation. These processes are separated into discrete domains, or zones, within the meristem that start to be set up as early as the beginning of embryogenesis. Antagonistic interaction between two plant hormones, auxin and cytokinin, appears to be a key mechanism for initial segregation of these domains and partitioning of cell identities during embryogenesis [13] and during shoot and root meristem development [14,15].

In a fully developed shoot meristem three main domains are set up: the center, carrying slowly dividing, true self-renewing 'stem cells'; a peripheral zone surrounding the center, which contains more rapidly dividing but still undifferentiated cells; and specific regions on the flanks of the meristem where the differentiation of leaf primordia takes place. Each of these domains is characterized by a unique hormonal profile accompanied by a specific gene-expression program [16]. It is now apparent that these hormone balances play central roles in the dynamic establishment of the meristem domains and the underlying differentiation and organogenesis programs. A common theme is the exclusion, and thereby the segregation, of opposing hormonal and gene activities. For example, areas of localized expression of the auxin-transport protein gene *PINFORMED1* (*PIN1*) mark auxin concentration peaks and the position of incipient future leaf primordia, but exclude the expression of *SHOOTMERISTEMLESS* (*STM*), a gene that maintains meristem cells in an undifferentiated state [17]. In contrast, the synthesis and action of cytokinin is necessary for the maintenance of an undifferentiated pool of stem cells in the center of the meristem, and is brought about by the upregulation of *STM* [16,18,19] and of *WUSCHEL* (*WUS*), an organizer of the stem-cell niche that is expressed in the underlying zone known as the rib zone [20]. While both *STM* and *WUS* suppress differentiation, their roles are different: *WUS*, the primary stem-cell organizer, acts on the very center of the meristematic dome, whereas *STM* prevents differentiation but allows faster proliferation at the meristem flanks at regions other than those of new primordia formation [21].

Cross-talk between the auxin and cytokinin pathways is enabled by genes such as *MONOPTEROS* (*MP*), which encodes an auxin-responsive transcription factor required for shoot meristem patterning during and after embryogenesis.

MP is primarily necessary to counteract the activity of *ALTERED MERISTEM PROGRAM1* (*AMP1*), a gene involved in cytokinin homeostasis [22]. In other words, cytokinin action seems integral to meristem function and stem-cell identity in the center of shoot meristems, whereas auxin acts as a critical differentiation signal for leaf primordia at the flanks. High auxin-to-cytokinin ratios at the flanks, and high levels of another class of plant hormones, gibberellins, at the emerging leaf primordia, determine the complementary expression domains of the transcription factors KNAT1 (a member of the KNOTTED1-LIKE family of transcription factors) and ASYMMETRIC LEAF1 (AS1) [15]. KNAT1 and related activities, including STM, are central to meristematic function, while AS1 expression marks cells being incorporated into leaf primordia.

Directed long-distance transport was previously thought fundamental to plant hormone action. However, recent studies on expression domains of the enzymes required for auxin and cytokinin biosynthesis show that these hormones are synthesized locally in specific groups of cells within the meristem, and that their long-distance transport perhaps only reinforces their function [23].

It is intriguing that the proliferation- versus differentiation-promoting roles of auxin and cytokinin are largely reversed in the root meristem. Auxin transport-driven auxin accumulation acts as a key morphogen, determining the establishment of an organizing center in the root and rapid cell division in the proximity of auxin concentration maxima [24]. On the other hand, cytokinin acts as a differentiation signal in roots and leads to reduction of the pool of dividing cells [25]. Nevertheless, the underlying transcriptional network regulating meristem function is to some extent similar in shoots and roots: both utilize WUS-related homeobox transcription factors to regulate stem-cell maintenance [26].

Translating gene-expression domains into organ growth

How do factors like plant hormones with a graded distribution program the growth and differentiation parameters of cells in a dose-dependent manner? It has been found that the PLETHORA (PLT) group of transcription factors is expressed in distinct but overlapping domains, spanning the meristematic and cell-elongation regions in the *Arabidopsis thaliana* root. The additive dose of PLT transcription factors at a given point is translated into distinct cellular responses: high PLT activity promotes stem-cell maintenance, intermediate levels promote cell proliferation, whereas a further fall in activity is required for cells to exit proliferation and to enter differentiation. Auxin distribution and response are essential for correct *PLT* gene transcription, indicating that PLT proteins function as a graded readout of auxin distribution [27]. Downstream targets for the PLT transcription factors are largely unknown, but it has been shown that *RETINBLASTOMA RELATED1* (*RBR1*), the plant homolog of a human tumor suppressor gene, restricts the stem cell- and cell-proliferation-promoting activity of *PLT* genes [27], indicating that PLT and RBR1 act on shared targets.

RBR1 is a transcriptional repressor that regulates stem-cell and cell-proliferation activity by being recruited to target genes, including cell-cycle genes, through the E2F transcription factors. Three E2Fs (E2FA, E2FB, and E2FC) that have the ability to interact with the RBR1 protein are present in *Arabidopsis* [28]. RBR1-free E2FA and E2FB are thought to function as transcriptional activators, whereas E2FC might work together with RBR1 as a transcriptional repressor, because decreasing the level of E2FC activates cell proliferation in mature leaves [29]. Constitutively elevated E2FA or E2FB activity stimulates cell division but inhibits growth because it represses cell-differentiation and cell-expansion programs [30]. Whether these transcriptional regulatory complexes compete with each other, or have distinct binding sites and thus regulate distinct sets of genes, is not known. These opposing transcriptional regulators are differentially stabilized by growth-promoting light signals [9] and by auxin [30]. RBR1 activity is regulated in accordance with the cell cycle, being inactivated through phosphorylation by cyclin-dependent kinases. Correspondingly, elevated cyclin D3 in *Arabidopsis* promotes cellular proliferation, whereas a decrease in cyclin D3 levels favors cell-cycle exit and entry into cellular differentiation [31].

Another transcription factor with an impact on cell proliferation, and a link to auxin, is AINTEGUMENTA (ANT). ANT is related to the PLTs and regulates the sizes of leaves and flowers in a dose-dependent manner. One of the target genes for ANT is that for the cell-cycle driver cyclin D3;1 (*CYCD3;1*) [32]. While what determines the spatial distribution of ANT is not fully understood, an upstream gene, *ARGOS*, has been identified. *ARGOS* promotes cell proliferation, and is itself an auxin-induced gene. Genetic interaction studies with genes involved in auxin signaling confirm a link from auxin, via *ARGOS*, to *ANT* and eventually to cell proliferation and increased organ growth [33].

As well as being regulated by plant hormones, plant growth is affected by environmental factors such as nutrient availability. The WOX family of homeodomain transcription factors, including WOX9/STIMPY, distantly related to WUS, are essential for maintaining cell proliferation and preventing premature differentiation in embryos and in shoot and root organs. However, these actions are different from the hormonal control described above. Sucrose, which is capable of activating the cell cycle, is able to fully rescue a *wox9* mutant, whereas it cannot rescue mutants like *wus*. In addition, *WOX9* and its homologs have equivalent roles in

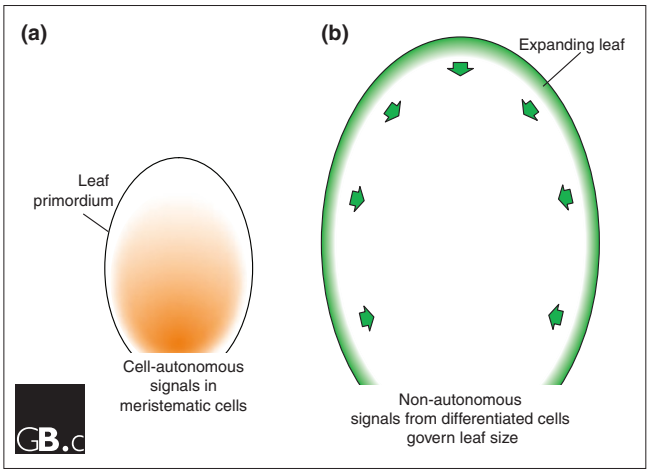

Figure 2
Distinct localization of growth- and size-regulatory mechanisms. **(a)** Cell-autonomous signals act (positively or negatively) on the proliferating cell pool in the meristems or young tissues. **(b)** Non-cell-autonomous signals, exemplified by KLUH and its expression domain in differentiated margin cells, act at a distance to determine the proliferation potential of meristematic cells or to restrict the transition between proliferation and differentiation. Organ expansion beyond a critical area would result in the KLUH signal reaching a critical low value, insufficient to maintain proliferation and thus allowing differentiation to take place. Signals from mature organs or from environmental inputs also act non-cell-autonomously.

cell proliferation in shoot and root meristems, rather than opposing roles like auxin and cytokinin [34,35].

Two other growth-promoting transcriptional regulators are JAGGED (JGD) and NUBBIN, two related zinc-finger domain proteins [36]. JGD was recently shown to act together with AS1 by repressing boundary-specific gene activities, including that of *CUP-SHAPED COTYLEDONS1* and *2* (*CUC1* and *CUC2*) [37]. Organ boundary-specific regions are important, in that at the stage of organ initiation they display the lowest cell-proliferation activity. Although *AS1* is considered a patterning gene, involved in setting up the region for leaf primordia initiation and in setting leaf polarity, recent work has shown that it might act by altering ribosome function. In an *as1* mutant background, mutations in the *PIGGYBACK* genes (*PGY1-3*), which all code for ribosomal proteins, cause ectopic outgrowths on the rosette leaves of *Arabidopsis* [38]. Perhaps, as in yeast, the expression of functionally distinct ribosomal protein variants could lead to ribosome heterogeneity, resulting in selective translation of distinct sets of genes [39]. Thus, patterning genes can act by altering the growth and proliferation potential of cells. In this regard, ErbB-3 epidermal growth factor receptor binding protein (EBP1) is thought to be a rate-limiting factor for ribosome biogenesis in plants. EBP1 is stabilized by auxin and promotes leaf growth by regulating both cell proliferation and cell enlargement in a dose-dependent manner [40]. EBP1 might regulate cell proliferation through the repression of *RBR1*.

Importantly, there are also genes that restrain growth. During leaf growth, a front of proliferation moves in a basipetal manner, beginning at the tip of the organ and progressing back onto the base, where cells that remain proliferative the longest reside. Genes that act to arrest proliferation include some identified by their impact on plant architecture (*TEOSINTE BRANCHED 1*) or petal shape (*CYCLOIDEA*); both these genes are prototypes of the so-called class II TCP genes. Others are *PEAPOD1* and *PEAPOD2*, *BIGPETAL* [2], and *DA1* [41]. Common to all these growth-promoting or growth-restraining classes of genes is the fact that their actions are confined to meristematic domains, and they cell-autonomously establish the sensitivities and capacities of cells to respond to growth-regulating cues (Figure 2).

Growth regulators acting distantly might constitute the measuring device for organ size

The locally acting growth-driving and growth-restraining mechanisms described above might, in principle, be sufficient to determine the extent of growth and the final size of organs - for example, in a scenario in which cells would grow and proliferate as long as they have a strong enough source of growth-promoting signals (Figure 2).

However, the discovery of genes that regulate organ growth non-cell-autonomously has unveiled other mechanisms (Figure 2). *Arabidopsis KLUH* (*KLU*) is a dose-dependent stimulator of organ growth: *klu* mutants form smaller leaves and flowers due to premature arrest of proliferation, whereas increasing *KLU* expression leads to organ overgrowth due to more cells [42]. *KLU* is not expressed in the regions of active cell proliferation, however, but appears to act from a distance at the basal margins of leaves and at the periphery of petals. *KLU* encodes a cytochrome P450, and was previously discovered as *CYP78A5* in *Arabidopsis*, a gene causing aberrant development when ectopically expressed [43]. P450 enzymes are known to modify small organic molecules, many of which serve as mobile growth regulators. One of the closest homologs of *Arabidopsis KLU*, maize *CYP78A1*, has a characterized catalytic activity: it omega-hydroxylates fatty acids, which suggests the nature of the compound generated by KLU [44].

How could the generation of a mobile signal at the organ periphery be used to define the final size limit an organ can grow to? Lenhard and colleagues [42] suggest that such expression at the margin could provide a readout for perimeter versus area ratio. Because geometrically the perimeter size only doubles at the same time as the area quadruples, the levels per unit area of a perimeter-generated signal would, as expansion progresses, decrease until they drop below the threshold level necessary to support cell proliferation at a distance. Similar mechanisms are used to regulate the size of the *Drosophila* wing, where a mobile

growth factor, Decapentaplegic (Dpp), is produced from a line of cells at the centre of the wing and forms a concentration gradient that is used to measure the size of the wing primordium [45].

KLU is not the only gene that acts at organ margins to produce diffusible signals. The leaf margin is an important location for auxin biosynthesis [46], and is a route of auxin flow [47]. The steroid hormone brassinolide is another growth-controlling plant hormone. Loss of the brassinolide receptor causes extreme dwarfism and lack of leaf expansion. This defect can be reversed by complementation of the receptor specifically in the epidermal cell layer, but not in the underlying tissues [48]. *DWF4* is one of the genes responsible for brassinolide biosynthesis and is expressed almost exclusively in the leaf epidermis [49]. Margin-specific complementation of a *dwf4* mutant restored leaf shape but not the defects in leaf size, implying that the whole epidermis must respond to the hormone for wild-type size to be achieved. The epidermis can also constrain growth physically. For example, when cell division is blocked specifically in the epidermal layer by the selective expression of the cell-cycle inhibitors *KIP RELATED PROTEIN 1* and *4* (*KRP1* or *KRP4*) in these cells, the underlying ground-tissue cells cannot expand, yet they continue to proliferate [50].

Not only can mature tissues influence the development of proliferating tissues, but the extent of cell proliferation can also influence the behavior of differentiated cells. The size of a plant organ can be maintained to a certain extent when cell proliferation, and thus cell number, is reduced, because that is compensated for by cell enlargement. This occurs post-mitotically through cell expansion. Thus, there should be some mechanism that records total cell numbers produced in an organ and, if required, induces the compensation mechanism in differentiated cells by stimulating cell enlargement to attain organ size homeostasis [51].

Is plant biomass globally coordinated within the plant?

A likely ortholog of *KLU* in rice is *PLASTOCHRON1* (*PLA1*), a timekeeper of leaf initiation [52]. Both *KLU* and *PLA1* are expressed at the periphery of the shoot apical meristem and in developing leaves, but act distantly at the meristem to determine leaf-initiation rate [52,53]. There are a number of genes similar to or acting in parallel with *KLU*/*PLA1*: one is *Arabidopsis AMP1*; another is that encoding the maize MEI2-like RNA-binding protein, *PLASTOCHRON2* (*PLA2*) [54], or its maize ortholog, *TERMINAL EAR1* (*TE1*) [55]; a third is the *Arabidopsis* microRNA miR156, which targets the *SQUAMOSA PROMOTER BINDING PROTEIN-LIKE* (*SPL*) genes to regulate the temporal pattern of leaf primordia formation [53]; and lastly are the *YABBY* genes [56], which act to determine organ dorsoventrality but also influence the phyllotactic pattern of initiation of new primordia. A common characteristic of all these genes is that they act non-cell-autonomously to inhibit leaf-initiation rate at the meristem by altering gene-expression patterns, restricting cell proliferation, and restricting growth at the central zone. Furthermore, these genes positively regulate organ size while extending plastochron length (that is, delaying the production of new leaves), thus providing a compensatory mechanism that links the rate at which leaves are produced to their final leaf size. Such a compensatory mechanism between organ size and organ initiation rate would mean that overall biomass production is kept relatively constant, but that it is achieved by producing either numerous small organs or fewer but larger organs. This phenomenon is well known to plant breeders: for example, some tomato varieties have large numbers of small fruits and others have fewer large fruits [57].

Mature leaves also integrate environmental signals, such as light quantity or carbon dioxide concentration, and distantly direct the morphology of newly initiated leaves in the meristem, leading to alterations in, for example, leaf thickness and stomatal density [58,59]. Several candidate systemic signals have been considered, including phytohormones, peptides, sugars and redox species [52].

Many of the growth-regulatory genes discussed above played an important part in plant domestication, which represents an accelerated form of evolution, resulting in exaggerated changes in organ shapes and sizes of the greatest interest to humans [60]. Understanding the mechanisms by which these genes operate in a regulatory network should allow further engineering of plant architecture and growth for future human needs.

Acknowledgements

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