Space to grow: interplay between growth and patterning in plant morphogenesis.

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2014-07-16

Keywords: Plants, Morphogenesis, Patterning, Growth, Auxin, PIN, KNOX.

Understanding the interactions between patterning and growth during morphogenesis has led to their study within biological models. In plants, maxima of the growth hormone auxin give positional information for patterning. Thus, a robust auxin signaling ensures correct organ patterning, underlining the necessity of a strong control and regulation of morphogenesis. The recent development of computational models and specific sensors of auxin signaling has improved the study of morphogenesis. However, despite the prominent role of auxin, pattern-generating mechanisms are diverse and it is still in discussion if auxin is the primary signal for founder cell specification.

Introduction

Morphogenesis refers to the shaping of organisms through the differentiation of cells, tissues and organs and their subsequent development. Genetic background and environmental conditions affect these multi-scale processes. In animals, morphogenesis occurs during embryogenesis and relies on growth and cellular movements. In plants, the presence of embryonic tissues both during embryonic and adult lives allows morphogenesis to occur all life long through differential growth. During morphogenesis, growth at the tissue level requires the coordination of mechanistic cellular activities consisting in changing cell shape, increasing the contact area between neighboring cells, and creating new cell walls during cell division. Subsequently, growth appears at the tissue level as the result of coordinated and controlled cell growth.

One major actor involved in growth during morphogenesis is the phytohormone auxin (see Box 1) and the accumulation of genetic data has shown that it plays various roles in all plant organs. Given the little integration between auxin and the gene network underlying morphogenesis, the use of modeling shows how patterns can emerge from local interactions in the gene network. Nevertheless, this approach is somewhat disconnected from growth and shape, and reveals the need to include the biophysical aspects of

Box 1. Glossary.

Angiosperms: The phylogenetic group of flowering plants.

Auxin: Refers to a class of phytohormones whose principal member is the indole-3-acetic acid (IAA). Auxin is produced at the shoot apex and in young leaves. Then, its polar transport establishes a morphogen-like gradient of concentration that gives positional information and promotes growth in concentration maxima.

Aux/IAA proteins: Short-lived nuclear proteins encoded by early auxin response genes They exhibit four conserved domains, the second of which, termed DII, is an auxin binding site involved in Aux/IAA protein degradation in presence of auxin.

Clonal analysis: Labeling of a group of cells and observation of their descendents (which constitute a clone) after mitotic divisions. This method enables to track cell fate and differentiation.

CUP-SHAPED COTYLEDON2 (CUC2): Transcription factor involved in the initiation of *Arabidopsis thaliana* leaf margin serrations.

Class I KNOTTED1-LIKE HOMEOBOX (KNOX1) genes: Encode homeodomain transcription factors involved in the shoot apical meristem (SAM) formation and maintenance and in leaf shape control.

Founder cell: The first initial and undifferentiated cell that is prone to become an organ or a cell type.

Phyllotaxis: Regular arrangement of leaves on the plant stem.

PIN-FORMED1 (PIN1): The most characterized auxin efflux carrier in *Arabidopsis*. Its polar localization is involved in polar auxin transport leading to the generation of local accumulation of auxin.

Polycomb-repressive complex2 (PRC2): One of the two classes of Polycomb-group Proteins (PcG), involved in the regulation of chromatin structure and subsequent epigenetic gene silencing. These proteins are conserved between plants and animals.

Root apical meristem (RAM): Pool of undifferentiated cells located at the tip of the root. The RAM sustains cells to elongate the primary root axis.

Shoot apical meristem (SAM): Pool of undifferentiated cells located at the shoot apex and responsible for the generation of lateral organs.

growth. Therefore, mathematics are used to simulate how complex shapes may arise from growth [1] and physical approaches give useful information to understand the mechanical processes at work during morphogenesis. Interactions between mechanically connected tissues and growth patterns participate in generalized growth, *i.e.* in growth at the organ level. For example, at the *Arabidopsis* shoot apex, mechanical stresses regulate microtubule orientations which contribute to morphogenesis [2]. Additionally, physical forces may influence the polarization of the auxin efflux carrier PIN-FORMED 1 (PIN1, see Box 1) [3]••, tightly coupling biological signals (auxin) to mechanical signals during morphogenesis.

Morphogenesis is also based on pattern formation, or patterning, which can be understood as the development of multicellular structures [4]. Thus, patterning is the regular organization of differentiated cells in a functional structure. In angiosperms (see Box 1), patterns arise from cell division, changes of cell shape, in the composition of cell walls and cytoskeleton and upon reaching a fully differentiated state [5].

Obviously, patterning and growth are firmly related to shape organisms and they have been well studied in recent years. In this review, I will address the role of auxin in the interplay between patterning and growth during plant morphogenesis.

Pattern emergence from auxin maxima in plants

While looking at a leaf, one often wonders how it was initiated at that precise position, or what makes a leaf different from that of an other species and what is responsible for the shape of its margin. So far, this non-exhaustive list raises the following question: how are patterns produced in plants?

Auxin-mediated patterning provides positional information

The leaves of *Arabidopsis thaliana* exhibit repeated margin protrusions, called serrations, where the growth hormone auxin, produced mainly from tryptophan [6] in young leaves and in the shoot apex, accumulates via its efflux carrier PIN1 and thus promotes localized growth by loosening cell walls (Figure 1.B). These zones of auxin accumulation are interspersed with zones where a growth repressor is expressed (CUP-SHAPED COTYLEDON2, CUC2, see Box 1, [7]••). The alternating pattern of auxin maxima and peaks of CUC2 expression is established by two feedback loops. The first loop promotes auxin accumulation via PIN1 that is polarly localized to the membrane adjacent to the neighboring cell with the highest auxin concentration, *i.e.* "up-the-gradient", in response to

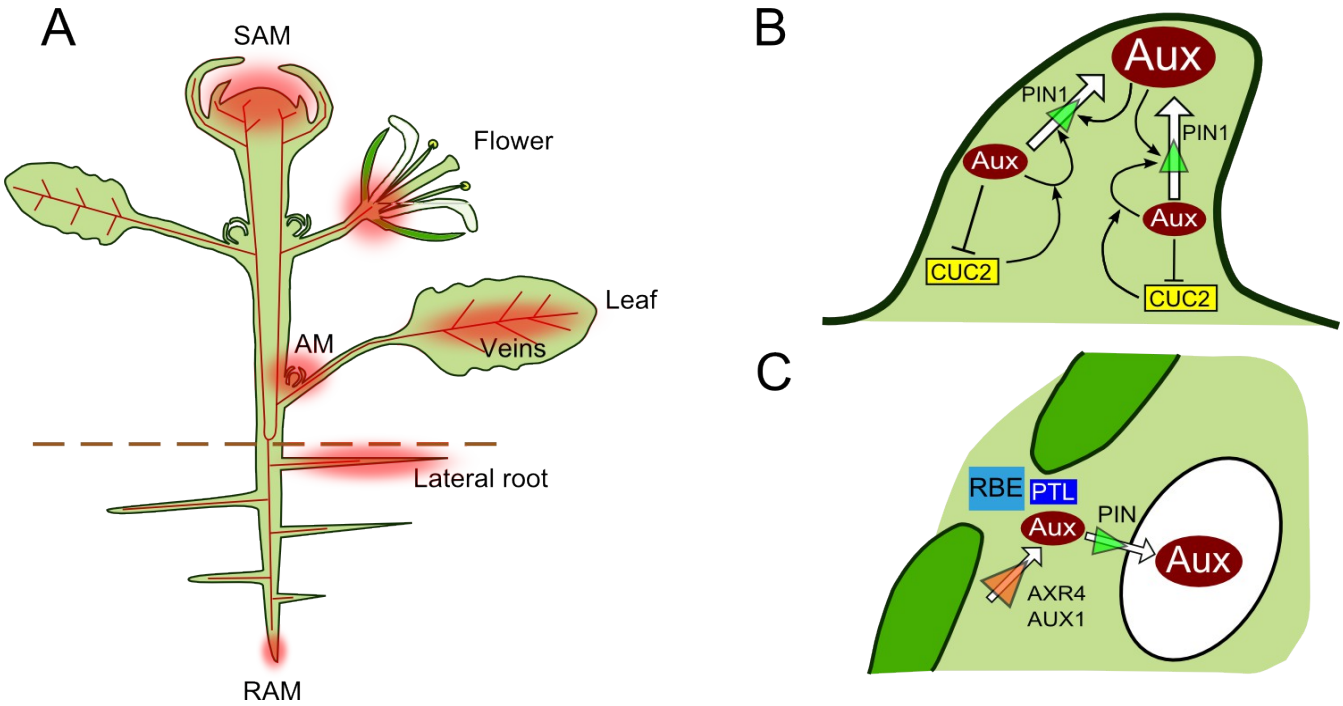

Figure 1. Pattern emergence from auxin maxima in plants. **(A)** Schematic representation of the plant model organism *Arabidopsis thaliana* showing zones (highlighted red and whose names are written next to them) where auxin accumulation provides positional information for organ patterning. High auxin concentrations induce lateral organ (leaves or flowers) initiation from the shoot apical meristem (SAM) and axillary meristems (AM), petal initiation in inter-sepal zones, leaf serration, root apical meristem (RAM) patterning, lateral root positioning and venation patterning. **(B)** Model for the regulation of *Arabidopsis thaliana* leaf margin development adapted from *Bilsborough et al.* [7]••. Auxin transport (white arrows) via PIN-FORMED1 (PIN1, green triangles) results in auxin accumulation. Auxin positively feeds back its transport by promoting PIN1 establishment up-the-gradient. A second regulation loop reorients PIN1 where CUP-SHAPED COTYLEDON2 (CUC2) is present and subsequently inhibits CUC2 by auxin. As a result, auxin maxima are stabilized. **(C)** Model for petal initiation in inter-sepal zones adapted from *Lampugnani et al.* [8]••. Two successive sepals are represented in dark green. In the inter-sepal zone, auxin is made available from two sources. One is based on growth repression by RABBIT EARS (RBE) and PETAL LOSS (PTL), and the other relies on the AUXIN-RESISTANT4 (AXR4)-AUX1 auxin influx pathway. Then, auxin transport via PIN proteins results in auxin accumulation in the petal initiation zone (white ellipsis).

auxin. It results in the formation of auxin minima and maxima. The second feedback loop consists in PIN1 reorientation in the presence of CUC2 and subsequent CUC2 inhibition by auxin. As a result, auxin maxima are spatially stabilized.

As in leaf margin protrusions, petal initiation in inter-sepal zones requires auxin accumulation from two sources [8]•• (Figure 1.C). One relies on growth repression by both the transcription factor PETAL LOSS (PTL) and the zinc finger regulatory protein RABBIT EARS (RBE). The other consists in an AUXIN RESISTANT4 (AXR4)-AUX1 influx pathway which makes auxin available for PIN-mediated transport towards the petal-initiation zone. In *ptl-1* mutants, the expression of the cytoplasmic auxin-inducible reporter *DR5rev:GFP-ER* is disrupted in cells at presumed sites of petal initiation, immediately internal to the inter-sepal zone where *PTL* is expressed in wild-type plants. It means that the loss of *PTL* function disrupts the auxin signaling of petal initiation and consequently impairs this morphogenetic process.

These two examples show the leading role of auxin on the morphological features of two organs: the leaf and the flower. Moreover, auxin plays a similar role on organ primordia themselves, meaning that it is involved not only when organs acquire their shape but also earlier, when they are initiated.

At the apex, auxin maxima act on boundaries between the shoot apical meristem (SAM, see Box 1) and leaves where they play an important role for pattern emergence (Figure 2.A). Lateral organs are reported to initiate in periphery of the SAM, where the expression of transcription factors, encoded by Class I *KNOTTED1-LIKE HOMEOBOX* (*KNOX1*, see Box 1) genes, is inhibited by auxin maxima. In *Arabidopsis thaliana*, mutations in *auxin response factor6* (*arf6*) and *arf8* cause abnormal expression of *KNOX1* genes [9]. This observation suggests that *KNOX1* repression in cells which will initiate leaves could be a direct read-out of auxin concentration [10]•, via the repression of *KNOX1* transcription by ARFs. It reveals the role of KNOX1 proteins in phyllotaxis patterning (see Box 1) and gives an example of how auxin concentration is interpreted into gene expression.

Additionally, more recent work has shown that a second path is at work during leaf differentiation (Figure 2.A), acting in parallel to that described above. The gene *KNAT2*, encoding another transcription factor, which belongs to the *KNOX1* gene family, is stably silenced by the complex composed of ASYMMERTIC LEAVES1 (AS1) and AS2 that physically interacts with Polycomb-repressive complex2 (PRC2, see Box 1) [11]• to give rise to a repressed chromatin state, somatically heritable and required for leaf differentiation.

In compound leaves, leaflet formation is dependent on maturation delay by KNOX1 proteins [12] and leaflets respond asymmetrically to auxin signaling according to their side in the leaflet primordium [13]. This direct consequence of the dynamic auxin transport in the SAM results in differential patterning of the proximo-distal axis on the left and right sides of the leaves.

Similarly to its role in leaf primordia, auxin is also involved in flower primordia initiation (Figure 2.B) where it activates the transcription factor MONOPTEROS (MP) that induces the expression of three genes encoding master regulators of flower development. These regulators are the floral fate specifier LEAFY (LFY) and two AINTEGUMENTA-LIKE/PLETHORA (AIL/PLT) transcription factors which regulate floral growth. In turn, LFY positively feeds back to the auxin pathway by increasing the expression o f *PINOID* (*PID*), which encodes a key regulatory kinase of auxin transport [14]•.

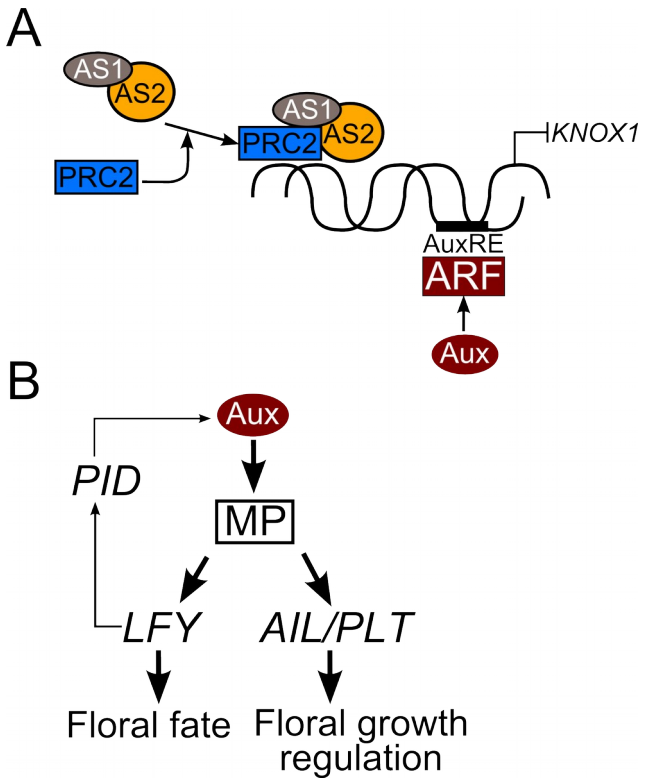

Figure 2. Auxin accumulation initiates new organs. (A) Auxin accumulation represses *KNOX1* gene expression in boundaries between the SAM and new leaves. Two parallel paths enable leaf differentiation. One relies on the repressive effect of AUXIN RESPONSE FACTORS (ARFs) that bind to Auxin Response Elements (AuxRE) when auxin is present. The other consists in the recruitment of the Polycomb repressive complex2 (PRC2) by the complex composed of ASYMMETRIC LEAVES1 (AS1)-AS2. The resulting repressive chromatin state is somatically heritable. **(B)** Auxin accumulation involvement in flower primordia initiation. Auxin activates the transcription factor MONOPTEROS (MP) that induces the expression of the floral fate specifier *LEAFY* (*LFY*) and two *AINTEGUMENTA-LIKE/PLETHORA* (*AIL/PLT*) transcription factors known to regulate floral growth. In turn, LFY increases the expression of *PINOID* (*PID*) that encodes a regulatory kinase involved in auxin transport.

Together, these examples underpin the fact that auxin concentrations provide positional information. Like in plant aerial parts, auxin-mediated patterning also occurs in lateral root positioning, root meristem patterning and vascular patterning (reviewed in [15], Figure 1.A). Nevertheless, the establishment of auxin differential concentrations requires a protein network that ensures its transport from its areas of production to its areas of action as a signaling molecule.

Auxin transport between and within cells

Models and mechanisms of polar auxin transport have been recently reviewed by Berkel *et al.* [16]•. The authors classify them into flux-based models and concentration-based models. In flux-based models, cells respond to the flux of auxin in a direction by promoting this transport in that direction. In concentration-based models, PIN efflux carriers are polarized up-the-gradient, requiring auxin concentrations to be sensed and compared between neighboring cells. In other words, if cell A has more auxin than cell B, PIN proteins in cell B will be polarized to the membrane adjacent to cell A, so that auxin accumulates into cell A.
Nevertheless, neither model fully explains the self-organization of auxin patterns. Additionally, microtubules indirectly influence PIN1 orientation within the cell [3]••. A local biomechanical signal can lead to microtubule reorientation and subsequent PIN1 repolarization. This change in PIN1 subcellular polarization deflects auxin flux and could be interpreted as a response to local cell expansion. Once into the cell, auxin accumulation is regulated, hypothetically by being transported from the cytosol to the endoplasmic reticulum. The recently discovered PIN-LIKES (PILS) proteins could be involved in this phenomenon and their activity might affect auxin nuclear signaling [17]. A similar role is expected for PIN5, an auxin efflux carrier located at the endoplasmic reticulum membrane [18].

The diversity of pattern-generating mechanisms

Differential auxin concentrations play a key role in pattern generation in plants as a source of positional information. However, activator-inhibitor systems and genetic oscillators are two other mechanisms at work that can even be included at certain levels into auxin-based patterning mechanisms.

In activator-inhibitor systems, both the activator and the inhibitor are initially present at the same concentration within a tissue. A locally higher concentration of the activator promotes the production of the inhibitor which diffuses faster than the activator and results in a high repression of the activator. In short, this model is characterized by a local activation together with a long-range inhibition and can be likened to a Turing mechanism since it relies on the difference of diffusivity between two factors to generate patterns in the absence of pre-existing patterns. In the case of organ initiation, models adapted from activator-inhibitor systems suggest that auxin maxima are responsible for local activation and that its depletion results in long-range inhibition [19]. Thus, local activation would rely on auxin directed transport but not on auxin self-production nor on its diffusion.

Alternatively, simple interactions can generate genetic oscillators which consist in the establishment of competence sites so that cells go through successive states. In *Arabidopsis*, root bending is cyclic and lateral root formation occurs within competent zones initiated periodically from the primary root tip by a set of oscillating genes [20,21]. Cyclic expression pulses of the auxin-signaling reporter gene *DR5:LUCIFERASE* mark the sites of future lateral root initiation, named prebranch sites. Yet, without exogenous hormone treatment, the expression of auxin inducible promoters fused with the coding region of the *LUCIFERASE* promoter does not have a detectable oscillatory behavior, suggesting that auxin is not sufficient to initiate a prebranch site. However, auxin may contribute to this initiation and participate in the final lateral root distribution pattern by modulating lateral root emergence. These findings question the relevance of an auxin-based oscillatory mechanism (reviewed in [22]).

Positional information provided by auxin concentration patterns is at the beginning of organ patterning, giving a “Russian doll”-like view of morphogenesis in which a global pattern stems from a smaller scale pattern. However, organ emergence from patterned cells at a specific position requires the contribution of directional growth to reach final size.

Interactions between patterning and generalized growth: a matter of tissue polarity

Key aspects of shape must be integrated in a dynamic growth model to understand the links between pattern-generating mechanisms and the distribution of growth that is generalized at the organ scale, by opposition to localized growth occurring at the cellular scale.

Clonal analyses (see Box 1) on the petal lobe of *Antirrhinum* (Snapdragon) revealed that petal asymmetry depends most on the direction of growth than on regional differences in growth rate [23]. It suggests that long-range signals maintain growth direction parallel to the proximo-distal axis along the petal, and it raises the issue of the nature of these long-range signals linking patterning and growth at the organ scale.

Combinatorial interactions between tissue polarity and growth result in the generation of diverse biological forms. Tissue polarity organizers are specific regions that anchor tissue polarity and define growth orientations [24]••. Principal orientations of specified growth are determined according to the propagation of polarity information towards or away from polarity organizers. Two views have been modeled to account for these particular orientations in a tissue. In axiality-based systems, orientations are defined through mechanical stresses, whereas in polarity-based mechanisms, genes influence the distribution of signaling molecules that establish a polarity field.
Evidence supporting an axiality-based system indicates that both cortical microtubule orientation and PIN1 polar localization can be controlled by the mechanical environment within the cell [2,3,25]. The orientations of stresses within a tissue are transduced and thus influence molecular properties of each individual cell. Since cell expansion is promoted by auxin, which

loosens cell walls, it is expected that PIN1 responds to the mechanical status of cell walls and also integrates auxin concentration in neighboring cells.
In polarity-based mechanisms, concentrations of signaling molecules such as auxin define a more local polarity at the cellular scale and mechanical constraints can influence resultant growth. In return, the resultant growth can influence polarity orientations in a feedback mechanism. The implementation of a polarity-based mechanism in Snapdragon flower development highlighted the fact that orientations can be specified regardless of stresses when generating complex tissue shapes and asymmetries [1].

In short, whatever the mechanism, tissue polarity stems from the contribution of signaling molecules and mechanical forces as well as their interaction, but the main difference lies in the nature of the primary signal triggering the establishment of polarity. Ultimately, tissue polarity is at the crossroads of the prior patterning and the forthcoming generalized growth.
The next question to address now is that of the regulation and control of morphogenesis in order to ensure the correct course of this complex developmental process.

Regulation and control of morphogenesis: one stimulus, various responses

Back at the cellular level, we must address the question of the regulation of morphogenesis. Cells are able to respond to competence factors only during particular developmental windows during which they will acquire their cellular fate. Otherwise, morphogenesis will exhibit a range of more and less severe alterations (Figure 3).

In the SAM, a pool of pluripotent cells is maintained by KNOX proteins, which are transcription factors regulating target genes involved in the control of hormone homeostasis. Lateral organ initiation occurs when *KNOX* gene expression is repressed by auxin maxima, at a specific time and a specific place. Several studies discovered the existence of windows of competence during which only competent cells are able to respond to *KNOX* expression, according to the context and the dose to which cells are exposed [10,12,26].
Cell-specific competence to respond to auxin has been recently mapped [27]••; transcriptomic analyses within four tissues of the *Arabidopsis thaliana* root showed that the response to auxin is interpreted differently according to cell types. Almost all auxin-regulated genes have a spatially-biased regulation, revealing that many cell type-specific auxin responses may not be detected at a larger scale (organ or organism scale) since local responses may go unnoticed among non-responsive cells. This study also showed an effect of auxin on transcriptional identity. For instance, genes that are relatively more expressed in the developing xylem are more strongly induced, compared to genes that are relatively more expressed in the maturing xylem. In this case, transcript sensitivity to auxin may predict the longitudinal expression of xylem-enriched genes in the root apical meristem (RAM, see Box 1).
A spatiotemporal control of lateral root development has been analyzed in both *Arabidopsis* and tomato plants [28]. In the auxin minimum zone and within a developmental window, pericycle cells respond more to auxin compared with other root cells and thus are prone to become lateral root founder cells (see Box 1).

As a result, a robust auxin signaling is required for correct patterning. The new sensor DII-VENUS enables the visualization of auxin signaling input [29]••. This sensor stems from the constitutively expressed fusion of an auxin-binding domain (DII, exhibited by several Aux/IAA proteins, see Box 1) to the fluorescent protein VENUS (a fast-maturating YFP variant). The DII domain responds to the local presence of auxin by targeting the sensor to the proteasome for degradation, meaning that the more auxin is present, the less DII-VENUS is detected. Thus, the local degradation of Aux/IAAs is monitored, as well as the input in the auxin signaling pathway. DII-VENUS degradation patterns indicate a high auxin signaling input in flower primordia, surrounded by cells with lower input. This is consistent with the fact that auxin is required for flower primordia formation [14]•. Interestingly, the use of DII-VENUS detected important temporal fluctuations in the auxin signaling input, whereas the *DR5::VENUS* sensor of auxin signaling output did not show such variations. In this sensor, the *VENUS* coding sequence is

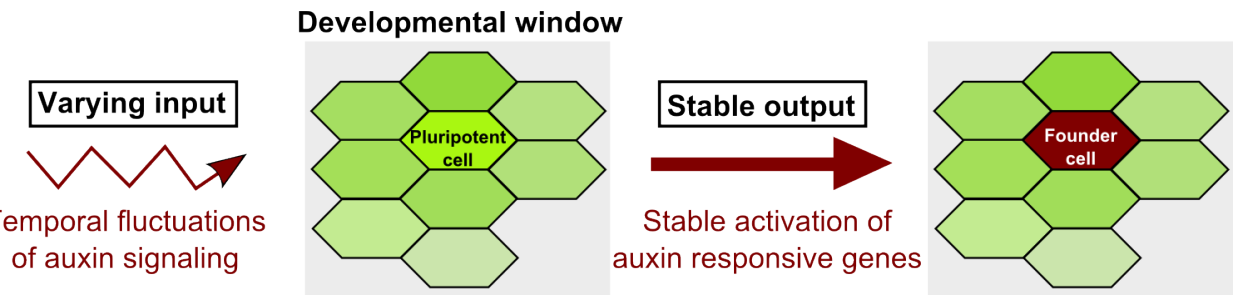

Figure 3. Founder cell specification by auxin signaling during developmental windows. In meristems, pluripotent cells (in green) perceive auxin signaling differently according to their cell type and to the dose of auxin to which they are exposed. In addition to spatial variations in auxin concentration (represented by cell color from light green to bright green), temporal fluctuations of auxin signaling contribute to its varying input. Pluripotent cell competence to respond to auxin signaling during a particular developmental window results in the stable activation of auxin-responsive genes leading to the specification of founder cells (in dark red) that will initiate a new organ. As a consequence, the stable output of auxin signaling buffers variations in the input and confers robustness to this mechanism.

downstream of the synthetic promoter *DR5rev* on which ARFs bind after their liberation consecutive to auxin-dependent Aux/IAA degradation. Thereby, *DR5::VENUS* monitors the final output of the auxin signaling pathway. The detection of a stable output was interpreted as a mechanism to buffer variations in the auxin signaling input within the SAM and thus leading to a stable activation of auxin-responsive genes. These findings pave the way for further investigation about the control of the read out of auxin signaling.

Discussion and future directions

Plants and animals, different tactics for a same struggle

Animals and plant kingdoms gather multicellular organisms with characteristic features of pattern formation. Some are shared but many remain unique to their respective clade or lineage [30] (Table 1).

Table 1. Shared and unique features of pattern formation in plants and animals

Actors involved in patterning	Multicellular organisms	
	Animals	**Plants**
Cell polarity modules	PAR proteins	PIN[1] proteins
Developmental TFs[1]	Hox genes	MADS-box genes
Interaction toolkit molecules[2]	Notch-BMP[1] Wnt-Hedgehog Cadherins-ECM[1]	Auxin Adhesive components
Regulators of chromatin state	PcG[1] proteins	
Mechanical forces	Reorient mitotic spindle	Relocalize PIN1 Reorient microtubules

[1] Abbreviations: BMP, Bone Morphogenetic Protein; ECM, Extracellular Matrix; TFs, Transcription Factors; PcG, Polycomb Group; PIN, PIN FORMED.
[2] Animal molecules are cited together with their respective ligand (molecule-ligand).

Development requires a set of toolkit genes differing between organisms but acting towards a same function. For example, cell polarity involves PIN-polarity modules in plants but PAR-polarity modules in animals [31]. Many toolkit genes are developmental transcription factors, encoded by MADS-box genes in plants and Hox genes in animals. Additionally, important toolkit molecules mediate interactions and communication between adjacent cells. In plants, they include the phytohormone auxin and adhesive components. In animals, it is Notch, Wnt and cadherins together with their ligands (BMP4, Hedgehog and extracellular matrices respectively). For instance, their periodic activity positions somites along the antero-posterior axis [32] and the auxin-dependent oscillating expression of auxin-responsive genes positions plant lateral roots [20]. The role of these molecules stems in pattern formation and morphogenesis in multicellular organisms, on account of the physical processes they participate at the mesoscale. In fact, the signaling role of mechanical properties during animal development is widely accepted [25]. As PIN1 relocalization and microtubule orientation in plants, the animal mitotic spindle orientation depends on mechanical forces [33]. Thus, these forces constraint the emergence of shape both in plants and animals. Moreover, given that the local chromatin state participates in developmental gene expression, Polycomb group (PcG) proteins are a prominent example of chromatin state regulators shared by both plants and animals.

In short, organisms belonging to different phyletical groups share analogous structures settled by the activity of homologous toolkit genes.

Looking for a primary signal for founder cell specification

A primary signal for founder cell specification is required for organ initiation but its identity remains unknown. Founder cells are able to respond to an induction signal in a specific manner. Auxin may be this induction signal but auxin is received by epidermal cells whereas the first signs of organogenesis are detected in underlying layers [8]••, raising the issue of the presence of an earlier signal, like the *DORNRÖSCHEN-LIKE* (*DRNL*) gene, which marks all floral organ founder cells in *Arabidopsis* [34].
Cytokinin signaling may be an alternative signal for founder cell specification. Indeed, cytokinin inhibits cell division and pattern formation [35] revealing an essential cytokinin-auxin antagonism during lateral root organogenesis as well as during the formation of adventitious roots [36].
Alternatively, transient manual root bending is sufficient to induce lateral root formation [37], suggesting that mechanical forces acting within the root can trigger organ formation. These forces may act by locally altering tissue mechanical properties (cell wall stiffness) via PIN1 repolarization and subsequent modulation of the auxin flux that triggers cell wall acidification and loosening.

In conclusion, plants, as well as animals, have evolved tightly regulated mechanisms occurring at precise time points that shape their organs and consequently their global body form. The integration of patterning and growth into computational models has improved our understanding of morphogenesis. Yet, many issues still remain, especially concerning the unknown into the auxin-signaling pathway or the nature of the primary signal for founder cell specification.

Acknowledgments

I thank Dr. Jean-Nicolas Volff and Dr. Dali Ma for their advice and critical reading of the manuscript. I also thank Dr. Angela Hay who suggested the subject of this review. Thanks to Dr. Antoine Corbin for his help. Finally, warm thanks to Sylvie Clappe for her friendship and her support during the hardworking days I spent to write this first review.

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