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MECHANISMS OF PATTERN FORMATION IN PLANT EMBRYOGENESIS

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Key Words *Arabidopsis*, cell fate, polarity, auxin, cytokinesis, cell division

■ **Abstract** Many of the patterning mechanisms in plants were discovered while studying postembryonic processes and resemble mechanisms operating during animal development. The emergent role of the plant hormone auxin, however, seems to represent a plant-specific solution to multicellular patterning. This review summarizes our knowledge on how diverse mechanisms that were first dissected at the postembryonic level are now beginning to provide an understanding of plant embryogenesis.

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INTRODUCTION

Multicellular animals and plants develop from the single-cell zygote. Divisions of the zygote, which are precisely controlled in many organisms, give rise to a population of cells, different from one another and from their progenitors, that will form the body plan of the embryo. The process by which cells are specified in three dimensions has been termed pattern formation. Mechanisms of pattern formation in plants can be put into context by comparing the well-studied fruitfly *Drosophila melanogaster* with the flowering plant *Arabidopsis thaliana*. In insects like *Drosophila*, the adult differs radically from the juvenile larva, but postembryonic development nevertheless uses the patterning information laid down during embryogenesis as a reference (189). A similar situation holds true also for flowering plants. The difference in appearance between the young seedling, which is the end result of plant embryogenesis, and the mature plant derives mostly from the later activity of local mitotic cell populations, the meristems. Although the mature plant is almost exclusively derived from the postembryonic activity of meristems, the overall organization of the plant body and hence the activity of the meristems appear to be conditioned by patterns generated in the embryo (74). Thus, mechanistic understanding of pattern formation in plants has to start from the embryo. Nevertheless, patterning mechanisms have been studied primarily at the postembryonic stage because of the relative inaccessibility and the lack of differentiation landmarks of the higher plant embryo. Here we focus on postembryonic patterning mechanisms that have emerged, compare them with animal counterparts, and finally describe how these mechanisms have helped to elucidate embryonic pattern formation in synergy with focused studies on plant embryo development. Several aspects of plant embryogenesis have been reviewed (73, 74, 82, 153, 175); here we attempt to highlight the mechanisms underlying patterning.

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PATTERNING MECHANISMS IN ANIMALS: LESSONS FROM FLIES

Genetics, experimental embryology, and molecular studies have combined to provide remarkable insights into the mechanisms involved in patterning the *Drosophila* embryo (67, 115). Formation of a patterned *Drosophila* embryo is the result of a cascade of gene activities that establish the body plan along the antero-posterior and dorsal-ventral axes. Along the antero-posterior axis, maternal gene products laid down in the egg are translated after fertilization. They provide positional information that regulates zygotic gene expression to specify a pattern of master regulatory genes encoding transcription factors in the segments and to stabilize the parasegment and the segment boundaries.

Different mechanisms are involved in specifying regions of the *Drosophila* embryo. Examples for the most important ones are briefly described here.

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1. *Combinatorial codes*: Region identity is established by the spatially specific transcriptional activation of an overlapping series of master regulatory genes, the homeotic selector genes, that encode transcription factors. The combined expression of the *Ultrabithorax*, *Abdominal-A*, and *Abdominal-B* genes of the *bithorax* gene complex is required to specify parasegment and segment identity (96). Combinatorial codes of transcription factors with overlapping expression domains give cells unique "addresses" and allow the transcription of cell-specific target genes, leading ultimately to differentiated characteristics (68).
2. *Feedback signaling in boundary formation*: The *engrailed* (*en*) gene, which encodes a homeodomain transcription factor, is expressed in cells along the anterior margin of the parasegment. These cells also express the segment polarity gene *hedgehog* (*hh*) and secrete Hh protein. Hh activates and maintains expression of the segment polarity gene *wingless* (*wg*) in the adjacent cells across the compartment boundary, and *wg* feeds back on *en*-expressing cells to maintain the expression of *en* and *hh*. These interactions stabilize and maintain the compartment boundary (174).
3. *Stochastic mechanisms*: Definition of fine-grained patterns (e.g., spacing of the ommatidia in the eye of *Drosophila* and the specification of neuroblasts by DELTA-NOTCH interactions) occurs by a process called lateral inhibition, in which a noncell-autonomous signal from a differentiating cell influences the differentiation choice of immediately adjacent cells (11).
4. *Gradients of signaling molecules* (*morphogens*): In the unfertilized egg, *Bicoid* mRNA is localized to the anterior end. After fertilization, the Bicoid transcription factor diffuses from the anterior end and forms a concentration gradient along the antero-posterior axis (34). Morphogens required for patterning also operate postembryonically during formation of the appendages of adult flies. These appendages develop from imaginal discs, which are monocellular epithelial layers consisting of undifferentiated, proliferating cells (78). In the wing disc the formation of an antero-posterior boundary is established by a pattern-organizing center. In the organizing center (OC), *decapentaplegic* (*dpp*) is expressed in a narrow stripe of anterior cells as a response to secreted hh from the posterior side (192). At the boundary of the anterior compartment, *hh* also induces *Patched*, an Hh receptor that binds but does not transduce the Hh signal, restricting the range of its own effect and the range of Dpp action through this negative feedback loop. Dpp, in turn, defines the expression pattern of downstream targets (38).

Mechanisms such as those described for *Drosophila* are well conserved in many animals. Examples of conservation of mechanisms include the following: *Antennapedia* class *Hox* genes in mouse and humans, which show striking similarities in their organization, expression, and combinatorial coding to the selector genes of the Antennapedia complex of *Drosophila* (108); lateral specification in vulva precursor cells of *Caenorhabditis elegans* involves LIN-12, the orthologue

of NOTCH (51); and SONIC HEDGEHOG, an *Hh* homologue in vertebrates, and *dpp* homologues act together during limb development (119).

Whether the mechanisms of pattern formation described are unique for the animal kingdom or represent common and "unavoidable" principles can only be determined when pattern formation in other kingdoms has been studied to a comparable degree. In this respect, a comparison with plant development is informative (109). Plants differ dramatically from animals in their life strategy, and multicellularity in plants and animals evolved independently. Animal cells are capable for some time of adjusting to a new position during embryogenesis, but at gastrulation most cells lose this ability and develop autonomously. Plants, however, have the capacity to develop most organs continuously in the postembryonic phase and most, if not all, living cells remain totipotent. This strategy makes sense because plants are sessile organisms that cope with changing environmental conditions by translating stimuli from the environment into developmental decisions. The potential to develop new organs and to initiate new meristems focuses in the meristems and recapitulates aspects of embryonic pattern formation (157). Did plants evolve unique mechanisms to ensure this developmental flexibility?

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PATTERN FORMATION IN PLANTS: LESSONS FROM WEEDS

Flower Development: A Combinatorial Code of Homeotic Gene Products

The development of the *Arabidopsis* flower elegantly illustrates the existence of combinational codes of transcription factors for regional specification in plants. Flowers arise from floral meristems at the flanks of inflorescence meristems that, in turn, derive from the shoot apical meristem (SAM). Once the flower primordium is initiated, the floral homeotic genes establish regional identities within the radial axis of the developing flower to specify concentric domains (whorls) (Figure 1*A*). The ABC model describes this combinatorial interaction of floral homeotic genes (29, 184, 111). With the exception of *APETALA2* (*AP2*), these genes encode MADS box transcription factors (112).

Ectopic expression of the ABC genes alone in leaves is not sufficient to transform leaves into flowers. Floral organ specification is also dependent on MADS box proteins of the SEPALLATA (SEP) class, which act as cofactors in activating complexes with B and C class proteins (Figure 1*A*) (66, 122, 123).

LEAFY (LFY), a plant-specific transcription factor, is required for the transition of inflorescence meristems to flower meristems (183). In addition to this role in promoting flowering, LFY plays a key role in floral patterning. *AP1* is a direct target of LFY (179). LFY requires UNUSUAL FLORAL ORGANS (UFO), an F-box containing protein that forms a SCF^{UFO} complex (120, 182) and is spatially restricted in a ring-like domain in all meristems, to activate *AP3* in the B domain of the flower (120). LFY can bind to *AG* promoter elements and activate *AG* (22). One of the

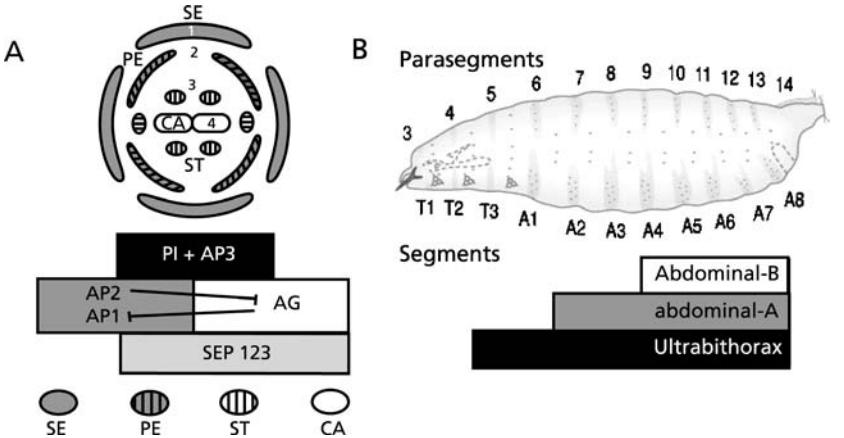

Figure 1 ABC model and the Ultrabithorax complex: examples of combinatorial codes of transcription factors involved in organ identity. *A*. The ABC model for *Arabidopsis* flower organ identity. Schematic representation of the flower, shown from above. The wild-type flower has a characteristic structure: sepals (SE) develop in the outermost whorl (whorl 1), petals (PE) in the second whorl, stamen (ST) in the third whorl, and carpels (CA) in the center (whorl 4). The floral homeotic genes are active in two adjacent whorls in the flower such that A alone specifies sepals, A and B specify petals, B and C specify stamen, and C alone specifies carpels. The homeotic genes are for A, *APETALA 1* and *2* (*AP1* and *2*); for B, *APETALA 3* (*AP3*) and *PISTILATA* (*PI*); and for C, *AGAMOUS* (*AG*). The combinatorial activity of three classes of homeotic gene products specifies floral identity: A (AP2, AP1) = SE, A + B (AP3 + PI) = PE, B + C (AG) = ST, and C = CA. Loss of one of the genes results in homeotic alterations. *B*. Combinatorial expression of genes of the bithorax complex characterizes each parasegment. Different homeotic transformations are found depending on the combination of residual genes. The absence of Abdominal-B, Abdominal-A, and Utralbithorax leads to conversion of parasegment 5–13 into 9 parasegments 4 (Modified from 126, 189).

cofactors required for this might be the homeobox transcription factor WUSCHEL (WUS) (101), which is expressed in the center of the meristems (86, 90).

The mechanism of a combinatorial code of overlapping transcription factors is reminiscent of that operating in *Drosophila*, but in plants it remains to be established how the spatial domains in the flower are set up in collaboration with earlier expressed meristem factors like UFO and WUS, and how these in turn are activated during embryogenesis.

An Organizing Center Under Feedback Control to Specify Stem Cells

The postembryonic SAM of *Arabidopsis* gives rise to leaves, stems, and flowers in a predictable and regular pattern. The SAM consists of a small dome of cells

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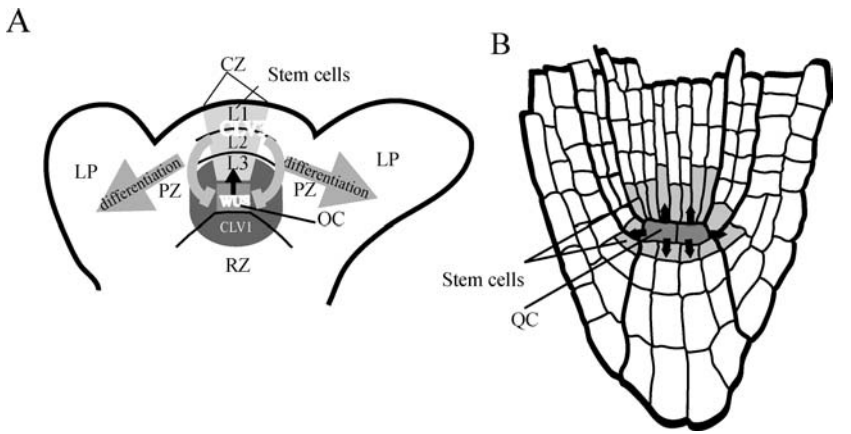

Figure 2 Organization and maintenance of the SAM. *A*. Schematic view of the different domains in the SAM. The central zone (CZ) contains slowly dividing cells (*in light gray*) that include the apical stem cells. Initiation of organ primordia takes place in the peripheral zone (PZ). Differentiation of central pith tissue is initiated in the rib zone (RZ). Different layers of the SAM are indicated with L1, L2, and L3. The mRNA expression domains of *CLV1*, *CLV3*, and *WUS* are depicted in dark, light-, and mid-gray, respectively. Model for shoot meristem maintenance: WUS expression in the OC promotes an as yet unidentified signal to specify stem cells. The stem cells restrict the range of WUS expression via CLV3 signaling. Cells that have passed the boundary defined by the *CLV* function establish organ founder cell populations. *B*. In analogy, the root meristem contains the QC, which promotes stem-cell identity of the surrounding cells (A: modified from 55, 142).

and it is organized into regions with different functions and fates. The SAM can be subdivided into layers and into zones. The cells of L1 layer divide anticlinally and therefore remain in this layer and eventually differentiate into epidermis. Cells in the L2 form a subepidermal cell layer and gametes. The third layer (L3) gives rise to the vascular system and the pith (Figure 2*A*). The central zone includes slowly dividing cells that replenish the peripheral zone and are required for maintenance of the SAM (69).

The *clavata* (*clv*) mutants accumulate too many cells in the central zone of the SAM and floral meristems (26, 27). *CLV1* and *CLV2* encode leucine-rich-repeat *trans*-membrane proteins, which can form a heterodimeric receptor molecule (28, 72). *CLV3* encodes a small polypeptide with an amino-terminal putative signal sequence (37). *CLV1* is expressed in the L3 layer of the central zone whereas *CLV3* is expressed in a central region of the L1 and L2 layers (Figure 2*A*). CLV1 and CLV3 likely undergo a receptor-ligand interaction (132). The active CLV receptor complex also contains one or more members of the Rop subfamily of Rho/Rac small GTPase-related proteins (170) and kinase-associated protein phosphatase (KAPP) (160, 186). CLV signaling restricts WUS, which is expressed in a subset

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of cells within the *CLV1* domain (Figure 2*A*) (83). In *wus* mutants, the meristem is not established during embryogenesis; after germination, axillary meristems are initiated and abort repeatedly, which is attributed to a failure to specify the central stem cells that are required to repopulate the peripheral meristem. *wus* mutations are epistatic to *clv1* (142), and *CLV3* is down-regulated in *wus* (20), suggesting that the CLV signaling pathway negatively regulates WUS activity. WUS is required for positive regulation of *CLV3* gene expression to promote stem-cell identity in the upper meristem layers (20, 142). Binding to the CLV1 receptor may prevent CLV3 from entering the WUS-expressing OC to repress *WUS* transcription there (88).

The current model for feedback regulation of stem-cell fate in the SAM of *Arabidopsis* postulates that the homeobox transcription factor WUS acts from an OC in the deeper layers of the meristem to specify stem cells in an overlying region. These stem cells express and secrete the CLV3 protein that activates a CLV1/CLV2 heterodimer and counteracts WUS activity (Figure 2*A*).

Thus, the size of a cell population in the SAM is controlled by a positive-negative feedback loop. The root meristem also contains an organizing center, the quiescent center, the existence of which was first inferred from laser ablation experiments (173) (Figure 2*B*). Overexpression of the CLV3 homolog CLE19 resulted in a restriction of root meristem size, suggesting that components of a CLV pathway also operate in roots, but in this case CLE19 affected the stem-cell daughters (25). Whether positive-negative feedback mechanisms keep animal stem-cell populations in check is unknown (155, 81).

Abaxial/Adaxial Fate Specification in Leaves and Boundary-Linked Organizers

Leaves are lateral organs of seed plants with proximal-distal and adaxial (central)-abaxial (peripheral) polarity. Leaves are derived from the flanks of the SAM and therefore possess an asymmetric relation to the rest of the plant, with the future adaxial leaf surface adjacent to the meristem and the abaxial surface distant from it (Figure 3*A*). Current models of the establishment of leaf polarity involve translation of a radial cue in the meristem into an adaxial/abaxial asymmetry in leaves.

An unknown signal from the SAM appears to activate the members of the *REVOLUTA* (*REV*)/ *PHABULOSA*(*PHB*)/ *PHAVOLUTA*(*PHV*) gene family. These genes encode homeodomain-leucine zipper (HD-ZIP) transcription factors containing a START domain, which may bind steroid-like ligands and/or miRNAs (35, 124, 130, 165). *REV/PHB/PHV* are first expressed in the SAM and uniformly within the organ primordia, but their expression becomes restricted to the adaxial side of the primordium as it initiates from the SAM. Dominant mutations and expression patterns suggest related roles for these three genes in promoting adaxial fate. Genes involved in promoting abaxial fate in leaves are members of the GARP family of putative transcription factors, *KANADI 1–3* (*KAN1-3*), and members of the *YABBY* family encoding for presumptive transcription factors such as *FILAMENTOUS FLOWER* (*FIL*) and *YABBY3* (35, 77, 136, 150). *Yabby* and *kanadi* double

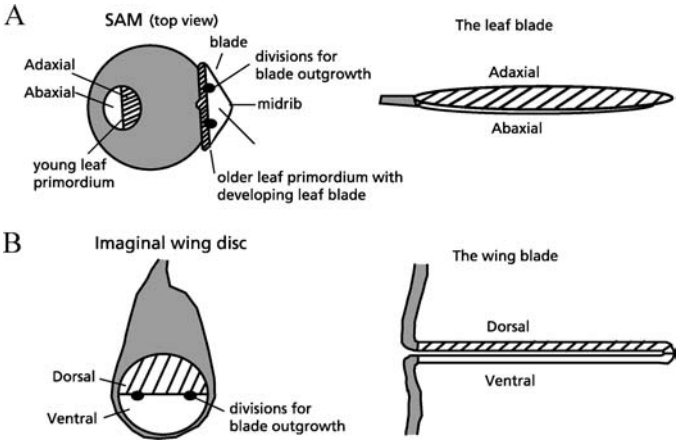

Figure 3 Boundary-linked organizers in outgrowth of *Arabidopsis* leaf and *Drosophila* wing. *A*. Schematic view of an *Arabidopsis* SAM shown from above, illustrating a model for leaf development. In this model, adaxial and abaxial domains of the leaf are specified early during leaf primordium development, while the primordium still resides within the SAM. The juxtaposition of adaxial and abaxial cell fates causes the subsequent development and outgrowth of the leaf blade. *B*. Schematic representation of the development of the wing blade from the imaginal disc. The dorsal and ventral surfaces start off in the same plane, but at metamorphosis, the sheet folds and extends, so dorsal and ventral surfaces come into contact with each other (modified from 107, 189).

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mutants show enhanced phenotypes, which suggests that these gene families are independently required for abaxial fate specification. Current models predict that the activated form of PHB or PHV acts as a repressor of *KAN1* and *KAN2* in the adaxial regions where continued abaxial expression in turn represses *PHB* and *PHV* (36). The *KAN* genes then activate members of the YABBY family on the side of the primordia away from the meristem, which leads to abaxial fate (18, 150). Interestingly, mutation of *KAN* and class *III HD ZIP* genes also perturbs central/peripheral patterning of vascular bundles (35).

The absence of an adaxial/abaxial boundary in many leaf polarity mutants results in the formation of radialized leaves without blade outgrowth (Figure 3*A*) (107, 180). Thus, the juxtaposition of adaxial and abaxial cell fates appears to be required for blade outgrowth. This resembles the wing disc organizer where the juxtaposition of an antero-posterior boundary promotes outgrowth of a wing blade from the wing imaginal disc (Figure 3*B*).

Radial Patterning: Moving Transcription Factors?

The distally located cortical stem cells in the *Arabidopsis* root meristem divide horizontally to give rise to daughters and new stem cells (33, 140). The stem-cell

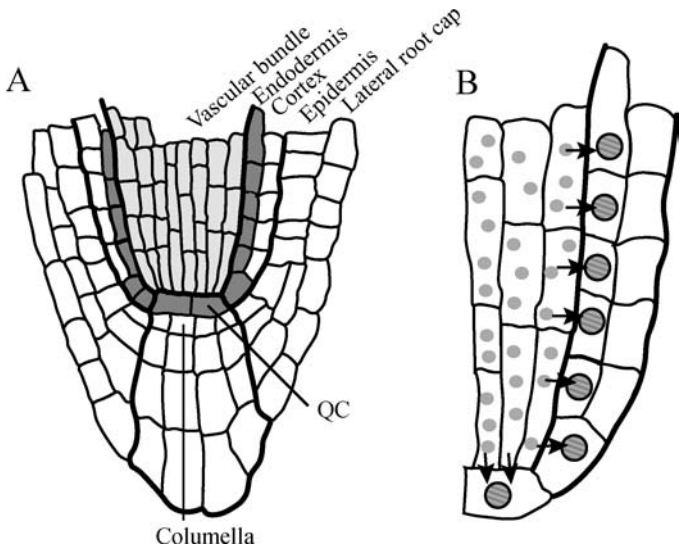

Figure 4 Schematic presentation of the cell-to-cell movement of the SHR transcription factor. *A*. mRNA transcription domains of *SCR* (*dark gray*) and *SHR* (*light gray*) in the *Arabidopsis* root tip. *B*. SHR protein (*light gray circles*) is moving from the vascular bundle to the nucleus of the endodermis, which is expressing SCR protein (*dark gray*).

daughters divide periclinally to give rise to endodermis and cortex. Two genes required for this aspect of radial pattern formation in the root are *SHORTROOT* (*SHR*) and *SCARECROW* (*SCR*) (13). SCR is essential for the rotation of cell division that separates cell layers (31, 139). In contrast, SHR plays a role in both cell division and specification of the endodermis.

SHR and *SCR* encode putative transcription factors of the GRAS family (63, 128, 191). *SCR* is expressed in the quiescent center (QC), cortex/endodermis initial and endodermis (Figure 4*A*) (191). Surprisingly, *SHR* is transcribed in the vascular bundle and not in the ground tissue cells where its action is required (Figure 4*A*) (63). Antibodies and a fusion protein between SHR and the green fluorescent protein (GFP) indicated that the protein is located in both the nucleus and cytoplasm of the stele, but appears to move into the nucleus of endodermal cells where its function is required (Figure 4*B*) (110).

The QC, a subset of four cells in the root tip, is required for maintaining the stem-cell population in the root meristem (173). Recently, it has been shown that SCR functions in the QC to maintain the stem-cell identity of root meristem initials (134). QC-specific expression of SCR in *shr* mutants did not rescue *shr* QC function, suggesting that SHR may also act in the QC by moving there (134). The data on SHR indicate that nonautonomous action of transcription factors can occur in the cytoplasmically connected cells of plant meristems (110). Recent results on

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ectopic SHR expression provide evidence for regulatory mechanisms that restrict SHR movement (146). Other moving transcription factors have been identified, but in contrast to SHR, the function of the movement of these transcription factors is unclear (93, 147).

In animals, movement of transcription factors occurs in the syncytium (a single-cell stage of embryogenesis with multiple nuclei), where, for example, Bicoid diffuses in a gradient from the anterior end to the posterior end to provide positional information for patterning the antero-posterior axis. We are not aware of examples of moving animal transcription factors as a patterning mechanism in multicellular stages.

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Epidermal Patterning by Lateral Inhibition

Plant epidermal cells specialize to produce hair-like structures separated by nonhair cells. In leaves, the initial patterning is stochastic so that hair cells (trichomes) arise randomly, but once formed, they inhibit neighboring cells from becoming trichomes. In the *Arabidopsis* root, the trichoblast always overlies the underlying cell wall between two cortex cells (33, 98). Basically the same genes pattern root-, leaf-, and stem-epidermal cell types. In trichomes, a cell-autonomous myb factor called GLABRA1 (GL1) was identified as a positive regulator of hair fate (97) and a related gene in atrichoblasts WEREWOLF (WER) is a positive regulator of nonhair fate (84). CAPRICE (CPC) and TRYPTYCHON (TRY), truncated Myb transcription factors, inhibit trichome and a-trichoblast hair fate (85, 137, 141, 177, 178).

WER in the root and GL1 in the shoot form a complex with a basic-helix-loop-helix (bHLH) transcription factor and a WD40 protein in vitro (121), which regulates GLABRA2 (GL2) transcription required for fate specification (131, 163). TRY and CPC interact in vitro with this complex, and genetic interactions suggest that this binding inactivates the complex (Figure 5*A*) (84, 85, 98, 137, 178). CPC and TRY presumably act as noncell-autonomous inhibitors of trichome and atrichoblast hair fate in the neighboring cells (Figure 5*A*) (85, 137, 177). In trichomes, where this process is unbiased, the first selected trichomes influence the fate of neighbors through these inhibitors. In the root epidermis, the relation to the underlying cortex cells biases this process in some way, but it is not yet clear how.

Neuronal specification in *Drosophila*, involving transmembrane signaling using the DELTA-NOTCH ligand-receptor pair, is a comparable lateral inhibition mechanism (Figure 5*B*) (8). Competitive inhibition of neighboring cells by TRY and CPC may also serve as an additional example of cell-to-cell movement of transcription factors, as described in the previous section.

Overview

Several mechanisms of plant pattern formation share similarities with those used in animals. The use of combinational codes for flower development and lateral inhibition for trichome and root hair outgrowth are prominent examples of such

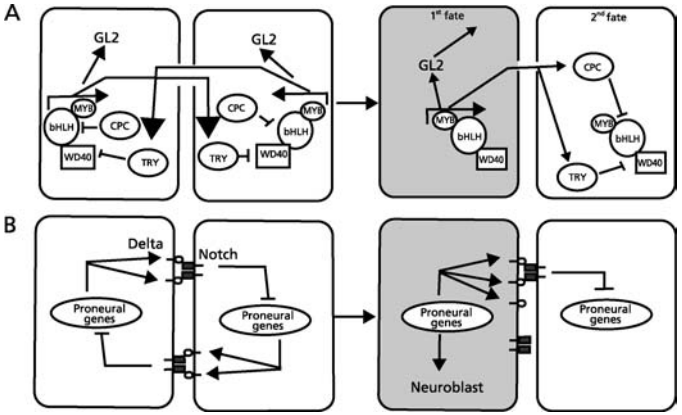

Figure 5 Lateral inhibition in *Arabidopsis* epidermis cells and *Drosophila* neurons. *A*. Model for epidermal patterning with an activator complex, consisting of myb, a bHLH protein, and a WD40 protein. The complex binds the promoter of GL2 to promote primary cell fate (root; atrichoblast; leaf:trichome). TRY and CPC inhibit the noncell-autonomous activator complex and small initial differences resolve into stable state in which one cell adopts primary cell fate and the other the second cell fate. *B*. Simplified model for neuroblast specification by lateral inhibition. DELTA is the ligand for the NOTCH receptor, both transmembrane proteins. Activation of NOTCH by DELTA leads to inhibition of the proneural genes and thus inhibits neuroblast fate. Small differences in Notch/Delta signaling between cells allow one cell to embark on the pathway to neural specification sooner than others; as a result, it sends a signal that prevents the other cell from a neural fate (modified from 138, 189).

similarities. However, some mechanisms may be plant specific. The negative feedback regulation of the WUS domain in the shoot meristem and the cell-to-cell movement of transcription factors to regulate gene expression serve as examples. Many genes involved in postembryonic patterning have specific expression patterns in the embryo, and ultimate understanding of pattern formation in plants will require determining how these expression domains are initiated. Therefore, a primary question in plant development remains: What is the origin of the distribution of transcription factors that set up cell-specification patterns? To find the origin of apical/basal, radial and bilateral patterns in plants, the genes involved in their initiation must be identified and analyzed.

IDENTIFICATION OF *ARABIDOPSIS* GENES INVOLVED IN EMBRYONIC PATTERN FORMATION

The principles of pattern formation during *Drosophila* embryogenesis have been used to categorize embryo-patterning mutants in *Arabidopsis*. In an attempt to isolate early patterning mutants, seedlings were analyzed and classified by loss

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or alterations in apical-basal or radial pattern elements at the seedling stage and the phenotypes were traced back to changes in regional division patterns in the embryo (104).

In assessing these embryo mutants, a distinction has emerged between pattern formation mutants, which are specifically affected in spatial control of position-dependent cell specification, and morphogenetic mutants, which can be affected in all processes leading to overall shape and variation in cell shape and number (15).

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Early Embryo Patterning Genes: Hints to Auxin-Response Factors

Alterations in embryonic cell divisions patterns in *monopteros* (*mp*) mutants indicated that these identified a candidate-patterning gene. The *Arabidopsis* zygote divides transversely into a small apical cell and a large basal cell. The apical cell results in most of the proembryo while the basal cell gives rise to the hypophyseal cell and the precursors of the distal root (Figure 6*A*). In wild-type embryos, the apical cell divides vertically, whereas in *mp* embryos the apical cell divides transversely. In later-stage *mp* embryos, procambium cells elongate inappropriately and hypocotyl and root development is abnormal (16). Later in development, MP is also required for continuous vascular tissue formation (127). The *MP* gene encodes a transcription factor of the AUXIN RESPONSE FACTOR (ARF) family (59), which binds to auxin-response elements in the promoters of genes inducible by this major plant hormone to regulate their transcription (166, 171).

mp-like phenotypes were also observed in *bodenlos* (*bdl*) and *auxin resistant 6* (*axr6*) mutant seedlings (58, 65). *bdl* carries a dominant mutation in *IAA12*, an early auxin-response gene of the Aux/IAA family, encoding short-lived, nuclear-localized proteins that contain four highly conserved domains (1–3, 57, 79). ARFs (like MP) interact with domains III and IV of these Aux/IAA proteins. The (semi-) dominant character of mutations in Aux/IAA genes such as *bdl* is thought to result from increased stability of the mutant protein (118, 190) or from the formation of nonfunctional dimers with Aux/IAA proteins or members of ARF class of proteins mediating auxin responses (52, 79, 172). Consistent with the possibility that BDL interacts with an ARF (i.e., MP), *mp* and *bdl* mutants show similar early embryo phenotypes, *mp* and *bdl* interact genetically, and two-hybrid studies indicate MP and BDL protein interaction (57). *MP* and *BDL* transcripts are gradually confined to subepidermal cells and eventually restricted to provascular cells and future QC, but only *MP* becomes expressed in the progenitors of the columella root cap. *MP* expression was detected in *bdl* early-embryos, showing that the *bdl* mutation does not interfere with *MP* transcription, a finding consistent with interactions between the gene products at the protein level (57). *NON-PHOTOTROPIC HYPOCOTYL4* (*NPH4*) encodes a member of the ARF family with amino acid sequence and overlapping expression patterns highly related to MP (60). MP and NHP4 can

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form heterodimers and can act redundantly in various processes, as is apparent under conditions with reduced MP activity (60).

In *axr6* embryos, abnormal orientation and timing of cell divisions are observed in the basal part of the embryo proper (65). AXR6 encodes the *Arabidopsis* CULLIN 1 (AtCUL1), a component of the SCF (for SKIP, CDC53/CULLIN, and F-box protein) TIR1 complex (64). The SCF^{TIR1} is a complex of ubiquitin ligases, binding Aux/IAA proteins (e.g., BDL) (49). SCF complexes attach a chain of ubiquitin molecules to target proteins, which leads to degradation of the tagged proteins by the 26S proteasome (12). The involvement of BDL, MP, and AXR6 in early root formation suggests that BDL and MP form a complex in vivo that prevents MP from activating target genes. In this scenario, BDL protein could be degraded in response to auxin by the SCF^{TIR1} complex, thus activating MP (57, 58, 64).

Early defects observed in *hobbit* (*hbt*) embryos resemble those found in *mp*, *bdl*, and *axr6* (187). Analysis of marker gene expression in the basal region of the early embryo and the homology of *HBT* protein to the CDC27/NUC2 component of the anaphase-promoting complex suggest that the *HBT* gene is required for cell division and progression of cell differentiation (17). Accumulation of IAA17/AXR3 in *hbt* seedlings suggests that HBT, as a component of the APC, may also be involved in targeting Aux/IAA proteins for degradation. The cell cycle–regulated *HBT* gene could couple cell division to auxin responsiveness by restricting certain auxin responses to dividing cells.

In contrast to the many transcription factors revealed by initial screens in early fly development, the *Arabidopsis* screens for early embryo patterning mutants revealed only a few transcriptional regulators, all suggesting a prominent role for the phytohormone auxin in early patterning. Given the wide range of physiological and developmental responses to ectopically provided auxin during regeneration in tissue culture, this is perhaps not surprising in hindsight.

Mechanisms of Meristem Formation During Embryogenesis

Analysis of mutant seedlings with specific shoot and root meristem defects provides valuable insights into pattern formation during embryogenesis. From the globular to the heart stage of embryogenesis, the apical region of the *Arabidopsis* embryo can be divided into three subregions that will give rise to cotyledons, cotyledon boundaries, and the SAM (6, 19, 91). The *CUP-SHAPED COTYLEDON* genes (*CUC1-3*), which encode transcription factors of the NAC family, are required for cotyledon separation and SAM formation (5, 164, 176). MP (see previous section) is also involved in cotyledon separation and in SAM formation (16). *mp cuc1* double mutants have enhanced numbers of fused cotyledons and *CUC1* and *CUC2*, normally expressed in a stripe between the cotyledon primordia at early heart stage, show altered expression in *mp* embryos. It was concluded that MP is required for repression of CUC1 in the cotyledons and for activation of CUC2 in cotyledon boundaries, but how *CUC1* gene expression is initiated remains

unclear. CUC1 is largely responsible for cotyledon separation in the *mp* mutant (7). Furthermore, *CUC1* and *CUC2* are expressed in the SAM and are redundantly required for SAM formation. CUC1 (and possibly CUC2) can activate *SHOOT MERISTEMLESS* (*STM*) expression in the SAM.

STM encodes a homeobox transcription factor of the *KNOX* family (92). Mature *stm* embryos lack a SAM and thus STM is required to maintain proliferation of cells in the SAM and/or prevent their differentiation from late-globular stage onward. Postembryonically, the cells at the position of the SAM are consumed by leaf primordia in *stm* mutants. Repression of differentiation by *STM* occurs mainly via repression of the MYB transcription factor ASYMMETRIC LEAVES1 (AS1), which is expressed in lateral organ primordia, because loss of *AS1* function in a *stm* mutant background rescues SAM formation (23).

The *WUS* gene, which is required for the maintenance of stem cells, is first expressed in the prospective L3 at the 16-cell stage. Later on in development, its expression is restricted to a subset of cells underneath the outer three cell layers of the SAM (in the L3) (101). The mechanisms or genes involved in initiation and asymmetric inheritance of WUS expression are not known. *wus* and *stm* mutants display different phenotypes, and recent evidence corroborates that WUS and STM act independently to generate a self-maintaining meristem. Ectopic expression of WUS and STM induces the expression of downstream target genes and meristem activity in the shoot (44, 87). Ectopic WUS expression in roots induces shoot-specific pattern elements, indicating that WUS establishes stem cells with intrinsic shoot identity (43). WUS induces expression of *CLV3*, but not *KNAT1* or *KNAT2*. STM does not regulate *CLV3*, but can induce *KNAT1* and *KNAT2*. Conversely, STM suppresses differentiation independently of WUS and is required and sufficient to promote cell division in stem-cell daughters before these cells are incorporated into organs (87).

The *PLETHORA* (*PLT1-2*) genes are required for generating a stem-cell niche in the embryonic root pole (Figure 6*B*) (4). The *PLT* genes encode AP2-class putative transcription factors, which are essential for QC specification and stem-cell activity and whose expression depends on auxin-responsive transcription factors. Ectopic expression of *PLT* genes in the early embryo transforms apical regions into hypocotyl and root identities, indicating that *PLT* genes play a role in the establishment of all basal embryo identities, which is reminiscent of the role of WUS in the SAM.

Interestingly, the early expression dynamics of the members of the *WUS RELATED HOMEOBOX* (*WOX*) gene family suggest that the specification of the embryonic meristem is presaged by a partitioning of cell fates along the apical-basal axis (Figure 6*A*) (54). Three *WOX* genes (*WOX2*, *9*, and *8*) partition in apical, central, and basal domains from the zygote to the eight-cell stage of embryogenesis. After the eight-cell stage, *WOX2* marks shoot-specific pattern elements and *WOX*5 marks the QC in the basal part of the embryo (Figure 6*A*). Detailed mutational analysis of the *WOX* genes, whose phylogenetic relationships suggest redundant activities, should indicate whether this partitioning into homeobox-expressing domains has a functional significance that resembles the

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partitioning of animal embryos in regions specified by combinatorial codes of homeobox proteins. The recent finding that a MAPKK, YODA, can influence cell fate of the zygotic daughter cell raises the question whether MAPK signaling might operate to partition fate determinants like the *WOX* genes (95).

In summary, the proper activation of critical patterning genes involved in both shoot- and root-meristem formation that have been identified so far suggests a role for auxin signal transduction in the early embryonic specification of meristem domains. Candidate factors involved in early partitioning of cell fates, which might set the stage for region-specific shoot and root meristem genes, have recently been identified, but their mode of action and their connection to later-acting transcription factors remain to be investigated.

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Role of Polar Auxin Transport During Embryogenesis

In *Arabidopsis* embryo patterning screens, mutations in the *GNOM/EMB30* (*GN*) gene were found to affect embryo polarity along the apical-basal axis and the orientation of early cell divisions (102, 104). *GN* encodes a Brefeldin A (BFA) sensitive membrane-associated guanine-nucleotide exchange factor on ADP-ribosylation factor G protein (ARF GEF) involved in vesicle trafficking (21, 148, 149, 159).

In *Brassica juncea*, a remarkable range of aberrations resembling embryos with mutations in the *GN* gene has been observed after exogenous application of auxins, auxin antagonists, and polar auxin transport (PAT) inhibitors (53). The induced phenotypes at later stages of development resembled mutations in the putative auxin efflux carrier *PIN-FORMED1* (*PIN1*) (53). The *pin1* mutant exhibits reduced polar auxin transport and develops naked, pin-shaped inflorescences and defects in cotyledon number, size, shape, and position (45, 116). PIN1, a putative auxin efflux facilitator postembryonically involved in polar auxin transport from the shoot to the root, is located at the basal end of vascular cells. PIN1 rapidly cycles between the plasmamembrane and endosomal compartments and is internalized upon treatment with BFA, an inhibitor of vesicle transport (47). During embryogenesis, the localization of PIN1 becomes polarized from midglobular stage onward, and coordinated polar localization of PIN1 is disrupted in *gn* embryos (159). Analysis in plants harboring a specific mutation in the BFA-interacting site of a still-functional GN protein showed that PIN1 localization was no longer sensitive to BFA whereas other trafficking processes remained sensitive. Thus, GN is specifically required for PIN1 recycling between the plasma membrane and endosomes (46) and defects in this process might lead to altered vesicle transport, resulting in abnormal localization of PIN1 protein. Internalization upon BFA treatment is also observed for other PIN family members (41, 50), which might indicate that GN could play a role in the localization of other PIN proteins. Analysis of partial loss-of-function alleles substantiates a role for GN in auxin transport during embryogenesis and postembryonic organ development (48).

Direct evidence for an important role of PIN proteins during embryo development comes from the analysis of PIN7 and PIN4. PIN7 is detected after the zygotic

division at the apical surface of basal cell descendants, and reverses orientation at the globular stage (40). PIN4 is detected from late-globular stage embryos onward along the surface of the hypophysis and at the basal end of the adjacent suspensor cell (39). These locations correlate with an auxin maximum in the apical cell at early stages of embryogenesis and relocation of this maximum to the basal pole at the globular stage (Figure 6*B*). Interestingly, *pin7* mutants failed to establish the apical auxin maximum in early stages of embryogenesis, which resulted in abnormal development of the first stages of embryogenesis, but recovery occurred from the globular stage onward (40). In *pin4* embryos, abnormal divisions were observed in the hypophyseal cell derivatives and suspensor cells with low percentage (39). Loss of multiple PIN family members in extreme cases phenocopied *gn* and effects of chemical inhibition of auxin transport, suggesting a high redundancy among PIN genes (40). Taken together, the phenotypes and the altered auxin distribution of mutants in putative auxin efflux carriers and in the ARF-GEF that regulates their trafficking are consistent with the notion that polar auxin transport plays an important role in embryo pattern formation.

The association of patterning elements and division activity in the root with an efflux carrier-dependent auxin-response maximum that appears from embryogenesis onward indicated that auxin distribution in maxima plays an instrumental role in root patterning and cell division (Figure 6*C*) (133). Interestingly, PIN-dependent auxin distribution might represent a common principle for embryonic and postembryonic development, where outgrowth of embryo regions and root and leaf primordia is always associated with distal auxin maxima (Figure 7*A*). The direction of the auxin flux around maxima in shoot primordia appears to be reversed from the flow in root primordia (Figure 7*B*,*C*) (14). In the shoot apical meristem, such a local accumulation and surrounding depletion of auxin may regulate primordial spacing or phyllotaxis (129).

In summary, distal accumulation of auxin in diverse primordia appears to be instrumental in primordium outgrowth and patterning, which indicates that auxin acts as a positional cue of principal importance that can be utilized in multiple developmental contexts. For the basal auxin maximum of embryo and root, the *PLT* genes have emerged as candidate downstream transcription factors, a finding that should allow for a further dissection of the mechanism by which embryonic auxin accumulation can generate region-specific responses (Figure 6*B*) (4). The mechanisms whereby auxin distribution patterns are set up and changed, and how these interact with transcription factors, remain to be elucidated.

ARABIDOPSIS EMBRYO MUTANTS IDENTIFY GENES INVOLVED IN CELL MORPHOGENESIS

In several plant screens for embryo patterning genes, mutants were categorized by early embryonic division patterns. Many of the mutants recovered were affected in the orientation and execution of cell division and found to be involved in basic

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cellular processes that consequently affect pattern formation. Why were those mutants not emphasized in the initial animal screens? The fly embryo is subdivided into segments that have characteristic differentiation landmarks (e.g., denticles), and can be used to select for alterations in the identity of cells in specific regions in the embryo. In plants, however, cell division planes have long been the only criterion on which to select for patterning mutants. In addition, plant embryos might tolerate gross changes in cellular processes with more flexibility, although these often lead to embryo lethality in animals (71, 125, 145).

Cytokinesis mutants in *Arabidopsis* were initially interpreted as radial pattern mutants because of defective epidermal cell specification (104). These mutants were later noted to have embryos with more general cellular defects such as incomplete cell walls and enlarged cells with one or more large nuclei (10, 94).

In plant cytokinesis, formation of a new cell plate occurs in the phragmoplast, a complex structure containing microtubules, microfilaments, and vesicles (62, 113, 156). At late anaphase, golgi-derived secretory vesicles carrying cell wall materials are transported to the equatorial zone of the phragmoplast. Fusion of these vesicles gives rise to a membrane-bound compartment, the cell plate. The cell plate expands until it reaches the division site on the mother cell wall (30). Once this attachment has taken place, the cell plate undergoes a complex process of maturation during which callose is replaced by cellulose and pectin (135). Two plant-specific cytoskeletal arrays of microtubules and actin filaments, the preprohase band and the phragmoplast, play central but as yet poorly understood roles in the orientation and expansion of the cell plate and in the execution of cytokinesis (9, 117, 162). Thus genes implicated in vesicle trafficking and fusion and cytoskeletal dynamics will affect plant cytokinesis. Indeed, isolation of cytokinesis mutants revealed genes involved in both processes.

1. *Vesicle trafficking and fusion*: Genes required for the execution of cytokinesis are *HINKEL/NACK1*, *KNOLLE* (*KN*), and *KEULE* (*KEU*). *HINKEL/NACK1* encodes a plant-specific kinesin-related protein required for the cell cycle–related reorganization of phragmoplast microtubules by regulating the activity and localization of ANP1/NPK1 (a MAPKKK), which is involved in cell plate expansion (114, 161). A complex of v-SNARE and t-SNARE (syntaxin) proteins mediates fusion of vesicles to their target membranes (185). *KN* encodes a cytokinesis-specific syntaxin (80, 94). *KEU* encodes the yeast Sec1 homologue (10). Sec1 proteins are key regulators of vesicle trafficking and specifically regulate the steps involved in tethering/docking and membrane fusion, by interacting with syntaxins (56). KEU interacts genetically and biochemically with KNOLLE (10, 181). In both *keule* and *knolle*, vesicles are transported to the equator of a dividing cell but do not fuse (181). *knolle keule* double mutants do not show defects in the cell cycle, but fail to undergo cytokinesis, which results in giant single cells with many nuclei (181). Therefore, *KN* and *KEU* cooperate to promote vesicle fusion in the cell division plane (152). Isolation of a KN interactor via a biochemical approach yielded AtSNAP33, a homologue of the animal t-SNARE SNAP 25, required for plant cytokinesis. AtSNAP33 belongs to a small AtSNAP25 gene

family (61). Studies in animals show that t- and v-SNARE proteins are involved in fusion of vesicles to plasma- and endomembranes (42). Further research on t- and v-SNARE complexes should provide links to dissect the various requirements for vesicle trafficking during embryo development.

2. *Cytoskeletal dynamics*: An example of a gene required for proper orientation of the plane of division is *FASS/TONNEAU2*, (104, 151, 162, 168). *fass* mutant embryos are made up of irregularly shaped, enlarged cells that are not arranged in regular rows (168). TONNEAU2/FASS encodes a type 2a protein phosphatase (24), and it remains to be investigated how it is involved in formation of the preprophase band and ordered microtubular arrays that make up the plant cytoskeleton (105, 169).

Members of the *pilz* and *titan* groups of mutants also have abnormally formed embryos as a result of cytoskeletal defects that interfere with mitosis and cytokinesis. The endosperm of *ttn* does not cellularize and contains a small number of extremely enlarged nuclei (89). The *pilz* mutant embryos lack microtubules but contain actin, which results in a mushroom-shaped embryo with one or a few grossly enlarged cells containing one or more enlarged nuclei (103, 106). Several *ttn* mutants are allelic to *pilz* group mutants: *ttn1* is allelic to *champignon* and *ttn5* is allelic to *hallimash* (106). *TTN5* encodes a small G protein Arl2 with a predicted role in regulation of intracellular vesicle transport (106). Other genes of the *pilz* group encode orthologs of mammalian tubulin-folding cofactors (TFCs), which mediate the formation of α/β tubulin heterodimers in vitro (158). The availability of mutations in these genes paves the way for future studies on the requirement of the microtubular cytoskeleton for development of specific cell types (99). Similarly, the discovery of weak conditional alleles in actin polymerization factors in trichome mutants will allow future studies on the role of actin in pattern formation (100).

Mutations in genes involved in sterol biosynthesis *FACKEL/HYDRA2* (*FCK/HYD2*), *STEROL METHYLTRANSFERASE1/ CEPHALOPOD* (*SMT1/CPH*), and *HYDRA1* show pleiotropic defects during embryogenesis (32, 143, 144, 167). *FCK* and *SMT1* are expressed from the octant stage onward, and cell division and expansion defects in *fck*, *smt1/cph and hyd1* during early embryogenesis result in embryos with abnormally shaped cotyledons and reduced central and basal regions (32, 70, 143, 144, 187). These defects were postulated to be caused by alterations in unidentified steroid signals in these mutants (143, 144). Alternatively, these findings may reflect a role for bulk sterols during embryogenesis (154). In s*mt1*^{orc} seedling roots, cell-polarity defects were observed and localization of PIN1 and PIN3 was disturbed. These data suggested a link between sterol biosynthesis and efflux carrier positioning that may be explained either by defects in sterol trafficking (50) or by the existence of sterol-dependent membrane microdomains (187).

CONCLUDING REMARKS

Transcription factors identified by embryo-patterning screens have linked early patterning events with auxin-response factors. Other transcription factors with a role in embryonic patterning have been identified through the analysis of genes

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involved in postembryonic patterning processes. The shoot meristem and its stem cells are specified and maintained by two parallel mechanisms involving WUS and STM. Combinatorial activity of SCR, SHR, and PLT provides positional information for specifying the stem-cell niche in the root meristem. These factors exemplify the use of combinatorial coding in the plant embryo.

Differential auxin distribution has been correlated with a number of developmental responses during embryogenesis and organ outgrowth. The precise spatial auxin-distribution pattern during embryo development requires PIN protein activity, presumably through a plant-specific mechanism, that might be directly involved in activation of the patterning genes identified through postembryonic screens. For example, PLT activation in the basal domain of the embryo may be promoted by accumulation of auxin in an MP-dependent way to specify the root stem cells. Interestingly, the dynamic expression during embryogenesis of WOX homologs suggests even earlier partition events, but how and if the WOX dynamic expression is correlated with the expression of other transcription factors involved in embryo patterning and early auxin distribution patterns, discussed above, remains to be elucidated.

Identification of many genes from morphological mutants affecting cell polarity and auxin transport has provided specific entries into vesicle trafficking and cytoskeletal functions, which are essential for cytokinesis and influence cell division planes in the early embryo. The merger of these lines of investigation with the growing knowledge on transcription factors involved in embryonic patterning should allow the major mechanisms for plant embryonic pattern formation to be determined in the near future, thereby informing us on the universality of these mechanisms.

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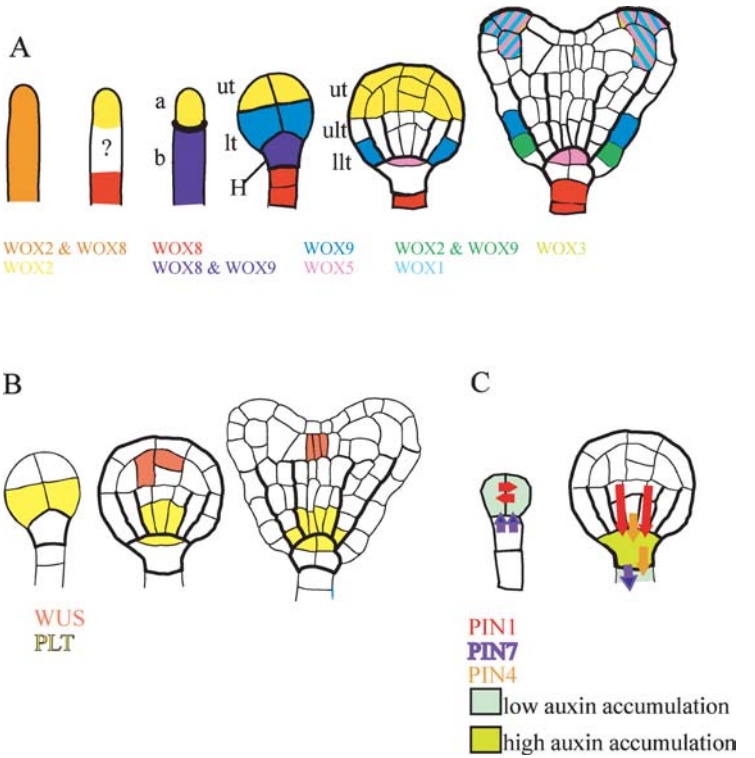

Figure 6 Embryo development. *A*. The temporary expression of different members of the WOX family during early embryo development. The egg cell and the zygote show overlapping *WOX2* and *WOX8* expression, which later on localize to the different poles of the zygote. After the first zygotic division, *WOX2* is localized to the apical cell (*a*) and the basal cell (*b*) expresses *WOX8* and *WOX9*. The basal cell will give rise to the suspensor, which expresses *WOX8*. WOX9 becomes restricted to the uppermost suspensor cell, the hypophyseal cell (*H*). The apical cell will form the embryo proper, which can be divided into an upper tier (*ut*) and a lower tier (*lt*). The upper tier will give rise to most of the shoot tissues and express only *WOX2*, and the lower tier gives rise to the hypocotyl and root and expresses only *WOX9*. *WOX9* later on during development becomes restricted to the protoderm layer [in the lower lower tier (*llt*) together with *WOX2*]. *WOX5* is turned on at later stages of development and is expressed in precursors of the QC. At heart stage, *WOX5* can also be detected in the cotyledon primordia together with *WOX1* and *WOX3*. *B*. Transcription domains of PLT and WUS stem-cell organizing genes during early stages of embryogenesis. *C*. PIN expression and presumed auxin distribution. Auxin accumulates in the apical cell of a two-cell stage embryo through PIN7-mediated auxin transport. Later on during development, auxin is transported to the hypophyseal cell in a PIN1- and PIN4-dependent manner. Auxin accumulation patterns inferred from auxin-responsive reporter genes. Accumulation of auxin (*green*) at different stages of development triggers organ-specific downstream events.

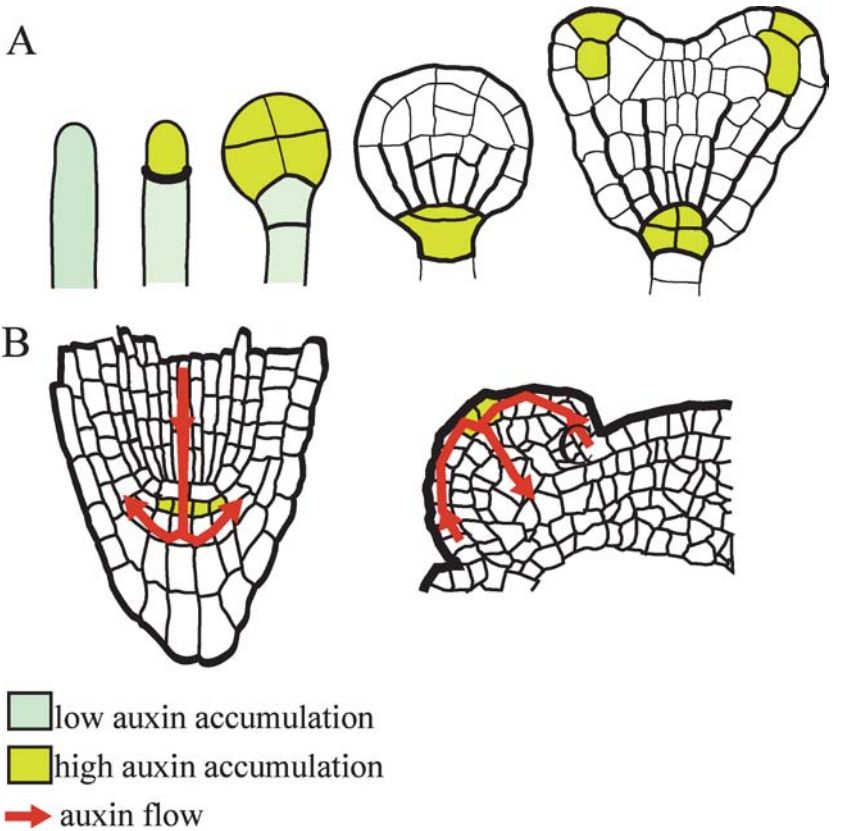

Figure 7 Auxin maxima during plant development. *A*. Inferred auxin distribution during early stages of embryogenesis. Overall low accumulation (*light green*) is gradually restricted to the apical cell eight-cell-stage embryo. At late-globular stage, auxin accumulates in the hypophyseal cell and from heart stage onward, additionally accumulation is detected in cotyledon primordia. *B*. Inferred auxin flow (*red arrows*) via the auxin maximum (*green*) in the root tip (*left*) is reverse of the auxin flow through maxima in leaf primordia (*right*).

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