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Minireview

Molecules and Cells

Interdomain Signaling in Stem Cell Maintenance of Plant Shoot Meristems

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The plant shoot meristem maintains a group of stem cells that remain active throughout the plant life. They continuously generate new cells that are then recruited for organ initiation in the peripheral zone. Stem cell proliferation and daughter cell differentiation has to be integrated with overall growth and development of the diverse functional domains within the shoot apex. Several studies have revealed extensive communication between these domains. The signaling mechanisms employed comprise diffusible peptides, directional transport of plant hormones, but also complex interactions between transcription factors, that together establish a panoply of regulatory inputs that fine-tune stem cell behavior in the shoot meristem.

INTRODUCTION

Postembryonic plant growth is based on the divisional activity of stem cells. Some stem cells are established already during embryogenesis at the opposite poles of the plant embryo and maintained during the entire life cycle. The organization, localization and maintenance of the tissues harboring stem cells, called meristems, depends on regulatory mechanisms involving cell-cell communication, hormone signaling, as well as small peptide signals and their corresponding signaling pathways. In this review, we will discuss the mechanisms of communication between different functional domains of a plant's shoot meristem with a specific view upon the regulation of stem cell fate.

Shoot meristem structure

The shoot apical meristem (or SAM) gives rise to the aerial parts of a plant. It can be subdivided into different domains on the basis of cell division rate and orientation, cell origin, cell morphology, as well as gene expression profiles. Slowly dividing stem cells are located in a central zone (CZ) at the tip of the SAM (Fig. 1). After a division, daughter cells are displaced from the center to the peripheral zone, either to contribute to the formation of new organs, or to create the boundary regions between them. The size of an SAM may change during development, but the overall shape is stably maintained. In a longitudinal section, three layers (L1 to L3) can be classified due to cell division plains and cell origin. L1 and L2 cells divide only anticlinally; their origin can be traced back to three stem cells for each layer. Cells of the L1 layer will form the epidermis. Mesophyll tissue of an organ is formed by L2 layer cells. The multilayered L3 shows anti- and periclinal cell divisions and forms the corpus of a plant. Stem cells are located in the upper 4-5 cell layers of the central zone and therefore contain cells of all three layers. Below the stem cells, a small cell population with a low cell division rate builds the organizing center (OC). The OC is required for the initiation of stem cells during embryogenesis and for their later maintenance. Cells below the OC, in the rib zone of the meristem, are responsible for the bulk growth. Differentiated vasculature that extends from the plant body into the meristem ends in the rib zone.

Intensive communication between CZ and OC

Signals from the OC are required to maintain the stem cell population. One of these signals is WUSCHEL (WUS), a homeodomain transcription factor expressed in OC cells. *wus* mutants fail to maintain stem cells, and misexpression experiments show that WUS is sufficient for stem cell induction in the upper layers of the SAM and at adaxial positions of lateral organs, but not in the whole plant (Brand et al., 2002; Schoof et al., 2000). WUS activity is counteracted by the CLAVATA signaling pathway, comprising the signaling molecule *CLAVATA3* (*CLV3)*, and several receptor proteins. Stem cells express the small and secreted 12aa peptide CLV3, which belongs to the *CLE* (*CLAVATA3/ESR related*) family (Brand et al., 2000; Fletcher et al., 1999; Kondo et al., 2006). A reduction in stem cell number during growth will cause reduced *CLV3* expression and release *WUS* from *CLV3* dependent repression. Stem cell overproduction would in turn restrict or eliminate *WUS* activity. Together, WUS dependent stem cell induction and CLV3 dependent *WUS* repression act as a feedback regulator that can adjust stem cell number during growth (Brand et al., 2000; Schoof et al., 2000). However, large fluctuations in the relative sizes of CZ and OC have been observed under variable growth conditions, indicating that the CLV3/WUS system is not sufficient to set a defined CZ size (Geier et al., 2008). This is further supported by the observation that *CLV3* expression levels may change over a tenfold range before phenotypical effects become apparent (Müller et al., 2006).

The CLV3 signal is transmitted through two receptor com-

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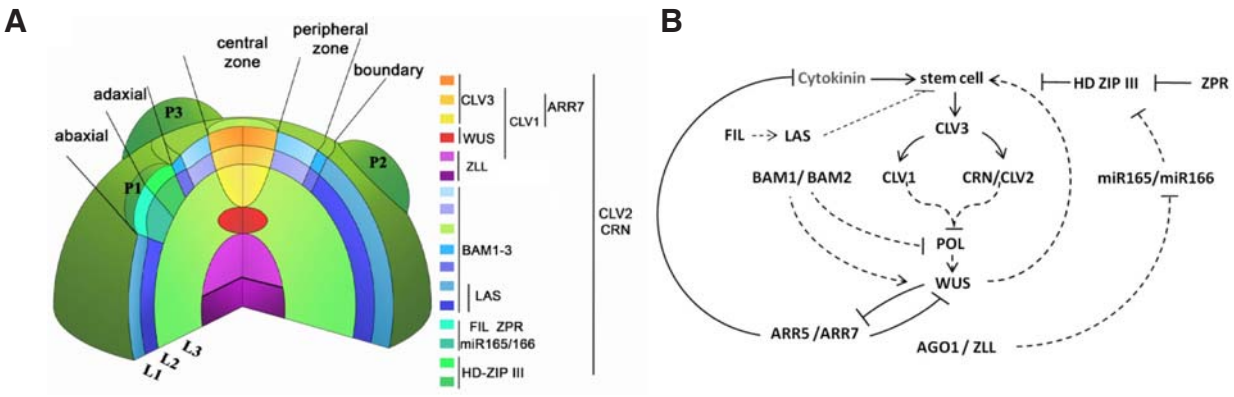

Fig. 1. (A) SAM domain structure, based on differences in expression patterns, cell division rates and cell division planes. (B) Model for signaling interactions controlling stem cell maintenance.

plexes, which probably act independently of each other. *CLAVATA1 (CLV1)* encodes a membrane associated LEUCINE RICH REPEAT (LRR) receptor kinase (Clark et al., 1997), whose extracellular LRR domains was shown to bind CLV3 peptide (Ogawa et al., 2008). *CLV1* is expressed by the cells of the OC and from overlying cells of the L2 and L3 layers (Clark et al., 1997). CLAVATA2 (CLV2), a LRR receptor protein, acts with CORYNE (CRN), a membrane associated protein kinase, in a second pathway to transmit the CLV3 signal (Müller et al., 2008). These two receptor systems (CLV1, and CLV2 with CRN) are not redundant, because both contribute equally to restrict WUS activity.

Components of the intracellular signaling pathway, acting between receptors and WUS, are KINASE ASSOCIATED PROTEIN PHOSPHATASE (KAPP), which is likely to be involved in the regulation of CLV1 kinase activity (Williams et al., 1997; Stone et al., 1998), as well as POLTERGEIST (POL) and POLTERGEIST LIKE1 (PLL1), two closely related protein phosphatases 2C, which positively regulate WUS transcription, and can even inhibit cell differentiation when overexpressed (Song et al., 2006; Yu et al., 2000; 2003). There is a range of other, less defined factors that may influence the size of the stem cell population. This includes signals from the L1, the vasculature, primordia and from the boundaries, which we will discuss in the following sections.

Down from the top: signals from the L1

The epidermis controls development of the plant. This is nicely illustrated by brassinosteroid mutants, defective in either biosynthesis of the hormone or lacking a functional receptor, that show a range of phenotypes, including dwarfism. This growth defect can be rescued (independent of other defects) by reactivating the biosynthesis or signaling pathway specifically in the epidermis, but not in other layers of the corresponding mutant (Savaldi-Goldstein et al., 2007). Further support for a vital role of the L1 (and signals from this domain) comes from cell ablation experiments. Ablating L1 cells in the central or peripheral zone leads to disorganized cell divisions in the L2, while L1 ablation of a primodium inhibits cell divisions in the L2 and L3 (Reinhardt et al., 2003). Signal exchange between layers may involve both symplastic and apoplastic communication. Meristem cells are connected via plasmodesmata. Their permeability can be regulated by structural change, or by deposition of callose (Benitez-Alfonso et al., 2009; Kurata et al., 2003; 2005). Microinjection of fluorescence dyes showed that the plasmodesmata between central and peripheral zone are blocked (Rinne and van der Schoot, 1998) but the symplastic transport of KNOX proteins, like KNOTTED1, from the L1 in deeper cell layers indicate the importance of directional protein transport between cells in SAM regulation (Kim et al., 2002). There are number of transcription factors that are specifically expressed in the L1, from embryogenesis onwards, and apparently redundantly required for L1 establishment. These are the homeodomain-GLABRA2 (HD-GL2) transcription factors *Arabidopsis thaliana MERISTEM LAYER 1* (*ATML1*) and its close homologue *PROTODERMAL FACTOR2* (*PDF2*) (Lu et al., 1996). Double mutants of *atml1;pdf2* suffer from severe defects in epidermal cell differentiation (Abe et al., 2003). Target genes activated by *ATML1/PDF2* are the prolin rich cell wall protein *PDF1* and the receptor kinase *Arabidopsis CRINKLY4* (*ACR4*), which are involved in epidermis establishment. *ACR4* itself and related family members are here of particular interest, because *ACR4* was recently found to respond to CLE peptides in the control of root stem cell development (Stahl et al., 2009). Thus, *ACR4* may present a node that integrates intralayer signaling (within the L1) with communication between domains.

Bottoms up: signals from the vasculature

Expression of *ZWILLE* (*ZLL*) in the provasculature, underneath the OC, is required to establish a functional SAM during embryogenesis. Both *ZLL* and the related gene *ARGONAUTE1 (AGO1)* belong to the Argonaute protein family and are known to be involved in miR165/miR166 dependent gene regulation. *zll* mutants show no defect in the establishment of *WUS* or *CLV3* expression, but after torpedo stage, expansion of the *CLV3* expression domain from the L1 to the cells of the L2 and L3 layers fails, although *WUS* expression itself increases. Interestingly, *ZLL* expression is specifically required in the vascular domain, which was shown by the failure to rescue the meristem defects of *zll* mutants by expressing a functional *ZLL* gene in other regions. Furthermore, *WUS* seems to act through *ZLL* and *AGO1*, because both gene functions are necessary to induce the specific phenotypes caused by *WUS* misexpression (Tucker et al., 2008). *zll* and *ago1* mutants show increased miR165 and miR166 levels in the central zone, which lead to the downregulation of transcription factors belonging to the HD-ZIP III family. The HD-ZIP III protein family has the five members *PHABULOSA(PHB), PHAVOLUTA(PHV), REVOLUTA (REV), CORONA(CNA)* and *ATHB8,* which encode homeodomain transcription factors containing a leucin zipper motive and

Table 1. Genes, predicted protein classes and proposed functions for signaling components (see Fig. 1B for interactions).

Gene name	Annotation	Protein class	Expression pattern	Proposed function
WUS	AT2G17950	Homeodomain transcription factor	OC	Maintenance of stem cell pool; ↑ CLV3
CLV3	AT2G27250	Secreted signal peptide	CZ	Promotes stem cell differentiation; ↓ WUS
CLV1	AT1G75820	Membrane associated LRR receptor kinase	OC and surrounding cells	Promotes of stem cell differentiation; ↓ WUS
CLV2	AT1G65380	Membrane associated LRR receptor protein	SAM	Promotes of stem cell differentiation; ↓ WUS
CRN	AT5G13290	Membrane associated receptor kinase	SAM	Promotes of stem cell differentiation; ↓ WUS
ARR7	AT1G19050	Transcription factor, two component response regulator	CZ	↓ Cytokinin signaling, ↓ WUS
ARR5	AT3G48100	Transcription factor, two component response regulator	SAM	↓ Cytokinin signaling, ↓ WUS
FIL	AT2G45190	Transcription factor, YABBY family	Abaxial side of organs	Regulation of organ polarity, ↓ WUS
LAS	AT1G55580	Transcription factor of the GRAS family	Boundary	Initiation of axillary meristem; ↓ WUS
PHB	AT2G34710	Transcription factor of the HD ZIP III family	Adaxial side of organs and SAM	Establishment of organ polarity; SAM maintenance
PHV	AT1G30490	Transcription factor of the HD ZIP III family	Adaxial side of organs and SAM	Establishment of organ polarity; SAM maintenance
REV	AT5G60690	Transcription factor of the HD ZIP III family	Adaxial side of organs and SAM	Establishment organ of polarity; SAM maintenance
miR165	AT1G01183	miRNA, gene silencing	Abaxial	Target PHB/PHV/REV for degradation
miR166	AT2G46685	miRNA, gene silencing	Abaxial	Target PHB/PHV/REV for degradation
BAM1	AT5G65700	Membrane associated LRR receptor kinase	Peripheral zone	↑ Stem cell population
BAM2	AT3G49670	Membrane associated LRR receptor kinase	Peripheral zone	↑ Stem cell population
BAM3	AT4G20270	Membrane associated LRR receptor kinase	Peripheral zone	↑ Stem cell population
ZLL	AT5G43810	Argonaute protein, gene silencing	Vascular tissue, adaxial	Establishment of Organ polarity by repressing HD-ZIP III
AGO1	AT1G48410	Argonaute protein, gene silencing	Vascular tissue, adaxial	Establishment of Organ polarity by repressing HD-ZIP III
POL	AT2G46920	Membrane associated protein phos phatase 2C	SAM	↑ WUS Expression

a putative sterol/lipid-binding domain (START domain). *PHB*, *PHV* and *REV* acting redundantly to establish organ polarity (Byrne, 2006), but they also influence meristem size. The meristem arrested in triple mutants (Emery et al., 2003), and dominant HD-ZIP III alleles that carry a mutation in the miRNA recognition site show enlarged meristems. *REV* is expressed in the SAM and, like the other HD-ZIP III genes, also on the adaxial side of primordia, indicating a functional continuity between meristem and adaxial organ domain. Furthermore, HD-ZIP III proteins were found to promote vascular development and differentiation. The expressivity of the *zll*-mutant phenotype is highly variable, which may be due to concentration differences of the miRNAs that target HD-ZIP III proteins (Liu et al., 2009). Nevertheless, detailed analysis of *zll* mutant alleles showed a severe downregulation of HD-ZIP III gene expression in both meristem and vasculature. Although these observations do not allow to directly pinpoint a target site for HD-ZIP III activity, the fact that *ZLL* expression in the vasculature, but not in the meristem can rescue *zll* dependent meristem defects indicates that either HD-ZIP III activity itself, or a signal generated by HD-ZIP III in the vasculature is required for stem cell maintenance.

Outside in: signals from the periphery

Laser ablation experiments indicated extensive crosstalk between periphery and central zone. The ablation of the meristem centre (including CZ and OC) leads to the *de novo* formation of an OC and a new CZ within a few days, while primodia initiation is not affected. Domain reorganization starts with *WUS* expression in some of the surrounding cells of the ablated region, followed by stem cell initiation. The simplest interpretation of these results is that signals from the meristem centre (CZ or OC) inhibit cells in the periphery to acquire stem cell identity during normal development. Ablation experiments eliminate the cells that send these (so far unknown) signals, and permit for-

mation of a new central region from peripheral cells (Reinhardt et al., 2003). A partial ablation of the periphery leads to a decreased *WUS* expression domain, indicating positive signals from the periphery. Possible candidates for signaling components are the LRR receptor kinases *BARELY ANY MERISTEM1 to 3* (*BAM1 to 3*), which are closely related to *CLV1*. These three receptors are expressed in the peripheral zone and redundantly promote meristem growth, because *bam1/bam2* double mutants were found to carry smaller SAMs, while the loss of all three BAM receptors leads to an SAM arrest (DeYoung et al., 2006). Interestingly, mutations in BAM can at least partially suppress *clv3* mutants. One suggested explanation is that CLE peptides that are expressed in the peripheral zone are inhibited from entering the SC and OC region by binding to BAM receptors. In *bam* mutants, these CLE signals gain access to the meristem center, where they can partially compensate for a loss of *CLV3* (Deyoung and Clark, 2008).

During the transition from the vegetative to the inflorescence phase, SAM size rapidly increases almost twofold due to increased cell division rates, before it slightly decreases again. Detailed analyses of the *CLV3* and *WUS* expression domains showed that while the *CLV3* expressing stem cell domain remains almost stable, *WUS* expression increases twofold (similar to SAM size itself) (Geier et al., 2008). This uncoupling of CZ and OC indicates that other factors stabilize the stem cell population independent of WUS expression. Higher cell division rates during the floral transition suggest a role for cytokinins in meristem size regulation. The size of the meristem can be modified by changing cytokinin levels, e.g. overexpression of a cytokinin oxidase/dehydrogenase which degrades cytokinins, or the loss of several redundant cytokinin receptors leads to a reduction of meristem size (Nishimura et al., 2004; Werner et al., 2003). WUS acts by repressing expression of several *ARABIDOPSIS RESPONSE REGULATORs* (*ARR*s) (Leibfried et al., 2005), which are negative feedback inhibitors of cytokinin signaling, thereby promoting overall meristem growth. ARRs in turn provide a negative feedback control on *WUS*. However, regulation of cytokinins cannot be the sole function of WUS, because cytokinin treatment is not sufficient for stem cell initiation.

The phytohormone auxin is actively transported from cell-to-cell via the combined activity of PIN efflux carriers and AUX1/LAX1 influx carriers (Bainbridge et al., 2008; Carrier et al., 2008). In the shoot, PIN1 is localized in the L1 of the peripheral zone, such that auxin accumulates at organ initiation points in the periphery (Wisniewska et al., 2006). Drainage of auxin away from the young leaf primordium through the developing vasculature then causes a depletion of auxin in the surrounding area of the peripheral zone. Auxin can even enter the stem cell region, and computer simulations predicted auxin accumulation in the central zone (de Reuille et al., 2006). In root development, auxin is vital for stem cell maintenance. Whether auxin, together with cytokinins, acts from the periphery to regulate stem cell behaviour in the shoot meristem remains to be investigated.

Beyond borders: signals from the primordia

The establishment of an adaxial-abaxial polarized organ is required for the formation of new meristems (Eshed et al., 2001). Failure to specify adaxial fates results in failure to make axillary meristem and in extreme cases, failure to make the SAM. However, induction of ectopic adaxial identity results in the formation of ectopic buds.

Primodia are initiated in the peripheral zone of a meristem, marked by auxin accumulation. The formation of the organ axes depends on signals from the SAM, which was shown through a now classical experiment: surgical isolation of young primordia from a potato meristem caused organ radialization, because no adaxial side developed (Sussex, 1951). Similarly, laser ablation of the L1 layer between primodium und central zone leads to the formation of radialized leaves (Reinhardt et al., 2005). Do primodia signal to the SAM? Many genes which are involved in the adaxial-abaxial patterning of a primodium show also effects on SAM development, and new axillary meristems arise only on the adaxial side of organs. Adaxial identity depends on HD-ZIP III function, which is also involved in SAM regulation. The function of HD-ZIP III proteins is inhibited on the abaxial side by the leucin zipper containing protein LITTLE ZIPPER (ZPR), which heterodimerizes with HD-ZIP III and interferes with their DNA binding activity (Wenkel et al., 2007). In addition to ZPR, abaxial organ identity is positively regulated by KANADI (KAN), YABBY(YAB) and AUXIN RESPONSE FACTORS (ARF3 and ARF4) (Bowman et al., 2002; Eshed et al., 2004; Kumaran et al., 2002; Siegfried et al., 1999). KANADI (KAN)1-3 belong to the GARP protein family, which appears to influence the stem cell population, because overexpression of KAN1 proteins can lead to early SAM arrest during embryogenesis (Emery et al., 2003; Eshed et al., 2001; 2004; Pekker et al., 2005). *YAB* genes, like *FILAMENTOUS FLOWER (FIL)/YAB1* or *YAB3*, are essential for the establishment of abaxial cell fate (Goldshmidt et al., 2008), but also involved in a short range signaling pathway to restrict stem cell population. Leaves with reduced *YAB1* activity develop ectopic SAMs, indicating that *YAB1* inhibits SAM establishment on the abaxial side (Kumaran et al., 2002). Importantly, *fil* or *fil/yab3* double mutants show an enlarged *CLV3* and *WUS* expression domain. Because neither *FIL* nor *YAB3* are normally expressed in the meristem center, and neither mRNA nor protein is transported, other signaling intermediates need to be involved. Genetic screens then identified the *LATERAL SUPRESSOR (LAS*) gene, which is expressed specifically in the boundaries of the SAM, as a mediator between organ and meristem centre (Goldshmidt et al., 2008). This suggests a signaling mechanism, reaching from the abaxial organ side via the boundary domain to the meristem centre, which aligns stem cell activity with the requirement for new cells for lateral organ initiation.

OUTLOOK

We described the different domains of the SAM that differ in function and gene expression patterns and the corresponding signals from these domains which influence the stem cell population. Some facets have been identified by now, and a picture begins to emerge that paints the stem cells as senders and receivers of signals that integrates their proliferation and development with formation of the entire shoot tip.

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