Long- and short-distance signaling in the regulation of lateral plant growth

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Lateral growth of shoot and root axes by the formation of secondary vascular tissues is an instructive example for the plasticity of plant growth processes. Being purely postembryonic, lateral growth strongly depends on environmental input and is tightly regulated by long- and short-distance signaling. In general, plant vasculature represents the main route for long-distance transport of compounds throughout the plant body, thereby providing also a fast and efficient signaling pipeline for the coordination of growth and development. The vasculature consists of three major tissues; the xylem conducts water and nutrients, the phloem transports mainly organic compounds and the vascular cambium is a group of undifferentiated stem cells responsible for the continuous production of secondary vascular tissues. Notably, the close proximity to functional vascular tissues makes the vascular cambium especially accessible for the regulation by long-distance-derived signaling molecules as well as by the physical and physiological properties of transport streams. Thus, the vascular cambium offers unique opportunities for studying the complex regulation of plant growth processes. In this review, we focus on recent findings about long- and short-distance signaling mechanisms regulating cambium activity and, thereby, lateral expansion of plant growth axes by the formation of additional vascular tissues.

Introduction

In multicellular organisms, communication among cells is essential for coordinated growth and development. In plants in particular, the flexible regulation of cellular properties by cell-to-cell communication is important throughout the whole life cycle. This is because plants cannot escape from adverse conditions and continuously need to adapt their growth and development to a changing environment. The basis of this growth plasticity is the activity of local stem-cell niches located at the tips and along the flanks of plant growth axes called meristems. Plant meristems provide protective environments that allow maintenance and proliferation of embedded stem cells. Regulation of these meristems is mediated by a combination of receptor–ligand signaling systems (Aichinger et al. 2012). Ligands travel along symplastic or apoplastic routes and bind to receptors sitting in the plasma membrane, in the cytosol or in the endomembrane system. In addition, more direct effectors like transcriptional regulators travel symplastically along plasmodesmata establishing continuity between the cytoplasm of neighboring cells.

Abbreviations – ACC, 1-aminocyclopropane-1-carboxylic acid; CLE, CLAVATA3/ESR-RELATED; ERF, ETHYLENE RESPONSE FACTOR; GA, gibberellin; HD-ZIP, HOMEODOMAIN-LEUCINE ZIPPER; IAA, indole-3-acetic acid; JA, jasmonic acid; JAZ10, JASMONATE ZIM-DOMAIN10; KAN, KANADI; LRR-RLK, leucine-rich repeat receptor-like kinase; PXY, PHLOEM INTERCALATED WITH XYLEM; RAM, root apical meristem; SAM, shoot apical meristem; SL, strigolactone; TDIF, tracheary element differentiation inhibitory factor; TDR, TDIF RECEPTOR; WOX, WUSCHEL-RELATED HOMEOBOX.
and non-cell autonomously induce or repress the expression of their target genes.

The cambium is a meristematic tissue in which the stem cells are a priori arranged in a single-cell layer that forms a closed cylinder along the periphery of stems and roots (Sanchez et al. 2012, Fig. 1A, B). These stem cells, which are also called initials, divide, thereby renewing themselves and providing cells for secondary xylem toward the center of the stem (adaxially) and secondary phloem toward the outside (abaxially, Fig. 1B). Thus, in a first approximation the cambium can be considered as a collection of concentric cylinders of cell layers with different cell identities and degrees of differentiation but which are still dividing. In light of the complex anatomy and growth dynamics, intensive communication between cambium cells harboring different states is essential. However, a fine mapping of cell states and functional subdomains within the cambium area and a detailed description of their mutual interactions are still pending. In particular, the mechanisms balancing the bidirectional recruitment of cells into new layers of secondary vasculature have hardly been touched so far. This lack of knowledge is remarkable considering the essential role of lateral growth for plant performance and terrestrial biomass accumulation.

Communication between growing organs – the long-distance interaction between the shoot apex and the cambium

Auxin has been extensively characterized in the context of long-distance regulation of lateral growth. The key observation is that decapitation of shoots results in the loss of cambial activity, which however can be restored by the apical application of auxin (e.g. Ko et al. 2004). Further support for an important role of auxin in lateral growth came from direct auxin measurements in *Populus* and *Pinus* trees. In both species, the concentration of the major endogenous auxin, indole-3-acetic acid (IAA), peaks in the center of the cambial zone and declines to both sides toward the xylem and phloem (Ugglà et al. 1996, 1998). This observation led to the idea that auxin determines cell fate during lateral growth in a dose-dependent manner (Bhalerao and Bennett 2003). Collectively, it is believed that auxin is mainly biosynthesized in the shoot apex, transported basipetally along the shoot via the cambium and/or the phloem (Lachaud and Bonnemain 1984) and distributed laterally via polar auxin transport across the cambial zone. Consistent with this model, various genes encoding for auxin transporters like PIN-FORMED (PIN) efflux and AUXIN RESISTANT 1 (AUX1)-like influx carriers are differentially expressed across the cambial zone in *Populus* (Schrader et al. 2003). However, more direct evidence for lateral transport of auxin within the cambium area is missing.

Besides polar auxin transport, auxin signaling provides another regulatory layer in cambium regulation. Similar to auxin transporters, transcription of genes encoding for auxin signaling components showed a strong positive correlation with the pattern of auxin levels across the cambium area in *Populus* (Schrader et al. 2003). However, the expression maxima of auxin-responsive genes were rather found in the developing xylem (Nilsson et al. 2008). This indicates not only a role for auxin in xylogenesis but also an indirect relationship between auxin concentration and transcriptional activation of most of the auxin-responsive genes that are expressed in the cambium area. Consistent with this observation, xylem cell expansion was more sensitive than cambium proliferation to reduced auxin responsiveness, which was achieved by expressing a transcriptional repressor of auxin signaling (PtTIAA3) throughout the plant (Nilsson et al. 2008). Interestingly, trees overexpressing PtTIAA3 also showed an enlarged zone of anticlinal divisions (Nilsson et al. 2008) usually characteristic of cambial initial cells (Fig. 1B, Schrader et al. 2004). This observation may indicate that auxin signaling not only positively regulates cambium activity but also spatially restricts stem-cell characteristics in the cambium area.

How is auxin signaling translated into cambium activity? Lately, it was demonstrated that strigolactone (SL) signaling directly in the cambium area is important in this respect (Agustí et al. 2011a). This conclusion was based on the observation that cambium sensitivity to auxin was reduced in SL biosynthesis and signaling mutants. Conversely, treatments with the SL analog GR24 resulted in the activation of cambium activity at a similar rate in wild-type and auxin-resistant1 (axr1) mutants impaired in auxin signaling, suggesting that auxin signaling is not required for an SL effect on cambium activity (Agustí et al. 2011a). Furthermore, restoring SL signaling specifically in the cambium of the SL signaling mutant more axillary branches2 (max2) was sufficient for complementing defects in cambium activity. These findings argue for a role of local SL signaling downstream of the auxin signaling pathway in lateral growth regulation.

Gibberellins and brassinosteroids: candidates for balancing the formation of cambium-derived tissues

Gibberellins (GAs) are important endogenous regulators of cambial activity and, in this context, derive
presumably from leaves (Dayan et al. 2012). In general, exogenous GA treatments stimulate cell divisions in the cambial region. However, GA-induced cells did not display the typical appearance of cambium cells and also did not differentiate properly in Populus (Björklund et al. 2007). This indicates that GA alone is not sufficient for promoting all aspects of lateral growth. Consistently, co-application of auxin and GA led to proper induction and differentiation of cambium cells and a stronger enhancement of cambial activity than either individual hormone treatment, indicating that these two hormones function synergistically (Björklund et al. 2007). This synergy might be explained at least partially by the stimulatory role of GA on auxin transport on one side and the promoting effect of auxin on GA biosynthesis on the other side (Björklund et al. 2007). Analysis of the distribution of bioactive GAs in Populus stems showed that, in contrast to auxin, GA levels do not peak in the cambium but in the adjacent domain of xylem cell expansion, supporting a role of GA in the promotion of cell division and differentiation in cells committed to the xylem cell fate (Israelsson et al. 2005). Such a role was further suggested by transgenic trees ectopically expressing GA 20-oxidase, which resulted in enhanced GA levels as well as increased xylem fiber cell number and length (Eriksson et al. 2000). More recently, it was found that GAs also act as a mobile signal in Arabidopsis that, upon flowering, is transported from shoots to hypocotyls where it triggers the formation of xylem cells (Ragni et al. 2011).

Brassinosteroids also play a role in the formation of cambium-derived tissues. Exogenously applied brassinosteroids promoted the differentiation of tracheary elements and regulate the expression of xylem-related genes in a xylogenic culture system of Zinnia mesophyll cells (Yamamoto et al. 2001 and references therein). Furthermore, gas chromatography–mass spectrometry analysis of the cambial zone of Pinus trees identified two bioactive brassinosteroids specifically present in this meristem (Kim et al. 1990). A potential role for brassinosteroids in balancing cambium-dependent tissue production is further supported by an enlarged secondary phloem and reduced secondary xylem in vascular bundles of Arabidopsis mutants defective in brassinosteroid biosynthesis and signaling (Caño-Delgado et al. 2004).
Cytokinins stimulate cambium activity

A role of cytokinins in stimulating cambium activity is well established. In particular, recent studies show that reductions in cambial cytokinin levels, achieved through the expression of cytokinin degrading enzymes or by combining mutations in the cytokinin biosynthesis pathway, substantially impair lateral growth in *Populus* and *Arabidopsis*, respectively (Matsumoto-Kitano et al. 2008, Nieminen et al. 2008). In addition, single and double *Arabidopsis* mutants of the cytokinin receptors ARABIDOPSIS HISTIDINE KINASE2 (AHK2) and AHK3 display reduced (pro)cambial cell numbers and lack secondary growth (Hejatko et al. 2009). The site of cytokinin production does not seem to be crucial in this context because grafting experiments showed that wild-type shoots or roots could restore cambium activity in roots or shoots, respectively, impaired in cytokinin biosynthesis (Matsumoto-Kitano et al. 2008).

The mechanisms mediating endogenous cytokinin function in cambium regulation and their interaction with other signaling pathways are still poorly understood. Transcriptional profiling across the vasculature of *Populus* showed that genes encoding cytokinin receptors and a cytokinin primary response gene (*PtRR7*) are especially active in the cambial zone (Nieminen et al. 2008). Moreover, the His kinase CYTOKININ-INDEPENDENT1 (CKI1), implicated in the perception of cytokinins, is expressed in (pro)cambial cells of the vascular bundles in *Arabidopsis* stems (Hejatko et al. 2009). Reduced CKI1 transcript levels resulted in reduced (pro)cambial cell divisions similar to ahk2 single and ahk2;ahk3 double mutants, indicating that cytokinin signaling in the cambium itself is required for proper cambium function (Hejatko et al. 2009).

Stress-induced cambium activity: ethylene and jasmonic acid

Ethylene is a gaseous signaling molecule that is important for plant development. Its function in lateral growth regulation has been initially addressed by exogenous hormone application experiments. Both treatment with the ethylene precursor 1-aminocyclopropane-1-carboxylic acid (ACC) and local application of gaseous ethylene to *Populus* stems stimulated lateral growth (Junghans et al. 2004, Love et al. 2009). In addition, it was recently shown that *ethylene overproducer1* (*eto1*) mutants show an increased number of (pro)cambial cells in *Arabidopsis* (Etchells et al. 2012). On the contrary, mutations in the positive regulators of ethylene signaling ETHYLENE INSENSITIVE2 (EIN2), EIN5 and ETHYLENE RECEPTOR1 (ETR1) dramatically enhanced the defect in (pro)cambium proliferation observed in phloem intercalated with xylem (pxy) mutants (Etchells et al. 2012, see below). Interestingly *ein2*, *ein5* and *etr1* single mutants do not display any alterations in cambial cell number, indicating compensatory functions of ethylene signaling in the absence of PXY (Etchells et al. 2012). The mechanism triggering an ethylene-dependent cambium response is not clear, but the biosynthesis of ethylene in general is activated in response to many environmental cues and particularly increases during the formation of tension wood in response to mechanical stress induced by bending tree stems (Andersson-Gunneras et al. 2003). To address the role of ethylene in tension wood formation, Love et al. (2009) engineered ethylene-overproducing and -insensitive *Populus* lines. These lines displayed increased xylem formation and reduced tension wood formation, respectively (Love et al. 2009). Notably, the ethylene-insensitive trees were not reported to show reduced lateral growth in the absence of bending-induced mechanical stress (Love et al. 2009), arguing that ethylene signaling is not essential for cambium activity under normal growth conditions, but rather becomes active as a response to different stresses.

More recently, it was demonstrated that the jasmonic acid (JA) signaling pathway is involved in the stimulation of cambial activity (Sehr et al. 2010). Initially, it was found that the touch- and JA-inducible repressor of JA signaling JASMONATE ZIM-DOMAIN10 (JAZ10) is active in laterally growing *Arabidopsis* stems (Sehr et al. 2010). Mutants defective in *JAZ10* displayed enhanced cambial activity, whereas mutants impaired in CORONATINE INSENSITIVE1 (COI1) or JASMONATE INSENSITIVE1 (JIN1/MYCC), two positive regulators of JA signaling, showed reduced cambium proliferation (Sehr et al. 2010). Interestingly, Zhu et al. (2011) demonstrated that JA is able to enhance the activity of transcription factors that mediate plant response to ethylene signaling (Zhu et al. 2011). This observation provides a potential framework how mechanosensing through the JA signaling pathway might be converted into enhanced cambial activity via ethylene signaling during reaction wood formation.

Stem-cell maintenance in the cambium

Despite the substantial anatomical differences between shoot and root apical meristems (SAM and RAM) and the vascular cambium, central molecular mechanisms controlling both meristem types appear to be similar. The first indication in this direction was provided by the discovery of the CLAVATA3/ESR-RELATED (CLE) peptide TDIF (tracheary element differentiation inhibitory factor),...
which was identified as a repressor of xylem differentiation and promoter of cell proliferation in the *Zinnia* cell culture system (Ito et al. 2006). The two *Arabidopsis* TDF homologs, CLE41 and CLE44, are expressed in the phloem and secreted into the apoplastic space. In the neighboring (pro)cambium they induce stem-cell proliferation and inhibit tracheary element differentiation (Fig. 1C; Hirakawa et al. 2008, Whitford et al. 2008, Etchells and Turner 2010). This indicates that CLE41/44 signaling mediates both the proliferation of vascular stem cells and the inhibition of xylem differentiation, reminiscent of the situation in apical meristems where other CLE peptides fulfill similar roles (Schoof et al. 2000, Stahl et al. 2009).

CLE41/44 signaling in the vascular stem cells is perceived by the leucine-rich repeat receptor-like kinase (LRR-RLK) PXY, also known as TDR (Fisher and Turner 2007, Hirakawa et al. 2008, Etchells and Turner 2010). PXY is expressed in the *Arabidopsis* cambium and presumably targeted to the plasma membrane. pxy mutants display interspersed phloem and xylem tissues and defects in the orientation and number of (pro)cambial cell divisions (Fig. 1C; Fisher and Turner 2007, Hirakawa et al. 2008, Etchells and Turner 2010). Thus, the PXY/CLE41/44 module seems to provide positional information similar to LRR-RLK/CLE-dependent cell-to-cell communication found in SAM and RAM (Schoof et al. 2000, Stahl et al. 2009). However, while in apical meristems the LRR-RLK/CLE signaling modules inhibit meristematic activity, the PXY/CLE41/44 module stimulates cambium proliferation (Hirakawa et al. 2008, 2010), indicating either substantial differences in the regulation of apical meristems and the cambium or the existence of yet uncharacterized signaling components. Support for the latter hypothesis is provided by the identification of additional cambium-specific LRR-RLKs (Agustí et al. 2011b, Bryan et al. 2012, Wang et al. 2013). One of them, MORE LATERAL GROWTH1 (MOL1), indeed acts as a negative regulator of cambium activity (Agustí et al. 2011b).

CLE41/44 signaling stimulates cambium activity by promoting the expression of the WUSCHEL-RELATED HOMEBOX4 (WOX4) gene in a PXY-dependent manner (Hirakawa et al. 2010). WOX4 activity is essential for maintaining stem-cell fate in the cambium (Hirakawa et al. 2010, Suer et al. 2011) equivalent to the roles of WUSCHEL (WUS) and WOX5, two other members of the WOX gene family active in SAM and RAM, respectively (Schoof et al. 2000, Sarkar et al. 2007). Strikingly, WOX4 expression in the stem is also induced by auxin independently from PXY (Suer et al. 2011). Thus, WOX4 seems to integrate the inputs of long-distance-derived signals acting in parallel to the PXY/CLE41/44 module. Recently, another member of the WOX gene family, WOX14, was shown to be expressed in the cambium (Etchells et al. 2013). wox4 single mutants show no alterations in vascular stem-cell number, whereas wox4;wox14 double mutants display a stronger reduction of vascular cell division than wox4 single mutants. Therefore, WOX14 acts, at least partially, redundantly to WOX4 in mediating (pro)cambium activity (Fig. 1C; Etchells et al. 2013).

The regulatory networks acting downstream of WOX4/14 are still largely uncharacterized. Recent data indicate that the ethylene-responsive ETHYLENE RESPONSE FACTOR (ERF) transcription factors ERF1, ERF018 and ERF109 promote vascular cell divisions downstream of PXY and WOX4. In pxy and wox4 mutants, activity of the ERF1, ERF018 and ERF109 genes is enhanced partially masking defects caused by disturbed PXY or WOX4 functions (Etchells et al. 2012). In conclusion, WOX4 seems to mediate the interaction between auxin and ethylene signaling and integrate also other pathways to control the rate of cell divisions in plant vascular tissue.

### Setting the polarity of the cambium

Whether the strict bidirectional polarity of tissue production by the cambium is the output of a constant signaling process along the radial axis of the cambium zone or whether this is implemented during cambium establishment and then maintained is unclear. However, there are indications that an early establishment of the adaxial–abaxial polarity is crucial. For example, tissue production in tissue blocks from interfascicular regions in *Ricinus communis* maintained its original polarity even when these blocks were excised before any sign of cambium formation and inserted in reversed orientation (Siebers 1971). Importantly, cambium formation happens when surrounding organs have already established an overall adaxial–abaxial polarity (reviewed in Husbands et al. 2009) and factors active in adaxial or abaxial domains presumably transfer spatial information to (pro)cambium cells. For example, class III HOMEODOMAIN-LEUCINE ZIPPER (HD-ZIPIII) transcription factors are important for organ polarization and are expressed in adaxial tissues of young leaves, roots and stems including the developing xylem (e.g. Emery et al. 2003). Reduction of HD-ZIPIII expression led to decreased organ polarity and, at the same time, to defects in xylem differentiation (Ilegems et al. 2010). Conversely, KANADI (KAN) transcription factors are expressed in abaxial organ domains including the phloem (Emery et al. 2003). No direct effect of KAN transcription factors on phloem specification and/or differentiation has been reported, but *Arabidopsis*...
activity has also been reported for hd-zipIII mutants (Ilegems et al. 2010). Enhanced cambium at the center of vascular bundles and increased cambium display an expansion of the (pro)cambium domain in Agustí et al. 2011b, Ragni et al. 2011, Suer et al. 2011). 

In addition to an inherent polarity of the cambium, it is also possible that phloem and xylem specification is induced or supported by signals derived from differentiated tissues and transported along the growth axis to ensure continuity of vascular transport routes. One candidate for this is xylegen, a proteoglycan-like factor polarly localized in cell walls of differentiating tracheary elements and essential for xylem continuity (Motose et al. 2004). On the other side, OCTOPUS (OPS), a protein of unknown function, is polarly localized to the plasma membrane of provascular and protophloem cells and promotes phloem continuity (Truernit et al. 2012).

**Conclusion**

Our current understanding of lateral plant growth regulation is more than fragmentary. This becomes especially obvious when considering the lack of knowledge of how different signaling pathways interact with each other on the level of cambium cells, which signaling components act in different cambium subdomains, how these subdomains interact or how environmental input is integrated. These aspects are particularly difficult to address because lateral plant growth is a late process during plant development and many essential regulators may also have functions during earlier growth phases. Therefore, distinguishing between primary and secondary effects is often challenging when applying standard genetic tools. Moreover, interpreting short-term effects of pharmacological treatments or induced changes of gene activities has to be done with caution as no live cell imaging during logical treatments or induced changes of gene activities is possible. Encouragingly, Arabidopsis thaliana is becoming established more and more as a model for lateral plant growth and exploitation of genetic and molecular tools available in this reference plant has already provided important novel insights (Ito et al. 2006, Fisher and Turner 2007, Hirakawa et al. 2008, Melzer et al. 2008, Etchells and Turner 2010, Agustí et al. 2011b, Ragni et al. 2011, Suer et al. 2011). These advancements are promising and considering the conservation of key regulators of lateral growth among dicotyledonous species, transferability of findings to a broader spectrum of species is very likely. After all, the integration of individual interactions into comprehensive regulatory models that are also able to reproduce interspecies and intraspecies variations will be essential for establishing a systemic view on a process of such fundamental importance for plant growth and development.

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