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Genetic and hormonal control of vascular tissue proliferation

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Abstract

The plant vascular system develops from a handful of provascular initial cells in the early embryo into a whole range of different cell types in the mature plant. In order to account for such proliferation and to generate this kind of diversity, vascular tissue development relies on a large number of highly oriented cell divisions. Different hormonal and genetic pathways have been implicated in this process and several of these have been recently interconnected. Nevertheless, how such networks control the actual division plane orientation and how they interact with the generic cell cycle machinery to coordinate these divisions remains a major unanswered question.

Introduction

Vascular tissues form an efficient fluid conducting system that stretches throughout the entire plant body. Besides providing long-distance transport of water, sugars, nutrients, hormones and other signaling molecules, it also contributes to mechanical support. Broadly speaking, the vascular system consists of three major tissue types: xylem, phloem and (pro)cambium cells (**Figure 1**). Based on ontogeny and anatomical studies during embryogenesis and in the primary root meristem, it seems that all vascular cell types are derived from procambium cell divisions [1-4]. Although the organization of vascular tissues differs tremendously between species, within different organs and even depending on the developmental stage, procambium is in general located between xylem and phloem cell types (**Figure 1**). Xylem tissues differentiate into several cell types including tracheary elements, xylem fibers and xylem parenchyma cells. Each of these xylem cell types contain distinct lignified secondary walls that combine the required mechanical strength with connectivity between cells [5,6]. Phloem on the other hand, consists of sieve elements, companion cells, phloem fibers and phloem parenchyma cells. Intriguingly, the different vascular cell types described above all originate from only a few procambium initial cells in the early embryo. Unlike for example epidermis and cortex, procambium cells thus need to develop into a vast array of cell identities; a process that is dependent on specific oriented cell divisions.

In the following, we will illustrate how these oriented cell divisions are critically involved in developing an efficient vascular system and we will highlight how genetic and hormonal regulatory networks control vascular proliferation. Because most of these interaction networks have been best described in *Arabidopsis thaliana*, we will focus on this model species. For a more comprehensive overview of the different vascular cell types and their function, we refer to some excellent recent reviews [7-11].

Oriented cell divisions shape the vascular cell lineage

Because plant cells have rigid cell walls and are immobilized within a tissue context, cell expansion and oriented cell divisions are the main mechanisms to shape a three-dimensional organ and eventually the entire plant body. Two basic types of divisions occur in plants: perpendicular (anticlinal) and parallel (periclinal) to the surface of the plant (**Figure 1**). An

anticlinal cell division (AD) adds a new cell to an existing cell file and is thus the main driver of longitudinal growth along the main body axis of the plant. A periclinal cell division (PD) however provides an increase in the number of cell-files and thus control radial growth. These divisions often result in daughter cells of different size or identity and are therefore also referred to as 'formative divisions'[12]. The existence of these clearly distinct division types also suggests that control mechanisms must be present to specifically position the division plane and control its orientation. This process plays vital roles throughout plant development, starting with the very first division of the zygote [13,14]. Later during embryogenesis, specific anticlinal and periclinal cell divisions generate all major tissue types of the plant [1,2]. Post-embryonically, cell division orientations have also been shown to be of vital importance in e.g. root stem cells [15], stomatal development [16] and lateral root formation [17,18].

Although a tight control of cell division orientation is important throughout plant development, this is specifically true for vascular tissues. During the early globular stage of embryogenesis, four procambium cells expressing early vascular marker genes [19] will undergo a series of PDs giving rise to a fully patterned vascular bundle containing about 25 cell files (excluding pericycle cells) in a mature embryonic root (**Figure 1**). In Arabidopsis, the young root vasculature is organized in a bisymmetric pattern with a central one-cell wide xylem axis, flanked by two phloem poles and separated by procambium. Additional rounds of post-embryonic PDs in the meristematic vascular tissues will further increase the number of vascular cell files from 25 just above the quiescent center to about 30 in the elongation zone (**Figure 1**). Of particular interest in this case is the phloem cell lineage. Here, a single procambium cell undergoes a PD resulting in another procambium cell and a sieve element precursor cell. The latter undergoes another round of PD, generating a proto- and a meta-phloem cell file (**Figure 1**). Two more PD events generate the companion cell files on each side of the sieve element cell files from neighboring procambium cells [20,21].

Later in development during secondary growth, subsets of procambium cells will develop into vascular cambium; a meristem responsible for the secondary radial growth of stem and root tissues (**Figure 1**). During secondary growth, PDs are responsible for the dramatic increase in size of the vascular bundle. The organization of the root vascular tissues also changes during this process in which xylem proliferates in the center, phloem at the periphery and cambium in the middle [11]. In the stem, cambium in the vascular bundles is first connected via

interfascicular cambium that will then generate more phloem and xylem cells [8]; resulting in an organization similar to that of the mature root (**Figure 1**).

Genetic and hormonal control mechanisms

Over the past few years, our understanding of the hormonal and genetic control mechanisms of vascular development has increased tremendously. Genetic players ranging from early embryogenesis to late differentiation are now identified. However, despite the importance of oriented cell divisions for the vascular cell lineage, only a few pathways have been implicated in this process so far. Here, we will briefly discuss these pathways that act during primary and secondary growth and highlight how these interact in controlling vascular proliferation.

A major pathway controlling vascular PDs acts during early embryogenesis and also at least in the post-embryonic root. The auxin dependent bHLH transcription factor *TARGET OF MONOPTEROS5* (*TMO5*) is first expressed in the four procambium cells during early globular stage of embryogenesis [22]. TMO5 and its closest homologs form heterodimer complexes with another bHLH transcription factor called LONESOME HIGHWAY (LHW) and its respective homologs [23,24] (**Figure 2**). Loss-of-function of *TMO5* or *LHW* clade members results in strongly reduced vascular cell file numbers, whereas ectopic expression of both TMO5 and LHW is able to ubiquitously induce PDs in the root [23,25,26]. Intriguingly, the expression of both bHLH transcription factors overlaps in young xylem cells while the PDs mostly take place in the neighboring procambium cells, suggesting that a mobile signal acts downstream [23]. The cytokinin (CK) biosynthetic gene *LONELY GUY4* (*LOG4*) and its close homolog *LOG3* were identified as direct targets of the TMO5/LHW dimer complex [3,27]. CK is a good candidate to act as this mobile signal because CK-signaling is clearly required for PD. This is reflected by the fact that mutants in the biosynthetic pathway (e.g. *log1,2,3,5,6,7,8* [28,29]), perception by the CK receptors (e.g. *wooden leg* [20]) and mutants in downstream signaling events (e.g. *arr1,10,12* [30,31]) all show strongly reduced PDs in the vascular bundle. In all these mutants, patterning within the vascular bundle is also disturbed, indicating that cell division orientation and patterning events are tightly linked. Although TMO5/LHW-dependent CK production along the xylem axis is able to trigger PDs in neighboring procambium cells, it seems unlikely that this pathway also controls the high number of PDs in the more distantly positioned phloem cell lineage, suggesting the existence of a yet unidentified factor controlling phloem cell proliferation.

The TMO5-LHW dimer was very recently linked to another pathway controlling PD through the *ACAULIS5/THICKVEIN* (*ACL5/TKV*) gene [32-34]. Loss of ACL5 function causes vascular cell proliferation in combination with increased xylem cell differentiation [35,36]. The polyamine thermospermine produced by ACL5 has been shown to repress the translational inhibitory effect of the up-stream open reading frames (uORFs) located in the 5' leader sequence of several genes, including *SUPRESSOR OF ACAULIS51* (*SAC51)* and the closely related *SAC51-LIKE* (*SACL*) genes. These encode yet another clade of bHLH transcription factors [35], which also form heterodimer complexes with LHW [23,24,37,38]. This way, SACL proteins compete with TMO5 for the LHW binding partner, reducing the amount of active TMO5-LHW [37,38]. As *ACL5* and *SACL* genes themselves are downstream targets of TMO5-LHW, these factors constitute a negative feedback loop that controls TMO5-LHW activity at the post-translational level [37,38]. Intriguingly, TMO5-LHW overexpression shows vascular differentiation phenotypes similar to the *acl5* mutant [37]. This suggests that the TMO5-LHW pathway might control both vascular proliferation and differentiation processes [37,38].

Furthermore, *ACL5* is under transcriptional control of both MP and the auxin-dependent homeodomain - leucine zipper (HD-ZIPIII) protein ARABIDOPSIS THALIANA HOMEOBOX 8 (ATHB8) [39-41] (**Figure 2**). Strikingly similar to TMO5-LHW misexpression and the *acl5* mutant, loss-of-function of *HD-ZIPIII* genes show increased vascular PDs in the hypocotyl and root. Increased *HD-ZIPIII* levels however, show strongly reduced root vascular cell numbers [42,43], analogous to *tmo5* or *lhw* higher order mutants [23] or SACL overexpression [37,38]. It will be interesting to see if the HD-ZIPIII family members will be linked further to TMO5-LHW, or whether they operate in parallel.

In conclusion, the pathways that control primary vascular tissue growth are slowly being linked. These are the first steps towards a full understanding of the integrated transcriptional network controlling vascular proliferation.

Later in development during secondary growth, PDs in the hypocotyl and stem are controlled by the CLE41/44 or TRACHEARY ELEMENT DIFFERENTIATION INHIBITORY FACTOR (TDIF) peptide and its PHLOEM INTERCALATED WITH XYLEM / TDIF RECEPTOR (PXY/TDR) receptor [44-46] (**Figure 2**). This CLE-type peptide, produced in the secondary phloem, travels to the cambium where it binds the PXY/TDR receptor and induces the expression of the WUSCHEL-RELATED HOMEOBOX4 (WOX4) and WOX14 transcription factors [44-48]. Mutants in these factors all show reduced numbers of vascular

cell files, indicating a key role during lateral growth both in Arabidopsis and poplar [48]. Moreover, WOX4 and WOX14 act redundantly in controlling the number of vascular cell files within the cambium as the *wox4/wox14* double mutant shows a further reduction in cell files compared to the *wox4* single mutant [47,49]. This regulatory pathway is also profoundly controlled by hormonal input. For example, similar to primary vascular proliferation, CK is required for secondary growth, as procambium divisions are absent in a CK biosynthesis mutant and can be reinstalled by CK treatments [50]. Also, *WOX4* was shown to be auxin-responsive in a PXY/TDIF independent manner, while *ETHYLENE RESPONSE FACTORs* (*ERFs*) are upregulated in the stem and hypocotyl of the *pxy*/*tdr* and *wox4* single mutants. Additionally, the *pxy erf109 erf018* triple mutant shows a reduction of vascular cell files within the hypocotyl [51].

Intriguingly, the networks controlling vascular proliferation during primary and secondary growth are clearly distinct with no overlaps or interactions uncovered so far. It remains to be seen if this is truly the case, or whether it reflects a more historical perspective in the sense that research into these processes has focused on specific pathways. Despite this consideration, the genetic and hormonal pathways discussed above all seem to control vascular proliferation. However, it remains entirely unclear how they exert their effect on the actual orientation of cell divisions in the vascular tissues. Indeed, there appears to be a gap in our understanding of how these regulatory networks are linked to cell division plane orientation.

Bridging the gap

A large number of proteins are required to correctly execute oriented cell divisions. Many of these affect actin or microtubule (MT) dynamics and organization during different stages of cell division, while others determine a plasma membrane domain where the cell plate will fuse at the end of cytokinesis [52-66]. In all cases, mutations do not cause a 90-degree rotation of the cell division plane, but result in randomly oriented cell divisions. Hence, these factors do not control the exact switching of the division plane between anticlinal or periclinal divisions, but are rather part of the canonical cell division machinery itself.

Nevertheless, as the preprophase band (PPB) normally forms in the same orientation as the cortical cytoskeletal organization [67], the switch in cell division orientation required to

generate a PD should be preceded by a similar 90-degree rotation of the cortical MT array from transverse to longitudinal. This type of cytoskeletal rotation can be induced by light stimulus in hypocotyl epidermis cells through KATANIN-dependent MT severing and plus-end polymerization [68] and TONNEAU2/FASS-dependent branching nucleation [69]. Similarly, short-term auxin treatments [70] also provoke similar interphase MT reorientations, although an opposite reorientation from longitudinal to transverse by auxin and auxin in combination with gibberellic acid treatments has also been reported [71]. Besides hormones, sensing physical pressure is also able to switch the orientation of cortical MT [72-75]. It is however not straightforward to imagine how cells in the vascular system would feel differential pressure, or how light could induce the required MT reorientation in root vascular cells. Despite these considerations, KATANIN and TONNEAU2/FASS are good molecular targets to act downstream of the genetic pathways we have described previously. Other candidates present in root vascular cells are AURORA kinases. Especially during lateral root development in *aur1-2 aur2-2* double mutants, the highly elongated pericycle cells frequently undergo PD, instead of the normal AD [76]. In contrast, a switch from PD to AD has been observed in loss-of-function mutant embryos of TORMOZ (TOZ) [77]. The *TOZ* gene encodes a nucleolar protein with WD40 repeats but its precise function remains unknown. It is conceivable that some or all of these molecular players will eventually be found as common downstream targets of the genetic pathways regulating vascular proliferation described above.

Future perspectives

In order to form functional vascular tissues, specifically oriented cell divisions have to occur in the correct cell at the right time, suggesting that this is a highly coordinated developmental process. Several genetic and hormonal pathways controlling vascular proliferation have been identified over the past years. A major future challenge will be to determine if these pathways independently provide cues for vascular proliferation or whether they all interconnect to control common target genes.

Another poorly explored level of regulation involves the spatial and temporal resolution. Although we know that several key factors are expressed in vascular tissues throughout plant development, most published information is limited to a specific developmental context. Therefore, a second challenge will be to evaluate if these factors act during other stages of development and in different parts of the plant.

Finally, it remains entirely unknown what might act downstream of these genetic factors to control the actual orientation of cell divisions in the vascular tissues. Whatever the identity of these downstream regulators might be, it is very likely that they will eventually control MT orientation and/or subsequent PPB positioning. Future work will have to show if such factors can be identified in vascular tissues or if for example cell polarity plays an important role; similar to stomatal development [78,79]. Finally, it remains possible that control of oriented cell divisions occurs through non-genetic determinants such as mechanical stress and light; or a combination of all these factors.

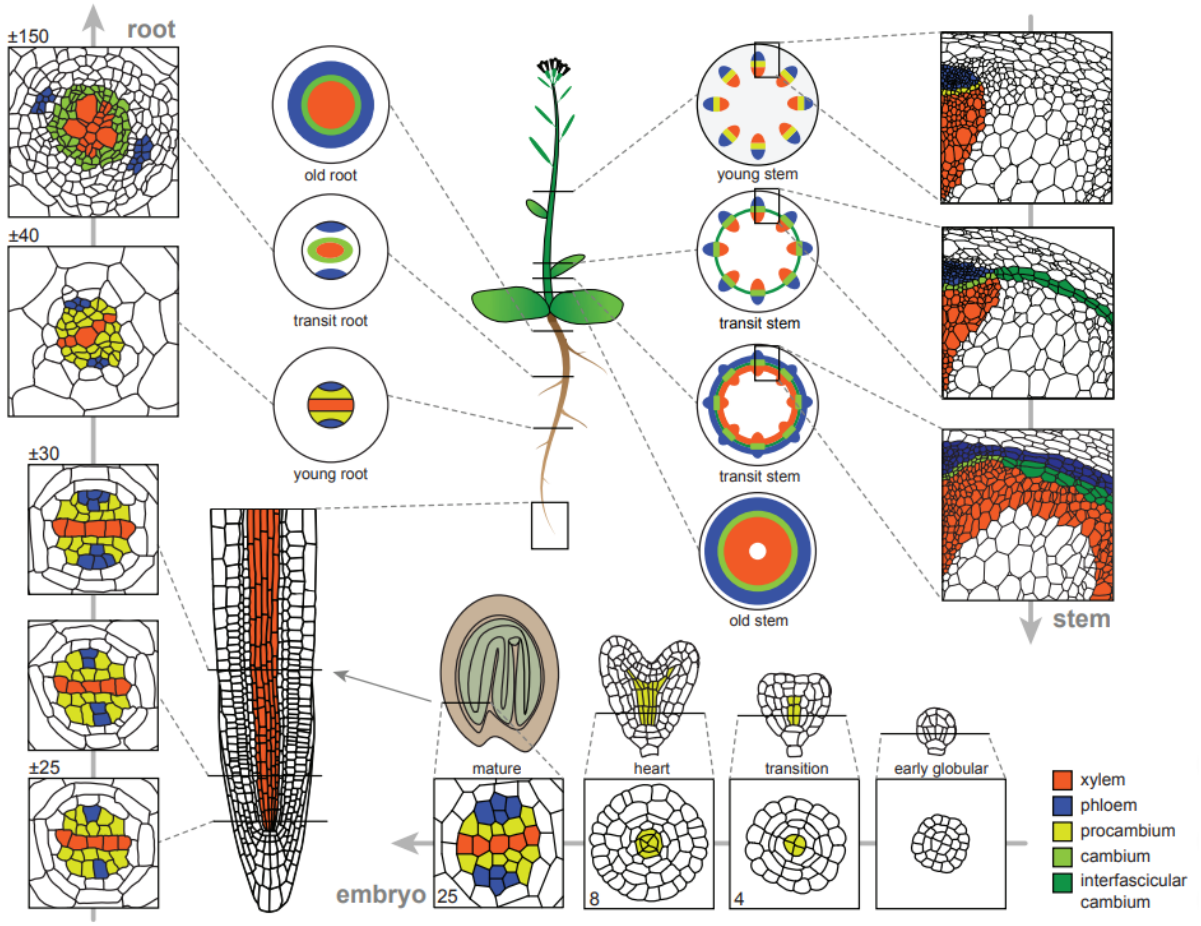

Figure 1: An overview of how periclinal cell divisions contribute to shaping the vascular cell lineage throughout plant development. Starting from only four procambium cells in the early embryo (bottom panel) periclinal divisions increase the number of vascular cell files both in root (left panel) and in stems (right panel). The vascular tissues of the shoot and root lateral organs are omitted for simplicity. The location of each cross section is indicated on a young *Arabidopsis thaliana* plant in the middle. The representative location of the section through the mature embryo in comparison to the post-embryonic root meristem is indicated with a thin arrow. The large gray arrows behind the cross sections represent the time axis during development and the numbers on or next to the cross sections represents the number of cells within the vasculature (excluding the pericycle cells). Note that two of the four procambium cells in the early globular stage embryo share a common cell wall, predicting the future xylem axis.

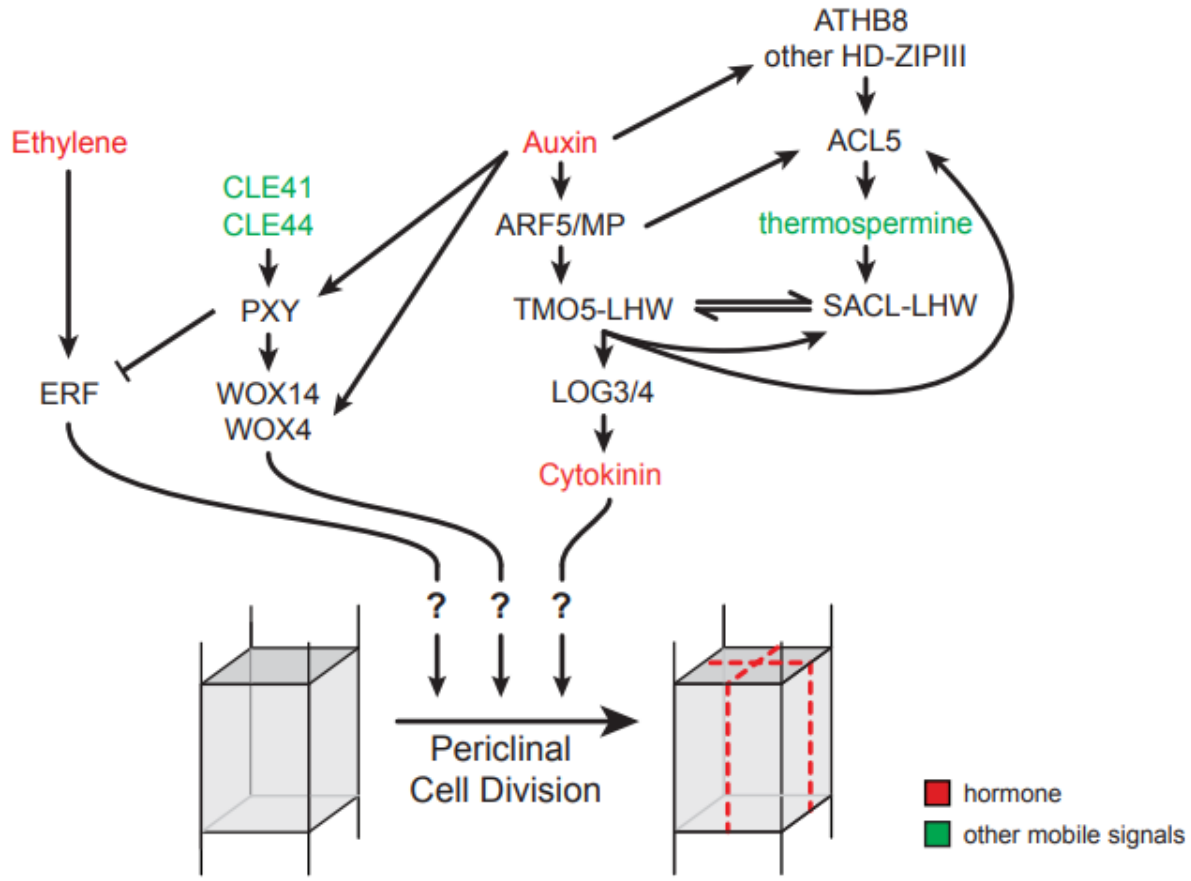

Figure 2: Schematic representation of the known hormonal and genetic pathways controlling vascular proliferation. Several pathways acting in different tissues during distinct developmental stages have been implicated in vascular proliferation (hormonal inputs to this network are highlighted in red, other mobile signals in green). The double arrow indicates competition for LHW in both heterodimer complexes. It remains unclear if these pathways control the same downstream target genes or whether they independently provide cues for cell division orientation. The downstream factors controlling the actual orientation of cell divisions remain unknown.

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Highlighted references:

● ● **[3]** The TMO5-LHW module directly induces expression of LOG4, a rate-limiting enzyme in CK biosynthesis, linking auxin and cytokinin in the control of periclinal cell division in vascular tissues.

● ● **[21]** The authors describe opposing activities of CLE45 and OPS dependent signals in sieve element precursors for the proper timing of protophloem specification and the progression of its differentiation.

● ● **[27]** The T5L1-LHW transcription factor dimer establishes xylem precursor cells as a signal center and thus promotes procambial cell proliferation via cytokinin response.

● **[39]** This work describes the feedback regulation between auxin, the HD-ZIPIII family transcription factor ATHB8 and the thermospermine synthase genes ACL5 and BUD2.

● ● **[47]** The authors show that WOX4 and WOX14, two transcription factors acting downstream of TDIF-PXY, act redundantly in controlling proliferation in the procambial cells of the stem.

● ● **[68]** KATANIN-mediated severing at microtubule crossover sites is regulated by blue light and functions to reorient the microtubule array.

● **[70]** The authors describe that application of exogenous auxin on elongating cells results in microtubule reorientation from transverse to longitudinal.

● **[71]** Hormonal treatment of hyopcotyl cells with auxin and gibberellic acid is shown to synchronously induce reorientation of the microtubule array