

Receptor Kinases in Plant Meristem Development

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Abstract Meristems are groups of cells that promote shoot and root growth, including the growth of new organs, and control vascular development throughout the life of a higher plant. Their continuous proliferation has to be coordinated with the growth requirements of the plant. Signalling systems that facilitate the intercellular communication in meristems have evolved to include the secretion of small signalling peptides, which are perceived by a set of corresponding receptor kinases. Studies on vascular, shoot and root meristems have uncovered surprising similarities and shared functions among these signalling components. One common feature of these meristems is their use of CLE peptides to signal, often *via* redundantly acting RLKs, to regulate the expression of homeodomain transcription factors. These peptide/RLK/homeodomain transcription factor modules control the proliferation and maintenance of stem cells in these meristems.

1 Regulation of Shoot and Floral Meristem Function by RLKs

Meristems are important as the building centres of the plant shoot and root. Primary meristems are initiated during embryogenesis and control growth along the main body axis of the plant. Secondary meristems are generated later and give rise to axillary shoot structures and flowers, or produce lateral roots. Roles for receptor kinases in meristem development were discovered using mutant analysis. Many mutations in meristem functions cause drastic developmental defects, which are obvious and were among the first to be identified and characterized during the early boom of plant developmental genetics and molecular biology in the 1990s. One of the first receptor kinases shown to regulate plant development was CLAVATA1

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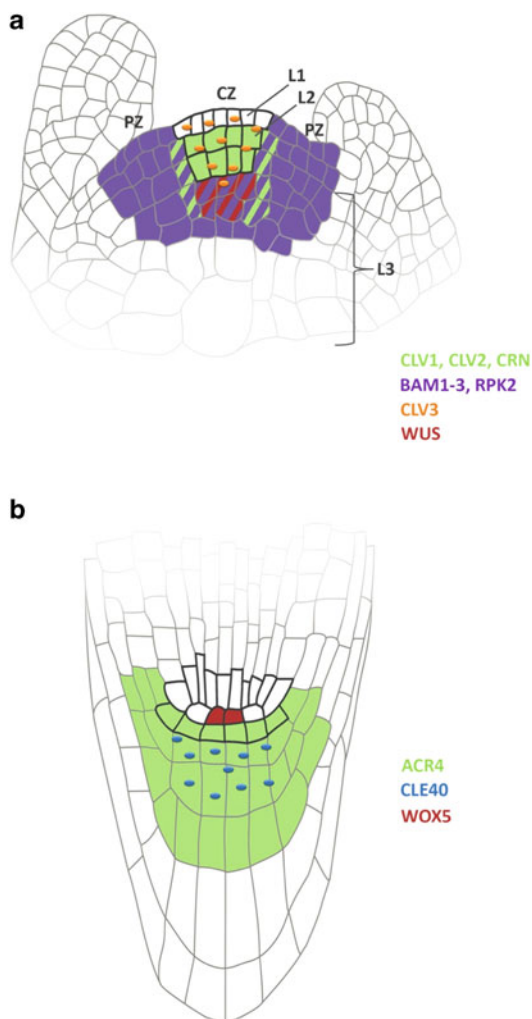
Table 1 Receptors involved in meristem maintenance

Gene	Annotation	Expression domain	Protein family	Putative ligand	Interaction with	Proposed function
CLV1	AT1G75820	OC	LRR-RLK	CLV3/CLEs	CLV1, BAMs	SAM maintenance
CLV2	AT1G65380	SAM	LRR-RLP	CLV3/CLEs	CLV2, CRN	SAM maintenance
CRN	AT5G13290	SAM	MA-RLK	–	CLV2	SAM maintenance
BAM1	AT5G65700	PZ	LRR-RLK	CLEs	unknown	SAM maintenance
BAM2	AT3G49670	PZ	LRR-RLK	CLEs	unknown	SAM maintenance
BAM3	AT4G20270	PZ	LRR-RLK	CLEs?	unknown	SAM maintenance
RPK2	AT3G02130	PZ	LRR-RLK	CLEs?	RPK2	SAM + RM maintenance
PXY	AT5G61480	VAS	LRR-RLK	CLE41/44	unknown	Stem cell maintenance in the vasculature
ACR4	AT3G59420	Distal RM	CR-RLK	CLE40	ACR4	Distal RM maintenance

OC organizing centre, *PZ* peripheral zone, *SAM* shoot apical meristem, *RM* root meristem, *VAS* vasculature, *LRR-RLK* leucine-rich repeat receptor-like kinase, *LRR-RLP* leucine-rich repeat receptor like protein, *MA-RLK* membrane associated receptor-like kinase, *CR-RLK* crinkly repeats receptor-like kinase

(CLV1) from *Arabidopsis thaliana* (Table 1). CLV1 contains an extracellular domain with 21 leucine-rich repeats (LRRs) (Clark et al. 1993, 1997), a single-pass transmembrane domain (TMD) and a cytoplasmic kinase domain with serine/threonine specificity. CLV1 controls the identity and behaviour of stem cells in the vegetative shoot meristem, the inflorescence meristem and the floral meristem. These meristem types share a simple organization (Barton 2009). They contain a small group of stem cells at the tip of the apical dome in the central zone (CZ), which is surrounded by cells of the peripheral zone (PZ) (Fig. 1a). Cell divisions in the CZ will shift daughter cells to a more lateral position into the PZ. At their new position, cells behave differently and start to divide more rapidly. New organ primordia such as leaves or new floral meristems are generated from the PZ. Stem cells within the CZ are controlled by uncharacterized signals from the underlying organizing centre (OC) cells. The expression of the homeodomain transcription factor WUSCHEL (WUS) in the OC is pivotal for stem cell maintenance in the CZ (Laux et al. 1996; Mayer et al. 1998; Schoof et al. 2000). CLV1 is expressed in and around the OC, and a *clv1* mutant fails to restrict WUS expression in the OC. The resulting expansion of WUS expression in *clv1* mutants will cause prolonged maintenance of stem cell identity, thereby causing CZ expansion (Schoof et al. 2000). Such a loss of stem cell control and unrestricted growth of

Fig. 1 Expression domains of receptors and ligands involved in shoot and root meristem maintenance. Schematic representation of the shoot apical meristem (**a**) and root meristem (**b**). Stem cells are outlined in *bold*. Expression domains are colour coded. CZ central zone, PZ peripheral zone



the CZ become evident by larger meristems that produce a fasciated (band-like) stem and flowers with extra floral organs. The production of more carpels, the central organ of the flowers, is very prominent and causes the formation of deformed siliques, reminiscent of clubs, or *clava* in Latin. Mutants in any of the three *CLAVATA* (CLV) genes (Clark et al. 1993, 1995; Kayes and Clark 1998) carry such club-shaped siliques, and this phenotype facilitated the identification of additional mutants affected in stem cell development.

Studies of the three CLV genes led to the model that CLV1 acts as a receptor kinase that is likely to be activated by binding of a small ligand, CLAVATA3 (CLV3), which is secreted from the stem cells of the CZ (Fletcher et al. 1999; Brand et al. 2000) (Table 1). CLV3 belongs to the large *CLAVATA3/ENDOSPERM*

SURROUNDING REGION (CLE) gene family that encodes small peptides which share a conserved C-terminal amino acid sequence, the CLE motif (Cock and McCormick 2001; Oelkers et al. 2008). Isolation and detailed analysis of CLV3 peptide from transgenic plant tissues revealed that the mature 13 amino acid peptide is proteolytically processed from a larger precursor protein (Kondo et al. 2006; Ohyama et al. 2009). Furthermore, two proline residues carry hydroxyl groups, which can be further modified by the addition of arabinofuranose residues. Such peptide modifications, which were also found for CLE2, could serve to protect the peptides from proteolysis in the extracellular space, or may change their binding affinities for specific receptors.

Further experiments led to a model that a negative feedback system is established which could serve to maintain a constant stem cell population. This model depends on a balance between the expression domains of *CLV3* and *WUS*, respectively. Any increase in stem cell number, for example after a burst of stem cell division activities in the shoot meristem, will cause the production of more CLV3 ligand, which in turn will downregulate *WUS* expression via CLV1 activation. Given that *WUS* serves to maintain stem cells, decreased *WUS* expression will allow cells at the CZ periphery to exit earlier from the stem cell state. The resulting drop in CLV3 levels, following a reduction in stem cell number, should then alleviate *WUS* repression, and allow in turn for more stem cells to be produced. In a similar manner, CLV3-dependent CLV1 signalling would be turned down when too few stem cells are available. *WUS* levels will then increase again and a normal stem cell number is restored. According to mathematical models, such a simple network based on negative feedback regulation can serve to maintain a stable stem cell population, and therefore guarantee meristem activity, albeit only within a limited range of parameters (Geier et al. 2008; Hohm et al. 2010).

Several *clv1* mutant alleles with missense mutations in the extracellular or kinase domain displayed stronger phenotypes than putative null alleles that disrupt the kinase domain, such as *clv1-6* or *clv1-7* (Dievart et al. 2003). Furthermore, transcriptional cosuppression of strong alleles resulted in partial suppression of the *clavata* phenotype, indicating that the mutant Clv1 proteins encoded by strong alleles can exert a dominant negative function, possibly by interfering with the activity of pathways that signal in parallel to *CLV1*. Screens for other mutants with a *clv* phenotype had previously identified *CLV2*, which encodes a receptor-like protein that contains LRRs, a TMD and a short cytoplasmic C-terminal region (Kayes and Clark 1998; Jeong et al. 1999). Loss-of-function mutants of either *CLV2* or *CLV1* caused an enlargement of the shoot and floral meristems. However, these single mutants were phenotypically less severe than mutants lacking the signalling peptide CLV3. Interestingly, *clv1/clv2* double mutants displayed an enhanced phenotype (Müller et al. 2008). This suggested that both receptors could act in parallel and potentially independent pathways to transmit the CLV3 signal. Both CLV1 and CLV2 proteins were then found to be capable of CLV3 binding (Ogawa et al. 2008; Ohyama et al. 2009; Guo et al. 2010). However, the mode of signal

transmission from CLV2 to the nuclear compartment, where *WUS* transcription is downregulated upon CLV3 signalling, remains unclear.

New light on the role of CLV2 in stem cell signalling came from genetic screens. Misexpression of CLV3, CLE40 or CLE19 had previously been found to affect not only stem cell maintenance in the above-ground meristems of *Arabidopsis*, but also root development (Casamitjana-Martinez et al. 2003; Hobe et al. 2003; Fiers et al. 2004, 2005). Seedlings overexpressing CLE peptides, or grown on medium containing synthetic CLE peptides, showed root growth retardation and premature differentiation of root meristem cells, indicating the activity of a CLV-related pathway (Hobe et al. 2003). However, the roots of *clv2* mutants (but not *clv1* mutants) were found to be resistant to treatment with CLE19 and other CLE peptides (Fiers et al. 2005). Two novel mutants (*SUPPRESSOR of LLP1/CLE19* overexpression, *sol1* and *sol2*) were isolated that suppressed the CLE19-dependent growth restriction. *sol1* was found to encode a Zn^{2+} -carboxypeptidase that is proposed to process CLE peptide precursors (Casamitjana-Martinez et al. 2003). *sol1* mutant roots were resistant to CLE19 overexpression, but still strongly affected when synthetic CLE peptides (representing the processed version of CLE19) was added externally to the growth medium. Thus, processing of the peptide from a larger precursor molecule was indeed required to generate an actively signalling molecule. The components of such a processing activity were partially purified and characterized from meristem extracts of cauliflower, and shown to be able to process not only CLE peptide precursors, but also related small peptide precursors such as the IDA peptides (Ni and Clark 2006; Stenvik et al. 2008; Ni et al. 2011).

Overexpression of *CLV3* causes shoot meristem arrest (Brand et al. 2000), and suppressor mutants were identified that suppressed the effects of increased CLV3 signalling in the shoot. As expected, not only new alleles of *clv1* and *clv2* were identified, but also mutations in *CORYNE (CRN)* (Müller et al. 2008). The predicted CRN protein contains a short extracellular domain, a TMD and a potentially cytoplasmic serine/threonine kinase domain. Kinase activity has not been shown so far, and attempts to complement a *crn* mutant with a presumed non-functional kinase mutant gave conflicting results (Betsuyaku et al. 2011; Nimchuk et al. 2011a). Cloning of *SOL2*, which was isolated based on its insensitivity to *CLE* gene overexpression, revealed that *CRN* and *SOL2* are allelic. This is consistent with the notion that *CRN* and *CLV2* function in a pathway that controls meristem maintenance in both shoot and root tissues (Miwa et al. 2008). *crn/sol2* mutants display enlarged shoot and floral meristems like *clv2* mutants, but are aphenotypic in the root (Müller et al. 2008). Double mutant studies then revealed that *CRN/SOL2* acts with *CLV2* in the same *CLV3* signalling pathway, in parallel to the *CLV1* pathway (Müller et al. 2008). At the molecular level, CRN and CLV2 could interact within membranes via their TMDs and their short juxtamembrane sequences to reconstitute a functional receptor kinase.

Attempts to isolate and identify the components of signalling complexes comprising CLV1 and CLV2 had been reported (Trotochaud et al. 1999). These early experiments suggested the formation of high-molecular-weight CLV complexes,

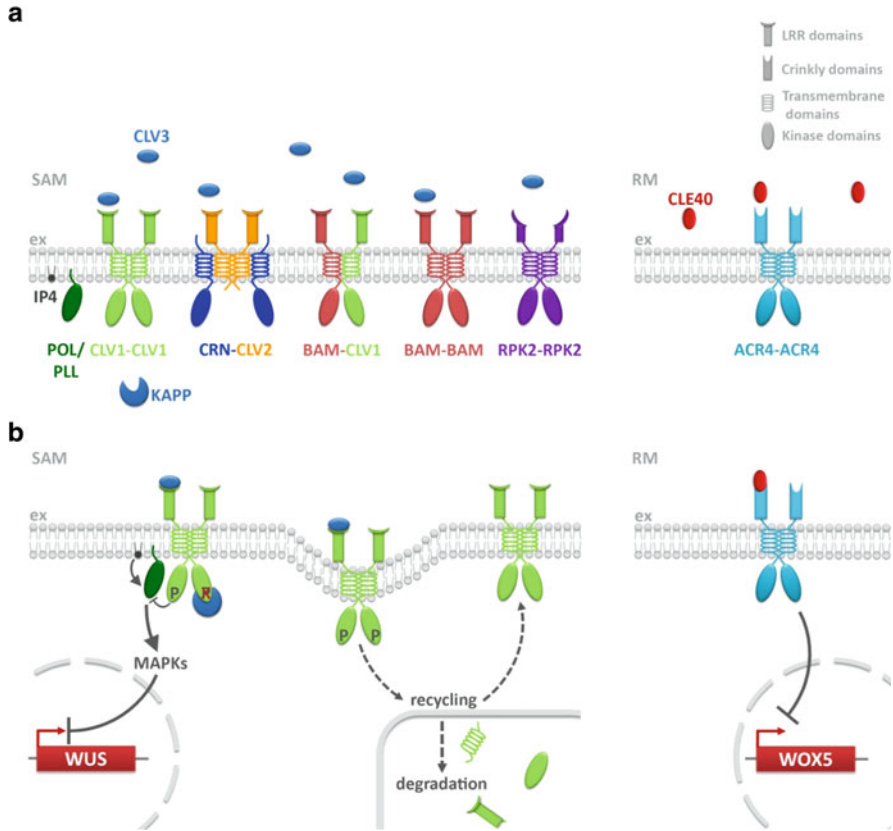


Fig. 2 Receptor complexes involved in meristem maintenance. **(a)** Schematic representations of receptor complexes present in the plasma membrane of the shoot apical meristem (SAM) and the root meristem (RM). The different receptors and their putative ligands are colour coded and shown in their proposed complexes. **(b)** Models of the signalling after receptor/ligand interactions including a proposed mechanism of recycling and degradation of CLV1. Arrows indicate positive regulation, barred lines indicate negative regulation. *ex* extracellular

however, later observations revealed that LRR containing proteins, such as CLV2 and related RLPs identified as receptors in plant pathogen signalling pathways, showed aberrant behaviour in size fractionation experiments (Rivas et al. 2002; Van Der Hoorn et al. 2003). Interactions between CLV2 and CRN were detected using epitope tagged receptors and co-immunoprecipitation, or the split-luciferase system and transient expression in *Arabidopsis* protoplasts or epidermal cells of *Nicotiana benthamiana* (Zhu et al. 2010) (Fig. 2). However, the significance of weak interactions between CLV1 and CRN remained unclear. Another study analysed the fusions of the receptor proteins CLV1, CLV2 and CRN with the fluorescent reporters GFP and mCherry (fluorescent proteins, FP) in transgenic *Arabidopsis* and

by transient expression in *N. benthamiana* (Bleckmann et al. 2010). These experiments showed that receptor proteins tend to form larger and potentially non-functional aggregates in the ER if misexpressed at high levels. Using estradiol-inducible gene expression of receptor fusion proteins, rescue of the corresponding mutants could be shown within a temporally limited window of expression, suggesting that the fusion proteins are fully functional when expressed at low levels. In both *Nicotiana* and *Arabidopsis* cells, CLV1-FPs localized to the plasma membrane, whereas CLV2-FP or CRN-FP remained in the ER when expressed separately. Only when coexpressed, CRN-FP and CLV2-FP were found at the plasma membrane. Interestingly, FRET analysis revealed that the TMDs of CLV2 and CRN are required for their specific interaction, which occurs earlier in the ER. Localization to the plasma membrane requires additional amino acid sequences from the juxtamembrane regions of both proteins. These experiments suggested that at least two independently acting receptor complexes exist: one consisting of CLV1 monomers and a second complex consisting of CLV2 and CRN, which reconstitute a functional receptor via their interaction through the TMDs. Crosstalk between these two complexes can be mediated by an interaction between CLV1 and CRN.

Furthermore, screens for *Arabidopsis* mutants that are insensitive to exogenous CLE peptides uncovered yet another receptor protein contributing to CLV3 signalling. Mutations in the gene *RECEPTOR-LIKE PROTEIN KINASE 2* (*RPK2*), previously identified as *TOADSTOOL2* (*TOAD2*, see Chapter “Experimental Evidence of a Role for RLKs in Innate Immunity”) (Nodine et al. 2007), cause an increase of the shoot and floral stem cell domains (Kinoshita et al. 2010). Although phenotypically slightly milder than mutants in *CLV1*, *CLV2*, *CLV3* or *CRN*, *rpk2* mutants are additive with *clv1* and *crn* or *clv2* mutants, suggesting that *RPK2* is a component of a third signalling pathway acting in parallel to CLV1 and CLV2/CRN. Protein interaction studies in the *N. benthamiana* transient expression system showed that *RPK2* can homomerize at the plasma membrane, but does not interact with the other components of the CLV3 signalling pathways (Betsuyaku et al. 2011). *RPK2* contains extracellular Leucine-rich repeats, a TMD and a cytoplasmic serine/threonine kinase domain, but belongs to a different subfamily of LRR-RLKs than CLV1. Whether *RPK2* is also able to directly bind CLE peptides has not yet been investigated. *RPK2/TOAD2* has multiple roles during plant development, and is required from embryogenesis onwards to specify cell types along the radial axis, generation of the root pole, and in tapetal cell fate specification (Mizuno et al. 2007; Nodine et al. 2007). Interestingly, overexpression of *RPK2* in the entire plant caused a reduction in vegetative growth, suggesting that *RPK2* function may be rate-limiting in a number of different developmental processes (Kinoshita et al. 2010). Although *RPK2* is likely to be involved in CLV3 perception and negative regulation of stem cell fate by repressing *WUS*, increased expression of *RPK2* led to a reduction in stem cell number and plant phenotypes resembling those of *wus* mutants. It is possible that *RPK2* could either autoactivate when overexpressed, or trigger the activation of the CLV1 or CLV2/CRN pathways independently of CLV3.

1.1 Regulation of Signalling

RPK2 is expressed in most plant tissues analysed, and RNA is found throughout the shoot and floral meristems of *Arabidopsis*. Expression of RPK2-GFP fusion proteins from the RPK2 promoter revealed localization of the receptor at the plasma membrane, but expression levels were clearly reduced in the central zone of inflorescence meristems (Kinoshita et al. 2010). This could suggest that the protein is undergoing cyclic degradation upon perception of the CLV3 signal. A similar scenario was recently proposed for the CLV1 receptor and suggested to be part of a compensatory mechanism that dampens CLV signalling (Nimchuk et al. 2011b) (Fig. 2b). Here, CLV1-GFP fusion proteins were found to be targeted towards the vacuole for degradation in a CLV3-dependent manner. However, overall CLV1 levels were not increased in *clv3* mutants compared with wild-type, suggesting that CLV3-dependent removal of CLV1 from the membrane mainly serves to compensate for the continuous de novo synthesis of CLV1 receptor. Interestingly, *WUS*, the main target of the CLV pathway, directly downregulates *CLV1* expression at the transcriptional level (Busch et al. 2010). Thus, CLV signalling will cause increased *CLV1* expression, which can be compensated by receptor degradation.

1.2 Role of CLV1-Related BAM Receptors in Meristem Signalling

Several LRR-RLKs that are closely related to CLV1 also contribute to meristem maintenance in *Arabidopsis*. Single mutations in *BARELY ANY MERISTEM1* (*BAM1*), *BAM2* or *BAM3* were aphenotypic, but double mutant combinations of *bam1* with *bam2* carried smaller shoot meristems, while *bam1 bam2 bam3* triple mutants even arrested growth or generated floral meristems lacking organs (DeYoung et al. 2006). Thus, BAM receptors appear to act antagonistically to CLV1 in meristem size control. However, expression of *CLV1* under the control of the *ERECTA* promoter, which is more broadly expressed than *CLV1*, could rescue *bam1 bam2* meristem defects, and expression of *BAM1* or *BAM2* in the shoot meristem was able to partially suppress *clv1* mutant phenotypes, indicating that these receptors are functionally interchangeable. Expression of *CLV1* is mostly confined to the centre of shoot and floral meristems. BAM receptors are expressed preferentially not only at the meristem periphery, but also in other tissues (DeYoung and Clark 2008). For example, *BAM1* and *BAM2* control cell division and cell type specification during anther development (see Chapter “Experimental Evidence of a Role for RLKs in Innate Immunity”). In meristems, BAM receptors can also affect development of the central meristem domain, because *clv1* mutants showed additive interactions with *bam1* and *bam2*. BAM receptors were reported to bind CLE peptides, although with a lower affinity than CLV1 (Guo et al. 2010) (Fig. 2a). It was proposed that BAM receptors in the outer meristem regions could partially shield the meristem centre from diffusing CLE peptides that originate from

the meristem periphery (DeYoung and Clark 2008), and are able to activate CLV signalling similarly to CLV3. The A-type CLE peptides CLE16, 17 and 27 were recently shown to be expressed also in shoot apical meristems, but misexpression of these peptides at high levels in the shoot meristem did not affect meristem maintenance (Jun et al. 2010). It is still possible that other peptides expressed at low levels or divergent in sequence from the CLE family act in parallel with CLV3 and bind the BAM receptors. Alternatively, BAM RLKs could function with the CLV signalling pathway not at the level of ligand sequestration, but further downstream at the regulation of common target genes.

1.3 Signal Transduction to the Nucleus

The precise mechanism of CLV signal transmission from plasma membrane binding sites to transcriptional responses in the nucleus is still not understood. However, genetic screens allowed the isolation of several genes whose products may mediate these signalling pathways. Mutations in the *POLTERGEIST* (*POL*) gene suppress the enlarged meristem phenotypes of *clv1*, *clv2* (Yu et al. 2000) and also *crn* mutants (Müller et al. 2008) (Fig. 2a, b). *POL* acts downstream of the *CLV* genes and encodes a protein phosphatase 2C that, with other members from the plant kingdom, belong to a unique subclass of phosphatases (Yu et al. 2003). *POL* and the related PLL1 (*POLTERGEIST*_LIKE-1) protein promote *WUS* expression in shoot and floral meristems (Song and Clark 2005; Song et al. 2006), but are also required for the specification of vascular cells and the root meristem during embryogenesis (Song et al. 2008). As a downstream intermediate, *POL* was suggested to be repressed by CLV signalling. The finding that *POL* and PLL1 require N-terminal myristoylation and palmitoylation to be localized to the plasma membrane significantly expanded the understanding of this signalling pathway (Gagne and Clark 2010). *POL* phosphatase activity is stimulated upon binding of phosphatidylinositol (4) phosphate (PI4P), suggesting that stem cell fate in meristems may be strongly influenced by the lipid composition of the plasma membrane. It is conceivable that preferential activation of CLV receptors by CLV3 at the apical side of a cell could then locally restrict PI4P availability. The resulting polar distribution of PI4P would cause a corresponding polar activation of phosphatases such as *POL*, which could underly the mechanism that generates asymmetries after stem cell division.

Another CLV signalling component is KAPP, a kinase-associated protein phosphatase that binds to phosphorylated peptides and serves to antagonize diverse RLKs in *Arabidopsis* (Williams et al. 1997; Stone et al. 1998; Ding et al. 2007). Interaction studies and phosphorylation assays suggest that the MAP kinase pathway is involved in transmitting the CLV3 signal to the nucleus (Betsuyaku et al. 2011). CLV3 was found to trigger CLV1 phosphorylation in an *N. benthamiana* transient expression system and to control MPK6 activity via the CLV receptors also in *Arabidopsis* seedling assays. Interestingly, this study indicates a differential effect of the CLV receptors on MPK6 activity, with RPK2 and CLV2 activating, but

CLV1 repressing MPK6 function (Betsuyaku et al. 2011). However, a more detailed investigation is needed to specifically resolve the roles of MAPKs in stem cell maintenance.

2 ACR4 Regulates Lateral Root Formation and Stem Cell Maintenance

The first indications that RLK-dependent signalling pathways regulate root meristem architecture or maintenance came from CLE peptide misexpression phenotypes in roots (Fig. 1b). As described above, exogenous application of or constitutive misexpression of CLV3, CLE40 or CLE19 caused inhibition of root growth, due to premature differentiation of meristem cells (Casamitjana-Martinez et al. 2003; Hobe et al. 2003; Fiers et al. 2004). These early results suggested that a *CLV*-like signalling pathway also operates in the root. However, knockout mutants in several root-expressed RLKs were aphenotypic, and only *CLV2* and *CRN*, which are both expressed in the vasculature of the root meristem, were found to be required for the growth-limiting phenotypes after high-level misexpression of CLE peptides (Fiers et al. 2005; Müller et al. 2008). Nevertheless, no loss-of-function phenotype was found for these receptors in root development.

Lateral roots are initiated from cells of the pericycle cell layer that are located opposite of the xylem poles. Two asymmetric divisions generate a core group of four small cells, which, after several rounds of periclinal cell divisions, will generate the lateral root primordium. Cell sorting and RNA analysis via microarray resulted in the identification of genes that are specifically expressed during these earliest stages of lateral root formation, among them the membrane-localized RLK *ARABIDOPSIS CRINKLY4* (*ACR4*) (De Smet et al. 2008). *ACR4* is a member of a small gene family, together with four closely related RLKs (*CRR1* – 4) (Cao et al. 2005). Previously, *ACR4* was found to control the maintenance of the outermost meristem cell layer, the L1, during embryonic development (Tanaka et al. 2002; Gifford et al. 2003; Watanabe et al. 2004). In the root, *ACR4* restricts the number and position of lateral root initiation events (De Smet et al. 2008) acting redundantly with the other family members, but also restricts the proliferation of stem cell layers at the distal position of the root meristem that generate the protective columella cells. A close inspection of *cle40* mutants revealed a similar proliferation defect of the columella stem cell layers as observed in *acr4* mutants (Stahl et al. 2009). *CLE40* is normally expressed in the differentiated columella cells. When *Arabidopsis* roots are grown on media containing synthetic CLE40 peptide, the distal root stem cells also acquired columella cell identity. This *CLE40* overexpression phenotype did not manifest in *acr4* mutants, suggesting that CLE40 could be a potential ligand that signals through ACR4 in columella stem cells.

These parallels to the regulation of the shoot stem cell system through the *CLV* pathway can be even further extended to the targets of the CLE peptide/RLK

signalling module. Root stem cells are highly specific and give rise to discrete cell types (Benfey and Scheres 2000). The stem cells surround the quiescent centre (or QC), a group of four cells that inhibits stem cells from differentiating. A candidate gene for stem cell maintenance that is specifically expressed in the QC is *WOX5*, a member of the *WUSCHEL-LIKE HOMEODOMAIN* (*WOX*) gene family, and *WOX5* is very closely related to *WUS* (Sarkar et al. 2007). Indeed, cross-complementation experiments showed that *WUS* and *WOX5* can functionally replace each other when expressed in the corresponding domains. *WOX5* was found to be a target for transcriptional regulation by the proposed *CLE40* – *ACR4* module (Stahl et al. 2009) and consistent with this, *wox5* mutants fail to maintain columella stem cells. The *CLE40* peptide is most closely related to *CLV3* and can replace *CLV3* function if expressed from the *CLV3* promoter (Hobe et al. 2003). Thus, the stem cell regulatory units consisting of a CLE peptide (*CLV3* or *CLE40*) and a target transcription factor (*WUS* or *WOX5*) are fully conserved between the shoot and the root. However, a different receptor type, one without LRRs, is employed for signal transmission in the root.

ACR4 contains seven CRINKLY repeats with a predicted β -propeller structure and a domain homologous to the Cys-rich repeats of tumor necrosis factor receptor (TNFR) in the extracellular region, followed by a transmembrane domain and a cytoplasmic kinase region. Complementation analysis showed that the TNFR-like domains are not required, and that also a kinase-null version of *ACR4* can still rescue *acr4* mutant phenotypes (Gifford et al. 2005). This could indicate that *ACR4* interacts with another RLK that provides the kinase activity. On a similar line, *CRR1* and *CRR2*, which were found to be kinase-dead, were shown to be the targets for phosphorylation by *ACR4* (Cao et al. 2005). This suggests that RLKs from the *ACR4*-family may act in larger complexes, and indeed, dimerization via their transmembrane domains has been confirmed for all of them (Stokes and Rao 2008).

Interestingly, *ACR4* shows a high degree of turnover, and both the TNFR domain and the cytoplasmic domain appear to be involved in controlling protein stability. Only the functional versions of *ACR4* that carry the CRINKLY repeats are rapidly endocytosed, suggesting that the removal of *ACR4* protein from the plasma membrane followed by degradation is triggered by ligand binding and serves to dampen signalling (Gifford et al. 2005). *ACR4* expression is also transcriptionally upregulated in the distal stem cell domain upon incubation of roots with excess *CLE40* peptide (Stahl and Simon 2009), suggesting that overall *ACR4* signalling activity is subject to both positive and negative feedback regulation.

3 Signalling Cell Fate in the Vascular Meristem

The procambium comprises the stem cells of the vascular system. The procambial strands are highly polarized, generating new cell layers along the radial axis that will differentiate into either phloem cells (outside) or into xylem cells (inside). A first hint of a specific role of RLKs in maintaining this organization came from a

biochemical tour-de-force, aimed at isolating diffusible factors that control cell differentiation in a tissue culture system (Ito et al. 2006). *Zinnia* cell cultures had long been used to study xylem tracheary element development, with specific emphasis on their ability to link up and form long, continuous vascular strands. A peptide belonging to the CLE family, TDIF (TRACHEARY ELEMENT DIFFERENTIATION INHIBITORY FACTOR), and its *Arabidopsis* homologues CLE41/CLE44 were shown to inhibit xylem cell differentiation. Both CLE41/44 are normally expressed from the phloem. When *Arabidopsis* seedlings were grown in liquid culture containing TDIF peptides, procambium cells proliferated at the expense of xylem differentiation (Hirakawa et al. 2008). A candidate receptor for CLE41 is PXY (PHLOEM INTERCALATED WITH XYLEM), an RLK closely related to CLV1 and the BAM receptors, which is expressed mainly in the procambium (Fisher and Turner 2007). *Pxy* mutants show aberrant arrangement of phloem and xylem cells, indicating that PXY controls oriented cell division of procambium descendants. CLE41 was found to bind to the extracellular domain of PXY (also known as TDR, for TDIF receptor) (Hirakawa et al. 2008) and control PXY/TDR activity in a dosage-dependent manner. A *cle41* mutant formed a thinner stele than wildtype plants (Hirakawa et al. 2010), whereas increased expression of CLE41 from the phloem caused procambium proliferation, albeit with normal vasculature organization (Etchells and Turner 2010). However, *CLE41* misexpression in specific vascular cell types disturbed the normal pattern of vascular development, and also downregulated expression of *PXY* itself. These observations suggest that the CLE41 peptide controls the rate of procambium proliferation and the orientation of cell divisions. This proposed gradient of CLE41 peptide, with phloem cells as a source and signalling competent, PXY-expressing procambial cells as sink would serve to maintain the procambial cells and act to balance phloem and xylem production. One of the targets regulated transcriptionally by the TDIF-PXY/TDR pathway is *WOX4*, another member of the *WOX* gene family (Hirakawa et al. 2010). Furthermore, *WOX4* expression in the procambium and cambium is needed for stem cell maintenance and continuous production of the vasculature. Thus, a CLE/RLK signalling module controls also stem cell behaviour during vascular development, but in contrast to the previous examples, by promoting rather than repressing the expression of a WUS-like homeodomain protein.

4 Evolutionary Considerations and Conclusions

We have discussed here the roles of RLKs in three different meristem systems: the shoot and floral meristems, the primary root meristem and the vascular meristem. In all three systems, RLKs play an important role in controlling the maintenance and proliferation of undifferentiated stem cells, and there are intriguing similarities in the molecular makeup of these signalling pathways. CLE peptides act as ligands that serve to control the communication between differentiated cells and stem cells. In the shoot meristem, three receptor systems have been identified which perceive

extracellular CLE peptides via their leucine-rich repeats, and signal through the cytoplasmic kinase domains. Both *CLV1* and *RPK2* have evolved early in the plant lineage, and homologues can be found in bryophytes such as *Physcomitrella patens* (Sawa and Tabata 2011). In *Lotus*, the *CLV1* and *RPK2* homologues have been identified as *HAR1* and *KLAVIER*, respectively, which interact and control not only shoot meristem development, but also formation of root nodules in a CLE-dependent manner (Okamoto et al. 2009; Miyazawa et al. 2010). The *CLV2/CRN* composite receptor appears to be a more recent innovation of vascular plants (Miwa et al. 2009). In addition to controlling stem cell fate in the shoot system, *CLV2/CRN* expression in the root has been exploited by parasitic nematodes as an access point to induce root cell proliferation via production of nematode CLE peptides (Replogle et al. 2011). *PXY*, belonging to the same subfamily of RLKs as *CLV1* and the BAMs, controls vascular development by promoting *WOX4* expression, and homologues from both *PXY/TDR* and *WOX4* were shown to be expressed in the procambium of important crop species such as poplar (Schrader et al. 2004).

For all the signalling systems discussed here, mutant identification provided a starting point for the genetic dissection of pathways. However, we now realize that the regulatory systems are more complex than initially thought. A single signalling molecule, such as *CLV3* peptide, can be perceived by at least three different receptor complexes. In addition, further biochemical studies revealed that many more receptors are able to bind the *CLV3* ligand and that an array of different CLE peptides can interact with the *CLV* receptors. An important question arising now is how signalling specificity is maintained. Given the huge number of receptor kinases that are expressed in plants and the tendency of most systems to operate via redundant receptors, which could provide a fail-safe mechanism, it is unlikely that we will be able to unravel the roles of all RLKs through mutant studies. Instead, we will need to study receptor expression, interaction, complex formation and activation *in vivo*, and perform these analyses in individual cells within a tissue context. To do this, novel and more sensitive techniques will have to be developed to allow RLK functional analysis in the developing plant meristems.

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