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REVIEW

CLAVATA-WUSCHEL signaling in the shoot meristem

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ABSTRACT

Shoot meristems are maintained by pluripotent stem cells that are controlled by CLAVATA-WUSCHEL feedback signaling. This pathway, which coordinates stem cell proliferation with differentiation, was first identified in *Arabidopsis*, but appears to be conserved in diverse higher plant species. In this Review, we highlight the commonalities and differences between CLAVATA-WUSCHEL pathways in different species, with an emphasis on *Arabidopsis*, maize, rice and tomato. We focus on stem cell control in shoot meristems, but also briefly discuss the role of these signaling components in root meristems.

KEY WORDS: CLAVATA-WUSCHEL, Shoot meristem, Signaling, *Arabidopsis*, Maize, Rice, Tomato

Introduction

The shoot apical meristem (SAM) is the primary stem cell niche in plant shoots (Nägeli, 1858; Steeves and Sussex, 1989). The SAM is organized into distinct clonal cell layers, with three layers (L1-L3) in *Arabidopsis* but different numbers in other species; for example, there are only two (L1 and L2) in maize (Abbe et al., 1951; Steffensen, 1968). The clonal layers are not fully maintained outside of the SAM, but in general the L1 forms the epidermis, the L2 forms mostly subepidermal tissues and the germline, and the L3 forms the remaining inner tissues of the shoot (Satina et al., 1940). The SAM can also be classified into different zones based on function, cytology and gene expression profiles. A stable pool of pluripotent stem cells is maintained in the central zone (CZ), and these divide slowly, displacing daughter cells into the peripheral zone (PZ). Here, the cells resemble transit amplifying stem cells and receive differentiation signals until they eventually form new organ primordia on the flanks of the SAM (Rembur and Nougarède, 1977; Ruth et al., 1985). A group of cells residing directly below the stem cells in the CZ is referred to as the organizing center (OC), since they are required to 'organize' or faithfully maintain the stem cell population (Mayer et al., 1998).

The SAM remains active through the entire life of the plant, for up to hundreds or thousands of years in trees, and stem cell proliferation thus has to perfectly balance the continuous loss of daughter cells to organ formation. The CLAVATA3 (CLV3)-WUSCHEL (WUS) signaling pathway has evolved as the central regulatory pathway that coordinates stem cell proliferation with differentiation. This coordination is achieved via an autoregulatory negative-feedback loop (Fig. 1) comprising the stem cell-promoting transcription factor WUS and the differentiation-promoting peptide CLV3 (Brand et al., 2000; Schoof et al., 2000). In this Review, we summarize the CLV-WUS pathway and highlight recent findings from studies of *Arabidopsis* and other species that have revealed important mechanistic details as well as new complexity in the CLV-WUS pathway. We also discuss evidence that this pathway has been a target of selection during crop domestication to enhance agricultural yields.

The generation of a signal: CLV3 and related peptides

CLV3 is a founding member of the CLAVATA3/EMBRYO SURROUNDING REGION (ESR) CLE peptide family, the members of which can be identified by sequence similarity to CLV3 and the maize *ESR* gene products, which are expressed in the developing endosperm surrounding the embryo (Clark et al., 1995; Opsahl-Ferstad et al., 1997). In *Arabidopsis*, there are 24 expressed CLE family members, which share a conserved 14 amino acid sequence motif termed the CLE-box and have been implicated in stem cell maintenance in the SAM, the root apical meristem (RAM) and the vascular cambium (Casamitjana-Martínez et al., 2003; Cock and McCormick, 2001; Fletcher et al., 1999; Ito et al., 2006; Stahl et al., 2009). CLV3 is expressed as a pre-pro peptide only in stem cells of the SAM, and the processed peptide is secreted (Fletcher et al., 1999; Rojo et al., 2002). In the underlying cells of the OC, CLV3 peptide is perceived by at least four different receptor-like proteins to repress WUS activity (Brand et al., 2000; Fiers et al., 2005; Hobe et al., 2003; Müller et al., 2008; Schoof et al., 2000). Accordingly, repression of WUS by CLV3 results in fewer stem cells being maintained, and, ultimately, in a reduction in CLV3 production (Brand et al., 2000; Schoof et al., 2000). This feedback loop enables the stem cell compartment and the OC domain to maintain their size, by adjusting relative to each other, and it was found that this system can robustly buffer SAM size when CLV3 levels are varied up to tenfold (Müller et al., 2006). For example, a surge in CLV3 signal activity would result in rapid downregulation of WUS, followed by a loss of responsiveness of the system to ongoing CLV3 signaling during a refractory period (Müller et al., 2006). What causes this loss of responsiveness is not known, but it could be due to depletion of receptors from the plasma membrane or the temporary modification of downstream signaling, such as hyperphosphorylation (Nimchuk et al., 2011b).

The first *CLE* genes identified outside of *Arabidopsis* were the *ESR* genes in maize, but *CLV3* orthologs have been best characterized in rice, where one was named after a mutant in the *FLORAL ORGAN NUMBER2* (*FON2*) gene (also identified and named independently as *FON4*) (Chu et al., 2006; Suzaki et al., 2006). Similar to *CLV3*, *FON2* is expressed in a few cells in the apical region of all shoot meristems, and *fon2* mutants, like *clv3* mutants, make additional floral organs (Chu et al., 2006; Suzaki et al., 2006). *FON2* overexpression affects floral meristems and inflorescence meristems, but not the vegetative SAM, suggesting developmental stage specificity (Suzaki et al., 2006). CLE peptides have also been studied by exogenous application of synthetic forms in order to mimic overexpression (Fiers et al., 2005). For example, exogenous FON2 peptide application in rice leads to vegetative

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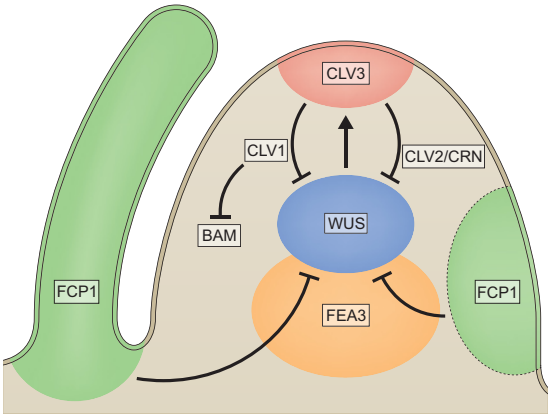

Fig. 1. CLV-WUS feedback pathways in shoot meristems. Hybrid model combining data from *Arabidopsis* and maize. The canonical CLV3-WUS negative-feedback loop is represented by positive and negative arrows. Negative regulation of *BAM* genes by *CLV1*, and of *WUS* by FEA3/FCP1 signaling from differentiating cells, are also illustrated.

SAM termination but, in contrast to CLV3 peptide application, does not have an obvious effect on root meristem development, suggesting that *CLV3* and *FON2* are functionally divergent and that other *CLE* genes function in rice root development (Chu et al., 2006; Suzaki et al., 2008).

Further studies in rice suggest that multiple CLV3 orthologs function in the SAM. A *FON2*-related gene, *FON2 SPARE1* (*FOS1*), which encodes a very similar CLE protein, was identified because its functional allele in indica varieties acts as a genetic suppressor of *fon2* mutants in japonica. *FOS1* is expressed in all SAMs, including the vegetative SAM, and *FOS1* overexpression causes SAM termination, although *FOS1* may act redundantly with FON2 in some rice accessions (Suzaki et al., 2009). A third rice *CLE* gene, *FON2-LIKE CLE PROTEIN1* (*FCP1*), also functions in vegetative SAM maintenance but is expressed more widely in shoot apices, including in leaf primordia (Kinoshita et al., 2007; Suzaki et al., 2008). Overexpression of *FCP1* leads to a reduction in SAM size and blocks the initiation of adventitious roots (Suzaki et al., 2008). *FCP2*, a close paralog of *FCP1*, is expressed similarly, and *FCP1;FCP2* RNAi plants fail to regenerate shoots, suggesting that *FCP1* and *FCP2* function redundantly (Suzaki et al., 2008). In summary, studies in rice suggest that multiple *CLE* genes function at different stages of development, with *FON2* and *FOS1* encoding likely CLV3 orthologs, and *FCP1* and *FCP2* predicted to encode related CLE peptides that are expressed more broadly but also function in SAM regulation.

A *CLV3* ortholog has not yet been functionally characterized in maize, but two candidates, *Zea mays* (*Zm*) *CLE7* and *ZmCLE14*, were identified by phylogenetic analysis, and both peptides encoded by these genes were shown to have a negative effect on SAM size when applied exogenously (Je et al., 2016). *ZmCLE7* is expressed in the ear inflorescence meristem, and it is overexpressed in the CLV-related mutant *fasciated ear3* (*fea3*) (Je et al., 2016). A third maize *CLE* gene, *ZmFCP1*, is expressed in leaf primordia, similar to the rice ortholog that gave it its name. *Zmfcp1* mutants also show a *clv*-like 'fasciated ear' phenotype, suggesting that this CLE peptide can regulate the SAM by signaling from differentiating cells (Je et al., 2016).

Tomato orthologs of CLV3 have been identified, and peptide treatments also confirmed their ability to inhibit root and shoot development (Xu et al., 2015; Zhang et al., 2014). In contrast to the situation in *Arabidopsis*, however, *S. lycopersicum* (*Sl*) *CLV3* is expressed in the inner layer cells of the SAM, above *SlWUS* expression, but notably is absent from the L1 layer (Xu et al., 2015). Flowers in *Slclv3* mutants have typical *clv* phenotypes, and *Slclv3* mutants also have abnormally branched inflorescences, suggesting crosstalk between the CLV-WUS and branching pathways (Xu et al., 2015).

Peptide processing and modification

CLV3 encodes a 96 amino acid precursor protein that contains a signal peptide to direct it into the secretory pathway (Fletcher et al., 1999; Rojo et al., 2002). The mature processed form of CLV3 was characterized by matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI-TOF MS) of peptides expressed in callus, and was found to be a peptide containing the 12 central amino acids of the conserved 14 amino acid CLE-box, with hydroxylation of two proline residues (Kondo et al., 2006). Subsequently, by applying nano-liquid chromatography-MS/MS analysis to apoplastic peptides of *Arabidopsis* plants, this was further refined to predict that the mature active form of CLV3 is a 13 amino acid arabinosylated glycopeptide carrying a chain of three L-arabinose residues on the second hydroxyproline (Ohyama et al., 2009). Molecular modeling suggests that the triarabinoside chain induces conformational changes that have important effects on the binding and specificity of CLV3 with its receptor proteins; the arabinosylated peptide possessed a higher receptor binding affinity *in vitro* and higher biological activity when applied exogenously to *Arabidopsis* plants (Ohyama et al., 2009; Shinohara and Matsubayashi, 2013).

The importance of arabinosylation for CLV3 activity was further demonstrated *in planta* in tomato: the *fasciated inflorescence* (*fin*) mutant, which carries a mutation in a gene encoding a hydroxyproline O-arabinosyltransferase (HPAT; glycosyltransferases that add arabinose sugars to proteins), exhibits *clv*-like phenotypes with a larger meristem and more floral organs (Xu et al., 2015). Furthermore, *fin* mutants can be complemented by the addition of arabinosylated CLE peptides, indicating that arabinosylation is essential for meristem maintenance in tomato (Xu et al., 2015). The related *fasciated and branched2* (*fab2*) and CRISPR-generated *reduced residual arabinose3* (*rra3*) tomato mutants, which are also fasciated, harbor mutations in genes that encode additional arabinosyltransferases (Xu et al., 2015). These mutant phenotypes indicate that sequential arabinosylation of CLE peptides by three enzymes is crucial to CLV signaling in tomato. The situation in *Arabidopsis*, however, is less clear, since null mutants for *HPAT* genes do not have a *clv* phenotype (MacAlister et al., 2016). It should also be noted that, although arabinosylation may increase the potency of some CLE peptides, other CLE peptides that are able to control meristem size have serine or alanine residues instead of the hydroxyproline at position 7 and presumably are not modified, suggesting that arabinosylation is not essential for CLE function, unless the first hydroxyproline at position 4 can be modified (Ohyama et al., 2009).

Receptor localization, interactions and turnover

Once secreted from stem cells, the CLV3 peptide is perceived in the underlying cells of the OC by plasma membrane-localized receptor-like kinases (RLKs), receptor-like proteins (RLPs) and receptor-like cytoplasmic kinases (RLCKs) (Fig. 2). Of these, the RLK CLAVATA1 (CLV1) plays a key role. *clv1* was one of the first meristem mutants identified, owing to its enlarged SAM phenotype

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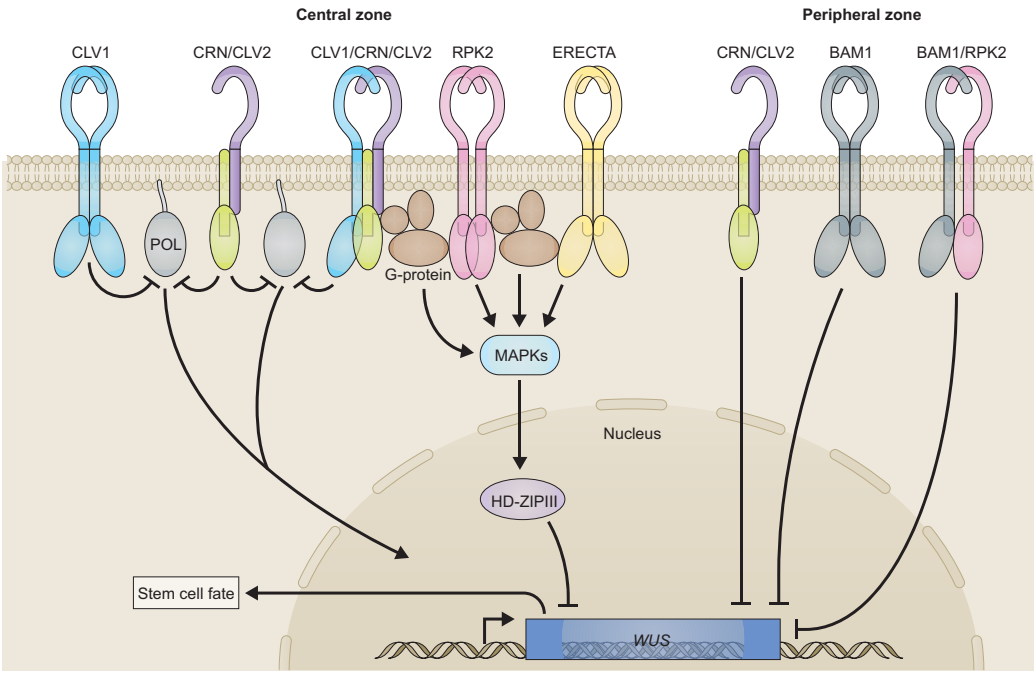

Fig. 2. Molecular components of the CLV-WUS pathway in *Arabidopsis*. Different plasma membrane-localized LRR-RLKs and RLPs in different meristem zones (the central zone and the peripheral zone) are shown with their putative interacting proteins and downstream effectors. Signaling via these receptors eventually leads to the repression of *WUS*, which would otherwise act to promote stem cell fate.

(Leyser and Furner, 1992). *CLV1* is expressed in the CZ of the SAM and encodes an RLK consisting of a receptor domain (RD) with 21 leucine-rich repeats (LRRs), a transmembrane domain (TMD) and an intracellular serine/threonine kinase domain (KD) (Clark et al., 1997). CLV1 was initially suggested to perceive the CLV3 peptide in a complex with the RLP CLAVATA2 (CLV2) (Clark et al., 1997; Jeong et al., 1999). Both *clv1* and *clv2* mutants generate siliques with additional carpels from enlarged floral meristems (Koornneef et al., 1983). CLV2 has a 21 LRR RD and a TMD similar to CLV1, but lacks an intracellular KD (Jeong et al., 1999). Although CLV2 was thought to act as a co-receptor for CLV1, only *clv1;clv2* double, but not single, mutants mimic the *clv3* phenotype in severity, suggesting at least partially independent roles for the two receptors (Jeong et al., 1999; Kayes and Clark, 1998). The co-receptor model was eventually modified when the cytoplasmic RLK CORYNE (CRN) was identified in an ethyl methanesulfonate mutagenesis screen for suppressors of *CLV3* overexpression (Müller et al., 2008). CRN lacks an extracellular RD and consists of a TMD with an intracellular inactive (pseudo)kinase domain (Müller et al., 2008; Nimchuk et al., 2011a). CRN and CLV2 were found to interact via their TMDs, thereby forming a full receptor-(pseudo)kinase complex, leading to a new model for stem cell maintenance, with the CLV3 signal transmitted by two parallel pathways: one signaling through CLV1; and a second, independent pathway signaling through a CLV2-CRN heterodimer (Bleckmann et al., 2010; Guo et al., 2010; Müller et al., 2008). Interestingly, in contrast to *CLV1*, *CLV2* and *CRN* are expressed throughout the entire SAM, and not only the CZ, raising the possibility that they could function not only in the central CLV3-WUS pathway, but also in a second pathway that could signal from the PZ into the CZ (Müller et al., 2008).

Receptor interactions, such as dimerization, appear to be a prerequisite for receptor activation and signaling activity. In the case of the CLV2-CRN receptor pair, heterodimerization is a prerequisite for the proteins to be exported from the endoplasmic reticulum (ER) to the PM (Bleckmann et al., 2010). CLV1 forms homodimers and also localizes to the plasma membrane in a dimeric form (Bleckmann et al., 2010). Interestingly, though, in all well-studied signaling pathways involving CLV1-related LRR-RLKs, such as FLAGELLIN SENSITIVE2 (FLS2) or BRASSINOSTEROID INSENSITIVE1 (BRI1), a co-receptor with a shorter LRR RD, such as BRI1-ASSOCIATED KINASE1 (BAK1), is required for stable peptide binding, indicating that the CLV1 homodimers might require such a partner as well (Santiago et al., 2013). However, thus far no such co-receptor is known, and it is unlikely that this co-receptor is CLV2 since it carries a large ectodomain with 21 LRRs and therefore could require a co-receptor itself. Once at the plasma membrane, the CLV1 homodimers bind the CLV3 peptide; CLV2 might be able to bind CLV3 under certain conditions but, in contrast to CLV1, does not exhibit a general binding specificity for CLV3 (Guo et al., 2010; Shinohara and Matsubayashi, 2015). Furthermore, whereas direct binding of CLV3 to the RD of CLV1 results in autophosphorylation of the CLV1 kinase, the CRN pseudokinase does not exhibit any autophosphorylation activity (Nimchuk et al., 2011a; Stone et al., 1998). Accordingly, it can be assumed that CLV1 is active in signaling on its own, whereas the CLV2-CRN complex requires another co-receptor to both aid CLV2 in binding to its peptide and, possibly, to transphosphorylate the CRN pseudokinase domain.

Following CLV3 perception and subsequent signaling, the CLV pathway must be downregulated to prevent complete repression of *WUS* transcription, which would lead to catastrophic meristem termination. In this context, it was found that the three CLV receptors aggregate in larger multimers within membrane microdomains following CLV3 perception (Somssich et al., 2015). This sequestration of the active signaling complexes could serve as a means of simultaneously downregulating these two otherwise independent and parallel pathways, thereby shutting down CLV3 signaling activity (Somssich et al., 2015). Following this sequestration the receptors might be internalized, as previously shown to be the case for CLV1 (Nimchuk et al., 2011b).

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Indirect receptor interactions fine-tune signaling activity

Several other genes encoding RLKs also influence meristem size and activity, or modulate the different *clv* mutants when perturbed. As we discuss below, these findings suggest that a whole suite of receptors acts to fine-tune the perception of, and signaling via, CLV3 in *Arabidopsis* and other plants.

BAM receptors

A search for *CLV1* homologs in *Arabidopsis* resulted in the identification of three BARELY ANY MERISTEM (BAM) LRR-RLKs (DeYoung et al., 2006). *bam1*, *bam2* or *bam3* single mutants do not exhibit any obvious phenotypes, but double and triple mutants show additive effects that lead to smaller meristems due to the loss of stem cell identity (DeYoung et al., 2006). *BAM1* and *BAM2* are expressed in the periphery of the SAM, and their expression is mostly excluded from the stem cell-containing CZ (DeYoung et al., 2006). *BAM1* expression appears to be repressed through a *CLV3*- and *CLV1*-dependent pathway (Nimchuk et al., 2015). Accordingly, *BAM1* is derepressed in the stem cells of *clv1* mutants, enabling it to take over at least some of the CLV1 functions (Nimchuk et al., 2015). This hypothesis is supported by the findings that BAM1 can bind CLV3, and that *clv1 bam1* double mutants have more severe phenotypes than *clv1* single mutants (DeYoung and Clark, 2008; Nimchuk et al., 2015; Shinohara and Matsubayashi, 2015). Moreover, *clv1 bam1 bam2* triple mutants exhibit a more severe phenotype than *clv3* mutants, indicating that there might be a second signal, possibly another CLE peptide, that is at least partially redundant with CLV3 (DeYoung and Clark, 2008; Nimchuk et al., 2015). This second CLE peptide, just like the BAM receptors, would normally only signal in the meristem periphery, but has the potential to take over CLV3 function in the CZ of *clv3* mutants, just as BAM1 can partially replace CLV1 in *clv1* mutants (DeYoung and Clark, 2008; Nimchuk et al., 2015). In addition to *CLV1*, *CLV2* and *CRN* are expressed not only in the CZ of the SAM, but also in the periphery, overlapping with *BAM1* and *BAM2* expression (Jeong et al., 1999; Müller et al., 2008). Therefore, the CLV2-CRN pathway could function in the PZ in parallel to the BAM1 pathway, which would be similar to recent findings in root meristem maintenance (Shimizu et al., 2015).

RPK2 and ERECTA

Another LRR-RLK involved in meristem maintenance is RECEPTOR-LIKE PROTEIN KINASE2 (RPK2), although its role remains somewhat enigmatic. RPK2 has 22 extracellular LRRs and an intracellular serine/threonine KD, and is similar to CLV1 but more distantly related than the BAMs (Mizuno et al., 2007). RPK2 was identified in a screen for insensitivity to exogenously applied synthetic CLV3 peptide (Kinoshita et al., 2010). This observation positioned RPK2 as another potential receptor for CLV3. In peptide binding assays, however, RPK2 does not bind CLV3 (Shinohara and Matsubayashi, 2015). Furthermore, *RPK2* is expressed preferentially in the PZ of the meristem, overlapping with *BAM1* expression, and not in the CZ (Kinoshita et al., 2010). RPK2 can interact with itself and with BAM1, but not with CLV1 or CLV2, in co-immunoprecipitation experiments (Kinoshita et al., 2010; Shimizu et al., 2015). *rpk2* mutants develop slightly enlarged meristems, a phenotype comparable in severity to *clv2* or *crn* mutants, and are additive to *clv1* and *clv2* (Kinoshita et al., 2010). These observations indicate that RPK2 is more likely to be involved in the BAM1 pathway than in the CLV pathway, which is also the case in the root meristem (Shimizu et al., 2015). An interesting possibility is that RPK2 could connect these two pathways once they are activated. This idea is supported by the observation that RPK2 does not interact with individual CLV receptors, but can interact with them if all three – CLV1, CLV2 and CRN – are co-expressed (Betsuyaku et al., 2011). As described above, CLV3 signaling via the parallel CLV1 and CLV2-CRN pathways leads to the accumulation of all three receptors in complexes within plasma membrane microdomains (Somssich et al., 2015), and the interaction of RPK2 with these oligomers, but not the dimers, suggests that RPK2 is part of these complexes (Betsuyaku et al., 2011). Furthermore, since receptor oligomerization is a result of strong signaling activity, it is possible that RPK2 (and possibly BAM1) is also active to support the CLV receptors and is therefore also sequestered. Alternatively, RPK2 might act downstream of the CLV receptors in the signaling cascade.

RPK2 could also provide a link to another LRR-RLK, namely ERECTA (ER), which is involved in SAM maintenance in a pathway parallel to the CLV pathway. *ER* is expressed in the SAM, and although *er* mutants do not exhibit any obvious meristem phenotype, mutants of *ER* and its family members *ERECTA-LIKE1* and *ERECTA-LIKE2* enhance *clv* meristem phenotypes (Durbak and Tax, 2011; Torii et al., 1996; Yokoyama et al., 1998). These effects of mutations in *ER* family genes on meristem size are the result of enhanced *WUS* expression, possibly via an HD-ZIPIII-dependent but CLV-independent signaling pathway (Chen et al., 2013; Mandel et al., 2014). In a more recent study, using mutant combination analysis with 2D sectioning of meristems, it was hypothesized that CLV3 controls meristem expansion along the apical-basal axis, while the ER family members control lateral expansion in a perpendicular orientation (Mandel et al., 2016). However, since the connection between the ER family and the CLVs is indirect, it is tempting to speculate that RPK2 could provide a link between the two pathways. Indeed, ER signals via the mitogen-activated protein kinase (MAPK) pathway, and the same pathway has been implicated for RPK2 in SAM maintenance (Bergmann et al., 2004; Betsuyaku et al., 2011). ER also signals via G proteins, in a pathway leading to resistance against necrotrophic pathogens (Ishida et al., 2014; Llorente et al., 2005).

ACR4: a role in both shoot and root

In roots, a different type of receptor, the CRINKLY repeat RLK ARABIDOPSIS CRINKLY 4 (ACR4), functions in RAM maintenance, where it interacts with CLV1 to perceive the CLV3-related peptide CLE40 (Stahl et al., 2013). A single row of columella stem cells is maintained in the root through the opposing signaling activities of the quiescent center-derived WUS-related WOX5 stem cell-promoting factor and the stem cell-repressing CLE40 signal coming from differentiating daughter cells (Sarkar et al., 2007; Stahl et al., 2009). Interestingly, CLV1-ACR4 complexes were found to localize preferentially to plasmodesmata, raising the possibility that CLE signaling through these receptors could regulate the cell-to-cell trafficking of proteins, such as transcription factors, through plasmodesmal channels (Stahl et al., 2013). In the shoot, *ACR4* functions in ovule and flower development, and is expressed in the L1 in all apical meristems (Gifford et al., 2003). Accordingly, ACR4 might also function in SAM organization, although there is as yet no direct evidence for this.

RLKs in other plant species

Multiple receptors also function in SAM development in other plants. The rice gene *FON1* encodes an ortholog of CLV1, and it was found that *fon1* mutants have extra floral organs but that the size of the vegetative SAM is unaffected, suggesting that *FON1*

Development (2016) 143, 3238-3248 doi:10.1242/dev.133645

functions exclusively in the floral meristem (Nagasawa et al., 1996; Suzaki et al., 2004, 2006). *FON1* is initially expressed at the periphery of the SAM, but after the inflorescence transition it is expressed throughout inflorescence and floral meristems (Nardmann and Werr, 2006; Suzaki et al., 2004). *fon1* mutants suppress the overexpression phenotypes of *FON2* (rice *CLV3*), indicating that *FON1* and *FON2* act in the same genetic pathway (Suzaki et al., 2006). However, *fon1* does not suppress *FOS1* or FCP1 overexpression phenotypes, suggesting that the CLV3-related FOS1 and FCP1 peptides function in independent pathways (Suzaki et al., 2008, 2009). Together, these data suggest that additional receptor(s) are required for FOS1 and FCP1 peptide function in rice.

In maize, *THICK TASSEL DWARF1* (*TD1*) encodes a FON1/CLV1 ortholog, and *FASCIATED EAR2* (*FEA2*) encodes an LRR-RLP that is orthologous to CLV2. *td1* and *fea2* mutants show striking enlargement/fasciation of inflorescence meristems and an increase in spikelet density with occasional abnormal floral phenotypes, indicating that TD1 and FEA2 are negative regulators of the SAM, as in *Arabidopsis* (Bommert et al., 2005; Taguchi-Shiobara et al., 2001). *TD1* transcripts are detected in the peripheral region of the maize vegetative SAM and in leaf primordia, but not in the CZ. In inflorescences, however, *TD1* is expressed throughout the outer cell layers of the inflorescence meristem and on its flanks at positions of spikelet pair meristem (SPM) initiation (Bommert et al., 2005). The implications of these changing expression patterns are unclear, since *TD1* functions more specifically in the inflorescence meristem, and its vegetative function is not clear. The vegetative expression of *TD1* (and rice *FON1*) is similar to that of the *BAM* genes, and clearly more work is needed to understand the intricacies of *CLV1-BAM* function in different species, but it is clear that multiple *CLV1* paralogs (in addition to multiple *CLE* genes) function in SAM regulation.

The phylogenies of these genes should also be revisited to understand whether maize *TD1* and rice *FON1* are orthologs of *CLV1*, or of *BAM* genes, or if they are co-orthologous. The expression pattern of maize *FEA2* has also been analyzed; in fact, *FEA2* was the first *CLV* gene to be functionally characterized outside of *Arabidopsis*. Similar to *CLV2*, *FEA2* is expressed broadly in maize, with no specific domain of expression in the SAM (Taguchi-Shiobara et al., 2001). A FEA2-GFP fusion localizes to the plasma membrane, suggesting that it might act as a co-receptor for a CLV1 homolog; however, the observation that *td1;fea2* double mutants show an additive genetic interaction provided the first evidence that CLV1 and CLV2 orthologs function in independent pathways (Bommert et al., 2005, 2013b; Taguchi-Shiobara et al., 2001). In CLE peptide assays, *fea2* mutants show resistance to a number of CLE peptides, including ESR2c, ZmFCP1 and maize CLV3 orthologs, so FEA2 might be a broad receptor of CLE peptides or, more likely, acts as a co-receptor for a number of LRR receptor kinases (Je et al., 2016).

A new *CLV*-type LRR receptor-like gene, *FEA3*, was recently identified in maize from studies of mutants that have strongly fasciated ears. *fea2;fea3* double mutants have synergistically enhanced phenotypes, suggesting that they function independently but might converge on the same downstream target (Je et al., 2016). In striking contrast to *CLV1* and *CLV3*, *FEA3* is expressed in and below the OC of the SAM, as well as in young leaf primordia, and expression of the maize *WUS* ortholog spreads downwards in *fea3* mutants, the opposite of what is observed in *Arabidopsis clv* mutants. A functional FEA3-RFP fusion localizes to the PM, and CLE peptide assays and epistasis experiments suggest that FEA3 is a receptor (or co-receptor) for ZmFCP1, with FEA3 and ZmFCP1 together defining a new CLV pathway that regulates meristem size using a CLE peptide expressed in differentiating primordia (Je et al., 2016). In support of this model, *ZmFCP1* overexpression driven by a leaf-specific promoter is sufficient to control SAM size (Je et al., 2016). This new FEA3-FCP1 pathway appears to be universal in plants, since *Arabidopsis fea3* ortholog RNAi lines are also fasciated, and are insensitive to a CLE peptide that is expressed in differentiating cells on the SAM periphery.

In tomato, *FASCIATED AND BRANCHED* (*FAB*) encodes a CLV1 ortholog. *fab* mutants have enlarged meristems, reminiscent of *clv1* mutants (Xu et al., 2015). Tomato *clv2* (*Slclv2*) CRISPR mutants are also weakly fasciated (Xu et al., 2015). *fab* meristems are insensitive to tri-arabinosylated SlCLV3 and SlCLE9, suggesting that FAB is a receptor of SlCLEs (Xu et al., 2015).

In summary, results in *Arabidopsis* show extensive cross-regulation and redundancy between several receptors that fine-tune the activity of the central CLV3-WUS negative-feedback loop. The BAM receptors, which are the closest homologs of CLV1, are transcriptionally regulated by the CLV receptors, as a further toehold to adjust signaling activity by deploying another otherwise redundant receptor if necessary. RPK2 seems to act at least partially in concert with BAM1 and downstream of the CLVs, and possibly at a conjunction of the CLV3-WUS and ER-WUS pathways. Because of this position, RPK2 could also interconnect the CLV3-WUS pathway to the partially redundant BAM pathway, and otherwise independent ER pathway, possibly allowing for co-regulation and adjustment of the signaling activity of all three pathways in a larger, organ-wide context. Although fewer mutants have been characterized in other species, work in maize has added a potentially new pathway that confers feedback from differentiating cells to the SAM. Clearly, much remains to be done to fully understand the complex architecture of receptor interactions in the SAM.

Downstream signal transduction

Curiously, little is known about the signaling pathways that act immediately downstream of the different SAM receptors in *Arabidopsis* (Fig. 2). Following perception of the CLV3 peptide, CLV1 becomes autophosphorylated, indicating activation of its intracellular KD (Stone et al., 1998). CRN, however, which is predicted to be a catalytically inactive pseudokinase, does not show any autophosphorylation activity *in vitro* (Nimchuk et al., 2011a). Interestingly, though, the KD of CRN is required for function *in vivo*, and when the predicted phosphorylation target serine is replaced with an alanine the resulting phosphomute CRN does not exhibit full function, whereas a putative phosphomimic (S→D) does (Somssich et al., 2016). This observation agrees with an earlier finding that demonstrated that CRN is phosphorylated at this site *in vivo* (Nühse et al., 2004). Therefore, it can be assumed that following CLV3 perception CLV1 autophosphorylates, whereas the CRN KD is transphosphorylated by an interacting kinase. Phosphorylation of the CLV1 and CRN KDs induces interaction with the protein phosphatase KINASE-ASSOCIATED PROTEIN PHOSPHATASE (KAPP), which interacts with both the CLV1 and CRN KDs in a phosphorylation-dependent manner and is thought to dephosphorylate and inactivate the kinases (Trotochaud et al., 1999; Zhao et al., 2011).

The POLTERGEIST (POL) and POLTERGEIST-LIKE1 (PLL1) protein phosphatases also function downstream of the CLV receptors (Song et al., 2006). These proteins are membrane-anchored by myristoylation and palmitoylation sites, bringing them

Development (2016) 143, 3238-3248 doi:10.1242/dev.133645

into proximity of the receptors (Gagne and Clark, 2010). Furthermore, they bind to phosphatidylinositol (4) phosphate [PI(4)P], which is enriched in detergent-resistant membrane fractions, again pointing to plasma membrane microdomains as a site of regulation for CLV receptor activity (Gagne and Clark, 2010). Mutations in *pol* and *pll1* suppress *clv* mutant phenotypes, indicating that they function downstream of CLV, and both *pol* and *pll1* are negatively regulated by CLV receptors (Song et al., 2006; Yu et al., 2000). Interestingly, they function in a dosage-dependent manner, since the ability to suppress *clv* correlates with the dosage of mutant alleles of the two genes (Song and Clark, 2005). In addition, both POL and PLL1 positively regulate *WUS* transcription; the repression of *WUS* by the CLV receptors could therefore be at least in part due to their negative regulation of POL and PLL1 (Song et al., 2006). This position of POL and PLL1 as signaling intermediates, connecting the CLV receptors and the WUS transcription factor, appears to be conserved in the root meristem, where it has been shown that POL and PLL1 are positive regulators of the WUS homolog WOX5 (Gagne et al., 2008). Taken together, this indicates that the concentration of phosphatases at the plasma membrane is important to regulate the signaling activity of the CLV3-WUS pathway. While POL/PLL1 abundance at the plasma membrane is connected to CLV3-WUS activity via the transcriptional regulation of these two genes by WUS, the fact that they function in a dosage-dependent manner could mean that there is competition between the different KDs for interaction with POL and PLL1 (Song et al., 2006).

Another pathway acting downstream of the receptors could involve MAPKs (Betsuyaku et al., 2011). In a set of *in vitro* experiments, it was suggested that CLV3 signaling via RPK2 and CLV2-CRN activates the MAPK cascade, whereas CLV3 signaling via CLV1 appears to function as a negative regulator of MAPK signaling (Betsuyaku et al., 2011). Interestingly, these CLV3-dependent effects on MAPK signaling were suppressed when cells expressing all four receptor proteins were treated with CLV3 (Betsuyaku et al., 2011).

A number of studies have also highlighted a role for G-protein signaling in the CLV pathway. In maize, COMPACT PLANT2 (CT2) was identified as a FEA2-interacting partner by map-based cloning of the *ct2* mutant. CT2 is a predicted α-subunit (Gα) of a heterotrimeric GTP-binding protein (Bommert et al., 2013b). *ct2* mutants resemble *fea2* mutants and show partial resistance to CLV3 peptide treatment in the root and SAM, suggesting that CT2 functions to transmit the CLV3 signal. CT2 interacts physically with FEA2 in co-immunoprecipitation assays, and double mutants show epistasis. These data suggest that CT2 transmits the CLV3 signal via FEA2, highlighting a new function for Gα signaling in plants (Bommert et al., 2013b). However, *ct2* mutant meristems are smaller than those in *fea2* mutants, suggesting that FEA2 signals through other pathways in addition to CT2/Gα to control SAM size (Bommert et al., 2013b). Heterotrimeric G-protein signaling also appears to be important in CLV signaling in *Arabidopsis*: β-subunit (Gβ) mutants (*agb1*) have large SAMs, and AGB1 interacts with RPK2 in transient assays in a CLV3-dependent manner (Ishida et al., 2014). Gγ alleles have also been identified as grain number quantitative trait loci (QTL) in grasses, suggesting that the entire heterotrimeric G-protein complex functions in SAM regulation (Huang et al., 2009).

WUSCHEL regulation

Transmission of the CLV3 signal into the nucleus eventually results in the transcriptional downregulation of WUSCHEL-RELATED HOMEOBOX (WOX) and HAIRY MERISTEM (HAM) transcription factor family members (Brand et al., 2000; Zhou et al., 2015). WUS acts non-cell-autonomously in the stem cell domain to promote stem cell fate (Daum et al., 2014; Haecker et al., 2004; Laux et al., 1996; Yadav et al., 2011).

WOX and HAM act as co-factors in different meristems in *Arabidopsis* (Zhou et al., 2015) and, just like *wus*, *ham* mutants were identified owing to their inability to maintain active shoot stem cell niches (Engstrom et al., 2011; Stuurman et al., 2002). In the SAM, WUS interacts with HAM1 and HAM2, while WOX4 interacts with HAM4 in the procambium, and WOX5 interacts with HAM2 in the RAM to regulate target gene expression and stem cell maintenance (Zhou et al., 2015). Interestingly, in the SAM, where WUS expression is confined to the cells of the OC, HAM1 and HAM2 are broadly expressed throughout the meristem (Zhou et al., 2015). However, WUS can move between cells within the meristem, and this movement is dependent on the size of the protein, suggesting that the movement is through plasmodesmata (Daum et al., 2014; Yadav et al., 2011). Accordingly, it is possible that large complexes of WUS and HAM1/2 are not able to traffic between cells, providing a unique patterning system with one mobile transcription factor and one local interaction partner that restricts movement in the destination cells.

In rice, the *WUS* ortholog *OsWUS* is expressed most highly in leaf margins but could not be reproducibly detected in the SAM (Nardmann and Werr, 2006). A mutant in *OsWUS* was identified as *tillers absent1* (*tab1*), although *tab1* mutant phenotypes are specific to axillary meristems, which arrest at various stages of the pre-meristem zone (Tanaka et al., 2015). *TAB1* is expressed transiently in the pre-meristem zone, and not in the axillary meristems once they form (Tanaka et al., 2015). However, it is unclear whether *TAB1* is expressed in the SAM, and *OSH1*, a SAM marker, accumulates normally in *tab1* mutants, suggesting that another gene plays the role of WUS in the rice SAM. A candidate for such a gene is rice *WUSCHEL-RELATED HOMEOBOX4* (*OsWOX4*), which is expressed in leaf primordia and in the SAM, as well as in procambium and vascular tissues, similar to *WOX4* in *Arabidopsis* (Ohmori et al., 2013). Downregulation of *OsWOX4* by RNAi leads to a smaller or flattened SAM, suggesting premature termination of the meristem, and constitutive expression mimics cytokinin action in callus (Ohmori et al., 2013), indicating that cytokinin function is somehow related to that of WOX4, as has been described for WUS in *Arabidopsis*.

A functional analysis of *WUS* orthologs has not been reported in maize, but the expression of two candidates – *ZmWUS1* and *ZmWUS2* – has been described. *ZmWUS1* is expressed in a small domain in the predicted OC position, and a ZmWUS1-RFP reporter construct was shown to be expressed in the predicted OC at the inflorescence transition stage (Je et al., 2016; Nardmann and Werr, 2006). *ZmWUS2* transcripts are detected on the flank of the SAM and in leaf primordia, similar to *TD1*, suggesting that TD1 signaling might function in a pathway with ZmWUS2 (Bommert et al., 2005; Nardmann and Werr, 2006). In tomato, *SlWUS* is expressed in the OC of the SAM and is overexpressed in *fab* and *fin* mutants, consistent with the *Arabidopsis* model (Muños et al., 2011; Xu et al., 2015). Therefore, *WUS* expression and function appear to be conserved in dicots, but have diversified in monocot species.

Feedback regulation, homeostasis and the role of plant hormones

In addition to its role in promoting stem cell fate in the CZ of the SAM, WUS also promotes its own expression in the OC through

Development (2016) 143, 3238-3248 doi:10.1242/dev.133645

modulating cytokinin signaling (Chickarmane et al., 2012; Gordon et al., 2009). This is achieved through local repression of several A-type ARABIDOPSIS RESPONSE REGULATOR (ARR) proteins, which are negative regulators of cytokinin signaling (Leibfried et al., 2005). Furthermore, cytokinin negatively regulates CLV1 expression, and thus local cytokinin in the OC suppresses CLV1 activity and thereby helps to define the boundary between the stem cell domain and the OC (Gordon et al., 2009; Lindsay et al., 2006).

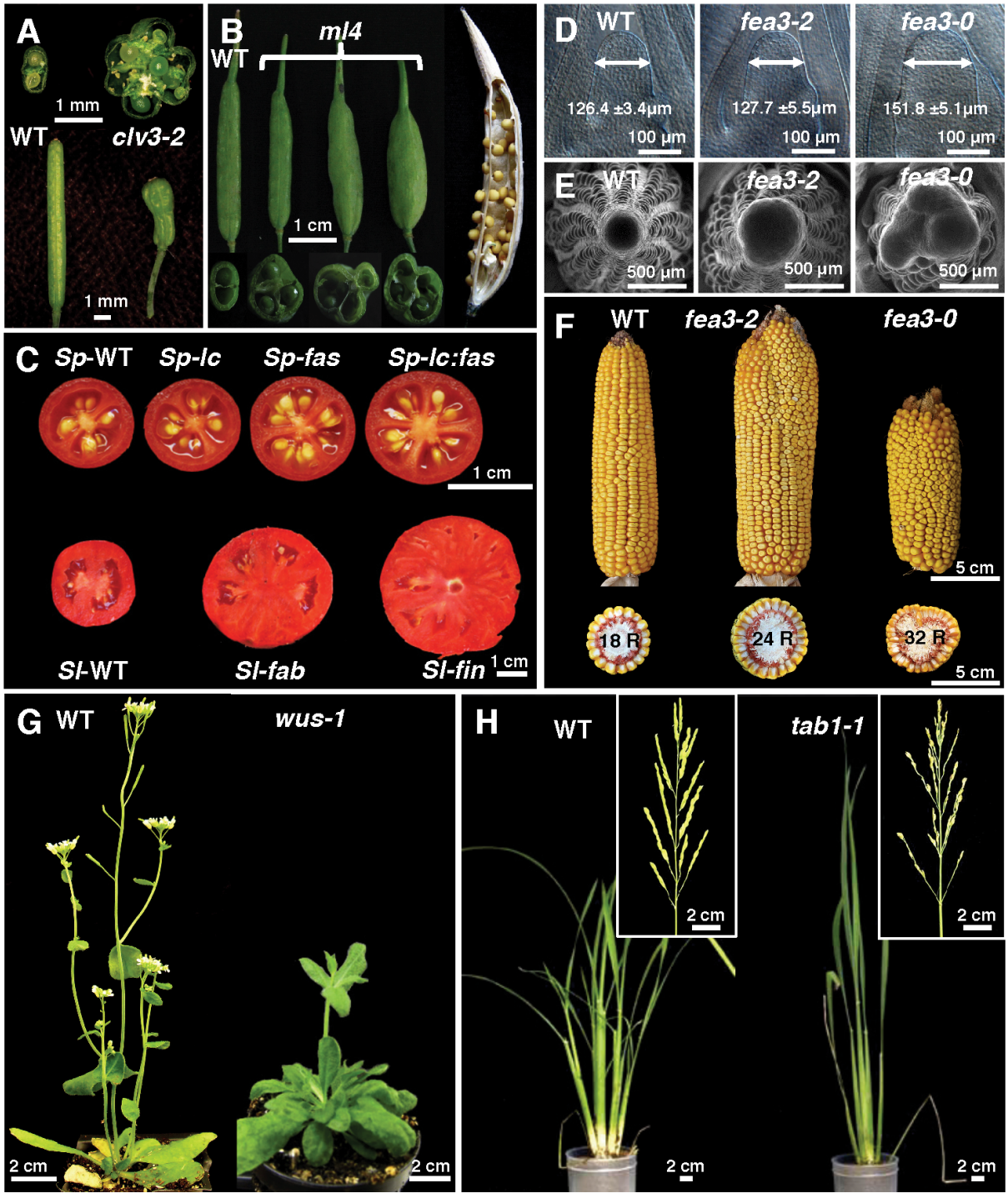

Fig. 3. Strong loss-of-function and weak QTL phenotypes in different species. (A) *Arabidopsis clv3-2* mutants exhibit multiple carpels. (B) In *Brassica*, conversion from two carpels (left) to four carpels is observed in *ml4* mutants. (C) Locule number is affected in *fas*, *lc* and *fas;lc* double mutants in the tomato wild ancestor *Solanum pimpinellifolium* (*Sp*), and increased locule number is observed in *fab* and *fin* mutants in *S. lycopersicum* (*Sl*). (D-F) SAM size (D), ear primordia (top view, scanning electron micrographs; E) and mature ears (F) of wild type, mild *fea3-2* and strong *fea3-0* alleles. Kernel row numbers are marked in ear transverse sections. (G) *Arabidopsis wus-1* mutants show irregular shoots and, after transition to flowering, produce just a few, defective flowers. (H) Rice *tab1-1* mutants lack tillers and have defective flowers (inset). WT, wild type. The images shown are modified with permission: in B from Fan et al. (2014); in C from van der Knaap et al. (2014) and Xu et al. (2015); in F from Je et al. (2016); in G from Ikeda et al. (2009); in H from Tanaka et al. (2015).

Development (2016) 143, 3238-3248 doi:10.1242/dev.133645

Cytokinin also plays an important role in the SAM of maize and rice. In maize *aberrant phyllotaxy1* (*abph1*) mutants, the SAM is enlarged and the phyllotactic pattern switches from alternate to decussate. ABPH1 is an A-type response regulator, a potential WUS target, which negatively regulates cytokinin signaling and also positively regulates expression of the PINFORMED1 auxin efflux transporter (Giulini et al., 2004; Lee et al., 2009). Cytokinin signaling is also important in rice, where the *LONELY GUY* (*LOG*) gene was found to encode an enzyme that converts cytokinin precursors into active hormone (Kurakawa et al., 2007). LOG is expressed in a small domain in the upper part of the SAM and axillary meristems. *log* mutants fail to maintain floral meristems, and *fon1* mutants are epistatic to *log*, indicating that cytokinin signaling might act upstream of CLV (Kurakawa et al., 2007; Yamaki et al., 2011).

Potential applications in agriculture

Compared with *Arabidopsis*, which has evolved in the wild as a 'weed' over millions of years, crop plants have undergone intense human selection over the past ∼10,000 years (Doebley et al., 2006; Kuittinen and Aguadé, 2000). Much of this selection has been for larger fruits, seeds or inflorescences – phenotypes that one naturally associates with CLV-WUS pathway genes. This might explain why CLV-WUS signaling is strongly buffered in *Arabidopsis* but can be easily disrupted by weak alleles in crop species (Müller et al., 2006) (Fig. 3). For example, during domestication, kernel row number in maize increased from two alternating rows in the slender inflorescences of teosinte to ∼18 or more kernel rows in modern maize (Doebley et al., 2006). QTL mapping and functional assays using weak alleles indicated that maize *FEA2* and *FEA3* may have contributed to domestication or subsequent crop improvement, since weak alleles of these genes make ears that are not fasciated but have more kernel rows and higher yields (Bommert et al., 2013a; Je et al., 2016).

In tomato, a fruit crop, variation from bilocular fruit of the tomato wild ancestor to large-fruited varieties having eight or more locules is controlled by *locule number* (*lc*) and *fasciated* (*fas*) loci (Barrero and Tanksley, 2004; Lippman and Tanksley, 2001; Tanksley, 2004). *SlWUS* is a candidate for the *lc* QTL, and *fas* was recently found to be caused by a genomic rearrangement that alters the expression of *SlCLV3* (Muños et al., 2011; Xu et al., 2015). Similarly, a naturally occurring *CLV3* mutation in mustard (*Brassica rapa*) corresponds to the *Multilocular* (more than two carpels) locus, which increases seed production (Fan et al., 2014). These diverse examples indicate that *CLV-WUS* genes have been selected in diverse crops during domestication, and could provide further crop yield increases – for example, by engineering weak alleles using CRISPR.

Conclusions and unsolved problems

The studies discussed above suggest that the basic mechanism of SAM homeostasis appears to be conserved in diverse monocot and dicot species; however, no one species has yet had all of its SAM homeostasis components functionally identified. Furthermore, despite the incredible conceptual advances gained in the ∼20 years since the isolation of the *CLV* and *WUS* genes, many important questions remain. At the level of CLE peptides, questions remain about the significance of arabinose modifications, which are crucial in tomato but appear less so in *Arabidopsis*. The *in vivo* localization of CLE peptides has not yet been studied, and we still know little about their range of movement in the SAM. Another key question is how CLV-WUS pathways integrate with abiotic or biotic stresses. Evidence for CLE crosstalk with defense receptor signaling is controversial, but it remains clear that stress leads to a general reduction in plant growth, and it will be interesting to see mechanistically how this affects CLV-WUS feedback (Lee et al., 2011, 2012; Mueller et al., 2012; Segonzac et al., 2012).

Some of these questions, including the issue of genetic redundancy, can now be easily addressed with recent advances in multiplex CRISPR mutagenesis, and similar approaches might also be used to further harness these pathways for crop improvement. However, since our appreciation of the complexity of the pathway is ever expanding, it is important to consider whether phenotypic differences between species represent different wiring of the pathways or, more trivially, a difference in genetic redundancy between species. In this respect, mathematical approaches could aid in producing unified models, bringing in data from diverse species and leading to computational simulations. For example, the FEA3-FCP1 regulation of *ZmWUS1* identified in maize was integrated into a recent *Arabidopsis* CLV-WUS feedback model, and helped explain how *WUS* is regulated from below the OC, something that was previously lacking from the models, and aspects of this new model were confirmed by experiments in maize and *Arabidopsis* (Chickarmane et al., 2012; Gruel et al., 2016; Je et al., 2016; Yadav et al., 2013). Such computational modeling is clearly becoming a powerful and complementary approach that can be used to understand the spatial patterning resulting from receptor-ligand signaling during SAM regulation.

Ian Sussex, who performed much of the early groundbreaking work on shoot meristems and inspired a whole generation of plant biologists, once commented that the shoot meristem is a black box and that seeking to obtain a molecular understanding was not a viable proposal. In this one case he was luckily proven wrong by the awesome power of genetics, which will no doubt continue to be the cornerstone of meristem research for many years to come.

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Competing interests

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