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REVIEW ARTICLE

Molecular Signaling Networks in the Shoot Apical Meristem

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Abstract Developmental growth and organ formation of all aerial parts of mature plants are thoroughly generated from stem cells in the shoot apical meristem (SAM). More interestingly, the SAM development is mainly established by multiple receptor-mediated signaling pathways induced by stem-cell-triggered peptides. For past few decades, various genetic and biochemical approaches have been employed to investigate the regulation of stem-cell functions through isolating peptide ligands, receptor complexes and early transcription factors that regulate stem-cell homeostasis. However, because signaling molecules have highly redundant properties, the receptor-mediated signaling cascade still remains unclear. Therefore, to better understand important aspects of intracellular signaling networks, this review is mainly focused on recently achieved findings involved in the molecular mechanisms of the SAM.

Keywords: MAPK cascade, Peptide-receptor signaling, Shoot Apical Meristem (SAM), Signaling network, Stem-cell homeostasis

Introduction

Plant growth and development are generated from the specialized tissues called meristems, which are located at the tips of shoots and roots. Plant meristems contain stem cells as an undifferentiated state during whole lifespan. Unlike most animals, plants are capable to undergo the distinct postembryonic development because plant stem cells retain the pluripotent ability in whole adult stage. Therefore, the maintenance of stem-cell population is an important source for the entire organ formation. Moreover, the balance between stem-cell homeostasis and developmental aging eventually influences the various longevities of plants.

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The shoot apical meristem (SAM) of higher plants contains the stem cells in the central zone (CZ) to supply new progenitor cells that provide the founder cells for all plant organs above the ground. The most well-known signaling mechanism in the shoot stem-cell niche is the negative feedback loop between *CLAVATA3* (*CLV3*) and *WUSCHEL* (*WUS*) for the regulation of stem-cell homeostasis (Aichinger et al. 2012). Normally, *CLV3* encodes the small size of protein, which is expressed in stem cells. CLV3 is further processed into the 12-amino acid (aa) or the arabinosylated 13-aa peptide sharing the conserved C-terminal CLE motif (Betsuyaku et al. 2011a). CLV3 peptide (CLV3p) secreted from stem cells spreads out through the apoplastic space between cells in stem-cell niche, which is perceived by CLV receptor complexes including CLAVATA1 (CLV1), CLAVATA2 (CLV2), SUPPRESSOR OF LLP1-2 (SOL2)/CORYNE (CRN) and RECEPTOR LIKE PROTEIN KINASE 2 (RPK2)/TOADSTOOL 2 (TOAD2) receptors (Lee et al. 2012a). Once CLV3p activates the receptor-mediated pathway, the intracellular signaling mechanism represses *WUS* expression. In the regulation of stem-cell homeostasis, *WUS* is the central player for the specification and proliferation of stem cells. *WUS* is a homeodomain transcription factor (TF) expressed in the organizing center (OC) cells of the rib zone (RZ) underneath the CZ, where a secreted CLV3p could not reach (Mayer et al. 1998; Schoof et al. 2000). Recently, it has been reported that WUS protein itself migrates toward stem cells via cell-to-cell movement and activates *CLV3* expression through the direct binding to its promoter (Yadav et al. 2011). In addition to CLV1, CLV2 and SOL2/CRN, other receptors including FLS2, RPK2, BAM1 and BAM2 have been known to perceive CLV3p through genetic and biochemical approaches (Guo et al. 2010; Kinoshita et al. 2010; Lee et al. 2011). Therefore, peptide-receptor signaling is the most fundamental regulatory framework in the SAM.

A Signaling Peptide, CLV3p in the SAM Development

Since a systemin has been isolated from tomato leaves as the first plant signaling peptide (Pearce et al. 1991), genetic and

biochemical approaches revealed that more than ten secreted peptides could function as regulatory signals in plant growth and development (Matubayashi 2011; Murphy et al. 2012). CLV3 has been first reported as a predicted extracellular protein and acts non-cell-autonomously to control the balance between cell proliferation and differentiation in the SAM (Fletcher et al. 1999). So far, the 12-aa and the arabinosylated 13-aa CLV3 peptides are identified as *in vivo* forms, which were purified from callus and culture medium of *A. thaliana* plants overexpressing *CLV3*, respectively (Kondo et al. 2006; Ohyama et al. 2009). Although the 12-aa CLV3p has two hydroxyproline residues at position 4 and 7 ($R^{1}TVPhSGPhDPLHH^{12}$), these post-translational modifications did not affect the inhibition of root growth (Kondo et al. 2006). More recently, complemented plants harboring each alanine-substitution of two hydroxyproline residues consistently showed the reduced SAM size of *clv3-2* and decreased *WUS* expression similar to that of wild-type (Song et al. 2012), suggesting that hydroxylation of proline residue rarely affects the activity of CLV3p in the growth of shoots and roots. Conversely, hydroxylation of proline residue is also known to be important for the binding and biological activity of the 13-aa CLV3p that is glycosylated at hydroxyproline (position 7) with three arabinose residues (Ohyama et al. 2009). Binding affinity of the arabinosylated 13-aa CLV3p to its receptor CLV1 (K_d = 1 nM) is about 100-fold higher than the 13-aa CLV3p without glycosylation (K_d = 280 nM) and 10-fold higher than the 12-aa CLV3p (K_d = 24 nM) (Ohyama et al. 2009). Notably, the 12-aa CLV3p has been recently reported to provide the immune protection in the SAM through the FLS2 receptor (Lee et al. 2011) and the 12-aa and the 13-aa CLV3 peptides showed different activities in immune responses (Lee et al. 2012b). Recent studies of molecular modeling for the arabinosylated 13-aa CLV3p displayed that arabinosylation causes the conformational distortion of the peptide, and gradually added arabinose residues from one to three proportionally increased biological activities of peptides (Shinohara and Matsubayashi 2012). However, since *in vivo* and *in vitro* alanine-substitution on arabinosylation residue hydroxyproline (position 7) rescued the lesion of enlarged *clv3* SAM size (Song et al. 2012; Song et al. 2013), various modifications on different mature CLV3 peptides may regulate the sensitive threshold of developmental activities in the SAM.

Intracellular Signaling Networks in the SAM Development

Since *CLV3*, *CLV1*/*CLV2* and *WUS* have been revealed to encode a peptide signal, receptor complex and a transcription factor in a signal transduction pathway (Clark et al. 1997; Mayer et al. 1998; Fletcher et al. 1999; Jeong et al. 1999), a kinase-associated protein phosphatase (KAPP) was reported as almost first possible signaling component in the CLV-WUS pathway. The KAPP could bind to the phosphorylated kinase domain of CLV1 and then dephosphorylated one *in vitro* (Williams et al. 1997; Stone et al. 1998), suggesting that the KAPP functions as a negative regulator of CLV1 receptor-mediated signaling. Another protein phosphatase type 2C (PP2C) proteins, POLTERGEIST (POL) and PLL1, can suppress phenotypes of *clv* mutants and positively regulate *WUS* expression to promote stem-cell population (Yu et al. 2000; Yu et al. 2003; Song and Clark 2005; Song et al. 2006). However, because the *pol pll1* double mutant is seedling lethal and shows pleiotropic phenotypes in grafted *pol pll1* double mutant (Song and Clark 2005; Song et al. 2006), the specific regulation of POL/PLL1 phosphatases in the CLV-WUS pathway needs to be further elucidated. More interestingly, recent findings proposed a new role of the POL/PLL1-dependent lipid signaling in the SAM (Gagne and Clark 2010). For the proper function, POL/PLL1 proteins were revealed to localize the plasma membrane through a myristoylation- and palmitoylation-dependent manner (Gagne et al. 2010). These PP2C proteins could bind to multiple lipids, such as phosphatidylinositol (PI) monnophosphates and phosphatidylserine (PS), and the phosphatase activity of POL proteins was catalytically stimulated by PI(4)P through an *in vitro* assay (Gagne and Clark 2010).

In addition to phosphatases, a Rho GTPase-related protein (ROP) as a possible signaling component has been biochemically identified through a co-immunoprecipitation with the active CLV1 receptor complex (Trotochaud et al. 1999). Arabidopsis 11 *ROP* genes are grouped into a novel, plant-specific subfamily, which are homologous with the Rho GTPase family belonged to the Ras superfamily in animals (Vernoud et al. 2003). Although ROP GTPases are known to function in plant growth and development including actin dynamics, cell polarity and reactive oxygen species production (Vernoud et al. 2003; Nibau et al. 2006), the molecular details involved in the SAM development remain elusive. Because protein phosphatases and Ras/Rho GTPases have been known to positively or negatively regulate the various signaling cascades through mitogen-activated protein kinase (MAPK) and phosphoinositide pathways based on the previous studies in eukaryotes (Van Aelst and D'Souza-Schorey 1997; Rodgriguez 1998; Bar-Sagi and Hall 2000; Tena et al. 2001), the role of MAPK cascade has also been long proposed as a plausible signaling network of the CLV-WUS pathway for several decades (Fig. 1) (Carles and Fletcher 2003).

In eukaryotes, MAPK cascade plays an important role in the signal transduction pathways regulating physiological and developmental processes through the sequential activation of three classes of kinases (Kültz 1998; Tena et al. 2001). Because the steady-state size of the shoot stem-cell population

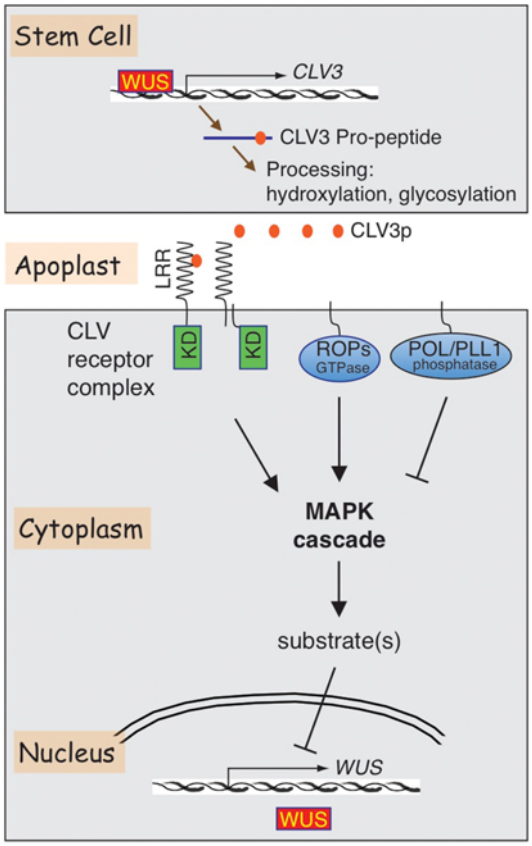

Fig. 1. A model of MAPK function in the shoot stem-cell homeostasis. CLV3 is only expressed in stem cells and encodes a pro-peptide. Then CLV3 peptides are processed through hydroxylation at proline residues and the glycosylation with three arabinose residues. Diffusible CLV3 peptides move via the apoplastic space, which are perceived by multiple CLV receptors. Based on previous studies of ROP small GTPase and POL/PLL1 protein phosphatases, MAPK cascade seems to be shown to play an important role in the intracellular signaling network to negatively regulate *WUS* expression.

seems to be established by the periodic fluctuation of secreted CLV3p, a transiently stimulating MAPK is most likely proper to the signaling networks connecting upstream receptor-mediated signal and downstream TFs in the negative feedback loop. However, since plant MAPK cascade genes are highly redundant compared to those of yeast and human (Sheen et al. 2008), MAPK members involved in stem-cell homeostasis of the SAM would be rarely isolated and studied through conventional genetic screens. Recent advances in the use of synthetic CLV3p as an input signal were able to study signaling cascades in a cellular level, which also make biochemical approaches more convenient (Kondo et al. 2006; Ohyama et al. 2009; Shinohara and Matsubayashi 2013). Sawa and collegues recently found the MAPK activation that could be triggered by the overexpression of CLV3 and proper receptors in *N. benthamiana* leaves and the exogenous treatment of synthetic MCLV3p to Arabidopsis seedlings (Betsuyaku et al. 2011b). Nevertheless, recent findings also raised the complex aspects of MAPK functions. In the absence of CLV3p, the phosphorylation of MPK6 was strongly increased in the *clv1* mutant and slightly decreased in the *clv2* mutant (Betsuyaku et al. 2011b), suggesting that the MPK6 activation is negatively and positively regulated by CLV1 and CLV2, respectively. Moreover, because CLV3p-dependent MPK6 activation was also negatively and positively regulated by CLV1 and RPK2/TOAD2, it suggests that the MAPK activation in the SAM seems to be complicatedly regulated by each receptor pathway (Betsuyaku et al. 2011b; Kiyohara and Sawa 2012).

Hormone Signaling Networks in the SAM Development

The negative-feedback loop conducted by peptide-receptor signaling of the CLV-WUS pathway is also tightly connected with the plant hormone cytokinin for the SAM development. Cytokinin signaling usually constitutes a phosphorelay two-component signaling system that transfers phosphoryl groups among sensors and regulators containing Histidine or Aspartate residues (Hwang et al. 2012). The level of cytokinin is positively regulated by another important meristem gene *SHOOT MERISTEMLESS* (*STM*) that is the Arabidopsis ortholog of the maize *KNOTTED* (*KN*) gene encoding a homeodomain protein (Hwang et al. 2012). STM directly induces the transcriptional activation of the cytokinin biosynthetic gene *ISOPENTENYL TRANSFERASE 7* (*IPT7*) in the SAM (Yanai et al. 2005). Because the strong *stm-1* mutant displays the complete elimination of a shoot meristem, the Arabidopsis *STM* gene is required for the initiation and maintenance of the SAM. Interestingly, since the exogenous treatment of cytokinin (zeatin) or expression of cytokinin biosynthetic gene through the *STM* promoter could partially rescue the *stm* mutant phenotype, it suggests that cytokinin signaling plays a significant role in the initiation of the SAM development (Yanai et al. 2005).

Another important function of cytokinin in the SAM seems to determine the spatial organization of stem-cell niche through the induction of *WUS* expression in the OC cells, because the expression domain of *WUS* was shown to overlap with that of the cytokinin receptor *ARABIDOPSIS HISTIDINE KINASE 4* (*AHK4*; cytokinin sensor) (Gordon et al. 2009). This cytokinin-mediated *WUS* expression can be more accelerated by the positive feedback loop through the inhibition of *Type-A Arabidopsis response regulators* (*ARRs*), *ARR7* and *ARR15*, by WUS. Usually, Type-A ARRs function as negative regulators of cytokinin signaling (Hwang et al. 2012). In addition, because *CLV3* expression was dramatically reduced by the artificial microRNAs of *ARR7* and *ARR15*, it suggests that *ARR7* and *ARR15* are also required for *CLV3* expression in the SAM (Zhao et al. 2010).

Another plant hormone auxin also involves in the regulation of stem-cell homeostasis through the crosstalk with cytokinin signaling in the SAM. Auxin is synthesized locally by *YUCCA* (*YUC*) genes in the CZ and induces downstream regulators including AUXIN RESPONSE FACTOR 5 (ARF5)/MONOPTEROS (MP) (Zhao 2008). Interestingly, recent findings revealed that *ARR7* and *ARR15* expression was strongly increased in the SAM of various high-ordered *yuc* mutants (auxin biosynthesis), *pin-1* and *pinoid* mutants (auxin transporter), and the *arf5*/*mp* mutant (auxin downstream factor), suggesting that auxin signaling represses *ARR7* and *ARR15* expression by the negative regulation of ARF5/MP TF (Zhao et al. 2010). Consequently, auxin signaling promotes cytokinin signaling in the SAM. ARF5/MP TF directly binds to the promoter of *ARR15* gene through AuxRE-like motifs. Notably, these AuxRE-like motifs were important for the repression of *ARR15* expression in the SAM, whereas they seemed to be involved in the activation in other tissues (Zhao et al. 2010). Consistent with this, auxin signaling antagonizes cytokinin signaling in embryonic root stem-cell niche through the activation of *ARR7* and *ARR15* expression (Müller and Sheen 2008). Taken together, feedback regulators, *ARR7* and *ARR15*, not only suppress cytokinin signaling but also integrate ARF5/MP-mediated auxin signaling in the CLV-WUS pathway for the SAM development.

Transcriptional Networks in the SAM Development

The SAM is an essential place for the postembryonic development of plants, which contains self-renewable stem cells and differentiating cells, and is functionally and anatomically separated into several zones and layers. Normally, stem cells are located at the tunica (comprising L1 and L2 layers) of the CZ and replenish new daughter cells toward the peripheral zone (PZ) and the RZ for the formation of lateral organs, including leaves and flowers, and stems, respectively. For the orchestration of plant growth and development, functional domains of the SAM must be regulated by different patterns of cell division and gene expression (Meyerowitz 1997; Yadav et al. 2009; Yadav et al. 2014). Indeed, the early target of the signaling cascade involved in stem-cell homeostasis is a homeodomain TF WUS. In addition, many types of TFs (e.g., MYBs, bZIPs, AP2, WRKYs, and AGLs) have also been revealed as key MAPK substrates through an *in vitro* protein microarray (Popescu et al. 2009), suggesting that the study of gene expression profiles represented in functional domains of the SAM is thought to be crucial to understand the molecular mechanisms of stem-cell functions.

Reddy and colleagues performed genomic analyses using the isolated cell-type specific populations, showing the highly sensitive expression profiles specific to spatial domains of the SAM (Yadav et al. 2009). In enriched stem cells, they could find the differentially expressed genes involved in DNA metabolism, replication and repair, indicating that error-free DNA replication is important for the correct proliferation of stem-cell population in the SAM (Yadav et al. 2009). In addition, because genes involved in chromosome organization and biogenesis were also enriched, the maintenance of genome stability and epigenetic regulation could be significant function in stem cells. Indeed, the genomic instability is represented as a hallmark of the eukaryotic aging processes (Yadav et al. 2009). More recently, they further dissected functional domains of the SAM by the separation of distinct clonal layers (Yadav et al. 2014). Notably, the meristematic cells of the L1 layer showed the enrichment of differentially regulated genes involved in the defense mechanisms against to bacterial and fungal pathogens. Genes involved in the maintenance of DNA fidelity and telomere length were preferentially accumulated in the cells of the L2 layer. Interestingly, unlike conventional idea of heterotrophic properties in the SAM cells (Fleming 2006), many genes enriched in the cells of the L3 layer have been revealed to encode proteins involved in photosystem (PS) I and II light-harvesting complexes, providing the possibility of autotrophic role in the SAM (Yadav et al. 2014). By high-resolution transcriptome analyses using separated cells and layers, 1225 TFs were detected in the SAM and 296 TFs of them were shown to be differentially expressed in clonal cell layers, suggesting that the complex transcriptional networks may be mediated by TFs in the SAM development (Yadave et al. 2014).

Conclusions

Stem cells in the SAM absolutely generate the aerial parts of mature plants. Thus, constant size of stem-cell population must be maintained for the correct growth and development. Because the SAM maintenance is triggered by CLV3p secreted from stem cells, the receptor-mediated signaling occurred in stem-cell niche seems to function as a key regulatory mechanism. However, since there are many receptors perceiving CLV3p (Lee et al. 2012a) and intracellular signaling components (e.g., ROP and MAPK cascade proteins) have the highly redundant properties, it suggests that the signaling network is likely composed of complex and highly branched pathways. Therefore, the molecular dissection of each receptor-mediated pathways is required for better understanding whole SAM activities (Fig. 2). To access this idea, we will have to elucidate the functional diversity of input signals such as the 12-aa and the arabinosylated 13-aa CLV3 peptides, isolate the marker

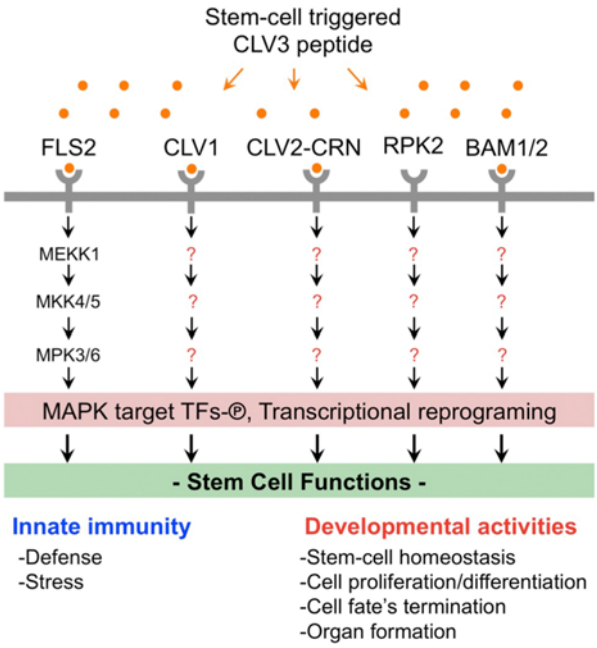

Fig. 2. Multiple pathways of peptide-receptor signaling in the whole SAM activities. CLV3 peptides secreted from stem cells are recognized by multiple receptor complexes identified by genetic and biochemical approaches. After perception of input signal, activated receptors trigger downstream mitogen-activated protein kinase (MAPK) cascade to phosphorylate substrate targets, especially transcription factors (TFs) that activate or repress developmental genes through the complex transcriptional networks.

genes representing each receptor-mediated pathway through the high-resolution transcriptome analyses in each receptor mutant and characterize the signaling module of MAPK cascade activated by each receptor.

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Author's Contributions

HL wrote and revised the manuscript. Author agreed on the contents of the paper and post conflicting interests.

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