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REVIEW

Control of cell fate during axillary meristem initiation

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Abstract
Axillary meristems (AMs) are located in the leaf axil and can establish new growth axes. Whereas their neighboring cells are differentiated, the undifferentiated cells in the AM endow the AM with the same developmental potential as the shoot apical meristem. The AM is, therefore, an excellent system to study stem cell fate maintenance in plants. In this review, we summarize the current knowledge of AM initiation. Recent findings have shown that AMs derive from a stem cell lineage that is maintained in the leaf axil. This review covers AM progenitor cell fate maintenance, reactivation, and meristem establishment. We also highlight recent work that links transcription factors, phytohormones, and epigenetic regulation to AM initiation.

Keywords Axillary meristem · Cell fate · Stem cell · Cell lineage · Gene regulatory network

Introduction

Unlike most animals, plants are ramifying systems with new cycles of growth throughout their lifespan. At one level, this constant growth is achieved by postembryonic organogenesis. The shoot apical meristem (SAM), which is formed during embryogenesis and harbors stem cells in its center, forms lateral organs such as leaves at its periphery. Thus, the SAM creates the shoot, i.e., the aboveground portion of a plant. Similarly, the root apical meristem gives rise to the entire underground root system. However, these two meristems only establish a single growth axis, and the periodic formation of branching meristems is needed to initiate new growth axes. In seed plants, branching is achieved by the axillary meristem (AM) formed at the leaf axil, where the boundary region separates the leaf from the stem. In the model plant *Arabidopsis thaliana* and many other species, an AM is associated with each leaf, which, together with an internode section, forms a developmental unit called a phytomere. AMs form axillary buds, which can either develop into a branch or remain dormant for a certain amount of time or even permanently. Axillary bud dormancy is strongly promoted by the SAM, and this phenomenon is termed apical dominance. Extensive studies have shown that auxin, strigolactone, and sucrose as well as light and other environmental signals all affect apical dominance. A number of excellent recent reviews have focused on axillary bud outgrowth [1–3]. In this review, we focus on AM initiation, which is an ideal system to study stem cell fate determination.

AM initiation is informative about cell fate, stem cells, and meristem organization

The origin of AMs has long been a matter of debate. Based on morphology, two theories have been proposed. The de novo theory posits that differentiated cells dedifferentiate to become stem cells and form AMs. The alternative detached theory proposes that some leaf axil cells remain undifferentiated and later form AMs [4]. Recent works identified a meristematic cell population in the leaf axil that is necessary for AM initiation [5]. However, this leaf axil population differs from the SAM cell population, as it does not express the stem cell markers *CLAVATA3* (*CLV3*) and *WUSCHEL* (*WUS*) [6–9]. These leaf axil meristematic cells undergo a maintenance phase, which is marked by low expression levels of the meristem gene *SHOOTMERISTEMLESS* (*STM*); a subsequent activation phase, in which *STM* expression increases; and finally an emergence phase, which is

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characterized by the establishment of the *WUS-CLV3* feedback loop (Fig. 1). This leaf axil meristematic lineage and AM initiation represent an ideal conceptual and technical framework for the study of cell fate, stem cells, and meristem organization [10]. Recent findings have shed light on the molecular regulation of each phase, and the following sections cover the regulation of stem cell fate during AM initiation. While this review focuses on vegetative stage branching, readers can refer to recent reviews on reproductive-stage branching, especially spike branching in grasses [11–16].

Distinct gene regulatory networks control postembryonic AM initiation

Because AMs have the same developmental potential as the SAM, a natural line of inquiry is whether AM initiation is under the same developmental regulation as embryonic SAM formation. There are indeed many similarities between the AM and SAM, particularly after the morphogenesis phase. In contrast, the maintenance and activation phases are largely specific to AM initiation and are not associated with SAM formation. Genes such as *LATERAL SUPRESSOR* (*LAS*) and *REGULATOR OF AXILLARY MERISTEMS* (*RAX*) in *Arabidopsis* have expression patterns highly specific to AM initiation. On the other hand, mutations in *STM* and *WUS*, both of which are required for SAM maintenance, also affect AM initiation.

STM regulates SAM maintenance, and is broadly expressed in the SAM since globular stage of embryogenesis [17, 18]. In the SAM, *STM* prevents meristematic cell differentiation. As mentioned earlier, *STM* is also profoundly involved in regulating AM initiation. Whereas strong *stm* alleles lack leaves, the intermediate/weak *stm-bum1* allele exhibits significantly reduced axillary buds formation [5]. *STM* expression is maintained in a small population of leaf axil cells, and these cells retain their meristematic identity and do not form vacuoles. Laser ablation of these *STM*-expressing cells abolishes bud formation, indicating that they are required to initiate axillary buds. The *STM* expression pattern in the leaf axil dynamically changes over the course of AM initiation (Fig. 1). During the earlier maintenance phase, the expression of *STM* is maintained but with a gradual decline. In the subsequent and activation phase, *STM* expression is significantly upregulated, which is accompanied by enhanced cell divisions [5]. It is important to note

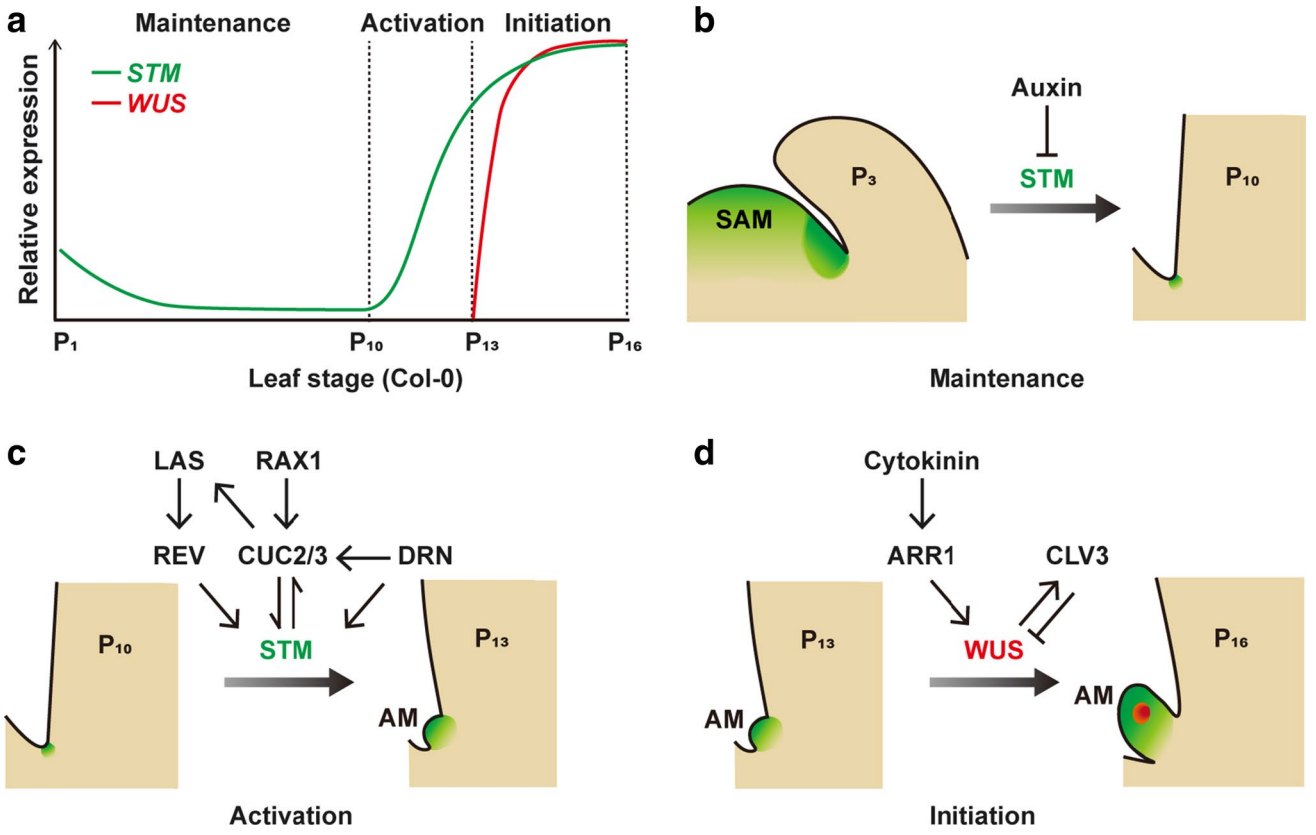

Fig. 1 Conceptual models of the different stages of AM initiation with a focus on the expression profiles of *STM* and *WUS*. **a** According to the expression levels of *STM* and *WUS*, AM initiation can be divided into three stages: maintenance, activation, and initiation (detailed in **b**–**d**). Arrows and inhibition symbols indicate activation and repression, respectively

that only cells with maintained *STM* expression can have high levels of *STM* expression during the activation phase to initiate AMs. In other words, there is no de novo establishment of *STM* expression. Based on its expression patterns, *STM* is a convenient marker for meristematic cell fate.

WUS is another crucial factor for SAM maintenance [19, 20]. During embryogenesis, *WUS* expression starts at the 16-cell stage, and its expression is constrained to the organizing center below the stem cells [19]. WUS is diffusible and directly activates the expression of the stem cell marker gene *CLV3* in the above stem cells [21–24]. In the organizing center, the expression of WUS-interacting HAIRY MERISTEM proteins prohibits WUS activation of *CLV3* expression [8, 9]. *CLV3* encodes a polypeptide hormone that represses *WUS* expression [23, 24]. The WUS-CLV3 feedback loop maintains stem cell niche homeostasis and according *wus* mutants are unable to maintain the SAM [20, 25]. *WUS* is also involved in AM initiation, as axillary buds are often completely absent or converted into one or a few leaf-like structures in *wus* mutants [6]. In contrast to *STM*, *WUS* expression in the leaf axil is not maintained. *WUS* expression is only detectable in mature leaf axils, around P_{13} (the thirteenth earliest leaf primordium) leaves in the Col-0 ecotype, when the AM has formed a visible bulge (Fig. 1a, d) [6]. *WUS* expression is initially scattered in a few cells, and gradually restrict to the organization center after *CLV3* expression becomes detectable [6–9]. In rice (*Oryza sativa*), mutation in the *WUS* orthologous gene *MONOCULM3* (*MOC3*, also named *TILLERS ABSENT1* and *STERILE AND REDUCED TILLERING1*) causes AM initiation defects and female fertility, with minimal effects on SAM maintenance [26–28].

Transcriptional regulation

To date, most of the identified regulators of AM initiation encode transcription factors (Fig. 2). Many of these genes are expressed specifically in the leaf axil and form a leaf axil-enriched gene regulatory network (GRN). Several key regulators of the GRN were initially identified by forward genetics, and have been used as 'anchor points' to pull out additional ones [29, 30].

LAS/MOC1

The *Arabidopsis LAS* gene specifically affects AM initiation and not the SAM. *LAS* encodes a GRAS family transcription factor, and is specifically expressed in the leaf axil [31]. *Lateral suppressor* (*Ls*), the *LAS* ortholog in tomato (*Solanum lycopersicum*), was first identified by forward genetic analysis. Tomato *ls* mutant plants lack axillary buds and also have petal development defects [32]. Using reverse genetics,

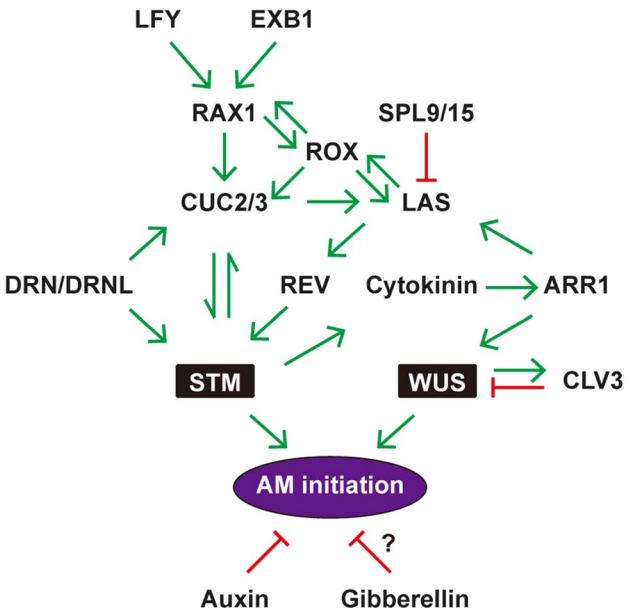

Fig. 2 Summary diagram of transcription factors and phytohormones controlling AM initiation. This diagram includes factors that function at different temporal stages. The black boxes denote the key meristematic factors STM and WUS. Green arrows and red inhibition symbols represent positive regulation and negative regulation, respectively

Arabidopsis las mutants were found to have severe defects in axillary bud formation but normal flower development [31]. Large-scale GRN analysis indicated that the *LAS* promoter is bound by many transcription factors and is likely to be a "regulatory hub" [30]. An independent forward genetic research identified *MONOCULM1* (*MOC1*), the rice *LAS* ortholog, which also exhibits boundary-specific expression. Rice *moc1* mutants have significantly reduced tiller number and inflorescence branching [33], suggesting that *MOC1* is involved in both vegetative and reproductive development. In rice, a co-activator of the cell cycle anaphase-promoting complex, TILLERING AND DWARF 1 (also named TILLER ENHANCER), targets MOC1 to the 26S proteasome for degradation in a cell cycle-dependent manner [34, 35]. At the protein level, rice MOC1 physically interacts with MOC3 and enhances MOC3 activation of *FLORAL ORGAN NUMBER1*, the *CLV1* ortholog in rice. Rice MOC1 promotes tiller bud outgrowth [36], which is distinct from the functions of its orthologs in *Arabidopsis* and tomato.

RAX

There are three paralogous *RAX* genes in *Arabidopsis*, all encoding R2R3 MYB transcription factors that redundantly regulate AM initiation. The *RAX* ortholog in tomato, *Blind* (*Bl*), was identified by forward genetic analysis of *bl* mutants lacking side shoots [37]. The three *Arabidopsis RAX* genes

similarly regulate early AM initiation. *RAX1* and *RAX3* expression domains are restricted to the center of the leaf axils and mark the positions where AMs initiate [38, 39]. In contrast, *RAX2* is more broadly expressed. Among the *RAX* gene mutants, *rax1* mutants have the strongest AM initiation defects, which are enhanced by *rax2* and *rax3* mutations. *rax1 rax2 rax3* triple mutants seldom develop axillary buds in either the rosette or cauline leaves [38].

CUC

In *Arabidopsis*, there are three NAC transcription factor-encoding *CUP-SHAPED COTYLEDON* (*CUC*) genes that redundantly regulate boundary formation. Two of them, *CUC1* and *CUC2*, are under miR164 regulation. *CUC1* and *CUC2* were first isolated for their redundant functions in embryonic SAM formation and cotyledon separation during embryogenesis, and the double mutant phenotype is characterized by occasionally fused cup-shaped cotyledons [40]. Similar mutant phenotypes were identified in petunia, *Antirrhinum*, and tomato [41–43]. *CUC* genes and their orthologous genes in other species redundantly affect phyllotaxis, leaf-stem separation, compound leaf formation or leaf margin serration, and carpel margin development [44–52], In *Arabidopsis*, *CUC* genes also redundantly promote AM initiation, with *CUC3*, and to a lesser extent *CUC2*, playing the leading roles. *cuc3* single mutants have dramatic AM initiation defects in rosette leaves, and both *cuc1* and *cuc2* mutations enhance the *cuc3* mutant phenotype. In *cuc1 cuc2 cuc3* triple mutant plants, almost all rosette and cauline leaves have barren leaf axils [53, 54]. In terms of their expression patterns, all three *Arabidopsis CUC* genes are restricted to the boundary regions. During embryogenesis, *CUC1* and *CUC2* are excluded from the uppermost layer, while *CUC3* expression is detected in this layer [40, 54, 55]. Consistent with this differential expression, only *CUC1* and *CUC2* transcripts are degraded by miR164. Among the three *MIR164* genes, *MIR164c* also exhibits boundary-specific expression [53]. Similar to *LAS*, the *CUC2* promotor is bound by a large number of transcription factors, including RAX1 [30]. It remains unclear if this RAX1 binding represents primary regulation or secondary feedback, as *CUC2* expression precedes that of *RAX1*. In terms of downstream regulation, *CUC* genes regulate *STM* and *LAS* [30, 40, 53, 56]. *STM* expression is lost in *cuc1 cuc2* double mutant heart-stage embryos, and CUC1 protein binds to the *STM* promoter to induce its expression [40, 55, 56]. In turn, STM protein binds to the *CUC1* promotor to activate *CUC1* expression, forming a positive feedback loop [56, 57]. The same regulatory mechanism may also function during AM initiation. In *cuc* triple mutant plants, *LAS* expression in the leaf axil is lost [53]. Consistently, CUC2 proteins directly bind to the *LAS* promotor and upregulate its expression [30].

REV

REVOLUTA (*REV*) has pleiotropic effects on shoot and root development, including SAM and floral meristem activity, leave and stem patterning and growth, vascular development, and root development [58, 59]. Notably, *rev* mutant plants lack axillary buds in both rosette and cauline leaf axils [58, 60, 61]. *REV* is broadly expressed in the SAM, leaf adaxial domain facing the SAM, center of the leaf axil proceeding AM initiation, and vascular tissues [5, 60–62]. *REV* encodes an HD-ZIPIII family transcription factor, which also includes *PHABULOSA* (*PHB*), *PHAVOLUTA* (*PHV*), *CORONA,* and *ATHB8* [60, 61]. The expressions of these HD-ZIPIII genes are regulated by *MIR165/6* [63, 64]. Nevertheless, only *rev* mutants have AM initiation defects, but not other single mutants for HD-ZIPIII genes [60]. On the other hand, dominant mutants of *PHB*, *PHV,* and *REV*, which escape from *MIR165/6* regulation, similarly exhibit adaxialized leaves and ectopic axillary buds surrounding the adaxialized leaves [61, 62, 65, 66].

REV is a downstream factor during AM initiation, and LAS promotes *REV* expression in the leaf axil [31]. REV in turn upregulates *STM* expression immediately prior to AM initiation by directly binding to the *STM* promoter region [5]. REV upregulation of *STM* requires prior *STM* expression and a permissive local epigenetic environment, which ensures that *STM* is not ectopically expressed in other tissues where REV is active [5]. Similar to the findings in *Arabidopsis*, rice HD-ZIPIII transcription factor LATERAL FLORET1 upregulates the expression of *OSH1*, a homolog of *STM*, to promote spikelet branching and to form extra florets [67].

Although the REV-related PHB and PHV proteins can similarly bind to *STM* and promote its expression [5, 68], the observed AM initiation defects are unique to *rev* mutants [60]. It is likely that among these genes, only *REV* is strongly expressed in mature leaf axils. On the other hand, *PHB*, *PHV*, and *REV* alleles that lead to ectopic expression of these genes all give rise to ectopic AMs on the abaxial leaf base, providing support for the de novo theory [65]. It is conceivable that ectopic activity of these HD-ZIPIII transcription factors could maintain *STM* expression in the leaf abaxial side and promote ectopic AM initiation.

LAX1/BA1/ROX

The *LAX PANICLE1* (*LAX1*) bHLH protein gene in rice was identified by forward genetic analysis, and mutation of this gene leads to defects in both vegetative and reproductive-stage branching [69]. Stage- and direction-specific LAX1 protein trafficking is essential for its function during AM initiation [70]. An independent forward genetic analysis showed that mutations in the orthologous *barren stalk1*

(*ba1*) gene in maize similarly lead to vegetative and reproductive branching defects [71]. *LAX1* and *ba1* orthologs broadly exist in many species [72]. Reverse genetic analysis showed that the *Arabidopsis* ortholog, *REGULATOR OF AXILLARY MERISTEM FORMATION* (*ROX*), also participates in AM initiation, but specifically affects early vegetative development [73]. *ROX* expression is restricted to the leaf axil, and is upregulated by both *RAX* and *LAS* [73]. The wild sunflower (*Helianthus annuus*) plants are highly branched with many small flowering heads. By contrast, domesticated sunflowers commonly produce a single large head. Recent studies showed that the *ROX* ortholog, *ROX-LIKE* (*Ha-ROXL*), was responsible for the plant architecture changes associated with domestication [74, 75]. Like rice and maize, but different from *Arabidopsis*, sunflower *Ha-ROXL* is responsible for both vegetative and reproductive-stage AM initiation. Furthermore, *HA-ROXL* promotes the expressions of *RAX*, *LAS,* and *CUC2* orthologs [74].

LAX2/BA2

Rice *LAX2* participates in AM initiation during both the vegetative and reproductive stages [76]. *LAX2* is broadly expressed in meristems and encodes a novel nuclear protein that contains a plant-specific conserved domain. BA2 is the LAX2 ortholog in maize, and it affects tiller bud formation, ear row number, and tassel branching [77]. The physical interactions of LAX2 with LAX1 in rice and BA2 with BA1 in maize are both known to regulate AM formation. However, both the *lax1 lax2* and *ba1 ba2* double mutants have much more severe bud formation defects than the single mutants [76, 77], suggesting the existence of additional interacting factors.

Other transcription factors

There are additional regulatory genes of AM initiation, and the majority of them encode transcription factors. A genome-scale yeast one-hybrid (Y1H) screen identified new transcription factors that bind to the promotor regions of *LAS*, *CUC2*, *RAX1,* and *STM* [30]. *LAS* and *CUC2* are putative regulatory hubs based on the abundance of transcription factors that bind to their promoters. SQUAMOSA PROMOTER-BINDING PROTEIN-LIKE 9 and 15 (SPL9/15) bind to the *LAS* promotor to suppress its expression, and mutations in *SPL9/15* lead to the formation of extra AMs, termed accessory meristems, in cauline leaf axils [30]. DORNRÖSCHEN (DRN, also known as ENHANCER OF SHOOT REGENERATION1, ESR1) and its homolog DRN-LIKE (DRNL, also known as ESR2) are required for AM initiation. In single and double *drn* and *drnl* mutants, a significant portion of the leaf axils are barren [30]. DRN and DRNL regulate AM initiation through various factors: both proteins bind to the *CUC2* promoter to promote its expression [30], and they also upregulate *CUC1* expression [78, 79].

Recent studies identified regulators of *RAX1*. *EXCESSIVE BRANCHES1* (*EXB1*, also named *WRKY71*) encodes a boundary-specific WRKY transcription factor, and *EXB1* overexpression leads to excessive AM initiation. Fusing EXB1 with an EAR repression domain to suppress downstream gene expression leads to inhibition of AM initiation. However, *exb1* mutant plants exhibit normal axillary bud formation, suggesting genetic redundancy. EXB1 also directly activates the expression of *RAX* genes [80]. LEAFY (LFY) is a master regulator of the reproductive-stage transition. An *LFY* allele with reduced floral function was used to show that LFY directly activates *RAX1* expression to promote AM initiation [81]. This finding also explains why AM initiation is much faster in cauline leaves, which are formed during reproductive-stage transition [82], compared to rosette leaves.

Genes with boundary-specific expression are often involved in AM initiation. One example is *LATERAL ORGAN FUSION1* (*LOF1*), which encodes an MYB transcription factor. *LOF1* weakly promotes AM initiation together with its homolog *LOF2* [83]. The tomato ortholog *Trifoliate* promotes compound leaf formation and also weakly affects AM initiation [84]. A recent leaf axil-specific translatome analysis also identified new regulators of AM initiation [29]. *HANABA TARANU*, which encodes a GATA transcription factor, promotes AM initiation in addition to its known roles in embryogenesis and meristem maintenance [85–88]. The translatome analysis also identified *RABBIT EARS*, which encodes a C2H2 family zinc-finger transcriptional repressor, as a suppressor of AM initiation.

A recent cell domain-specific transcriptome analysis showed that leaf axil boundary genes were also expressed in maize ligules, which separate grass leaf sheath and leaf blade [89]. This finding is supported by genetic analyses of the *BLADE-ON-PETIOLE* (*BOP*) genes in several species. The *BOP* genes were first identified in *Arabidopsis* as suppressors of lamina formation on the petiole [90, 91], and have later been associated with abscission zone formation, bract suppression, and floral patterning [92–94]. Notably, the barley *BOP* gene *UNICULME4* (*CUL4*) is expressed in the boundary and promotes axillary bud and ligule formation, as well as inflorescence development [95]. Furthermore, *Ligulum-a* (*ELI-a*) another related barley gene expressed in the preligular band and various other tissues is related to AM initiation. Mutations in *ELI-a* in combination with the *uniculm2* mutant, which lacks tillers, result in plants that restore tiller formation [96]. The functions of *BOP* appear to be highly diverged among different species. They control maize axillary bud outgrowth [97] and tomato inflorescence development [98]. However, *BOP* function in rice is restricted to

leaf development [99]. Nevertheless, the connection between AM initiation and ligule formation point to new approaches to identify novel genes that regulate AM development.

Phytohormones

Phytohormones play critical roles in various plant developmental process, and recent studies have linked some of them to AM initiation (Fig. 2).

Auxin

Whereas auxin maxima are often associated with organogenesis, such as the formation of leaves, flowers, and lateral roots, a low auxin environment is necessary for vegetative AM initiation in *Arabidopsis* and tomato [100, 101]. The DII auxin sensor, whose signal negatively correlates with auxin levels [102, 103], has strong signals in the leaf axil boundary region starting at leaf primordium emergence in *Arabidopsis*. DR5 signal, which correlates with auxin signaling, is excluded from the leaf axils in *Arabidopsis* and tomato. Consistent with these observed patterns, ectopic expression of the iaaM auxin biosynthesis enzyme in the leaf axil led to dramatically compromised AM initiation in *Arabidopsis* [100, 101]. Local auxin application in the leaf axil in tomato also blocks AM initiation [100]. The leaf axil auxin minimum depends on polar auxin transport, and both auxin efflux and auxin influx mutants exhibit varying degrees of axillary bud formation defects [100, 101]. Similar AM phenotype can also be obtained by treating *Arabidopsis* or tomato with auxin efflux inhibitor *N*-1-naphthylphthalamic acid [101]. In *pCUC2* ≫ *iaaM* plants with ectopic auxin biosynthesis in the leaf axil, *STM* expression is significantly reduced, disrupting *STM* maintenance [5]. Consistently, auxin signaling suppresses *STM* expression in the floral meristem [104].

In contrast to its effect on vegetative AM initiation, auxin promotes the formation of the floral meristem, which is considered a specialized AM [4], and probably also cauline leaf AMs, which form during the floral transition [82]. The formation of *Arabidopsis* floral primordia is further regulated by a reciprocal feedback loop between auxin levels and *LFY* expression. Auxin promotes *LFY* expression, and LFY feeds back onto multiple components of the auxin pathway [105–107]. A live-imaging analysis of *Arabidopsis* cauline leaf AMs showed high DR5 expression, which was similarly observed in tomato AMs, likely also after the floral transition [108]. The role of auxin in maize and rice spike branching has been more extensively studied [109].

In maize, auxin biosynthesis is required for AM initiation during vegetative development, in addition to promoting reproductive-stage AM initiation [110, 111]. Given that auxin is required for SAM homeostasis and maintenance [112], it is possible that auxin functions in a later step of AM initiation or bud maintenance. It remains to be determined if auxin is required for vegetative stage bud formation in eudicots, such as *Arabidopsis*.

Cytokinins

Cytokinins regulate SAM patterning and homeostasis [113–116], and are broadly involved in shoot meristem functions [117]. During AM initiation in *Arabidopsis*, a cytokinin signaling pulse, which can be monitored using the TCS cytokinin signaling sensor [118], is detectable just a few days prior to AM initiation in the center of the leaf axil [100]. Cytokinin signaling requires cytokinins, receptors, and signaling pathway components. STM promotes cytokinin biosynthesis in the SAM [119–121], and may function similarly in the leaf axil. AHK4, one of the three cytokinin receptors in *Arabidopsis*, is specifically detected in the leaf axil center [100]. Several type-B ARR transcription factors, which are downstream cytokinin signaling, are expressed or even enriched in the leaf axil [6, 100]. Cytokinin signaling in the leaf axil is causally related to AM initiation, and several combinations of cytokinin perception mutations lead to AM initiation defects. Mutants of type-B ARR transcription factor genes also show compromised AM initiation, with *arr1* having the strongest phenotype [100]. The leaf axil cytokinin signaling pulse depends on *LAS*, *RAX*, and *REV*. Moreover, ectopic cytokinin production in the leaf axil can rescue *rax* mutant phenotypes [100].

Cytokinin de novo activation of *WUS* expression in the leaf axil helps to establish functional AMs. Unlike *STM*, *WUS* expression is not maintained in the leaf axil. Soon after the leaf axil TCS signal, *WUS* expression is activated in TCS-expressing cells. At the molecular level, type-B ARR transcription factors, especially ARR1, directly bind to the *WUS* promoter to activate its expression [6]. Consistent with this activity, ectopic *WUS* expression rescues the AM initiation defect of the *arr1-4* mutant [6]. Similar to their function in AM initiation, type-B ARRs also activate *WUS* expression de novo during shoot regeneration from callus [122, 123]. In addition to binding to *WUS*, ARR1 also binds to the *LAS* promotor and activates its expression [30]. Cytokinins may also promote *STM* expression, which has been shown in the SAM [124].

Other phytohormones

Additional hormones may also contribute to AM initiation. For example, a recent study reported that gibberellin negatively regulates AM initiation [125]. DELLA proteins negatively regulate gibberellin signaling, and *della* pentuple

mutant plants have slightly reduced axillary bud numbers. Additionally, ectopic expression of the *GA20ox2* gibberellin biosynthesis gene in the leaf axil inhibits AM initiation [125]. DELLA proteins interact with SPL9 [126], which bind to the *LAS* promoter to repress its expression [30, 125]. These molecular links may contribute to AM initiation and warrant further confirmation.

Although there is no evidence that the growth-promoting brassinosteroid phytohormones interfere with AM initiation, they do affect organ boundary formation [127, 128]. Additionally, the expression levels of several AM initiation-related genes are altered in brassinosteroid signaling and biosynthesis mutants. Since many of these affected genes, such as *CUC* and *LOF1*, are involved in both boundary separation and AM initiation, it remains to be determined if brassinosteroids substantially affect AM initiation.

Epigenetic regulation

Epigenetic regulation allows differential expression of the same gene in different cell types from the same genome. Thus, epigenetic regulation is involved in virtually all developmental processes, including AM initiation. The above-mentioned transcriptional regulation of *WUS* and *STM* also depends on epigenetic regulation to ensure that their spatiotemporal expression patterns are precisely controlled. Neither REV, which activates *STM* expression, nor ARR1, which activates *WUS* expression, is limited to the leaf axil. Epigenetic regulation restricts the expression of both genes. The Polycomb group (PcG) complexes mediate histone 3 lysine 27 trimethylation (H3K27me3), which is a repressive mark. In differentiated tissues, such as mature leaves, both *STM* and *WUS* have high H3K27me3 levels. In contrast, these genes have a low level of H3K27me3 and a high level of H3Ac, a mark associated with active chromatin, in tissues containing the leaf axil *STM*-expressing cells [5]. It is likely that an open chromatin status is associated with the maintenance of *STM* expression. In PcG-related mutants, both *WUS* and *STM* expression levels are upregulated [5, 6, 129, 130]. Moreover, treating mature leaf cells with the histone deacetylation inhibitor trichostatin A leads to ectopic *WUS* expression [6].

Epigenetic regulation is more dynamic for *WUS*, whose expression is terminated in the leaf axil and then subsequently activated de novo [6]. In the leaf axil tissues of young leaf primordia, where *WUS* is not expressed, the *WUS* locus has abundant H3K27me3, but is depleted of H3/4Ac. Prior to *WUS* activation, the levels of the H3K27me3 repressive mark decrease, while the levels of the H3/4Ac active mark increase [6].

Perspectives

Phenotypic characterization of changes in AM initiation is often difficult due to strong apical dominance in many plant species, including the model plant *Arabidopsis*. Despite the identification of key transcription factors and phytohormones that regulate AM initiation (Fig. 2), there are clearly many "unknowns" in this research area. First, the leaf axil stem cell lineage warrants further characterization. Given that plant cells in general have higher plasticity than animal cells, this stem cell lineage provides an excellent system to study cell fate determination. It remains unknown how this stem cell lineage is maintained, how the epigenetic status is maintained, and to what extent the fate of this stem cell lineage is reversible. To answer these questions, new cellular resolution technologies are needed. Second, there are likely many unknown AM initiation regulators are awaiting to be uncovered. We need new tools for forward genetics and system biology to dissect the gene regulatory networks underlying AM initiation. Third, we need to better connect the known AM initiation regulators to obtain a plausible regulatory network. Finally, regulatory mechanisms other than transcriptional regulation need to be identified affecting AM initiation.

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