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All together now, a magical mystery tour of the maize shoot meristem

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Crop yield improvement requires optimization of shoot architecture, and can be facilitated by understanding shoot apical meristem (SAM) development. Maize, as one of the most important cereal crops worldwide, is also a model system and has significantly contributed to our fundamental understanding of SAM development. In this review, we focus on recent progress and will discuss communication between different meristem regulators, including CLAVATA receptors and ligands, transcription factors, small RNAs and hormones, as well as the importance of communication between different SAM regions.

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Introduction

The maize shoot system is derived from the shoot apical meristem (SAM), a pool of pluripotent stem cells which have the ability of self-renewal, and initiate new leaves and axillary meristems [1]. Due to its importance in determining shoot architecture and its self-organizing capability, the SAM has brought much attention to scientists for more than a century. As in other plants, the maize SAM is formed during embryogenesis, starting from ~7 days post pollination [2]. In contrast to animals, where organogenesis is usually complete during embryonic development, most new tissues and organs are formed during post-embryonic development in plants [3]. During maize embryogenesis, around five leaves are made before the seed matures and the embryo becomes dormant [4]. Upon germination, the SAM becomes active once more, and new leaves initiate continually until the transition stage, when the vegetative SAM transits to an inflorescence meristem (IM) that produces spikelets and flowers. Axillary meristems produced in association with leaf primordia can produce branches (tillers), or ear inflorescence shoots.

The SAM is comprised of different zones, based on their cellular activity. At the tip, the stem cell niche contains a pool of slowly dividing pluripotent stem cells, and is named the central zone (CZ). Surrounding the CZ is the peripheral zone (PZ), where cells divide more rapidly, and will generate leaf or axillary meristem primordia. Lastly, the rib zone (RZ) lies below the CZ, and cells dividing there will form the stem. A small group of cells called the organizing center (OC), sitting between the CZ and RZ was defined more recently based on molecular markers, and is important for communication between different zones (reviewed in [5,6]). A pioneering study showed that in some plants (though not in maize), the SAM can regenerate after the vast majority of cells are surgical removed [7]. This suggests that the SAM is not rigidly programmed, but can reestablish different zones and communication pathways to rebuild the structure of the meristem. Stem cell activity is at the heart of the SAM, and when this is disrupted by specific mutations, plant growth will be abnormal or will cease completely. In contrast, mutants that upregulate stem cell activity lead to bigger meristems with abnormally flattened and split stems and inflorescences, called fasciation. Such mutants have significantly contributed to our understanding of signaling and communication between zones of the maize SAM (summarized in Table 1). Recent progress has been rapid, fueled by advances in genomics, however the picture is still far from complete. In this review, we will synthesize findings from recent studies, focusing on receptor based communication between different zones of the maize SAM and intracellular signal transduction.

The classical CLAVATA (CLV)-WUSCHEL (WUS) model established in *Arabidopsis* is largely conserved in maize

The CLV-WUS model has long been recognized as a key feedback pathway that regulates communication between different zones in the *Arabidopsis* SAM [1]. It relies on communication between a series of receptors, peptide ligands and transcription factors that are expressed in different zones. Central to this complex network is WUS, a homeodomain transcription factor expressed in the OC to promote stem cell fate [8], and CLV3, a small peptide ligand that is secreted from cells in

Table 1

Summary of fasciated inflorescence mutants. Scanning electron microscopy images of wild-type and fasciated mutant ear primordia are presented, except for *Cg1*, for which a tassel primordium is shown. Inflorescence meristems are shaded in yellow. Protein structures are illustrated with indicated domains except for *Cg1*, a miRNA, for which transcript is illustrated. The references for the mutants are listed under their gene IDs. SP: signal peptide; LRR: leucine-rich repeat; TM: transmembrane; KD: kinase domain; bZIP: basic leucine zipper; CLE: Clavata3/Embryo Surrounding Region (ESR)-Related; SBP: SQUAMOSA promoter Binding Protein; SNH: Synovial Translocation (SYT) N-terminal Homology; PAZ: Piwi Argonaut and Zwille; dsRB: double strand RNA Binding

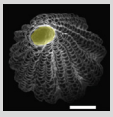
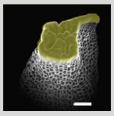
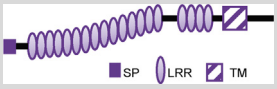
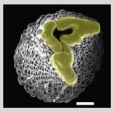
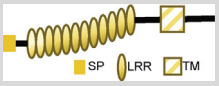
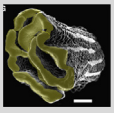
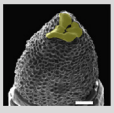
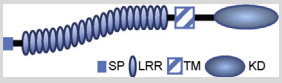
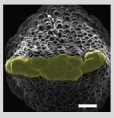
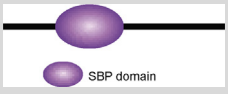
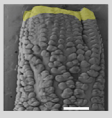
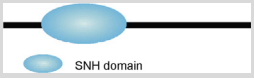
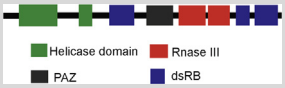
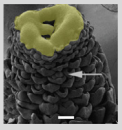
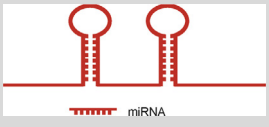
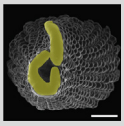
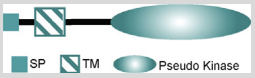
	IM	SAM size	Protein structure	*Arabidopsis* ortholog
WT		N/A	N/A	N/A
fea2 GRMZM2G104925 (14)		Enlarged		CLV2 (AT1g65380)
fea3 GRAZM2G166524 (19)		Enlarged		AtFEA3 (AT3g25670)
fea4 GRMZM2G133331 (47)		Enlarged		PAN (AT1g68640)
td1 GRMZM2G300133 (15)		Not determined		CLV1 (AT1g75820)
ct2 GRMZM2G064732 (21)		Enlarged		GPA1 (AT2G26300)
Zmfcp1 GRMZM2G165836 (19)		Enlarged		CLE27 (AT3G25905)
ub2,ub3 GRMZM2G160917 GRMZM2G460544 (42)		Not determined		AtSPL9 (AT2G42200) AtSPL15 (AT3G57920)
gif1 GRMZM2G180246 (45)		Not determined		AtGIF1 (AT5G28640)
fzt1 GRMZM2G040762 (65)		Not determined		DCL1 (AT1G01040)
Cg1 GRMZM2G022489 (67)		Not determined		miR156B (AT4G30972) miR156C (AT4G31877)

Table 1 (*Continued*)

	IM	SAM size	Protein structure	*Arabidopsis* ortholog
Zmcrn GRMZM2G032132 (28)		Enlarged		CRN (AT5G13290)

the CZ and perceived by leucine-rich repeat receptor-like kinases (LRR-RLKs), such as CLV1, and a leucine-rich repeat receptor-like protein (LRR-RLP) CLV2, resulting in the repression of WUS transcription [9–11]. Key to this feedback loop is the precise spatial expression of these components and the movement of CLV3 and WUS. CLV3 is secreted, and presumably moves through the extracellular matrix by diffusion, though the peptide has never been localized *in vivo*, and WUS protein moves cell to cell through plasmodesmata [12,13]. The CLV3 receptor *CLV1* is expressed below the CZ and surrounding the WUS domain, while *CLV2* is expressed broadly in the SAM and throughout the plant.

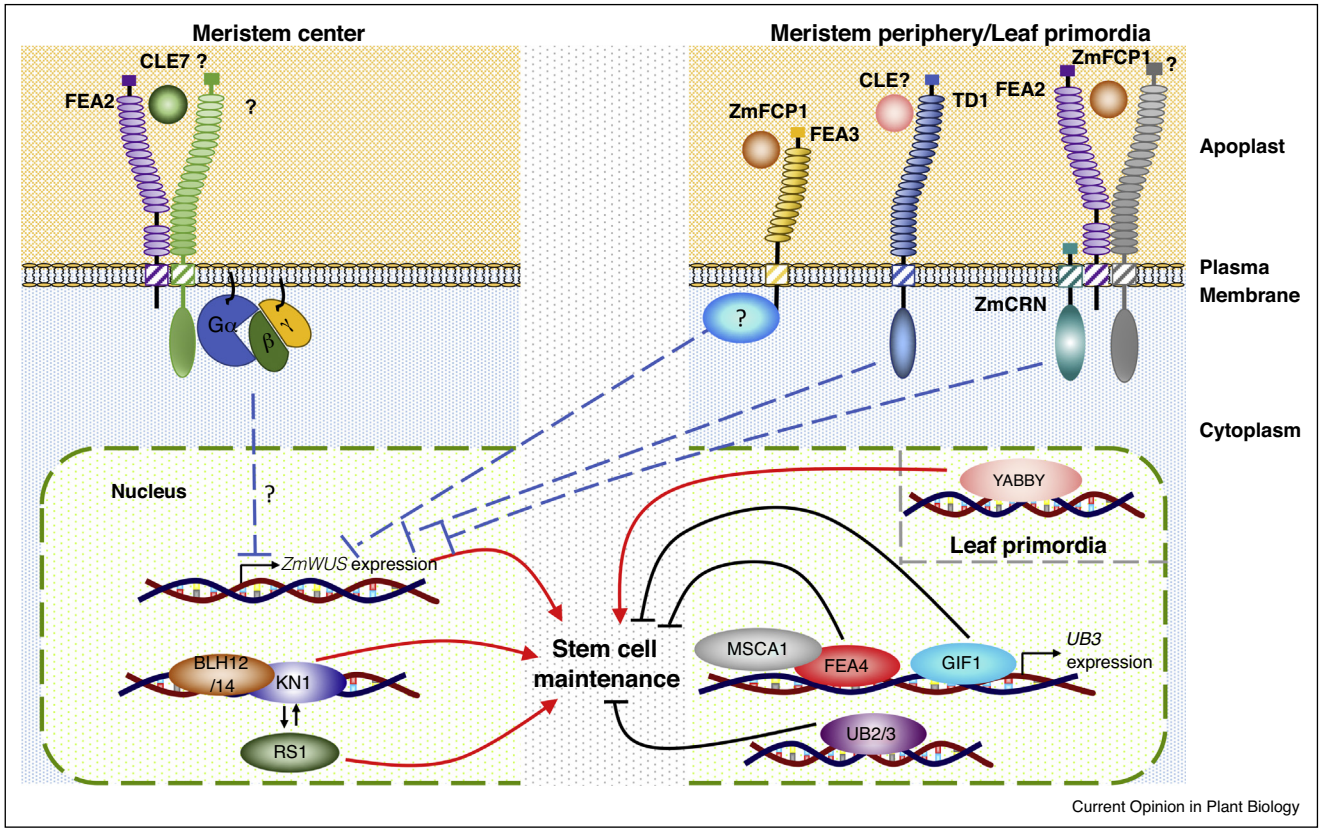
Conservation of the CLV-WUS pathway in maize is evident through studies using '*fasciated ear*' (*fea*) and similar mutants (Figure 1). For example, *FASCIATED EAR2* (*FEA2*) encodes an LRR-RLP that is orthologous to *CLV2*, and *fea2* mutants have enlarged vegetative SAMs and IMs [14]. Further evidence of conservation came from the cloning of *THICK TASSEL DWARF1* (*TD1*), which encodes a *CLV1* ortholog [15]. *td1* mutants have over-proliferating IMs, similar to *fea2* [15]. While additional LRR-RLKs, such as BARELY ANY MERISTEM*s* (BAM*s*), function redundantly with *CLV1* in *Arabidopsis* [16,17], it remains unclear whether the same is true for maize. Notably, *TD1* expression is similar to *BAM* genes, with expression high in the peripheral region of the vegetative SAM and in leaf primordia, and absent from the CZ [16,17]. More work is needed to understand the intricacies of the TD1-BAM clade in maize meristem regulation. Unlike the clearly defined *CLV1* and *CLV2* orthologs, maize has two *WUS* orthologs, *ZmWUS1* and *ZmWUS2*, however both are expressed at very low levels in the vegetative SAM [18]. However, *ZmWUS1* is clearly expressed in the OC of the inflorescence SAM, similar to *Arabidopsis* [19••]. *Zea mays* CLAVATA3/EMBRYO SURROUNDING REGION-RELATED7 (*ZmCLE7*) and *ZmCLE14* are candidates for maize *CLV3* orthologs, based on phylogenetic analysis [19••,20•], and treatment with these peptides affects SAM size in a predictable manner [19••], but functional characterization of *WUS* and *CLV3* orthologs is necessary to understand their true role in maize.

Signaling immediately downstream of the CLV receptors is poorly understood, possibly due to genetic redundancy or pleiotropy caused by converging signaling pathways. However, analysis of maize *compact plant2* (*ct2*) mutants, which also have fasciated ears and enlarged SAMs, reveals a role of heterotrimeric G-proteins in meristem regulation [21]. *ct2* mutants are partially resistant to CLV3 peptide treatment and *CT2*, which encodes Gα, is in a protein complex with FEA2, suggesting that CT2 and FEA2 together transmit the CLV signal. Heterotrimeric G-protein signaling also appears to be important in *Arabidopsis* meristem regulation, where the heterotrimeric G protein beta subunit, AGB1 interacts with another CLV-like receptor RECEPTOR-LIKE PROTEIN KINASE2 (RPK2) to control SAM size [22], but in the case of Gα is more redundant, since an increase in SAM size is only seen in quadruple mutants of *Gα* with 3 related '*eXtra-Large G protein*' genes [23]. Another downstream signaling component of CLV receptors is CORYNE (CRN), a transmembrane receptor-like pseudo-kinase [24–26]. In *Arabidopsis*, CRN directly associates with CLV2, though how this interaction mediates signal transduction remains unclear, since CRN lacks kinase activity [26,27]. A recent study shows that its maize ortholog, ZmCRN, also functions downstream of FEA2, the CLV2 ortholog. This study shows that FEA2 transmits signals from two distinct CLE peptides, ZmCLE7 and ZmFCP1 through specific interactions with CT2 and ZmCRN, respectively [28•]. This finding brings new insights into how LRR-RLPs can transmit different peptide signals through associating with different downstream signaling components. However details of these pathways are lacking, for example FEA2 is an LRR-RLP with no intracellular signaling domain, and *fea2* mutants are insensitive to treatments using several different CLE peptides [19••], so it is likely that FEA2 works as a co-receptor of multiple LRR-RLK receptors. The co-receptor idea is also based on results with CLV2, which cannot bind CLE peptides directly [29], so it will be interesting to identify the co-receptors that associate with FEA2 and bind CLE peptides (Figure 1).

Signaling from stem cell descendants back to the stem cell niche

In addition to the CLV-WUS pathway, which enables communication between cells within the SAM, recent studies in maize further highlight that stem cell descendants and initiating leaf primordia also send signals that feedback on SAM regulation. For example, the maize *YABBY* genes *DROOPING LEAF1* and *DROOPING*

Figure 1



Signal transduction in maize shoot meristems. In the center of the SAM, a putative CLV3 ortholog, ZmCLE7, interacts with FEA2 and a putative CLV1 ortholog, and the heterotrimeric G protein α subunit CT2 mediates CLV signaling by coordinating with FEA2. KN1 also functions in SAM maintenance, acting redundantly with RS1, and forms heterodimers with BLH12 or BLH14. Meanwhile, on the SAM periphery, FEA3 and a FEA2-CRN complex perceive signals from ZmFCP1, while the ligand of TD1 remains unknown. Signaling via CLV receptors leads to the repression of the stem cell promoter *ZmWUS*. Also on the SAM periphery, FEA4 interacts with MSCA1, and GIF1 regulates the expression of *UB3*, to inhibit stem cell maintenance. Lastly, acting from the leaf primordia, YABBY transcription factors promote SAM maintenance by an unknown signal.

LEAF2 (*DRL1*, *2*) were initially characterized due to their redundant effects on leaf angle, an important agronomic trait. DRL1 and 2 are expressed exclusively in leaf primordia, yet the double mutants have smaller SAMs, and similar findings in *Arabidopsis* also suggest that signals from organ primordia non-autonomously regulate SAM development [30,31•], however, the signaling mechanism remains elusive. Another example comes from the characterization of *fasciated ear3* (*fea3*) mutants. *FEA3* encodes an LRR-RLP similar to FEA2, but unlike other *CLV* genes that are expressed in stem cells and above and around the OC, *FEA3* is expressed within and below the OC, and in leaf primordia. FEA3 is involved in perception of a signal from the CLE peptide ZmFCP1, expressed in PZ and leaf primordia, and FEA3 inhibits the expansion of *ZmWUS1* downwards below the OC. Consistently, both *fea3* and *Zmfcp1* mutants have bigger SAMs and IMs, and *fea3* is epistatic to *Zmfcp1* with respect to SAM size [19••]. Therefore, FEA3 and ZmFCP1 define a new CLV feedback that appears to be conserved in *Arabidopsis* [19••], but a major question remains in the CLE field whether the CLE peptides move, as predicted, and whether it is by passive diffusion or active transport?

Additional transcription factors regulate the maize SAM

Besides WUS, additional transcription factors expressed in different SAM zones play important roles in maize development. One of the best studied is KNOTTED1 (KN1), the founding member of the KN1-related homeobox (KNOX) family [32–35]. Severe KN1 loss-of-function mutants fail to initiate or maintain the SAM, although in some genetic backgrounds somewhat normal plants survive albeit with smaller inflorescence and vegetative SAMs [32,34]. *KN1* is expressed throughout the SAM but excluded from leaf initiation sites, leaf primordia and the L1 layer [36], although KN1 protein traffics cell to cell through plasmodesmata into the L1, providing a possible mechanism to coordinate development of different cell

layers [37,38]. A recent study shows that KN1 forms heterodimers with BEL1-like homeobox transcription factors BLH12 and BLH14 [39]. *blh12,blh14* double mutants make slightly shorter but otherwise normal SAMs, but axillary meristems were not maintained, similar to the case in *kn1* mutants [39]. With the expanding use of transcriptome and ChIP-seq profiling, it was found that KN1 directly targets many developmental regulators, including transcription factors and genes participating in auxin and gibberellic acid hormonal pathways, revealing a complicated regulatory hierarchy for SAM development controlled by KN1 [40•,41]. However, the interaction between KN1 and ZmWUS still remains obscure, and seeking the common targets of both proteins could help to gain a better understanding of this question.

A major limitation of genetic analysis in plants is redundancy, as highlighted in a recent report [40•]. Expression of the *KNOX* gene *ROUGH SHEATH1* (*RS1*) overlaps that of *KN1* [40•], but *rs1* mutants have no obvious phenotype. However in double mutants, *rs1* exacerbates several aspects of the *kn1* phenotype. ChIP-seq experiments show that RS1 shares many *in vivo* binding targets with KN1, suggesting unequal redundancy between *KNOX* family members occurs at the level of transcriptional outputs. Overcoming genetic redundancy was also necessary to demonstrate that inflorescence development is regulated by SQUAMOSA PROMOTER BINDING (SBP)-box transcription factors UNBRANCHED2 (UB2) and UB3 [42••]. *ub2,3* double mutants have enlarged IMs and fasciated ears, and both genes are expressed throughout the periphery of the meristem. Previous studies raised the idea that weak alleles of fasciated mutants could enhance kernel row number (KRN) [19••,43••], an important agronomic trait, and fine-mapping of a major KRN quantitative trait locus (QTL), *KRN4*, found that a transposon insertion ~ 60 kb downstream of the *UB3* gene regulates its expression, and is responsible for maize KRN variation [44••]. More recently, *UB3* was found to be a transcriptional target of GROWTH-REGULATING FACTOR (GRF)-INTERACTING FACTOR 1 (GIF1) (Figure 1), and its expression is reduced in *gif1* mutants [45•]. Similar to *ub2,3* mutants, tassels and ears are fasciated in the *gif1* mutants. UB3 itself may function by regulating cytokinins, as it binds the promoters of *LONELY GUY1* (*LOG1*) and *TYPE-A RESPONSE REGULATOR* (*ARR*) genes that are involved in cytokinin biosynthesis and signaling [46].

Another gene critical to maize SAM regulation is *FASCIATED EAR4* (*FEA4*), which encodes a bZIP transcription factor orthologous to *Arabidopsis PERIANTHIA* (*PAN*) [47•]. *fea4* mutants have enlarged vegetative SAMs and very severely fasciated IMs, and double mutant analyses indicate that it functions as a negative regulator of meristem size in parallel to CLV-WUS signaling. However, *PAN* was previously reported as a controller of floral organ patterning but not meristem size [48], revealing the importance of studying basic processes in different model systems in order to reveal gene functions. Like *UB2* and *UB3*, *FEA4* is expressed in the SAM periphery, again highlighting the possibility that signals feedback from the PZ to the stem cell niche (Figure 1). FEA4 may be regulated by redox signaling in the SAM, since it interacts with a glutaredoxin protein MALE STERILE CONVERTED ANTHER1 (MSCA1) [49]. *msca1* loss-of-function mutants have smaller SAMs, whereas *MSCA1* misexpression in dominant *MSCA1-Aberrant phyllotaxy2* mutants leads to a bigger SAM and decussate phyllotaxy. The importance of redox signaling in the SAM was also recently discovered in *Arabidopsis*, where redox treatments and mutants alter SAM size [50]. Although it is confusing that so many factors control SAM size, genomic analysis can help clarify their relationships. In one example, ChIP-seq combined with RNA-seq profiling revealed that FEA4 and KN1 oppositely regulate a common set of target genes, suggesting that FEA4 functions in part in opposition to KN1 [47•]. A remaining question is how does MSCA1 interaction and redox signaling affect the function of FEA4?

Hormones crosstalk to regulate SAM development

Plant hormone signaling regulates development and communication between different regions of the SAM, converging with the pathways discussed earlier. The most well studied hormones are cytokinin and auxin, with cytokinin promoting meristem proliferation and auxin driving lateral primordium initiation. Insights have come from characterization of maize mutants with altered auxin biosynthesis, for example, the *sparse inflorescence1* (*spi1*) mutants that are defective in auxin biosynthesis have *pin*-like inflorescence meristems [51]. *SPI1* encodes a flavin monooxygenase similar to the *YUCCA* genes of *Arabidopsis*, which are involved in local auxin biosynthesis. Another example is *vanishing tassel2* (*vt2*). *VT2* encodes an ortholog of tryptophan aminotransferase of *Arabidopsis* (*TAA1*) that is also required for auxin biosynthesis [52]. *spi1* and *vt2* single mutants have reduced auxin levels, and the tassels are smaller and barren, lacking lateral branches and functional spikelets. The reduction in auxin levels in *spi1,vt2* double mutants is similar to single mutants, suggesting they work in a common pathway. Importantly, the finding that VT2 and SPI1 are epistatic led to a new hypothesis that TAA1 and YUCCA function in the same IAA biosynthetic pathway, which was later confirmed in *Arabidopsis* [53].

Analysis of additional *barren* mutants revealed important roles for auxin signaling and transport. *BARREN INFLORESCENCE1* (*BIF1*) and *BIF4* encode AUXIN/INDOLE-3-ACETIC ACID (Aux/IAA) proteins, key players in auxin signaling [54]. BIF1 and BIF4 control inflorescence axillary meristem initiation by regulating

the expression of *BARREN STALK1* (*BA1*), a basic helix–loop–helix transcription factor [55]. In addition, *BARREN INFLORESCENCE2* (*BIF2*) encodes a co-ortholog of the serine/threonine protein kinase PINOID (PID), and regulates auxin transport through affecting the subcellular localization of a PINFORMED1 auxin efflux transporter ortholog (ZmPIN1a) during maize inflorescence development [56,57]. The importance of auxin transport was also revealed by studies of the auxin influx carrier mutant, *Zmaux1*, which reduces tassel branch number and has fewer spikelets [58]. A study of the role of natural variation in meristem size control further showed that expression of its paralog, *ZmLAX2*, associates with SAM morphological diversity in a genome-wide association study (GWAS) [59•]. *In situ* hybridization revealed that *ZmLAX2* transcript accumulation coincided with PIN1 localization, suggesting that the balance between auxin efflux and influx needs to be balanced for proper SAM development, and that changes in *ZmLAX2* expression may be responsible for changes in SAM size [59•]. Earlier work also identified *ABERRANT PHYLLOTAXY1* (*ABPH1*) as a cytokinin-inducible type A response regulator, indicating that cytokinin controls SAM size and phyllotaxy [60,61]. *ABPH1* expression is dependent on auxin transport, and it activates *PIN1* expression [61] and therefore orchestrates phyllotaxy by restricting SAM size through negative regulation of a cytokinin signal and promoting leaf initiation by positively regulating auxin signaling, revealing a complex interaction between auxin and cytokinin in the SAM [61].

Additional pathways required for maize shoot meristem maintenance

Certain metabolites and mineral nutrients are also important for SAM maintenance. Mutations in a thiamine biosynthetic gene, *THAIMAMINE BIOSYNTHESIS2* (*THI2*), result in defects in meristem maintenance and a progressive reduction in SAM size that leads to premature shoot abortion, providing a new perspective on metabolic requirements of the SAM [62]. Mutations in *TASSEL-LESS1* (*TLS1*), which encodes an aquaporin family protein that facilitates the transport of boron also lead to similar defects in vegetative and inflorescence development [63]. Boron content is reduced in *tls1* mutants and application of boron can rescue the mutant phenotype, highlighting the importance of this mineral in meristem function. The recently characterized *narrow odd dwarf* (*nod*) mutants provide new insights into how cell expansion and division affects meristem development [64]. *NOD* encodes CELL NUMBER REGULATOR13 (CNR13) [64], and *nod* mutants have pleiotropic defects, including fewer and smaller leaf cells, dwarf and bushy shoots, reduced SAM size, barren tassels, as well as small, partially fertile ears. Remarkably, many of the differentially expressed genes in *nod* mutants overlap with KN1 targets, suggesting crosstalk between these two genes. Small RNAs, key players in many plant processes have also been implicated in meristem maintenance in maize. For instance, *FUZZY TASSEL* (*FZT*) encodes a homolog of DICER-LIKE1, a key enzyme in microRNA biogenesis. While null alleles are lethal, weak alleles are defective in the production of a subset of miRNAs, and exhibit fasciated inflorescences [65]. Overexpression of certain miRNAs also resulted in abnormal IM development. For example, the dominant mutant *Corngrass1* (*Cg1*), caused by the overexpression of miR156, has a fasciated inflorescence meristem similar to *fzt*; however, their genetic relationship remains obscure as miRNA156s level are not significantly changed in *fzt* mutants [66]. Remarkably, *Cg1* mutants have more severe phenotypes than plants overexpressing miR156 in *Arabidopsis*, suggesting that the buffering networks of miRNAs are more redundant in *Arabidopsis* [67,68]. Together, these studies suggest that the miRNA accumulation needs to be delicately controlled to orchestrate the expression of their target genes, such as SBP-box transcription factors, which are key regulators in meristem development [66].

Axillary meristems and tillering

Tillers are secondary shoots derived from axillary meristems produced at the base of each leaf [69,70]. Domestication of modern maize from the highly tillering ancestor, teosinte, strongly selected against tillering to enable high planting density and yield [71]. Among the major selected loci were *TEOSINTE BRANCHED1* (*TB1*), which encodes a TB1-CYCLOIDEA-PROLIFERATING CELL FACTOR (TCP) transcription factor that acts as a repressor of axillary bud growth [72], and *GRASSY TILLERS1* (*GT1*) [73]. *GT1* encodes an HD-ZIP I protein, and its expression is under the transcriptional control of TB1 and is dramatically reduced in *tb1* mutants. Recent characterization of a third mutant, *tassels replace upper ears1* (*tru1*) provides a new molecular mechanism for how *TB1* transformed teosinte into modern maize [74•]. *tru1* mutants cause maize to revert back to its highly branched ancestral state, much like *tb1*. *TRU1* encodes an ankyrin repeat protein and is expressed at the base of lateral organs during both vegetative and inflorescence development, but is absent from meristems. Genetic and molecular analyses suggest that *TB1* mediates suppression of axillary branches through direct activation of *TRU1*. Future work is needed to elucidate the downstream signaling pathways for these newly identified domestication targets.

Perspective

With the awesome power of genetics, which will no doubt continue to be the cornerstone for meristem research, a subset of key regulators has been identified in different plant species. Many key signaling pathways including CLV-WUS, KNOX, and plant hormones have conserved functions in maize and dicot species. Yet, the relatively

large meristem size and high genetic diversity make maize a powerful model, and can enable many new discoveries. For instance, the identification of FEA3 and its ligand leads to the discovery of new CLV feedback, which was missed in *Arabidopsis* genetic screens. The functional analysis of FEA4 highlighted its role in meristem regulation, with a much stronger effect than its ortholog in *Arabidopsis*, and led to the discovery of a new pathway acting in parallel with CLV-WUS. Despite the efforts of maize geneticists, many maize fasciation mutants have not yet been characterized, suggesting that meristem signaling pathways are more easily disrupted in maize than in *Arabidopsis*. One possible explanation for this is that maize has been subjected to human selection from ~10 000 years ago [71], while *Arabidopsis* is a wild species. One of the major targets for human selection was for larger ears, which is correlated with bigger meristems [43••]. Thus, the alleles that provide redundancy and buffering of meristem size may have been selected against in modern maize cultivars, providing a great opportunity to use maize as a model system to identify novel meristem regulators.

Genetic redundancy may have hindered discoveries of redundant components in the past, but with the advance of gene editing techniques, it is routine to generate multiplex knockouts. Therefore, progress in addressing many unanswered questions in meristem regulation will speed up in the next decade. For example, the complexity of receptor complexes for recognition of CLE peptides remains to be explored, and *in vivo* localization of CLEs is still missing. So far, only one CLE, ZmFCP1, has been functionally investigated in maize. Additional CLEs and their crosstalk need to be studied. In addition, very little is known about downstream signaling and how the signal is transduced from the membrane to the nucleus. Moreover, it will be interesting to learn more about the interaction between KNOX and CLV-WUS pathways, for example do they share common targets and how do they coordinate? Studies of SAM regulation in maize not only deepen our understanding of basic biological questions, but also enable potential application in agriculture. Our ancestors have successfully selected spontaneous mutations in the key SAM regulators, such as *WUS* and *CLV*, to domesticate wild species into modern cultivars with favorable traits and higher yield [75,76]. Advancing genomic and genome editing technologies may allow us to identify more SAM regulators and precisely fine-tune them to further boost crop yields. Recent work found that CRISPR mutagenesis of tomato *CLV3* cis elements could enhance yield [77••], and engineering of FEA2 and FEA3 by generation of weak alleles increased maize seed production and yield [19••,43••]. All of these examples suggest that the tremendous efforts that have been made toward understanding the SAM development are paying back and could help feed a growing world population.

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