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REVIEW

Out of step: The function of TALE homeodomain transcription factors that regulate shoot meristem maintenance and meristem identity

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Abstract **The indeterminate growth pattern displayed by shoots is mediated by the proper maintenance of the shoot meristem. Meristem maintenance is dependent upon the balance of stem cell perpetuation in the central zone (CZ) and organogenesis in the peripheral zone (PZ). Although the mechanisms that coordinate CZ and PZ function is not understood, meristem cell fate is likely achieved by the spatial interplay between gene regulatory networks and hormone signaling pathways. During shoot maturation, the identity of the shoot meristem as well as the lateral organs are transformed during the vegetative and reproductive transitions. Studies in model plant systems indicate that three amino acid extension (TALE) homeodomain proteins integrate signaling events that transform the identity of the shoot meristem and establish reproductive patterns of growth. This review will highlight the function of TALE homeodomain transcription factors that regulate shoot meristem cell fate and also function with phase specific regulators to maintain shoot meristem identity.**

Keywords shoot development, meristem, flowering, patterning, homeodomain

Shoot development

Plants undergo extensive and elaborate programs of development post-embryonically due to the activity of shoot and root apical meristems (Steeves and Sussex, 1989; Lyndon, 1998). All of the above ground organs originate from shoot meristems, which are subdivided into three functional zones (Bernier, 1988; Steeves and Sussex, 1989; Lyndon, 1998). Stem cells are maintained in the central zone (CZ), which is located at the apical region of the shoot meristem. The peripheral zone (PZ), which surrounds the CZ, acts to buffer the stem cells from the programs of differentiation, which are activated in lateral organs that emerge on the flanks of the shoot meristem. In the PZ, mechanisms that establish positional cues are essential for allocating the appropriate number of cells into leaves and axillary meristems. Cell division in the rib meristem (RM) gives rise to the pith cells of the stem. The activity of the RM plays a fundamental role in meristem morphology, as cytohistological analyses indicate that the RM plays an essential role in regulating the floral evocation (Bernier, 1988, 2011) and bud dormancy and release (van der Schoot and Rinne, 2011). The meristem-organ boundary is also essential for meristem maintenance as it acts to limit programs of differentiation from altering the fate of the cells in the meristem (Aida and Tasaka, 2006). In addition, the lack of cell division at the meristem-organ boundary is essential for the physical separation of leaves and axillary meristems from the SAM.

During plant development, shoots often sustain a period of indeterminate growth, which is dependent on the identity and function of the shoot apical meristem (SAM) (Steeves and Sussex, 1989; Lyndon, 1998). The indeterminate activity of the SAM depends upon the balance of stem cell maintenance and allocation of cells into initiating primordia (Vollbrecht et al., 2000). This hypothesis predicts that a loss of stem cell maintenance and/or mechanism of cell allocation will eliminate and/or dramatically perturb shoot growth. Recent reviews focused on stem cell maintenance and the plant hormones that regulate meristem function and organogenesis have been published (Bleckmann and Simon, 2009; Dodsworth, 2009; Shen and Xu, 2009; Braybrook and Kuhlemeier,

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2010; Vernoux et al., 2010). This review is focused on the function of KNOTTED1-like homeobox (KNOX) and BELL1-like homeodomain (BLH) transcription factors in regulating meristem cell fate and meristem identity during shoot development.

The role of KNOTTED1-Like homeodomain transcription factors in meristem function

Class I KNOX transcription factors regulate meristem function as well the morphology of shoots, flowers and leaves (Hake et al., 2004; Hamant and Pautot, 2010; Hay and Tsiantis, 2010). In maize, *knotted1* (*kn1*) is expressed in CZ, PZ and RM of the shoot meristem; however, transcription of this homeobox gene is inactivated in the incipient leaf primordia (Smith et al., 1992; Jackson et al., 1994). Consistent with this expression pattern, loss of function mutations in *kn1* disrupts meristem function (Kerstetter et al., 1997; Vollbrecht et al., 2000). Interestingly, the severity of the *kn1* phenotype is related to the height of the shoot meristem (Vollbrecht et al., 2000). In this case, loss of *kn1* function in inbred lines with smaller meristems frequently gives rise to plants with a terminal shoot phenotype after the initiation of the coleptile. Cell divisions in the RM play a role in regulating the height of the SAM (Bernier, 1988; Lyndon, 1998). Therefore, shoots with a less active RM may be more dependent upon KNOX function. Analysis of *kn1* phenotype suggested that this homeobox gene specifies meristem cell fate by maintaining meristematic cells in an undifferentiated state (Kerstetter et al., 1997; Vollbrecht et al., 2000). In *Arabidopsis*, the KNOX protein SHOOT MERISTEMLESS (STM) appears to function in an analogous manner as KN1 (Barton, 2010). In plants harboring *stm* null alleles, shoot growth terminates after the production of two partially fused cotyledons (Barton and Poethig, 1993; Long et al., 1996). Both KN1 and STM are expressed in all shoot meristem types, which display indeterminate and determinate patterns of growth (Smith et al., 1992; Jackson et al., 1994; Long et al., 1996).

KNOX proteins such as KN1 and STM appear to maintain meristem cell fate in a number of different ways. First, KN1/STM may act in the PZ to maintain the meristem-organ boundary, which separates the meristem from the developing leaf (Kerstetter et al., 1997; Long and Barton, 1998; Aida et al., 1999; Vollbrecht et al., 2000; Takada et al., 2001). In this light, KN1 and STM act at the meristem-organ boundary to restrict gene expression profiles that promote leaf and organ differentiation. Ectopic expression of KN1 in maize leaf margins results in the reestablishment of the proximal-distal patterning event (Ramirez et al., 2009). The reiteration of this patterning event suggests KN1 regulates the proximal identity of the leaf; therefore, in the absence of KN1 function, leaves fail to form because the proximal boundary is not defined (Ramirez et al., 2009). Experimental studies show that meristem-leaf boundaries are also crucial for the establishment and formation of axillary meristems (Aida and Tasaka, 2006). Analysis of different *stm* alleles indicates that this homeodomain specifies axillary meristems by maintaining meristem-leaf boundaries (Barton and Poethig, 1993; Kanrar et al., 2006; Takano et al., 2010). Therefore, KN1 and STM function at the meristem-leaf boundary to mediate the formation of the axillary meristems. Genetic studies indicate that KN1 and STM regulate meristem integrity and organization. For example, analysis of leaf initiation in different alleles of *stm* suggests that this homeodomain transcription factor regulates the integrity of the central region of the SAM (Endrizzi et al., 1996). Further, STM may regulate CZ function by maintaining a boundary between the CZ and PZ (Clark et al., 1996). Lastly, analysis of the hypomorphic *stm* allele, *gorgon*, suggests that STM also regulates the allocation of cells into initiating organ primordia (Takano et al., 2010). Taken together, KN1 and STM appear to regulate multiple pathways required for specifying meristem cell fate and maintaining meristem function.

Other class I KNOX transcription factors have been characterized and studies in *Arabidopsis* suggest that these homeodomain proteins also contribute to meristem maintenance but to a lesser extent (Hake et al., 2004). In *Arabidopsis*, mutations in *BREVIPEDICELLUS* (*BP*) and *KNOTTED1-like genes from Arabidopsis thaliana 6* (*KNAT6*) enhance weak alleles of *stm*, demonstrating role for these KNOX transcription factors in meristem maintenance (Byrne et al., 2002; Belles-Boix et al., 2006). Interestingly, recent studies indicate that BP regulates inflorescence architecture by repressing *KNAT6* and *KNAT2* in the internode and pedicels (Ragni et al., 2008).

KNOX regulation of gibberellin and cytokinin biosynthesis and signaling

Plant hormones play a fundamental role in meristem function (Shani et al., 2006). Gibberellin (GA) is a plant hormone that regulates seed germination, flowering and cell elongation (Itoh et al., 2008). Experimental studies in several plant species suggest that KNOX proteins regulate meristem function in part by repressing a key GA biosynthetic gene, GA20 oxidase (Sakamoto et al., 2001; Chen et al., 2004; Jasinski et al., 2005; Yanai et al., 2005). In addition, recent studies show that KN1 promotes transcription the GA2 oxidase gene, *ga2ox1*, which may serve to catabolize GA that moves into the shoot meristem via the leaves and stems (Bolduc and Hake, 2009). Thus, according to current models, the repression of GA biosynthesis and activity by KNOX proteins is essential for meristem function. However, experimental studies provide evidence that GA acts as florigenic molecule that moves from the leaves to the shoot meristem to evoke flowering in plants such as *Arabidopsis* and *Lolium* (King and Evans, 2003; Eriksson et al., 2006). In

the shoot meristem, flower specification is controlled by inflorescence meristem identity genes, *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS* (*SOC1*) and *AGAMOUS-LIKE 24* (*AGL24*), which are positively regulated by multiple flowering time pathways including GA (Lee and Lee, 2010). Interestingly, in the absence of the photoperiod florigenic signal, FLOWERING LOCUS T (FT), *stm-10* often initiates inflorescences that fail to form flowers despite that fact that *SOC1* and *AGL24* are expressed in the shoot meristem (Smith et al., 2011). In light of these studies, STM may function with *AGL24-SOC1* to mediate flower specification in response to GA. Therefore, the interplay between KNOX and GA appears to be complex and likely controlled by phase specific meristem identity transcriptional regulators.

Cytokinin (CK) plays a fundamental role in regulating meristem formation, integrity and maintenance (Kyozuka, 2007). Experimental evidence suggests that KNOX and CKs form a positive feedback loop, which is required for meristem function (Shani et al., 2006). Consistent with this model, growing a null allele of *stm* in the presence of CK partially rescues the terminal shoot phenotype (Yanai et al., 2005). In addition, a mutation in the CK receptor called *WOODEN LEG* (*WOL*) enhances a weak allele of *stm* (Jasinski et al., 2005). At the molecular level, STM positively regulates CK biosynthesis by activating *ISOPENTENYL TRANSFERASE 7* (*IPT7*) (Jasinski et al., 2005; Yanai et al., 2005). However, at the same time, STM also appears to activate *ARABIDOPSIS RESPONSE REGULATOR 5* (*ARR5*), a negative regulator of CK signaling (Jasinski et al., 2005; Yanai et al., 2005). Although the regions in the SAM in which STM regulates *IPT7* and *ARR5* are not known, STM and related KNOX proteins may regulate CK signaling at multiple levels to ensure meristem function is properly maintained.

Regulation of meristem function by association of KNOX proteins with BELL1-like homeodomain proteins

Molecular studies in several plant species indicate that KNOX proteins selectively associate with specific members of the BELL1-like homeodomain (BLH) proteins in plants (Hake et al., 2004; Hamant and Pautot, 2010). At the molecular level, biochemical studies indicate that the formation of KNOX-BLH complexes increases the DNA binding affinity for the TGACAGG/CT DNA-motif (Smith et al., 2002). KNOX and BLH proteins interact through large evolutionarily conserved domains in the N terminus of the proteins called the MEINOX domain and BELL or MID domain, respectively (Hake et al., 2004; Mukherjee et al., 2009).

The *Arabidopsis* genome contains 13 *BLH* genes and at least three of these homeodomain transcription factors regulate meristem cell fate and identity (Roeder et al., 2003; Smith et al., 2004; Mukherjee et al., 2009). Loss of function mutations in *PENNYWISE* (*PNY*: also known as *BELLRINGER*, *REPLUMLESS* and *VAAMANA*) disrupt internode and fruit patterning during reproductive development (Byrne et al., 2003; Roeder et al., 2003; Smith and Hake, 2003; Bhatt et al., 2004). In contrast to *pny*, shoot development is not altered in *pound-foolish* (*pnf*), the paralog of *PNY*. Both PNY and PNF are expressed in vegetative, inflorescence and floral meristems (Smith et al., 2004). Although meristem maintenance is not visibly altered in *pny* and *pnf* single mutants, the shoot meristem of *pny pnf* plants often terminates after the production of 3-4 leaves (Smith et al., 2004; Rutjens et al., 2009). In addition, the indeterminate behavior of inflorescence meristem is reduced in *pny PNF/pnf* plants (Smith et al., 2004). Recent studies indicate that PNY and PNF control the integrity of the shoot meristem by maintaining a boundary between the CZ and PZ (Ung et al., 2011). In addition, PNY and PNF regulate the meristem-leaf boundary, as there is a significant increase in the number of meristem cells allocated into leaf primordia in *pny pnf* plants (Smith et al., 2004; Ung et al., 2011). Finally, PNY and PNF maintain the boundary between the inflorescence and floral meristem, since the inflorescence shoots of *pny PNF/pnf* plants display fusions of pedicels to the main stem (Smith et al., 2004). The fact that PNY and PNF associate with STM is further evidence that these homeodomain proteins regulate meristem cell fate (Byrne et al., 2003; Bhatt et al., 2004; Kanrar et al., 2006; Rutjens et al., 2009). Genetic studies show that combining mutations in *pny* with weak alleles of *stm*, including *stm-11*, results in terminal shoot phenotype after the cotyledons are produced (Byrne et al., 2003; Bhatt et al., 2004; Kanrar et al., 2006). Lastly, the reduction in meristem indeterminacy displayed in *pny PNF/pnf* inflorescence shoots is greatly enhanced in *pny PNF/pnf STM/stm-11* shoots (Kanrar et al., 2006). Therefore, we propose that PNY-STM and PNF-STM regulate meristem integrity and function by maintaining boundaries in the shoot meristem.

The *ARABIDOPSIS THALIANA HOMEOBOX 1* (*ATH1*) encodes a BLH homeodomain that is structurally and phylogenetically distinct from PNY and PNF (Mukherjee et al., 2009). During vegetative growth, *ATH1* is expressed in the shoot meristem and developing leaves (Proveniers et al., 2007; Gómez-Mena and Sablowski, 2008). In contrast to PNY and PNF, transcript levels for *ATH1* rapidly decline in the shoot meristem upon floral induction (Schmid et al., 2003; Proveniers et al., 2007). During vegetative growth, ATH1 functions to maintain the basal boundary between the stem, meristem and leaf (Gómez-Mena and Sablowski, 2008). Moreover, a role for ATH1 in meristem maintenance is demonstrated through its physical interaction with STM and the fact that *stm-11 ath1* mutants produce a terminal shoot phenotype after the initiation of cotyledons (Rutjens et al., 2009). Genetic studies show that *ath1* also enhances the *pny pnf* terminal shoot phenotype, such that vegetative shoots terminate after two leaves are produced (Rutjens et al., 2009). The fact that *pny pnf ath1* did not produce a phenotype similar

to null alleles of *stm* suggests that other BLH proteins regulate meristem maintenance in association with STM and/or other KNOX partners.

Vegetative development is mediated by the interplay between MADS-box and homeodomain transcription factors

Plants maintain a vegetative growth pattern as a means to build up energy reserves needed to initiate and sustain reproductive growth. In *Arabidopsis*, specific members of the MADS-box transcription factors are expressed in temporal and/or spatial manner and function in a cooperative manner to regulate distinct phases of plant development (Becker and Theissen, 2003). During early stages of shoot development, the MADS-box protein FLOWERING LOCUS C (FLC) regulates the vegetative phase change and represses flowering in winter annual ecotypes prior to vernalization (Amasino, 2010; Crevillén and Dean, 2011; Willmann and Poethig, 2011). *FLC* is positively regulated by FRIGIDA (FRI) and negatively regulated by vernalization in an epigenetic manner (Amasino, 2010; Crevillén and Dean, 2011). FLC promotes vegetative growth in part by negatively regulating key flowering time genes, including the florigenic signal, *FT* and another MADS-box proteins *SOC1* (Helliwell et al., 2006; Hepworth et al., 2002; Searle et al., 2006).

As stated above, *ATH1* is expressed in vegetative shoot meristems and leaf primordia but downregulated upon flowering (Proveniers et al., 2007). The temporal expression pattern of *ATH1* displays a similar transcript profile for floral repressors such as *FLC* (Michaels and Amasino, 1999; Proveniers et al., 2007). A recent study showed that ectopic *ATH1* delays flowering in the *Arabidopsis* C24 ecotype (Proveniers et al., 2007). However, after vernalization, the shoots of the C24 plants expressing high levels of ATH1 are induced to flower in long-day photoinductive conditions. In contrast, expression of antisense *ATH1* transcripts results in an early flowering phenotype. At the molecular level, ATH1 delays flowering by positively regulating *FLC* in a FRI dependent manner (Proveniers et al., 2007) (Fig. 1). Interestingly, *Lolium perenne* plants expressing high levels of *ATH1* displays a late flowering phenotype indicating that the function of this homeodomain protein is conserved in dicot and moncots (van der Valk et al., 2004). In monocots, such as wheat and barley, VERNALIZATION2 (VRN2) encodes a zinc finger protein, which acts as a floral repressor with a similar function as FLC in *Arabidopsis* (Yan et al., 2004; Dubcovsky et al., 2006; Trevaskis et al., 2006). Although *Arabidopsis* and winter cereals utilize distinct floral repressors, FLC vs. VRN2, the function of ATH1 appears to be conserved. Taken together, ATH1 not only acts to regulate meristem maintenance, but this key vegetative specific BLH protein functions to specify vegetative meristem identity.

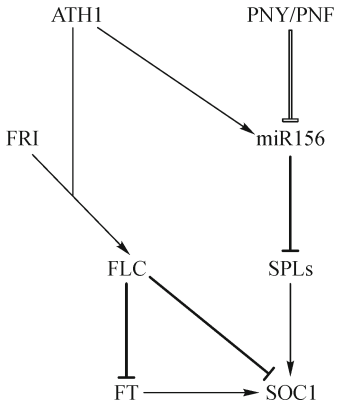

Figure 1 The role of ATH1 and PNY/PNF in regulating vegetative meristem identity. In this model, we propose that *ATH1* and *PNY/PNF* act in an antagonistic manner to regulate the temporal levels of *miR156*. In addition, ATH1 promotes vegetative shoot identity by activating *FLC* in a FR1 dependent manner. Positive regulation of *miR156* and *FLC* by ATH1 results in the repression *FT* and *SPL* expression. Ultimately, inflorescence identity is repressed in part through the inactivation of *SOC1* expression. The solid line depicts known regulatory events while the white filled line indicates a proposed regulectory event.

Networks that mediate the floral transition and flower specification in *Arabidopsis*

In *Arabidopsis*, FT acts as the long-day photoperiodic signal that moves from the leaves to the SAM to evoke flowering and promote flower specification (Amasino, 2010; Fornara et al., 2010). At the molecular level, FT induces flowering in part thought its association with the b-ZIP transcription factor, FD (Abe et al., 2005; Wigge et al., 2005). The tomato and rice FT homologs, SINGLE FLOWER TRUSS and Heading date 3a (Hda3), have been shown to associate with 14-3-3 proteins (Pnueli et al., 2001; Purwestri et al., 2009; Taoka et al., 2011). A recent study in rice suggests that 14-3-3 protein called GF14c acts as a molecular scaffold that bridges Hda3 with the *Oryza sativa* FD (Taoka et al., 2011). Based on this study, it is likely that the formation of FT-GF14c-FD complex, which has been termed the florigen activation complex (FAC), acts to regulate gene expression in the shoot apical meristem. Therefore, the FAC somehow mediates the floral transition by activating *SOC1* and a related MADS-box protein, *FRUITFULL* (*FUL*) in order to promote inflorescence meristem identity, in *Arabidopsis* (Schmid et al., 2003; Abe et al., 2005; Teper-Bamnolker and Samach, 2005; Wigge et al., 2005; Searle et al., 2006; Wang et al., 2009). Experimental studies suggest that TWIN SISTER OF FT (TSF), a FT-related protein, acts redundantly with FT to regulate reproductive development (Jang et al., 2009). SOC1 forms a MADS-box complex with AGL24 which is also upregulated in the SAM upon floral induction (Yu et al., 2002; Michaels et al., 2003; de Folter et al., 2005; Lee et al., 2008). Molecular studies show that FUL interacts with SOC1 and AGL24 indicating

that these three MADS-box proteins form a higher order complex to specify inflorescence meristem identity (de Folter et al., 2005) (Fig. 2). A subset of the *microRNA156* (*miR156*) targeted SQUAMOSA PROMOTER BINDING PROTEIN-LIKE (SPL) transcription factors define an endogenous flowering time pathway that appears to act both downstream and in parallel with FT (Wang et al., 2009). Further, SPLs promote the floral transition by activating inflorescence meristem identity genes, *SOC1* and *FUL* (Wang et al., 2009; Yamaguchi et al., 2009). In conclusion, both the photoperiodic and endogenous flowering time pathways converge on *SOC1* and *FUL* to mediate the floral transition and specify inflorescence meristem identity (Fig. 2).

In a recent review, it was proposed that the floral stimulus is a two-component system that involves the synthesis and movement of FT/TSF and cytokinin (CK) from the leaves to the SAM (Bernier, 2011). Recent studies have begun to shed light on the relationship between CK and the gene regulatory networks, which promote floral evocation at the SAM. In *Arabidopsis* and *Sinapis*, application of CK induces *SOC1* expression in the SAM (Bonhomme et al., 2000; Bernier, 2011; D'Aloia et al., 2011). Experimental studies show that applications of CK promotes flowering by activating *TSF* in the leaves of *Arabidopsis* (D'Aloia et al., 2011). Further, CK promotes flowering in a TSF dependent manner indicating that activation of *SOC1* by CK may be mediated by TSF. Taken together, CK appears to play a fundamental role in regulating florigen in the leaves and the mitotic activation event during floral evocation (Bernier, 2011; D'Aloia et al., 2011).

In *Arabidopsis*, flowers are specified on the flanks of the inflorescence meristem by the activity of LEAFY (LFY), an early flower meristem identity factor. Studies in *Arabidopsis* and Petunia, suggest that LFY regulates late flowering meristem identity genes in association with the F-box protein UNUSUAL FLORAL ORGANS (UFO)/DOUBLE TOP (DOT) (Chae et al., 2008; Souer et al., 2008). To date, the biochemical significance of UFO/DOT in regulating gene expression is not known. The initial upregulation of *LFY* is observed in a small group of cells in the PZ of the SAM, before any visible signs of flower development (Weigel et al., 1992). Once established, LFY activates a number of late flower meristem identity genes including *APETALA1* (*AP1*), a MADS-box gene (Parcy et al., 1998; Wagner et al., 1999; William et al., 2004; Saddic et al., 2006; Winter et al., 2011). The expression of *AP1* is first detected in the cells of the floral buttress on the flanks of the inflorescence meristem (Gustafson-Brown et al., 1994). Regulation of *LFY* is quite complex as this gene is activated and maintained by inflorescence and late flower meristem identity MADS-box transcription factors, respectively. Based on recent studies, it is likely that the initial upregulation of *LFY* in the PZ of the inflorescence meristem is directly mediated by the SOC1-AGL24 complex (Lee et al., 2008; Liu et al., 2008). In addition, genetic evidence suggests that FUL also participates in the activation of *LFY* indicating that this MADs-box protein is a component of the SOC1-AGL24 complex (Ferrándiz et al., 2000). SOC1 and FUL do not appear to be involved in the maintenance of *LFY* expression, since transcripts for these MADS-box genes fail to accumulate in the cells of the floral buttress (Mandel and Yanofsky, 1995; Samach et al., 2000; Yu et al., 2002; Michaels et al., 2003). In

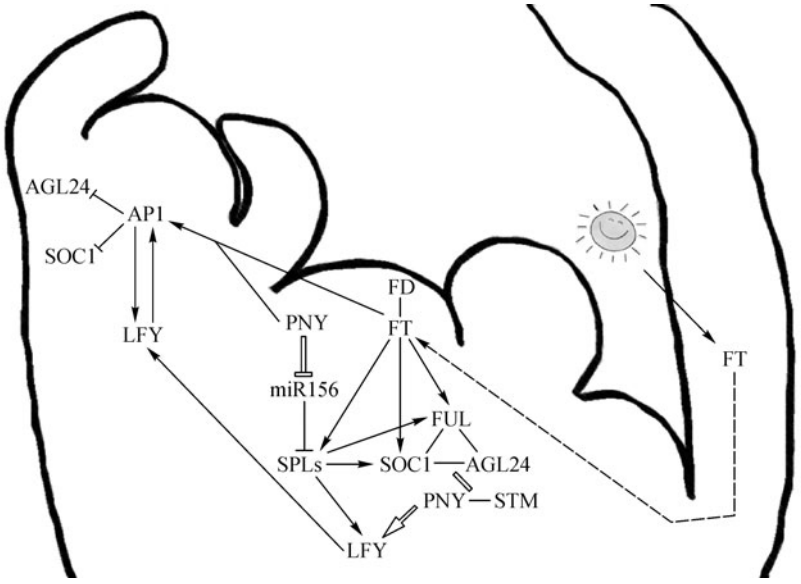

Figure 2 The role of PNY and PNF in regulating flower specification. Based on this model, we propose that PNY (as well as PNF) acts to regulate flower specification by down-regulating *miR156*, which allows for optimal *SPL* gene expression. In addition, PNY-STM (as well as PNF-STM) heterodimer may associate with SOC1-AGL24-FUL to promote the upregulation of *LFY*. Lastly, the FT activates *AP1* and *SPLs* in a PNY (as well as PNF) dependent manner. The solid lines and arrows depict known interactions and regulatory events while the white filled lines and arrows suggest possible interactions and regulatory events.

contrast to SOC1 and FUL, *AGL24* appears to play a transient role maintaining flower meristem identity together with *AP1* and *SHORT VEGETATIVE PHASE* (Gregis et al., 2008). Genetic and molecular studies indicate that a positive feedback loop between LFY and AP1 maintains flower meristem identity (Bowman et al., 1993; Schultz and Haughn, 1993; Liljegren et al., 1999). Therefore, AP1 acts to sustain flower meristem identity by maintaining *LFY* expression. In addition, AP1 represses inflorescence meristem identity by negatively regulating *SOC1*, *FUL* and *AGL24* (Yu et al., 2004; Liu et al., 2007; Gregis et al., 2008). AP1 is also directly activated by FT-FD complex, which acts in parallel with LFY to specify floral meristem identity (Abe et al., 2005; Wigge et al., 2005). A complete understanding of FT function appears to be incomplete as loss of function mutations in *fd*, fail to suppress the early flowering phenotype associated with *Arabidopsis* plants overexpressing *FT* (Abe et al., 2005; Teper-Bamnolker and Samach, 2005). Therefore, GF14c may act to bridge other meristem functioning transcription factors with FT in order to mediate the floral transition and flower specification.

The role KNOX and BLH transcription factors in regulating reproductive meristem identity

KNOX proteins, such as STM, function in the SAM to specify meristem cell fate (Hake et al., 2004; Scofield and Murray, 2006; Hay and Tsiantis, 2009). In the absence of STM, the cells in the SAM terminally differentiate (Barton and Poethig, 1993; Long et al., 1996). During reproductive development, weak *stm* alleles, display defects in inflorescence patterning events such as axillary meristem formation, flower meristem identity and internode development (Clark et al., 1996; Endrizzi et al., 1996; Kanrar et al., 2006). Given that STM is an essential regulator of meristem cell fate, the defects in reproductive patterning events may simply result from a decrease in meristem function. However, genetic studies indicate that FT and STM function together to regulate axillary meristem formation and flower meristem identity (Smith et al., 2011). In the *stm-10 ft-2* non-flower producing inflorescences, both *SOC1* and *AGL24* are expressed in the SAM, while the levels of *LFY* are low. This observation indicates that the function of SOC1 and AGL24 may be partially dependent upon STM for specifying flower meristem identity. Taken together, STM may function to integrate gene regulatory networks that specify meristem formation and identity to ensure that the function of the shoot meristem is maintained during each phase of development. It should also be pointed out that the levels of FT are crucial for regulating meristem determinacy and dormancy (Shalit et al., 2009). Therefore, meristem identity proteins may also function to regulate and modulate basic meristem function.

One of the intriguing features of *pny pnf* plants is the inability of the mature shoots to produce axillary meristems, which give rise to coflorescences and flowers (Smith et al., 2004; Rutjens et al., 2009). It has been postulated that PNY and PNF function to establish positional cues in subset of cells in PZ that develop into axillary meristems (Kanrar et al., 2008). Therefore, in the absence of PNY and PNF function, meristem cells allocated during organogenesis are unable to reorganize in order to form axillary meristems. During inflorescence development, it is well known that LFY and FT function to specify flower meristem identity (Kobayashi and Weigel, 2007); however, analysis of *lfy ft* inflorescences also indicates that these proteins cooperatively act to specify axillary meristems that develop into coflorescence shoots (Ruiz-García et al., 1997). Interestingly, the empty cauline leaf axil phenotype is also observed in the inflorescences of *pny lfy* and *pny ft* plants (Kanrar et al., 2008). Moreover, the decrease in the specification of axillary meristems in the axils of cauline leaves is further enhanced in *pny ft PNF/pnf* and *pny lfy PNF/pnf* plants. Therefore, FT and LFY appear to perform basic function with PNY and PNF in the formation of axillary meristems that give rise to coflorescence shoots and flowers.

PNY and possibly PNF also specify flower meristem identity. The inflorescences of *pny lfy* plants display complete conversion of flowers into shoots, producing reproductive shoots that are phenotypically similar to *lfy ft* and *lfy fd* (Kanrar et al., 2008). The fact that *pny ft* inflorescences displayed a minor conversion of flowers into shoots suggests that these proteins function in the same pathway to specify flower meristem identity (Kanrar et al., 2008). Consistent with this hypothesis, genetic studies show that FT is dependent upon the function of PNY and PNF. This is supported by the fact that flower formation is severely attenuated in *pny pnf* plants ectopically expressing *FT* (Kanrar et al., 2008). A molecular understanding that describes the interplay between FT and STM-PNY/STM-PNF will shed light on how these proteins regulate the specification of axillary and flower meristems, and possibly meristem determinacy.

In addition to promoting the floral transition, *miR156* targeted SPLs also function to directly activate *LFY* and *AP1* (Yamaguchi et al., 2009). Experimental studies suggest that the ability of FT to regulate the *miR156* targeted *SPLs* is dependent upon PNY and PNF (Lal et al., 2011). Furthermore, PNY and PNF also are required for the downregulation of *miR156*, since the levels of this microRNA fail to decline in the mature shoots of *pny pnf*. Based on biochemical and sequence alignment studies, KNOX and BLH proteins associate with similar DNA binding motifs, TGACAG/CT (Hake et al., 2004). The TGACAG sequence is conserved in nearly all *miR156* molecules that have been identified in plants (Lal et al., 2011). Therefore, PNY and PNF may directly bind to all *miR156* loci to repress their transcription of these microRNAs. As stated above, ATH1 promotes vegetative identity by activating *FLC* (Proveniers et al.,

2007). Interestingly, plants with increased levels of *FLC* display an extended juvenile phase (Martínez-Zapater et al., 1995; Telfer et al., 1997; Lee et al., 2000; Willmann and Poethig, 2011). Thus, ATH1 may act to promote vegetative growth and juvenile identity by positively regulating *FLC* and possibly *miR156*. Interestingly, loss of ATH1 function in *pny pnf* partially restores reproductive development (Rutjens et al., 2009). Although the levels of *miR156* have not been examined in *pny pnf ath1* shoots, reducing the activity of this microRNA in *pny pnf* plants results in the production of cauline leaf bearing inflorescences similar to *pny pnf ath1* (Lal, S. and Smith, H.M, unpublished data). Therefore, it would be interesting to know if the ability of *pny pnf ath1* plants to produce inflorescence shoots is due to a decrease in the levels of *miR156*. Taken together, the levels of *miR156* may be regulated by the binding of PNY/PNF and ATH1 to the TGACAG sequence in *miR156*. In this context, the ratios of PNY/PNF and ATH1 in meristem cells may coordinate the temporal levels of *miR156* during plant development.

In animals and yeast, homeodomain proteins function as cofactors for transcriptional complexes that regulate cell fate determination (Messenguy and Dubois, 2003; Moens and Selleri, 2006). In light of these studies, KNOX-BLH heterodimers may also function as cofactors for transcriptional complexes that control meristem cell fate and meristem identity. Recent studies indicate that FT controls reproductive development independent of FD, possibly by interacting with other meristem functioning transcription factors (Abe et al., 2005; Teper-Bamnolker and Samach, 2005). Genetic analyses show that FT functions with STM during inflorescence development (Smith et al., 2011). Further, the floral meristem specification activity of FT is dependent on PNY and PNF (Kanrar et al., 2008). Thus, FT may regulate floral meristem identity and meristem determinacy by directly interacting with the STM-PNY/PNF heterodimer or a transcription factor that associates with this KNOX-BLH complex. Interaction between homeodomain and MADS-box transcription factors have been described in yeast and animals (Messenguy and Dubois, 2003). In *Arabidopsis*, experimental evidence demonstrates that the founding member of the BLH family, BELL1, associates with ovule specific MADS-box proteins, AGAMOUS and SEPALLATA3 to specify ovule identity (Brambilla et al., 2007). The association of homeodomain and MADS-box transcription factors may be evolutionarily conserved in animals, yeast and plants. Therefore, individual KNOX or BLH proteins as well as KNOX-BLH heterodimers may serve as cofactors for MADS-box complexes in plants. In accordance to this model, PNY and PNF or possibly STM-PNY/PNF heterodimers may associate with SOC1-AGL24-FUL complexes to promote the initial upregulation of LFY in the PZ of the inflorescence meristem. Attempts to detect interactions between PNY/PNF/STM and SOC1/FUL/AGL24 have not been successful (unpublished data). Therefore, it may be possible that the association of STM-PNY/PNF with SOC1-AGL24-FUL is more complex in that the interaction may require a molecular scaffold, such as DNA or a nucleoplasmic structure. In addition, little is known about post-translational modifications of KNOX and BLH proteins, which may also serve to stabilize the association of these transcription factors with the inflorescence meristem identity complexes. Future studies are aimed at determining the link between PNY/PNF-STM and the regulatory proteins that control meristem identity.

Conclusions

In conclusion, STM-PNY/PNF complexes appear to regulate shoot meristem maintenance and integrity by controlling CZ-PZ, meristem-leaf, and inflorescence-floral meristem boundary. Experimental evidence indicates that STM-ATH1 complexes maintain the boundary between the meristem, stem and leaf. Therefore, TALE homeodomain complexes appear to play a major role in meristem maintenance and integrity by controlling boundaries within the meristem and between the meristem and lateral organs, axillary meristems and the stem. Genetic studies suggest that STM-ATH1 and STM-PNY/PNF complexes also control meristem identity by possibly interacting with and/or regulating phase specific transcriptional regulators. In addition, these TALE homeodomain complexes may act as molecular beacons that target phase specific transcriptional regulators to the appropriate loci in the genome. The vegetative phase change may be regulated in part by PNY/PNF and ATH1, which function in an antagonistic manner to modulate the levels of *miR156*. Experimental evidence indicates that KNOX proteins control meristem maintenance by regulating the biosynthesis and activity of CK and GA. However, this regulatory circuit may be more complex given that CK and GA act in the shoot meristem to promote floral evocation. Understanding how KNOX-BLH complexes coordinate meristem maintenance and meristem identity can be in part addressed by determining the biochemical function KNOX-BLH complexes and identifying the target genes regulated by these complexes in phase specific manner.

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