International Journal of Plant Developmental Biology ©2007 Global Science Books

KNOXing on the *BELL*: *TALE* Homeobox Genes and Meristem Activity

Laura Ragni • Elisabeth Truernit • Véronique Pautot

Laboratoire de Biologie Cellulaire, IJPB, Institut National de la Recherche Agronomique, Route de St Cyr, 78026 Versailles cedex, France

Corresponding author: * **pautot@versailles.inra.fr**

ABSTRACT

All plant organs are derived from meristems. The shoot apical meristem (SAM) produces the aerial part of the plant. It has two main functions: the maintenance of a group of stem cells at the center of the meristem and the initiation of organs at its periphery. The organs are initiated in a regular spatial pattern, referred to as phyllotaxy, and are separated from the surrounding tissue by a boundary domain. The KNOTTED-like homeobox (KNOX) family of transcription factors plays a key role in the control of SAM activity. These proteins belong to the three amino acid loop extension (TALE) homeodomain superclass and form heterodimers with other TALE proteins belonging to the BEL1-like (BELL) family. The KNOX proteins regulate the different activities of the SAM. They control SAM maintenance, boundary establishment, the correct patterning of organ initiation and the development of axillary meristems. They exert their effects through the regulation of several hormonal pathways. KNOX proteins repress gibberellin (GA) biosynthesis and activate cytokinin (CK) synthesis and signaling. In addition to their role in the SAM, they contribute to leaf form diversity. In plants with simple leaves, *KNOX* genes are expressed in the SAM and downregulated in leaf primordia, whereas in plants with dissected leaves their expression is reactivated in leaves.

Keywords: *Arabidopsis*, *BELL* (*BEL1*-like) genes, organ boundaries, *KNOX* (*KNOTTED*-like homeobox) genes, shoot apical meristem (SAM)
Abbreviations: ***BELL***, *BEL1*-like; **CK**, cytokinin; **GA**, gibberellin; ***KNAT***, *KNOTTED*-like from *Arabidopsis thaliana*; **TALE**, three amino acid loop extension; **SAM**, shoot apical meristem

CONTENTS

INTRODUCTION

Homeoproteins are a family of transcription factors that share a homologous DNA-binding domain, the homeodomain (Burglin 1997). They were first discovered in the fruitfly *Drosophila melanogaster*, in which their inactivation leads to homeotic mutations (McGinnis *et al*. 1984). Homeoproteins were subsequently found in animals, in many angiosperms, gymnosperms, ferns, mosses, algae and fungi. Some members of this family are key regulators of the body plan, as they are required to specify organ identity in animals, including nematodes, fruitflies and vertebrates (McGinnis and Krumlauf 1992; Burglin 1994). Plant homeobox genes, unlike their counterparts in animals, are generally not associated with organ identity. The BEL1 protein is an exception to this rule: it controls ovule integument identity (Reiser *et al*. 1995). The plant homeotic genes belong to another family of transcription factors, the MADS-box gene family (Rijpkema *et al*. 2007). Plant homeobox genes have been classified into several families and have been shown to control diverse developmental processes, including the maintenance of stem cells, ovule development, leaf polarity, and trichome elongation (Ito *et al*. 2002). In this review, we focus on the first homeoprotein family identified in plants, the KNOX family, and its role in meristem activity.

THE SHOOT APICAL MERISTEM

Plant growth results from the activity of groups of cells called meristems (for review see Traas and Vernoux 2002). The shoot apical meristem, located at the tip of the shoot,

Received: 6 March, 2007. Accepted: 16 April, 2007.

Invited Mini-Review

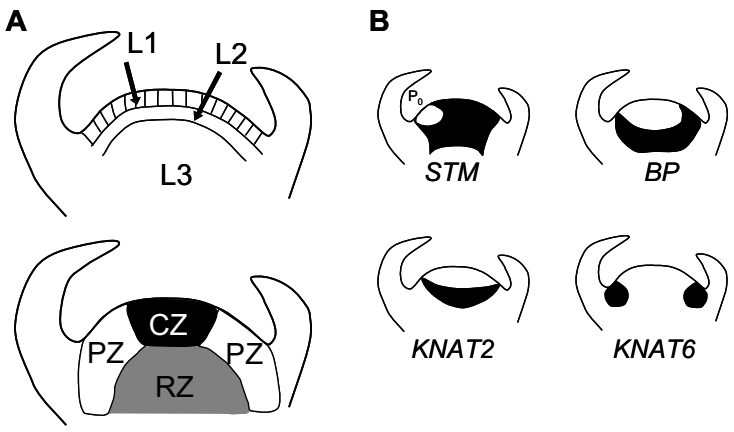

Fig. 1 Organization of the shoot apical meristem and expression of *KNOX* genes in *Arabidopsis*. (**A**) The SAM can be divided into a central zone (CZ), a rib zone (RZ) and a peripheral zone (PZ). These zones are superimposed on an organization of layers (L1 to L3). (**B**) Domains of expression (shown in black) of the *KNAT* class I genes *STM*, *BP/KNAT1*, *KNAT6*, and *KNAT2* in the SAM.

produces the aerial parts of the plant. It is established during embryogenesis and dictates the architecture of the plant, as it is responsible for initiating leaves, internodes, axillary meristems and flowers. The plant body consists of repeating units called phytomers, each comprising a stem fragment (internode) and one or several organs with a meristem in its axil (node). In most dicots, the SAM is organized into three distinct layers (**Fig. 1A**). The use of chimeric lines demonstrated that the L1 layer forms the epidermis whereas the L2 and L3 layers provide cells for the inner part of the organs. Intercellular trafficking of signaling molecules through the plasmodesmata within and between layers coordinates SAM function. The SAM can also be divided into distinct zones with specific functions, superimposed on the layered organization. It contains a population of slowly dividing stem cells located in the central region of the meristem. These cells are involved in SAM maintenance and provide cells for the peripheral and rib zones in which cell differentiation occurs. The rib zone contributes to stem formation, whereas the peripheral zone produces lateral organs. The initiation of an organ is accompanied by the creation of a boundary domain that separates the organ from the surrounding tissue (for review see Aida and Tasaka 2006). Organs are initiated successively on the flanks of the SAM in a regular pattern, referred to as phyllotaxy. In *Arabidopsis*, the organs are initiated in a spiral pattern, with an angle of divergence between successive primordia of about 137.5° (Peaucelle *et al*. 2007). The balance between the allocation of cells to the developing primordia and the perpetuation of pluripotent cells in the central zone maintains the SAM constant in size (Laufs *et al*. 1998).

THE *KNAT* (FOR *KNOTTED*-LIKE FROM *ARABIDOPSIS THALIANA*) FAMILY

The *KNOX* genes play a critical role in controlling meristem activity. These genes encode homeodomain transcription factors of the three amino acid loop extension (TALE) superclass. These proteins are conserved among eukaryotes and are characterized by a three-amino acid extension to the loop connecting the first and second helices of the homeodomain (Burglin 1997). *KNOX* genes can be divided into two classes based on sequence similarity within the homedomain, the positioning of introns and expression patterns (Hake *et al*. 2004). Class I contains genes expressed mainly in the shoot meristem whereas class II genes are more widely expressed. In *Arabidopsis*, the class II genes are *KNAT3*, *KNAT4*, *KNAT5* and *KNAT7*. Their function remains unclear as loss-of-function and overexpression mutants for *KNAT3*, *KNAT4* and *KNAT5* have wild-type phenotypes (Serikawa and Zambryski 1997; Truernit *et al*. 2006). However, the regulated expression of these genes in the root suggests that these genes play a role in root development (Truernit *et al*. 2006). To date, *KNAT7* is the only class II member for which a function has been proposed: phenotypic mutant analysis and transcriptional data have indicated that KNAT7 is involved in xylem formation (Brown *et al*. 2005). The *Arabidopsis* class I genes are *SHOOT MERISTEMLESS* (*STM*), *BREVIPEDICELLUS* (*BP*)/*KNAT1*, *KNAT2* and *KNAT6*. *STM* is expressed in the dome of the meristem, whereas *KNAT1* and *KNAT2* are expressed in the peripheral zone, and *KNAT6* is expressed in the boundary between the meristem and organs (Lincoln *et al*. 1994; Dockx *et al*. 1995; Long *et al*. 1996; Belles-Boix *et al*. 2006). None of these genes is expressed in the regions giving rise to leaf primordia (**Fig. 1B**).

MOVEMENT OF KNOX PROTEINS

The pattern of KNOX mRNA accumulation does not always match protein localization. Some KNOX proteins are able to move from cell-to-cell. This was first discovered when analyzing a dominant mutation of the maize homeobox gene *knotted1* (*kn1*). A signal originating from the internal layers was found to induce knots in the epidermis, indicating that *kn1* acts non-autonomously in maize (Hake and Freeling 1986). A comparison of the localization of KN1 protein and *kn1* RNA confirmed this observation. The protein was found in all layers of the SAM, whereas *kn1* mRNA was not detected in L1 (Jackson and Hake 1994). Microinjection and graft experiments subsequently showed that the KN1 protein could move through the plasmodesmata and transport its own mRNA (Lucas *et al*. 1995). Further experiments showed that KN1 trafficking is regulated during development. KN1 protein moves in both directions in the SAM, whereas it moves only from the mesophyll layers to the epidermal layer in leaves (Kim *et al*. 2002). Complementation experiments have shown that KNOX proteins differ in their trafficking ability. Movement was observed for STM and BP, although BP was less mobile, but not for KNAT2 and KNAT6 (Kim *et al*. 2002, 2005). Finally, the homeodomain has been shown to be necessary and sufficient for intercellular protein and mRNA trafficking (Kim *et al*. 2005). The trafficking of KNOX proteins probably establishes gradients essential to their function in the SAM (Jackson 2002).

KNAT GENE FUNCTION

SHOOT MERISTEMLESS is essential for meristem initiation during embryogenesis and meristem maintenance during post-embryonic development (Clark *et al*. 1996; Endrizzi *et al*. 1996; Long *et al*. 1996). Strong alleles of *stm* mutants fail to form a meristem and to produce lateral organs. In addition to its role in the SAM, *STM* contributes to organ separation, as *stm* strong alleles show a fusion of the cotyledon petioles (Endrizzi *et al*. 1996). Phyllotaxy defects were described in weak alleles of *stm*. *Stm-2* seedlings have a single leaf primordium and no shoot meristem, indicating that the meristematic cells have been consumed by the formation of the sole primordium. After embryogenesis, *stm-2* mutants form axillary meristems that give rise to primordia with an aberrant spatial organization. However, these defects may result from the abnormal structure of the

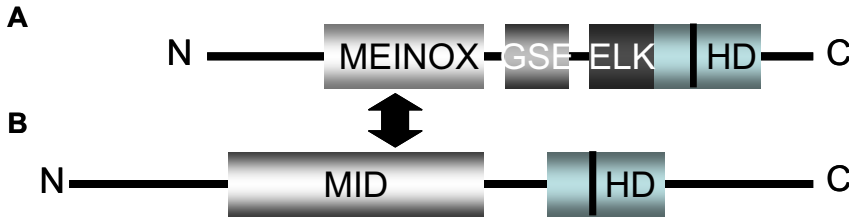

Fig. 2 Schematic representation of KNOX and BELL protein structures. (**A**) KNOX proteins contain a MEINOX domain, a GSE domain, an ELK domain and a TALE homedomain. (**B**) BELL proteins contain a MID domain and a TALE homeodomain.

SAM and are probably indirect. The *stm-2* inflorescence terminates prematurely in fused organs (Endrizzi *et al*. 1996). Thus, STM is primarily involved in SAM and boundary maintenance.

BREVIPEDICELLUS (*BP*)/*KNAT1* primarily plays a role in internode development, as *bp* mutants have short internodes and pedicels, bends at nodes and downward-oriented flowers and siliques (Douglas *et al*. 2002; Venglat *et al*. 2002). The reduced length of internodes and pedicels results from defects in both cell division and cell expansion (Douglas *et al*. 2002). In addition to their smaller size, *bp* inflorescences have stripes of achlorophyllous tissue in internodes, and abnormal vascular differentiation in internodes and pedicels. *BP* was subsequently shown to regulate the lignin biosynthesis pathway during internode development, preventing the premature accumulation of lignin (Mele *et al*. 2003). A role for *BP* in the promotion of stem growth is consistent with its expression in the stem cortex. In addition to its role in inflorescence differentiation, *BP* is redundant with *STM* in the SAM, as it reduces the meristematic potential of the weak *stm-2* allele (Byrne *et al*. 2002).

KNAT2 and *KNAT6* are the most closely related members of the *KNAT* family. *Knat2* and *knat6* single and double mutants show no abnormal phenotype (Belles-Boix *et al*. 2006). Genetic analysis has shown that *KNAT6* plays a redundant role with *STM* in meristem maintenance and organ separation (Belles-Boix *et al*. 2006). *KNAT6* inactivation abolishes the residual meristematic activity of *stm-2*. *KNAT6* makes a more substantial contribution to meristem maintenance than *BP*. The *knat6 stm* double mutant exhibits a fusion of the cotyledons that extends to the blade, indicating a specific role for *KNAT6* in organ separation. This role is consistent with *KNAT6* expression in the boundary domain (Belles-Boix *et al*. 2006). The role of *KNAT2* in the SAM remains unclear. *KNAT2* inactivation does not aggravate the phenotype of *stm* mutants or *knat6 stm* double mutants (Belles-Boix *et al*. 2006).

Loss-of-function mutants of *KNAT* class I genes show defects in meristem maintenance or meristem activity. Conversely, the ectopic expression of *KNAT* class I genes leads to the maintenance of an indeterminate state in various tissues. *KNOX* overexpression inhibits leaf differentiation, leads to the formation of lobes and, in the most severe cases, to the production of ectopic meristems (Sinha *et al*. 1993; Chuck *et al*. 1996). In addition, the ectopic expression of *KNAT*2 and *KNAT6* genes in ovules leads to the homeotic conversion of the nucellus into carpeloid structures (Pautot *et al*. 2001 and our unpublished data). Thus, KNOX genes confer indeterminacy on a normally determinate organ.

STRUCTURE OF KNOX PROTEINS AND THEIR INTERACTION PARTNERS

KNOX proteins have several conserved domains (**Fig. 2A**). The homeodomain (HD), consisting of three α-helices with a helix-turn-helix structure, is located near the C-terminus. The third helix is responsible for DNA binding (Gehring *et al*. 1994). KNOX HDs have three extra amino acids (PYP) between the first and the second helices, and therefore they belong to the TALE superclass (Bertolino *et al*. 1995; Burglin 1997). The PYP domain is also involved in DNA binding (Nagasaki *et al*. 2001). The ELK domain is located upstream from the HD. It has an amphipathic helix structure, which may serve as a nuclear sorting signal (Meisel and Lam 1996). In addition to the conserved ELK and HD motifs, KNOX proteins contain the MEINOX domain (from MEIS "Myeloid ecotropic viral integration site" and KNOX). This domain contains two subdomains, KNOX1 and KNOX2, separated by a flexible linker (Burglin 1997). The MEINOX domain mediates interactions with other KNOX and TALE proteins (Bellaoui *et al*. 2001; Müller *et al*. 2001; Smith *et al*. 2002). The formation of KNOX/KNOX homo- and heterodimers requires both the HD and MEINOX domains (Nagasaki *et al*. 2001). KNOX proteins interact specifically with members of another TALE class, the BELL family. The MEINOX domain binds to the N-terminal domain of the BELL protein, named the MEINOX interacting domain (MID) (**Fig. 2B**). The MID domain is a bipartite domain composed of the SKY and BELL regions. The interaction of KNOX and BELL proteins results in high DNA binding affinity and may also play an important role in localizing the KNOX-BELL complex to the nucleus (Bellaoui *et al*. 2001; Müller *et al*. 2001; Smith *et al*. 2002; Smith and Hake 2003; Byrne *et al*. 2003; Bhatt *et al*. 2004). The GSE domain, located between the ELK and MEINOX domains, is thought to be involved in protein stability (Nagasaki *et al*. 2001).

KNOX-BELL HETERODIMERS REGULATE SAM ACTIVITY

In *Arabidopsis*, the *BELL* family comprises 13 members (Smith *et al*. 2004). The first to be identified was designated *BEL1*, as the *bel1* mutant had bell-shaped ovules (Robinson-Beers *et al*. 1992; Modrusan *et al*. 1994; Ray *et al*. 1994). In addition to its role in ovule integument development, a function for BEL1 in maintaining the inflorescence meristem has been proposed (Bellaoui *et al*. 2001). The inflorescence of *bel1* mutants terminates in a floral structure similar to the inflorescence of *terminal flower 1* (*tfl1*) mutants. The patterns of *BEL1* and *STM* expression overlap in the inflorescence apex, and the BEL1 protein interacts with the STM protein in yeast two-hybrid studies (Bellaoui *et al*. 2001). *PENNYWISE (PNY)*, another member of the *BELL* family also known as *BELLRINGER* (*BRL*), *REPLUMLESS* (*RPL*), or *VAAMANA* (*VAN*), has also recently been shown to control inflorescence architecture (Byrne *et al*. 2003; Smith and Hake 2003; Bhatt *et al*. 2004). Loss-of-function *pny* mutants are smaller than wild-type plants and show a loss of apical dominance and aberrant organ positions. The regular spiral pattern of organs is disrupted in *pny* mutants and internode size is irregular. Lateral organ initiation is more frequent in the absence of *PNY* (Byrne *et al*. 2003). Like *BP* and *KNAT6*, *PNY* contributes to SAM maintenance in the absence of *STM* (Byrne *et al*. 2003; Bhatt *et al*. 2004). It makes a more substantial contribution than *BP* but a lesser contribution than *KNAT6*. Further genetic and expression analyses have shown that *BP* and *PNY* control inflorescence stem growth (Smith and Hake 2003). The *pny bp* double mutant has an additive phenotype, with extremely short internodes, downward oriented organ clusters and increased branching (Byrne *et al*. 2003; Smith and Hake 2003). *Pny bp* double mutant inflorescence stems also display higher levels of cellular disorganization than observed in single mutants. These two genes are expressed in overlapping domains in the inflorescence meristem and their proteins interact physically (Smith and Hake 2003; Bhatt *et al*. 2004). In addition to their phyllotaxy defects, *pny* mutants display abnormal fruit

development. Their siliques have defects in replum differentiation and in the fusion of the septum (Roeder *et al*. 2003). Moreover, *pny* flowers from old terminating shoots may display homeotic conversions of sepals to carpels (Bao *et al*. 2004).

Studies of the interaction between PNY and its closest relative in the BELL family, POUNDFOOLISH (PNF) revealed a role for *PNY* in the response to floral induction signals (Smith *et al*. 2004). The *pnf* mutant has a wild-type phenotype, suggesting that *PNY* can compensate for the loss of *PNF* activity. In contrast, *PNF* cannot compensate for the loss of *PNY* function, probably because it is expressed too weakly (Kanrar *et al*. 2006). Double mutants in which both PNY and PNF activities are compromised do not flower. Genetic analysis has indicated that *PNY* and *PNF* may regulate floral meristem identity genes in response to floral induction and may control the morphological changes required for flowering. In particular, *PNY* and *PNF* control expansion of the peripheral and rib zones of the meristem. These zones are narrower in the *pny pnf* double mutant. These genes also control the correct allocation of cells to organs, as *pny pnf* SAMs often terminate. They are also required for the correct pattern and rate of leaf initiation, as spiral phyllotaxy is transformed into a decussate-like pattern in double mutants (Smith *et al*. 2004). Inflorescence development is sensitive to gene dosage effects, as a single functional copy of the *PNF* allele restores flowering capacity. *Pny/pny pnf/+* inflorescences have more severe defects than those of *pny* single mutants. In particular, pedicels are often fused to the main stem or to each other, indicating a lack of maintenance of the boundaries between organs in *pny/pny pnf/+* mutants. In contrast, genetic analysis has indicated that *PNF* is not required for the early stages of meristem development. It does not aggravate the deficiencies in meristematic activity of the weak *stm-10* allele and cannot substitute for the loss of PNY activity in *pny stm-10* double mutants. These findings are consistent with the absence of *PNF* expression in the embryonic SAM (Kanrar *et al*. 2006). Genetic analysis has suggested that PNY/BP and PNF/BP heterodimers control internode patterning, whereas PNY/STM and PNF/STM heterodimers regulate floral specification, internode patterning, and boundary maintenance (Kanrar *et al*. 2006). Preliminary evidence also suggests a role for other BELL members in the regulation of flowering time. *ATH1*, a BELL gene whose expression is light regulated, interacts with *STM* and *PNY* to control SAM activity and floral competency (Quaedvlieg *et al*. 1995; B. Rutjens and M. Proveniers pers. comm). An effect of TALE proteins on flowering time was also mentioned in Cole *et al*. (2006). While overexpression of *ATH1* delayed the transition to flowering, the overexpression of *BLH3* and *PNY* (*BLH9*) caused an early flowering phenotype (Cole *et al*. 2006).

TALE PROTEINS INTERACT WITH OVATE PROTEINS

New partners of TALE proteins, the OVATE proteins, were recently identified during a large-scale yeast two-hybrid analysis (Hackbusch *et al*. 2005). This plant-specific class of proteins was first characterized in tomato, in which an OVATE protein was found to control fruit shape (Liu *et al*. 2002). Nine members of the *Arabidopsis* OVATE family interact with TALE proteins. The function of OVATE proteins in SAM development has not yet been studied. However, there is evidence to suggest that OVATE proteins may interact with TALE proteins to regulate GA content in the SAM. Coexpression studies have also shown that these proteins may regulate the intracellular localization of homeodomain proteins. Further studies are required to investigate this complex network and to determine the role of OVATE-TALE protein interactions in SAM development.

KNOX FUNCTION IS INTEGRATED INTO A HORMONAL NETWORK

The link between *KNOX* genes and hormonal pathways became evident from studies of *KNOX* overexpressors. *KNOX* overexpressors display some of the features of cytokinin overproducers: alteration of leaf shape, production of ectopic meristems, higher regeneration rate and delayed leaf senescence (for review see Hay *et al*. 2004; Ori *et al*. 2006). Consistent with this, KNOX overproducers have been shown to have high cytokinin levels (Kusaba *et al*. 1998). Conversely, plants overproducing cytokinins have higher levels of *KNAT1* and *STM* mRNA (Rupp *et al*. 1999). Further studies investigated the molecular link between KNOX proteins and CK. The activation of KNOX proteins leads to an increase of cytokinin biosynthesis by up regulating the accumulation of isopentenyl transferase 7 (*AtIPT7*) mRNA levels, and to the activation of ARR5, a cytokinin response factor. The expression of a cytokinin biosynthesis gene under control of the *STM* promoter partially rescued the *stm* mutant. Thus, the maintenance of the SAM by KNOX proteins involves the regulation of CK biosynthesis (Jasinski *et al*. 2005; Yanai *et al*. 2005). However, no direct molecular link between *KNOX* genes and CK has yet been demonstrated. In addition to changes in cytokinin levels, decreased levels of GA have been detected in *KNOX* overexpressors of several species. KNOX proteins have also been shown to act as GA biosynthesis repressors: the tobacco KNOX protein NTH15 binds to *Ntc12*, a gene encoding a GA-20-oxidase required for GA biosynthesis. Consistent with these data, exogenous GA partially rescues the lobed leaf phenotype of *KN1* and *KNAT1* overexpressors (Hay *et al*. 2002). Conversely, the *stm-2* phenotype was enhanced in the constitutive GA signaling mutant *spindly* (*spy*) (Hay *et al*. 2002). In addition, both KNOX proteins and CK activate a GA-2 oxidase gene triggering GA catabolism, thereby excluding GA from the SAM (Jasinski *et al*. 2005). The detrimental effects of constitutive GA signaling and low CK levels on meristem activity have been further demonstrated in *Arabidopsis.* A gene encoding a cytokinin oxidase that deactivates CK was introduced into the *spindly* (*spy*) mutant background leading to plants with no meristem and organ fusion defects (Jasinski *et al*. 2005). Thus, maintenance of the SAM by KNOX proteins involves the repression of GA and the activation of CK biosynthesis.

The link between *KNAT2* and GA was less clear than those for *STM*, *KN1* and *BP/KNAT1*. KNAT2 activation leads to the repression of GA biosynthesis, but this effect is less rapid than that of STM. Furthermore, GA application does not rescue the lobed leaf phenotype associated with *KNAT2* overexpression (our unpublished data). However, an antagonistic interaction between *KNAT2* and ethylene has been reported (Hamant *et al*. 2002). The *KNAT2* overexpressor phenotype is partially rescued by the application of an exogenous ethylene precursor and in the constitutive ethylene response *ctr-1-10* mutant. In addition, the domain of *KNAT2* expression was restricted in the presence of ethylene and in the *ctr1* mutant, but enlarged in the *etr1-1* ethylene-resistant mutant (Hamant *et al*. 2002). Indeed, the number of cells in the *KNAT2* expression domain was smaller in the *ctr-1-10* mutant. This defect was corrected by KNAT2 activation (Hamant *et al*. 2002). These findings suggest that ethylene may be involved in regulating meristem activity. **Fig. 3** summarizes the integration of each *KNAT* gene into the hormonal regulation of SAM development.

REGULATORS OF *KNOX* GENES

The *CUC* (CUP-shaped cotyledon) genes, encoding the NAC (NAM ATAF1 CUC2) transcription factors, are positive regulators of *KNOX* genes. During embryogenesis, the *CUC1*, *CUC2* and *CUC3* genes play a crucial role in establishing the SAM and organ separation (Aida *et al*. 1999; Takada *et al*. 2001; Vroemen *et al*. 2003; Hibara *et al*.

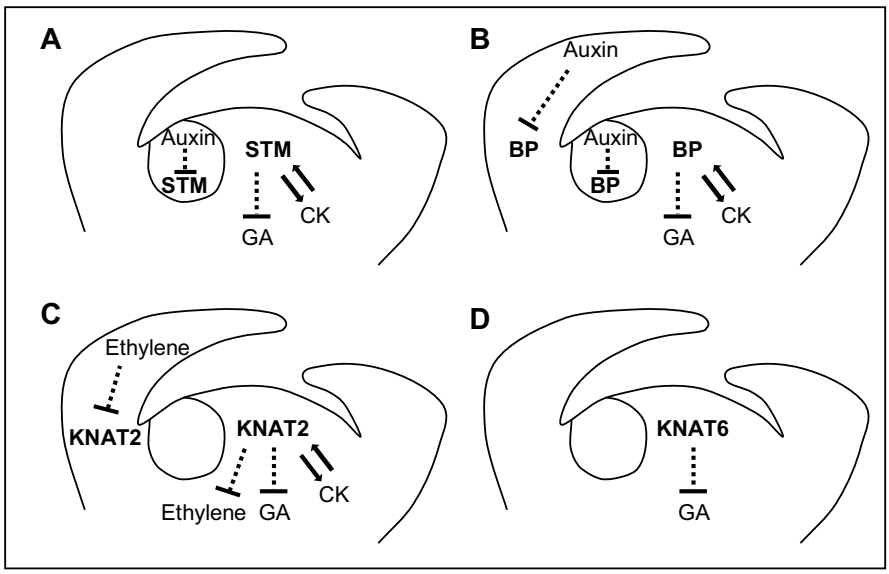

Fig. 3 KNAT interactions in the SAM. Summary of the known interactions of each KNAT member with hormones: STM (**A**), BP/KNAT1 (**B**), KNAT2 (**C**) and KNAT6 (**D**). GA, gibberellin; CK, cytokinins.

2006). The *CUC1* and *CUC2* genes play redundant roles in cotyledon separation and SAM formation *via* activation of the *STM* gene. In turn, during the later stages of embryogenesis, *STM* is required for correct *CUC2* expression and, to a lesser extent, *CUC1* expression. The role of KNAT6 and STM in SAM maintenance and boundary establishment has recently been shown to involve the regulation of *CUC* gene activity (Belles-Boix *et al*. 2006).

Only a few positive regulators of *KNOX* gene activity are known, but many negative regulators have been identified through analyses of mutants with abnormal leaf shapes resembling KNOX overexpressors. Indeed, many of these mutants display ectopic KNOX gene expression. One of these regulators, the myb AS1 (asymmetric leaves 1) transcription factor, which promotes adaxial leaf fate, plays a key role in downregulating *KNAT* class I genes in leaves. Genetic and expression analyses have demonstrated that STM represses *AS1* expression in the SAM and that AS1 downregulates *BP/KNAT1*, *KNAT2* and *KNAT6* expression in leaves (Byrne *et al*. 2000). AS2, from the lateral organ boundaries-domain (*LOB*) gene family (Semiarti *et al*. 2001), is another regulator. AS2 specifies adaxial fate by repressing *BP/KNAT1*, *KNAT2* and *KNAT6*, but not *STM* expression. Genes involved in abaxial organ identity, such as the *YABBY* genes, repress *KNAT* class I genes, including *STM*, on the abaxial sides of leaves (Kumaran *et al*. 2002). The *BLADE ON PETIOLE1 (BOP1)* and *BOP2* genes are members of a family of genes encoding proteins with ankyrin repeats and a BTB/POZ domain. They are expressed in the proximal domain of lateral organs, where they repress the *BP/KNAT1*, *KNAT2 and KNAT6* genes (Ha *et al*. 2003, 2004; Norberg *et al*. 2005). SERRATE, a zinc finger protein that regulates expression of the HD-Zip III gene PHABULOSA (PHB) via a microRNA (miRNA) gene-silencing pathway, and PICKLE, a chromatin-remodeling enzyme, seem to limit the ability to respond to KNOX activity in leaves (Ori *et al*. 2000; Grigg *et al*. 2005). Furthermore, HIRA, a histone chaperone, has been shown to interact with AS1 to maintain *KNOX* gene silencing (Phelps-Durr *et al.* 2005). However, the initial down-regulation of *KNOX* genes in the incipient leaf primordia is maintained in all of these mutants. Regulation *via* micro RNA (miRNA) gene silencing pathways would be an efficient way of downregulating *KNOX* gene activity in the P_0 primordia. However, no miRNAs targeting *KNOX* genes have yet been identified, and the initial downregulation of *KNOX* genes in mutants impaired in miRNA pathways such as *hyl1-1*, *dcl1-9* and *argonaute* was maintained (P. Laufs, pers. comm). Recent evidence suggests that auxin may play a major role in downregulating KNOX genes during the first steps of leaf primordium formation. In maize, a direct link between auxin and KNOX has been reported in studies of plants treated with auxin transport inhibitors. KNOX accumulation extended into the leaf primordia in NPA-treated plants (Scanlon 2003). Genetic analysis in *Arabidopsis* of the *pin1 pinoid* double mutant, in which auxin flux is disrupted, showed that auxin was required for *STM* downregulation to promote cotyledon formation (Furutani *et al*. 2004). The finding of a correlation between auxin maxima and the initial downregulation of *KNOX* genes in the incipent leaf primordium extends this conclusion to leaf primordia formation (Heisler *et al*. 2005; de Reuille *et al*. 2006). However, further genetic analyses are required to demonstrate this conclusively. Recent genetic analyses of mutants impaired in auxin signaling (*axr1*) or auxin transport (*pin1*) have shown that the auxin and *AS1* pathways converge to repress *BP* and to promote leaf development. *Pin1*, *as1* and *axr1* mutants were found to have defects in leaf number and leaf development. The defects were enhanced in *axr1 as1* or *pin as1* double mutants and were associated with the ectopic expression of *BP*. The reduction in leaf number of the *pin* mutant was partially rescued by *BP* inactivation, suggesting that the auxin-dependent repression of *KNOX* genes is required for primordium formation (Hay *et al*. 2006). However, the expression of *KNOX* genes in primordia anlagen of these mutants was not investigated (Hay *et al*. 2006). The initial downregulation of *KNOX* expression in *Arabidopsis* probably requires the convergence of several redundant pathways.

KNOX GENES CONTRIBUTE TO LEAF DIVERSITY IN SPECIES WITH DISSECTED LEAVES

In species with simple leaves, correct leaf differentiation requires the downregulation of *KNOX* genes at sites of leaf primordium initiation. The overexpression of *KNOX* genes in simple-leaved species leads to the production of lobes and the inhibition of leaf differentiation (for review see Hake *et al*. 2004). In contrast, this overexpression increases leaf complexity in species with dissected leaves (Hareven *et al*. 1996). A study of *KNOX* expression in various vascular plants revealed a correlation between *KNOX* expression and leaf form (Bharathan *et al*. 2002). *KNOX* class I genes are downregulated at the sites of leaf primordium initiation in all species, but are subsequently reactivated in the leaves of species with complex leaves. This reactivation of *KNOX* expression in leaves promotes the formation of leaflets. However, final leaf shape cannot necessarily be inferred from *KNOX* expression patterns. Leaves from some eudicot species, such as *Lepidium oleraceum*, form complex leaf primordia with the corresponding pattern of *KNOX* gene expression, but subsequently undergo secondary morphogenesis to form simple leaves (Bharathan *et al*. 2002). Another exception is found in legumes: pea has complex

leaves, but does not accumulate KNOX proteins in leaf primordia, suggesting that other mechanisms may control or regulate leaf shape in this species (Gourlay *et al*. 2000; Hofer *et al*. 2001). The molecular basis of differences in leaf shape was recently investigated in more detail in *Cardamine hirsuta*, a wild relative of *Arabidopsis* (Hay and Tsiantis 2006). This species has dissected leaves and displays *KNOX* expression in leaves. The downregulation of *STM* expression by RNA interference (RNAi) in *C. hirsuta* reduces leaflet initiation. Conversely, the overexpression of *KNOX* genes leads to the formation of additional leaflets. Thus, KNOX proteins are both necessary and sufficient for leaflet production in *C. hirsuta*. AS1 regulation contributes to leaf shape in many species with compound leaves (Kim *et al*. 2003). The production and function of the *C. hirsuta* AS1 protein were therefore investigated to determine whether AS1 regulation in *C. hirsuta* differed from that in *Arabidopsis*. *C. hirsuta AS1* was found to be functionally equivalent to *Arabidopsis AS1*, as it complemented the *Arabidopsis as1* mutant and repressed *KNOX* gene expression in *Arabidopsis*. Moreover, the regulation of *C. hirsuta AS1* expression was conserved: *C. hirsuta* AS1 was excluded from the SAM and accumulated in leaves. Promoter-swap experiments indicated that the differences in *BP* and *STM* expression between *Arabidopsis* and *C. hirsuta* were associated with differences in promoter *cis* regulatory sequences. Finally, the isolation of a *C. hirsuta as1* mutant, *chas1-1*, with additional orders of leaflets showed that *C. hirsuta* AS1 controls leaflet number and arrangement along the proximo-distal axis of the leaf. Thus, whereas the mechanism of *KNOX* gene regulation by AS is conserved between the two species, differences in leaf form result from differences in *KNOX* promoter sequences.

CONCLUDING REMARKS

In recent years, progress has been made towards elucidating the role of *KNOX* genes in plant development. It has become increasingly evident that KNOX proteins interact with different protein partners, resulting in flexibility in the regulation of distinct aspects of development. There also seems to be functional redundancy within the complex KNOX protein interaction network. This redundancy may ensure developmental robustness, by facilitating compensatory interactions. Further genetic analyses for each member of the *KNAT*, *BELL*, and *OVATE* gene families is required to determine the specific roles of these genes both within and outside the SAM.

ACKNOWLEDGEMENTS

We thank Isabelle Bohn-Courseau and Patrick Laufs for critical reading of the review. Laura Ragni and Elisabeth Truernit were supported by the European Marie-Curie (FP6) Program.

REFERENCES

Aida M, Ishida T, Tasaka M (1999) Shoot apical meristem and cotyledon formation during *Arabidopsis* embryogenesis: interaction among the CUP-SHAPED COTYLEDON and SHOOT MERISTEMLESS genes. *Development* **126**, 1563-1570

Aida M, Tasaka M (2006) Genetic control of shoot organ boundaries. *Current Opinion in Plant Biology* **9**, 72-77

Bao X, Franks RG, Levin JZ, Liu Z (2004) Repression of AGAMOUS by BELLRINGER in floral and inflorescence meristems. *Plant Cell* **16**, 1478-1489

Bellaoui M, Pidkowich MS, Samach A, Kushalappa K, Kohalmi SE, Modrusan Z, Crosby WL, Haughn GW (2001) The *Arabidopsis* BELL1 and KNOX TALE homeodomain proteins interact through a domain conserved between plants and animals. *Plant Cell* **13**, 2455-2470

Belles-Boix E, Hamant O, Witiak SM, Morin H, Traas J, Pautot V (2006) KNAT6: An *Arabidopsis* homeobox gene involved in meristem activity and organ separation. *Plant Cell* **18**, 1900-1907

Bertolino E, Reimund B, Wildt-Perinic D, Clerc RG (1995) A novel homeobox protein which recognizes a TGT core and functionally interferes with a retinoid-responsive motif. *The Journal of Biological Chemistry* **270**, 31178-31188

Bharathan G, Goliber TE, Moore C, Kessler S, Pham T, Sinha NR (2002) Homologies in leaf form inferred from KNOXI gene expression during development. *Science* **296**, 1858-1860

Bhatt AM, Etchells JP, Canales C, Lagodienko A, Dickinson H (2004) VAAMANA – a BEL1-like homeodomain protein, interacts with KNOX proteins BP and STM and regulates inflorescence stem growth in *Arabidopsis*. *Gene* **328**, 103-111

Brown DM, Zeef LA, Ellis J, Goodacre R, Turner SR (2005) Identification of novel genes in *Arabidopsis* involved in secondary cell wall formation using expression profiling and reverse genetics. *Plant Cell* **17**, 2281-2295

Burglin TR (1994) A Caenorhabditis elegans prospero homologue defines a novel domain. *Trends in Biochemical Science* **19**, 70-71

Burglin TR (1997) Analysis of TALE superclass homeobox genes (MEIS, PBC, KNOX, Iroquois, TGIF) reveals a novel domain conserved between plants and animals. *Nucleic Acids Research* **25**, 4173-4180

Byrne ME, Barley R, Curtis M, Arroyo JM, Dunham M, Hudson A, Martienssen RA (2000) Asymmetric leaves1 mediates leaf patterning and stem cell function in *Arabidopsis*. *Nature* **408**, 967-971

Byrne ME, Groover AT, Fontana JR, Martienssen RA (2003) Phyllotactic pattern and stem cell fate are determined by the *Arabidopsis* homeobox gene BELLRINGER. *Development* **130**, 3941-3950

Byrne ME, Simorowski J, Martienssen RA (2002) ASYMMETRIC LEAVES1 reveals knox gene redundancy in *Arabidopsis*. *Development* **129**, 1957-1965

Chuck G, Lincoln C, Hake S (1996) KNAT1 induces lobed leaves with ectopic meristems when overexpressed in *Arabidopsis*. *Plant Cell* **8**, 1277-1289

Clark SE, Jacobsen SE, Levin JZ, Meyerowitz EM (1996) The CLAVATA and SHOOT MERISTEMLESS loci competitively regulate meristem activity in *Arabidopsis*. *Development* **122**, 1567-1575

Cole M, Nolte C, Werr W (2006) Nuclear import of the transcription factor SHOOT MERISTEMLESS depends on heterodimerization with BLH proteins expressed in discrete sub-domains of the shoot apical meristem of *Arabidopsis thaliana*. *Nucleic Acid Research* **34**, 1281-1292

de Reuille PB, Bohn-Courseau I, Ljung K, Morin H, Carraro N, Godin C, Traas J (2006) Computer simulations reveal properties of the cell-cell signaling network at the shoot apex in *Arabidopsis*. *Proceedings of the National Academy of Sciences USA* **103**, 1627-1632

Dockx J, Quaedvlieg N, Keultjes G, Kock P, Weisbeek P, Smeekens S (1995) The homeobox gene ATK1 of *Arabidopsis thaliana* is expressed in the shoot apex of the seedling and in flowers and inflorescence stems of mature plants. *Plant Molecular Biology* **28**, 723-737

Douglas SJ, Chuck G, Dengler RE, Pelecanda L, Riggs CD (2002) KNAT1 and ERECTA regulate inflorescence architecture in *Arabidopsis*. *Plant Cell* **14**, 547-558

Endrizzi K, Moussian B, Haecker A, Levin JZ, Laux T (1996) The SHOOT MERISTEMLESS gene is required for maintenance of undifferentiated cells in *Arabidopsis* shoot and floral meristems and acts at a different regulatory level than the meristem genes WUSCHEL and ZWILLE. *Plant Journal* **10**, 967-979

Furutani M, Vernoux T, Traas J, Kato T, Tasaka M, Aida M (2004) PIN-FORMED1 and PINOID regulate boundary formation and cotyledon development in *Arabidopsis* embryogenesis. *Development* **131**, 5021-5030

Gehring WJ, Affolter M, Burglin T (1994) Homeodomain proteins. *Annual Review of Biochemistry* **63**, 487-526

Gourlay CW, Hofer JM, Ellis TH (2000) Pea compound leaf architecture is regulated by interactions among the genes UNIFOLIATA, cochleata, afila, and tendril-less. *Plant Cell* **12**, 1279-1294

Grigg SP, Canales C, Hay A, Tsiantis M (2005) SERRATE coordinates shoot meristem function and leaf axial patterning in *Arabidopsis*. *Nature* **437**, 1022-1026

Ha CM, Kim GT, Kim BC, Jun JH, Soh MS, Ueno Y, Machida Y, Tsukaya H, Nam HG (2003) The BLADE-ON-PETIOLE 1 gene controls leaf pattern formation through the modulation of meristematic activity in *Arabidopsis*. *Development* **130**, 161-172

Hackbusch J, Richter K, Muller J, Salamini F, Uhrig JF (2005) A central role of *Arabidopsis* thaliana ovate family proteins in networking and subcellular localization of 3-aa loop extension homeodomain proteins. *Proceedings of the National Academy of Sciences USA* **102**, 4908-4912

Hake S, Smith HM, Holtan H, Magnani E, Mele G, Ramirez J (2004) The role of knox genes in plant development. *Annual Review of Cell and Developmental Biology* **20**, 125-151

Hake S, Freeling M (1986) Analysis of genetic mosaics shows that the extra epidermal cell divisions in Knotted mutant maize plants are induced by adjacent mesophyll cells. *Nature* **320**, 621-623

Hamant O, Nogue F, Belles-Boix E, Jublot D, Grandjean O, Traas J, Pautot V (2002) The KNAT2 homeodomain protein interacts with ethylene and cytokinin signaling. *Plant Physiology* **130**, 657-665

Hareven D, Gutfinger T, Parnis A, Eshed Y, Lifschitz E (1996) The making of a compound leaf: genetic manipulation of leaf architecture in tomato. *Cell* **84**, 735-744

Hay A, Barkoulas M, Tsiantis M (2006) ASYMMETRIC LEAVES1 and auxin activities converge to repress BREVIPEDICELLUS expression and promote

leaf development in *Arabidopsis*. *Development* **133**, 3955-3961

Hay A, Kaur H, Phillips A, Hedden P, Hake S, Tsiantis M (2002) The gibberellin pathway mediates KNOTTED1-type homeobox function in plants with different body plans. *Current Biology* **12**, 1557-1565

Hay A, Tsiantis M (2006) The genetic basis for differences in leaf form between *Arabidopsis* thaliana and its wild relative *Cardamine hirsuta*. *Nature Genetics* **38**, 942-947

Heisler MG, Ohno C, Das P, Sieber P, Reddy GV, Long JA, Meyerowitz EM (2005) Patterns of auxin transport and gene expression during primordium development revealed by live imaging of the *Arabidopsis* inflorescence meristem. *Current Biology* **15**, 1899-1911

Hibara K, Karim MR, Takada S, Taoka K, Furutani M, Aida M, Tasaka M (2006) *Arabidopsis* CUP-SHAPED COTYLEDON3 regulates postembryonic shoot meristem and organ boundary formation. *Plant Cell* **18**, 2946-2957

Hofer J, Gourlay C, Michael A, Ellis TH (2001) Expression of a class 1 knotted1-like homeobox gene is down-regulated in pea compound leaf primordia. *Plant Molecular Biology* **45**, 387-398

Ito M, Sato Y, Matsuoka M (2002) Involvement of homeobox genes in early body plan of monocot. *International Review of Cytology* **218**, 1-35

Jackson D (2002) Double labeling of KNOTTED1 mRNA and protein reveals multiple potential sites of protein trafficking in the shoot apex. *Plant Physiology* **129**, 1423-1429

Jackson D, Hake S (1994) Expression of maize KNOTTED1 related homeobox genes in the shoot apical meristem predicts patterns of morphogenesis in the vegetative shoot. *Development* **120**, 405-413

Jasinski S, Piazza P, Craft J, Hay A, Woolley L, Rieu I, Phillips A, Hedden P, Tsiantis M (2005) KNOX action in *Arabidopsis* is mediated by coordinate regulation of cytokinin and gibberellin activities. *Current Biology* **15**, 1560-1565

Kanrar S, Onguka O, Smith HM (2006) *Arabidopsis* inflorescence architecture requires the activities of KNOX-BELL homeodomain heterodimers. *Planta* **224**, 1163-1173

Kim JY, Rim Y, Wang J, Jackson D (2005) A novel cell-to-cell trafficking assay indicates that the KNOX homeodomain is necessary and sufficient for intercellular protein and mRNA trafficking. *Genes and Development* **19**, 788-793

Kim JY, Yuan Z, Cilia M, Khalfan-Jagani Z, Jackson D (2002) Intercellular trafficking of a KNOTTED1 green fluorescent protein fusion in the leaf and shoot meristem of *Arabidopsis*. *Proceedings of the National Academy of Sciences USA* **99**, 4103-4108

Kim M, McCormick S, Timmermans M, Sinha N (2003) The expression domain of PHANTASTICA determines leaflet placement in compound leaves. *Nature* **424**, 438-443

Kumaran MK, Bowman JL, Sundaresan V (2002) YABBY polarity genes mediate the repression of KNOX homeobox genes in *Arabidopsis*. *Plant Cell* **14**, 2761-2770

Kusaba S, Kano-Murakami Y, Matsuoka M, Tamaoki M, Sakamoto T, Yamaguchi I, Fukumoto M (1998) Alteration of hormone levels in transgenic tobacco plants overexpressing the rice homeobox gene OSH1. *Plant Physiology* **116**, 471-476

Laufs P, Grandjean O, Jonak C, Kieu K, Traas J (1998) Cellular parameters of the shoot apical meristem in *Arabidopsis*. *Plant Cell* **10**, 1375-1390

Lincoln C, Long J, Yamaguchi J, Serikawa K, Hake S (1994) A knotted1-like homeobox gene in *Arabidopsis* is expressed in the vegetative meristem and dramatically alters leaf morphology when overexpressed in transgenic plants. *Plant Cell* **6**, 1859-1876

Liu J, van Eck J, Cong B, Tanksley SD (2002) A new class of regulatory genes underlying the cause of pear-shaped tomato fruit. *Proceedings of the National Academy of Sciences USA* **99**, 13302-13306

Long JA, Moan EI, Medford JI, Barton MK (1996) A member of the KNOTTED class of homeodomain proteins encoded by the STM gene of *Arabidopsis*. *Nature* **379**, 66-69

Lucas WJ, Bouche-Pillon S, Jackson DP, Nguyen L, Baker L, Ding B, Hake S (1995) Selective trafficking of KNOTTED1 homeodomain protein and its mRNA through plasmodesmata. *Science* **270**, 1980-1983

McGinnis W, Krumlauf R (1992) Homeobox genes and axial patterning. *Cell* **68**, 283-302

McGinnis W, Levine MS, Hafen E, Kuroiwa A, Gehring WJ (1984) A conserved DNA sequence in homoeotic genes of the *Drosophila* Antennapedia and bithorax complexes. *Nature* **308**, 428-433

Meisel L, Lam E (1996) The conserved ELK-homeodomain of KNOTTED-1 contains two regions that signal nuclear localization. *Plant Molecular Biology* **30**, 1-14

Mele G, Ori N, Sato Y, Hake S (2003) The knotted1-like homeobox gene BREVIPEDICELLUS regulates cell differentiation by modulating metabolic pathways. *Genes and Development* **17**, 2088-2093

Modrusan Z, Reiser L, Feldmann KA, Fischer RL, Haughn GW (1994) Homeotic transformation of ovules into carpel-like structures in *Arabidopsis*. *Plant Cell* **6**, 333-349

Müller J, Wang Y, Franzen R, Santi L, Salamini F, Rohde W (2001) *In vitro* interactions between barley TALE homeodomain proteins suggest a role for protein-protein associations in the regulation of Knox gene function. *Plant Journal* **27**, 13-23

Nagasaki H, Sakamoto T, Sato Y, Matsuoka M (2001) Functional analysis of the conserved domains of a rice KNOX homeodomain protein, OSH15. *Plant Cell* **13**, 2085-2098

Norberg M, Holmlund M, Nilsson O (2005) The BLADE ON PETIOLE genes act redundantly to control the growth and development of lateral organs. *Development* **132**, 2203-2213

Ori N, Eshed Y, Chuck G, Bowman JL, Hake S (2000) Mechanisms that control knox gene expression in the *Arabidopsis* shoot. *Development* **127**, 5523-5532

Pautot V, Dockx J, Hamant O, Kronenberger J, Grandjean O, Jublot D, Traas J (2001) KNAT2: evidence for a link between knotted-like genes and carpel development. *Plant Cell* **13**, 1719-1734

Peaucelle A, Morin H, Traas J, Laufs P (2007) Plants expressing a miR164-resistant CUC2 gene reveal the importance of post-meristematic maintenance of phyllotaxy in *Arabidopsis*. *Development* **134**, 1045-1050

Phelps-Durr TL, Thomas J, Vahab P, Timmermans MC (2005) Maize rough sheath2 and its Arabidopsis orthologue ASYMMETRIC LEAVES1 interact with HIRA, a predicted histone chaperone, to maintain knox gene silencing and determinacy during organogenesis. *Plant Cell* **17**, 2886-2898

Quaedvlieg N, Dockx J, Rook F, Weisbeek P, Smeekens S (1995) The homeobox gene ATH1 of Arabidopsis is derepressed in the photomorphogenic mutants *cop1* and *det1*. *Plant Cell* **7**, 117-129

Ray A, Robinson-Beers K, Ray S, Baker SC, Lang JD, Preuss D, Milligan SB, Gasser CS (1994) *Arabidopsis* floral homeotic gene BELL (BEL1) controls ovule development through negative regulation of AGAMOUS gene (AG). *Proceedings of the National Academy of Sciences USA* **91**, 5761-5765

Reiser L, Modrusan Z, Margossian L, Samach A, Ohad N, Haughn GW, Fischer RL (1995) The BELL1 gene encodes a homeodomain protein involved in pattern formation in the *Arabidopsis* ovule primordium. *Cell* **83**, 735-742

Rijpkema AS, Gerats T, Vandenbussche M (2007) Evolutionary complexity of MADS complexes. *Current Opinion Plant Biology* **10**, 32-38

Robinson-Beers K, Pruitt RE, Gasser CS (1992) Ovule development in wild-type *Arabidopsis* and two female-sterile mutants. *Plant Cell* **4**, 1237-1249

Roeder AH, Ferrandiz C, Yanofsky MF (2003) The role of the REPLUM LESS homeodomain protein in patterning the *Arabidopsis* fruit. *Current Biology* **13**, 1630-1635

Rupp HM, Frank M, Werner T, Strnad M, Schmulling T (1999) Increased steady state mRNA levels of the STM and KNAT1 homeobox genes in cytokinin overproducing *Arabidopsis* thaliana indicate a role for cytokinins in the shoot apical meristem. *Plant Journal* **18**, 557-563

Scanlon MJ (2003) The polar auxin transport inhibitor N-1-naphthylphthalamic acid disrupts leaf initiation, KNOX protein regulation, and formation of leaf margins in maize. *Plant Physiology* **133**, 597-605

Semiarti E, Ueno Y, Tsukaya H, Iwakawa H, Machida C, Machida Y (2001) The ASYMMETRIC LEAVES2 gene of *Arabidopsis thaliana* regulates formation of a symmetric lamina, establishment of venation and repression of meristem-related homeobox genes in leaves. *Development* **128**, 1771-1783

Serikawa KA, Zambryski PC (1997) Domain exchanges between KNAT3 and KNAT1 suggest specificity of the kn1-like homeodomains requires sequences outside of the third helix and N-terminal arm of the homeodomain. *The Plant Journal* **11**, 863-869

Sinha NR, Williams RE, Hake S (1993) Overexpression of the maize homeo box gene, KNOTTED-1, causes a switch from determinate to indeterminate cell fates. *Genes and Development* **7**, 787-795

Smith HM, Boschke I, Hake S (2002) Selective interaction of plant homeodomain proteins mediates high DNA-binding affinity. *Proceedings of the National Academy of Sciences USA* **99**, 9579-9584

Smith HM, Campbell BC, Hake S (2004) Competence to respond to floral inductive signals requires the homeobox genes PENNYWISE and POUNDFOOLISH. *Current Biology* **14**, 812-817

Smith HM, Hake S (2003) The interaction of two homeobox genes, BREVI PEDICELLUS and PENNYWISE, regulates internode patterning in the *Arabidopsis* inflorescence. *Plant Cell* **15**, 1717-1727

Takada S, Hibara K, Ishida T, Tasaka M (2001) The CUP-SHAPED COTY LEDON1 gene of *Arabidopsis* regulates shoot apical meristem formation. *Development* **128**, 1127-1135

Traas J, Vernoux T (2002) The shoot apical meristem: the dynamics of a stable structure. *Philosophical Transactions of the Royal Society B: Biological Sciences* **357**, 737-747

Truernit E, Siemering KR, Hodge S, Grbic V, Haseloff J (2006) A Map of KNAT gene expression in the *Arabidopsis* root. *Plant Molecular Biology* **60**, 1-20

Venglat SP, Dumonceaux T, Rozwadowski K, Parnell L, Babic V, Keller W, Martienssen R, Selvaraj G, Datla R (2002) The homeobox gene BREVI PEDICELLUS is a key regulator of inflorescence architecture in *Arabidopsis*. *Proceedings of the National Academy of Sciences USA* **99**, 4730-4735

Vroemen CW, Mordhorst AP, Albrecht C, Kwaaitaal MA, de Vries SC (2003) The CUP-SHAPED COTYLEDON3 gene is required for boundary and shoot meristem formation in *Arabidopsis*. *Plant Cell* **15**, 1563-1577

Yanai O, Shani E, Dolezal K, Tarkowski P, Sablowski R, Sandberg G, Samach A, Ori N (2005) *Arabidopsis* KNOXI proteins activate cytokinin biosynthesis. *Current Biology* **15**, 1566-1571