



Stomatal development: cross talk puts mouths in place

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Stomata are crucial for the productivity and survival of land plants. Until recently, little was known about the events and molecular pathways required for stomatal development. Emerging data indicate that cell–cell signaling conveys spatial information about cell identity and location. Such information might pattern stomata by orienting the plane of asymmetric division and might control stomatal number by regulating division frequency. This pathway also provides an accessible model system for studying post-apical meristem stem cells that generate specific tissues.

Plant surfaces rarely contain openings except where they are adaptive, such as for pollen release from anthers or for gas exchange through stomata. But unlike anthers, which are desiccated when open, stomata function in turgid organs that can tolerate only limited water loss. Thus, not only must the width of stomatal pores be controlled, but also pore distribution itself must be regulated developmentally. Stomata are spaced so that they are separated by at least one cell [1]. This distribution enhances the efficiency of gaseous diffusion shells, evapotranspiration, ion exchange and the ratio between carbon dioxide uptake and photosynthetic capacity. In spite of the importance of stomata, little was known about the developmental mechanisms that control their distribution. However, recent work with *Arabidopsis* has revealed key features and genes in these pathways. Here, we review evidence that position-dependent cell signaling controls the number and spacing of asymmetric divisions in the developing leaf. These events are crucial for regulating stomatal patterning and density, and contribute to the construction of the leaf itself.

Stomatal formation and patterning

In contrast to monocots, where stomata develop serially in cell files, dicot stomatal formation is dispersed in time and space during the mosaic growth of the leaf. Studies of *Arabidopsis* leaf cells through time have made it possible to distinguish between rules of stomatal development that are fixed and those that are flexible. All *Arabidopsis* stomata form through at least one asymmetric and one symmetric division (Fig. 1; Box 1). The first division takes place in a presumed stem cell that has become committed to the stomatal pathway, the meristemoid mother cell (MCC) (Fig. 1, left). This asymmetric division

produces a small precursor, a meristemoid (M), which is eventually converted into a guard mother cell (GMC) [2]. The symmetric division of the GMC produces the two guard cells that make up the stoma. Thus, the terminal differentiation of a stoma occurs after a progression through the three types of precursor cells (MMC to M to GMC).

Two types of developmental plasticity occur in this pathway that are related to the behaviors of the smaller and larger daughter cells produced by asymmetric division. Both types of plasticity contribute to epidermal formation and to stomatal distribution. The first type of developmental plasticity concerns whether or not the smaller cell, the meristemoid, divides asymmetrically before assuming a GMC fate. Meristemoids that divide twice after their initial formation produce a stoma surrounded by three NCs that share the same lineage as the stoma (a monoclonal complex) [2–6]. In this case, successive asymmetric divisions occur in an inward spiral, and the plane of the last division is often roughly parallel to the subsequent symmetric division of the GMC [3,6]. Nothing is known about how these division planes are positioned with respect to each other over four sequential divisions. Regardless, meristemoids that divide once or not at all result in polyclonal stomatal complexes [2]. The existence of such complexes argues against an exclusively cell lineage-based mechanism of patterning [2,3,5,7]. Finally, meristemoid divisions produce many leaf epidermal cells, and the number of divisions is under genetic control.

The second type of developmental plasticity concerns the larger sister cell to the meristemoid. These NCs, as

Box 1. Abbreviations and definitions of terms

Guard mother cell (GMC): a terminal precursor that divides symmetrically and produces the two guard cells of a stoma.

Meristemoid (M): a precursor cell that divides asymmetrically 0–3 times, where each division regenerates a meristemoid; meristemoids eventually convert into guard mother cells.

Meristemoid mother cell (MMC): undergoes the first asymmetric division in the stomatal pathway to produce a meristemoid and a larger sister cell.

Neighbor cell (NC): an epidermal cell adjacent to a stoma, meristemoid or GMC.

Pavement cell (PC): a generic, terminally differentiated epidermal cell characterized by wavy walls and endoreduplication. Many PCs are produced from asymmetric divisions of the stomatal pathway.

Satellite meristemoid (SM): a meristemoid produced by the oriented asymmetric division of an NC. SMs are placed away from pre-existing stomata or precursors, which is a key event in stomatal patterning. The majority of stomata develop from SMs in the abaxial epidermis of the leaf.

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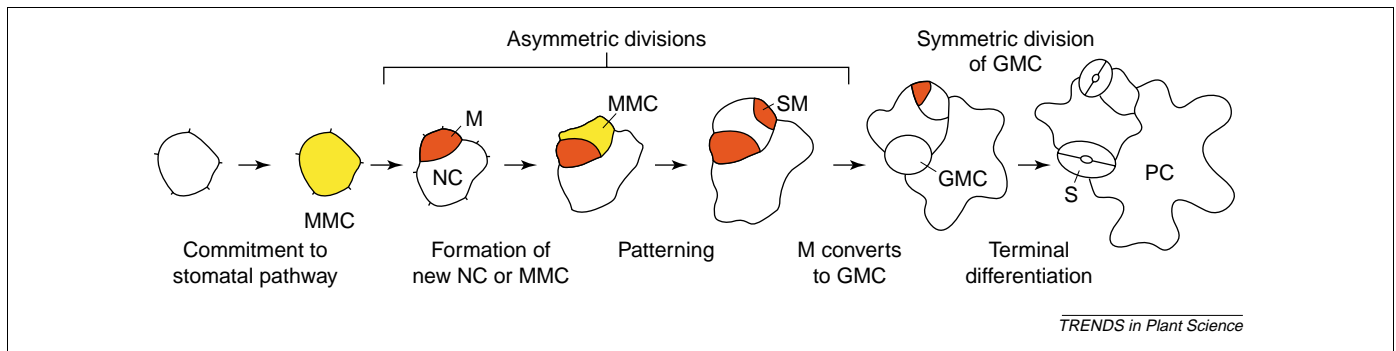


Fig. 1. *Arabidopsis* stomatal development. Initiation involves the selection of a meristemoid mother cell (MMC, yellow) that then divides asymmetrically producing a meristemoid (M, red) and a larger sister cell. A neighbor cell (NC) is considered to be any cell next to a stoma or a precursor. When meristemoids divide asymmetrically they regenerate a meristemoid and produce an additional NC. When the NC divides asymmetrically it functions as an MMC and intercellular signaling orients its division. The resulting smaller cell is termed a satellite meristemoid (SM) to highlight the importance of this class of asymmetric divisions in creating the minimal one-cell spacing pattern. Each meristemoid converts into a guard mother cell (GMC) that divides symmetrically producing a stoma (S). Pavement cells (PCs) make up a second type of terminally differentiated epidermal cell. Many PCs originate from asymmetric divisions in the stomatal pathway.

well as other NCs that are non-clonal, can follow several fates. Some recommit to the stomatal pathway and divide asymmetrically. Others do not divide and instead differentiate into pavement cells (PCs). How these cell fate choices are selected is largely undefined, although cell age is one factor. In young complexes, such as those around a meristemoid, all NCs are equally likely to divide whereas in older complexes, such as those around a stoma, usually only the smallest and youngest NC divides [6,8]. NC fate regulation is central for understanding how stomatal number is controlled because the asymmetric divisions of NCs produce the majority of stomata in the abaxial side of the leaf [2].

Given this plasticity, how is the fundamental aspect of stomatal patterning – the lack of stomata in direct contact – established? Analysis of cell behavior through time shows that this pattern is generated primarily by the orientation of asymmetric divisions in NCs [2]. By definition, a NC is a cell located next to a stoma, GMC or meristemoid. The plane of these divisions is placed so that the new satellite meristemoid does not contact the pre-existing stoma or precursor. Because correct division orientation is independent of relatedness within a cell lineage, intercellular signaling rather than mitosis-allocated

factors probably controls division orientation. Because this event is frequent and it spaces the pre-existing stoma apart from the new precursor, the orientation of NC divisions determines the patterns of most stomata in the abaxial leaf epidermis. This phenomenon underscores the widely recognized role of cell position in plant patterning and development [9,10].

A receptor and a protease regulate stomatal development

The isolation of mutations in the *TOO MANY MOUTHS* (*TMM*) and *STOMATAL DENSITY AND DISTRIBUTION1* (*SDD1*) loci has provided the first glimpses of the mechanisms controlling stomatal distribution. *tmm* has been found to randomize the plane and alter the number of asymmetric divisions in NCs [2]. As a result, many extra meristemoids are placed in contact with pre-existing stomata or precursors. These defects produce stomatal clusters that can be relatively large (Fig. 2) [11]. Therefore, *TMM* is required for the correct orientation of the plane of the asymmetric division that patterns stomata. *tmm* also allows divisions in cells that normally would not divide, those located next to two stomata and/or precursors (Fig. 2d). These phenotypes indicate that *TMM*

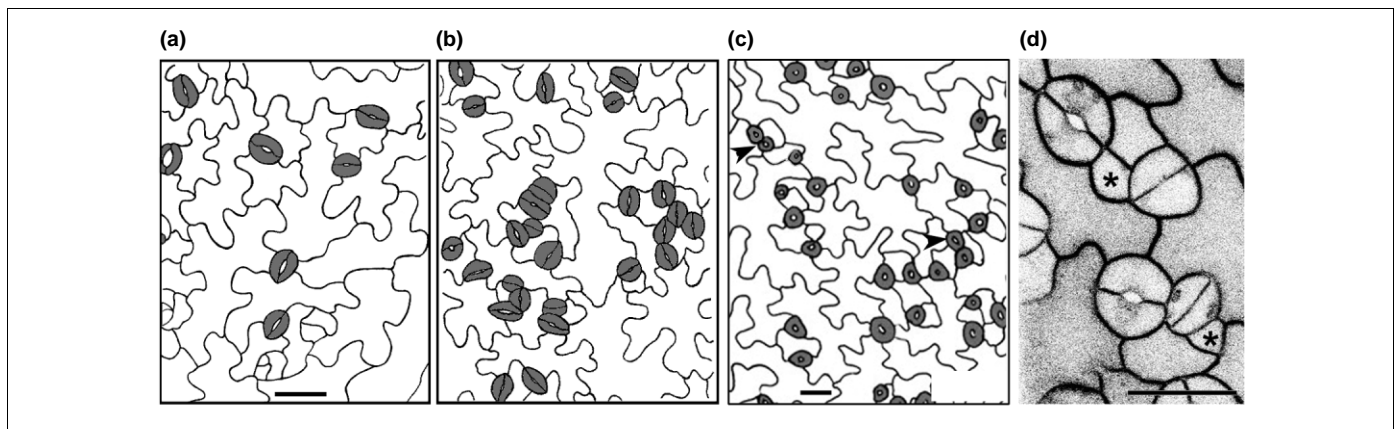


Fig. 2. Wild-type and mutant stomatal distribution. Compared to the wild type (WT) (a), *too many mouths* (*tmm*) (b) and *stomatal density and distribution1* (*sdd1*) (c) have excess stomata. *sdd1* has fewer stomata in direct contact than *tmm* does. *sdd1* tracing redrawn from [19]. (d) Confocal micrograph (inverted image) of *tmm* showing misoriented asymmetric divisions that incorrectly place satellite meristemoids (*). The satellite meristemoids shown resulted from the asymmetric division of cells located adjacent to two stomata and/or precursor cells, cells normally prohibited from dividing. All scale bars = 15 μ m. (a) and (b) are the same magnification.

functions in the perception or transduction of spatial cues that are normally used to orient division or to prevent division in cells in certain locations.

The identity of TMM is consistent with a probable role in the intercellular communication of positional signals. *TMM* encodes a leucine-rich repeat receptor-like protein (LRR-RLP) [12]. Like other LRR-RLPs, such as *CLAVATA2* (*CLV2*), *TMM* has no cytoplasmic kinase domain and thus would need to interact with other factors to participate in an intracellular signaling pathway. Based upon the subcellular localization of green fluorescent protein (GFP) as well as the presence of a signal peptide and predicted transmembrane domain, it is likely that *TMM* resides in the cell membrane, with most of the *TMM* protein being extracellular. Typically, extracellular LRR motifs found in plasma membrane proteins are believed to function in specific protein–protein or protein–ligand interactions that facilitate recognition events. In LRR-receptor-like kinases (LRR-RLKs), the recognition of a peptide or steroid ligand by extracellular regions in turn activates a cytoplasmic kinase domain, an event that transduces information to an intracellular signaling cascade. Signaling through LRR-RLKs controls other facets of plant development, such as meristem maintenance, hormone perception, organ shape and microspore formation [13–17]. At least one LRR-RLK, *CLV1*, is thought to form a heterodimer with an LRR-RLP, *CLV2*. This produces a receptor complex that apparently regulates the balance between stem cell proliferation and maturation in the shoot apical meristem [15].

The observed pattern of *TMM* expression agrees with its deduced roles in stomatal signaling [12]. *TMM* is expressed in stomatal precursors, in neighbor cells (NCs) (Fig. 3), and in some ‘isolated’ cells (non-neighbor cells). Expression would be expected in NCs because *TMM* is required for orienting the plane of division and restricting the frequency of asymmetric divisions in these cells. Expression in meristemoids makes sense because these

cells divide fewer times in *tmm*. Thus, *TMM* activity has the opposite effect in different cell types where it either increases or decreases division frequency.

The *TMM* expression pattern is strongly correlated with the pattern of divisions within a cell lineage because expression is highest in the youngest cells of a stomatal lineage [12]. Nonetheless, signaling crosses lineage boundaries by orienting division planes in NCs that are not clonally related [2]. This highlights the interplay between cell lineage-based events, such as the placement of new NCs through an inward spiral of asymmetric divisions, and positional signaling events, such as the control of NC division plane and frequency, events that together pattern much of the leaf epidermis.

The various functions of *TMM* – positive and negative cell-type-specific regulation of division frequency, and orientation of a class of asymmetric division in a particular spatial context – establish that *TMM* operates at several stages within the stomatal pathway. Indeed, the absence of stomata from *tmm* stems [5] shows that *TMM* can act early in the pathway in some organs.

The phenotypes of *sdd1* and *tmm* are similar in that both have many more stomata than wild-type leaves do, which indicates that both *SDD1* and *TMM* act as negative regulators of asymmetric division in NCs [2,6]. However, stomata in *sdd1* are more likely to be correctly patterned and *sdd1* has fewer and smaller clusters than *tmm* does (Fig. 2). So, although mutations in both loci disrupt the plane and frequency of NC asymmetric divisions, *TMM* seems to be more crucial for patterning and *SDD1* more crucial for limiting density. These two mutants also differ with respect to the distribution of their phenotypes. *sdd1* has an abnormally high stomatal density throughout the shoot, whereas *tmm* has stomatal clusters in leaves but virtually lacks stomata in some other regions [5].

SDD1 encodes a subtilisin-like serine protease [6]. The role of similar processing proteases in animal cell signaling

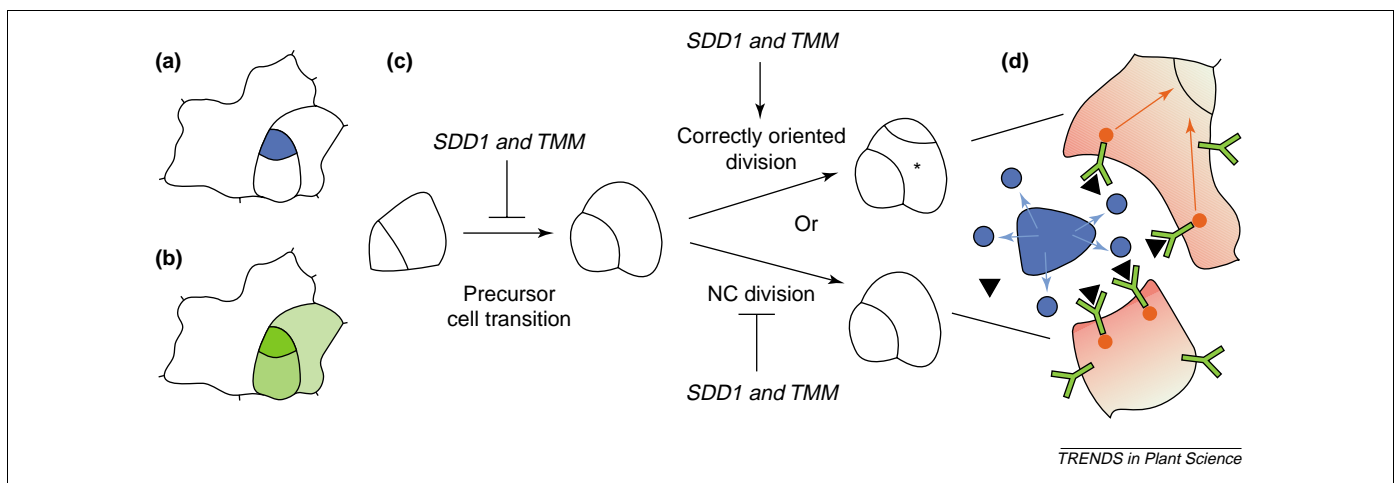


Fig. 3. Diagrammatic representation of *TOO MANY MOUTHS* (*TMM*) and *STOMATAL DENSITY AND DISTRIBUTION1* (*SDD1*) expression patterns and functions. (a) *SDD1* is expressed (blue) in meristemoids and guard mother cells (GMCs). (b) *TMM* is expressed (green) in GMCs, meristemoids and their recent sister cells. (c) Both gene products (1) promote meristemoid division thus delaying the transition to the GMC, (2) act as negative regulators of neighbor cell (NC) division (bottom 'T'), (3) prohibit asymmetric divisions in cells next to two stomata or precursor cells (asterisk at upper right), and (4) are required for the correct placement of patterning divisions in those neighbor cells (NCs) that are allowed to divide (top arrow). (d) Speculative model of signaling. Stomatal precursors broadcast an *SDD1* signal (blue) that might modify or interact with an unknown ligand (black triangles). This ligand could bind to receptor complexes (green 'Y's) that contain *TMM*. The resulting signaling through the receptor complex might set up a polarity that orients the plane of NC division (top). Alternatively, signaling might limit the number of NC divisions (bottom).

and the presence of diagnostic sequence elements in SDD1 are consistent with the idea that SDD1 functions in signaling by cleaving or modifying a developmental signal [18]. A function in intercellular signaling is supported by the likelihood that SDD1 is secreted. GFP–SDD1 fusion proteins localize near the cell membrane even though SDD1 lacks a transmembrane domain or post-translational membrane-association motifs. These data raise the possibility that SDD1 associates with the cell membrane through a protein complex or through interaction with a membrane-bound substrate.

The expression pattern of *SDD1* is consistent with the hypothesis that SDD1 helps produce a proximity signal that originates from stomatal precursors (Fig. 3). Both RNA *in situ* hybridization and promoter-reporter techniques show that *SDD1* expression occurs primarily in meristemoids and GMCs [19]. In leaves, SDD1 and TMM restrict the number of NC divisions and both are required for the correct division orientation (Fig. 3). However, *SDD1* is only expressed in precursor cells and not in NCs, which are the presumed targets of signaling, whereas *TMM* is expressed in both cell types.

The identity of SDD1 suggests that it can produce or activate an extracellular signal, whereas the identity of TMM indicates that it can receive positional signals [20]. One possible scenario is shown in Fig. 3d. SDD1 activity around the precursor might broadcast spatial cues into the surrounding apoplast that interact with extracellular domains of a TMM-containing receptor complex anchored in the NC cell membrane. The resulting intracellular signaling cascade might then either control the orientation of the division plane or limit the NCs that can divide.

Data that address the relationship between TMM and SDD1 function come from the overexpression of *SDD1* in wild-type and *tmm* backgrounds. Overexpression of *SDD1* from the CaMV 35S promoter in a wild-type background reduces the number of stomata and causes many GMCs to arrest – outcomes that are consistent with the overabundance of a negative regulator [19]. Thomas Altmann and co-workers showed that there is a probable feedback loop in which *SDD1* expression in precursor cells inhibits *SDD1* expression in adjacent cells [19]. The resulting restriction of *SDD1* expression could insure that only stomatal precursors produce directional cues. When this feedback loop is short-circuited by ectopic 35S expression, SDD1 produced by NCs might mimic the presence of adjacent precursors. In wild-type plants, one of the adjacent precursors usually dedifferentiates, thus restoring the spacing pattern [2]. Such a signaling mechanism might cause GMC arrest and reduce stomatal number in 35S *SDD1* plants. However, 35S-driven *SDD1* expression in a *tmm* background has no effect on stomatal number and does not cause GMC arrest [19]. The requirement for functional TMM hints that it might comprise part of the receptor complex that perceives SDD1-generated signals from precursors, but more work is needed to test this hypothesis. In addition, the relationship between TMM and SDD1 probably depends upon organ type and the stage of the pathway because different organs show different phenotypes in *tmm* and because their expression

patterns overlap at some, but not other, stages of the stomatal pathway.

Stem cells in epidermal development

Paradoxically, TMM restricts the number of NC divisions but its expression correlates with a propensity to divide. *TMM* expression is strongest in NCs that were produced most recently by asymmetric division, and such young NCs show the highest frequency of asymmetric division [6,8]. Similarly, the ‘isolated’ cells that express *TMM* are of a size and shape characteristic of cells observed to divide in the developing leaf epidermis [6,8]. However, more NCs express *TMM* than actually divide. Thus expression might indicate competence, but not necessarily a commitment, to divide [2,12]. Conversely, *TMM* expression is absent from terminally differentiated cells such as mature stomata and large pavement cells. Together, these data argue that TMM functions primarily in cells that are capable of dividing in the developing epidermis.

Often the timing, location and orientation of cell divisions are regulated to build functionally organized tissues in plants. Progress in understanding the stomatal system has provided insight into how the need for new cells is balanced with solidifying patterning elements through cell differentiation. Each cell lineage that ultimately produces a stoma also generates cells that can reiterate stomatal production. The stomatal lineage can be considered to originate from cells exhibiting characteristics reminiscent of animal stem cells. Stem cells are self-renewing and produce other daughter cells that terminally differentiate [21]. The progenitors of a stomatal lineage seem to fit these criteria because their divisions produce new cells that can act as MMCs. Controlling the behavior of stem cells is central to producing new cells in a spatially appropriate manner.

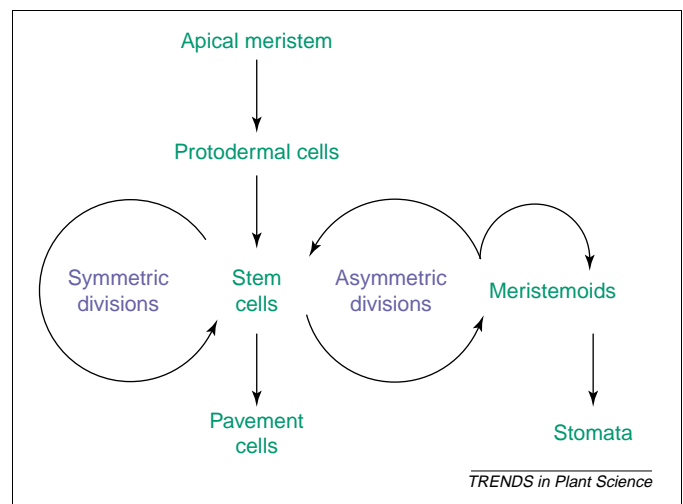


Fig. 4. Flux through the stem cell compartment involved in forming stomata and the leaf epidermis. In this model, stem cells derive from the protoderm and can divide symmetrically or asymmetrically. Each asymmetric division produces a stomatal meristemoid and a larger sister cell. The larger sister cell can divide symmetrically or asymmetrically. The pool of stem cells is replenished by meristemoid asymmetric divisions and by stem cell symmetric divisions. It is drained by the terminal differentiation of stomata and pavement cells. This balance regulates stomatal and epidermal cell number. Pavement cells differentiate from stem cells and their derivatives; they might also derive directly from selected protodermal cells (not shown).

TMM expression could, in part, mark a post-protodermal stem cell compartment, a view supported by the apparent confinement of *TMM* expression to the developing epidermis. By contrast, *SDD1* does not appear to be expressed in early stem cells and it is expressed below the epidermis (in the apical meristem and developing leaf mesophyll) [19]. Although neither gene seems to be required for stem cell formation, both regulate when and where stem cells divide to achieve a dynamic balance between division and differentiation. At the population level, this can be visualized as modulating the amplitude of arrows in the flowchart shown in Fig. 4. Presumably a crucial and early step in this pathway is the shift from protodermal cell identity to that of a *TMM*-expressing cell capable of dividing asymmetrically. *SDD1* could negatively regulate this step but because *SDD1* is only expressed in the epidermis after the first asymmetric division takes place, this function might instead be controlled through radial signaling from subtending leaf layers [19].

Once the first asymmetric division occurs, both *SDD1* and *TMM* promote the asymmetric division of meristemoids. This creates new NCs that replenish the pool of cells that can produce the next generation of meristemoids. At the same time, both gene products restrict the number of NCs that divide to form meristemoids. Thus, the stomatal index is regulated by the size of the pool of cells that can proliferate, the number of cells selected for the initial asymmetric division, and by the number of times each meristemoid divides. The pool of stem cells can also be replenished through symmetric division [8]. It is drained by the progressive terminal differentiation of meristemoids into stomata and of other cells into pavement cells [22].

A similar balance between proliferation and differentiation is a hallmark of apical meristem maintenance and activity, a parallel underscored by the finding that both developing leaves and meristems apparently use LRR-receptor like proteins to regulate this balance [13]. However, stem cell activity in developing leaves is different from apical meristem activity in that it is transient and dispersed. Other stem cell pathways, such as those that produce vascular tissue, also act outside the apical meristem. Thus, study of the stomatal pathway should help to identify gene classes and processes that will expand our understanding of plant stem cell compartments.

Concluding remarks

An emerging picture is that many types of plant cells are patterned via intercellular communication [9,10]. Depending upon the cell type, short-distance communication can occur through plasmodesmata or through the cell wall and then across the cell membrane [23]. Existing data tend to support the latter route for cross talk between stomatal precursors and adjacent cells. Relevant questions here are the identity of the substrate processed proteolytically by *SDD1*, whether *TMM* has a co-receptor, and the nature of a ligand that might activate a *TMM*-containing complex.

Regardless of the route of communication, the consequence is downstream signaling within the target cell, a process about which little is yet known. Several

additional questions concern this signaling as well as other events in stomatal patterning. One is how the asymmetry itself is set up. The smaller daughter cell invariably becomes the meristemoid, which indicates that an intrinsic polarity is established before division [2,24]. Although *tmm* sometimes disrupts this polarity [2], the genes required for the intrinsic asymmetry have not yet been identified. A second question is how intercellular signaling is superimposed upon and orients this intrinsic polarity. The challenge is to identify how the reception of spatial information from the precursor cell is then transduced to control cell-cycle progression and to specify correctly the plane of asymmetric division in the NC. A third question is how the planes of serial divisions are often coordinated through meristemoids (inward spiral) and then GMCs, a mechanism that could hypothetically allocate positional landmarks through successive mitoses.

Finally, the stem cell compartment marked by *TMM* expression needs further definition. Questions here include how protodermal cells differ from later-acting stem cells, the molecular events that mark the earliest commitment to asymmetric division and to entry into the stomatal pathway, and how the distribution of this compartment is regulated dynamically to populate the leaf epidermis and distribute stomata.

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