CHAPTER FOUR

Patterning at the shoot apical meristem and phyllotaxis

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Abstract

The shoot apical meristem (SAM) generates all above-ground organs throughout the life of plants. The development and maintenance of the SAM are crucial for building the plant architecture. The spatiotemporal patterning of lateral organs (leaves and flowers), called phyllotaxis, is one of the best-characterized self-organizing systems and has long been proposed to be driven by inhibitory fields generated by the existing organs and blocking new initiations in their vicinity. Recent years have seen impressive progress in our understanding of the molecular mechanisms controlling SAM function, and on how these mechanisms act in phyllotactic patterning. In this chapter, we first review the regulation of SAM stem cell activity and discuss how feedback signals

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coming from the differentiated organs affect stem cell homeostasis. Then we highlight experimental and theoretical works that have revealed the chemical and biophysical factors acting in the regulation of phyllotaxis. Finally, we summarize the important roles of SAM geometry in phyllotaxis.

1. Introduction

In contrast to animals, in which organogenesis occurs mainly during embryogenesis, plants continuously produce new organs during their post-embryonic development. This unique developmental ability is due to the existence of stem cell-containing tissues located at the growing apices of plants, called meristems. The shoot apical meristem (SAM), located at the shoot apex, and the root apical meristem (RAM), located at the root tip, give birth to all the aerial and underground parts of a plant, respectively. In several basal plants, the shoot apex is made of a single triangular cell (Golub & Wetmore, 1948). But in higher plants, like *Arabidopsis thaliana*, *Zea mays* (maize), and *Oryza sativa* (rice), the SAM is multicellular, with distinct cell layers and domains.

Both the SAM and the RAM are established during embryogenesis. Once environmental conditions, such as temperature and humidity, are suitable for germination, the meristems are activated to initiate organogenesis (although for some species like maize, organogenesis by the SAM is already active during embryogenesis), which is repetitive and modular. The modules are called phytomers (Hay & Tsiantis, 2010; Teichmann & Muhr, 2015). During the vegetative phase of development, each phytomer consists of a compressed internode, a leaf on the node, and an axillary meristem in the leaf axil. When plants reach the floral transition stage, internodes start elongating, and leaves are narrower, and their axillary meristems develop into branches. Later in the reproductive phase, phytomers bear flowers, with axillary leaves often being absent. Meristem activity is not only controlled by molecular and hormonal networks in the stem cells and surrounding regions but also by feedback regulation through long-distance signals from the differentiated cells in the previously formed organs. We will discuss these regulatory mechanisms below.

Phyllotaxis (from ancient Greek: *phýllon* refers to "leaf" and *táxis* means "arrangement") refers to the spatial organization of lateral structures (leaves, branches, flowers, etc.) along the stem. Phyllotaxis has been attracting the attention of mathematicians, physicists, and biologists for several centuries (for review, Adler, 1997; Galvan-Ampudia, Chaumeret, Godin, & Vernoux, 2016;

Kuhlemeier, 2017; Traas, 2013). In nature, there are different types of phyllotactic patterns, including alternate (distichous), opposite (decussate), whorled, and spiral. Among these, spiral phyllotaxis is the most frequent (Jean & Barabe, 1998), with an average divergence angle between single consecutive organ primordia close to 137.5°, the so-called "golden angle" defined from the Fibonacci series. The primary determinant of phyllotaxis is the spatiotemporal pattern of organogenesis in the meristem (Fig. 1A). During development, these patterns sometimes shift (Bartlett & Thompson, 2014). For example, in *A. thaliana*, the cotyledons and the first pair of true leaves are initiated in a nearly opposite decussate pattern, while all the following leaves and flowers initiate following a spiral pattern and later, during flower formation, floral organs are arranged in whorled patterns.

In contrast to the extensive modeling work available, it is only in the early 21st century that the molecular mechanisms underlying phyllotactic patterning in the SAM started to be uncovered. In this chapter, we will discuss our current knowledge of these mechanisms. We will first present a brief overview of the development of the SAM, of its organization and of the regulation

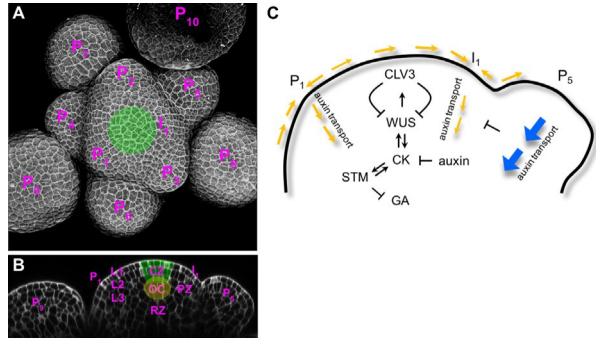

Fig. 1 The inflorescence shoot apical meristem of *A. thaliana* and its regulatory network controlling stem cell activity. (A) Top view of the SAM showing the center zone (CZ) and sequentially initiated primordia, with P_1 referring to the youngest primordium, P_2 the second youngest one, and so on; I_1 refers the oldest incipient primordium. (B) Side view of the SAM indicating the different structural organizations: three specific cell layers (L1, L2, and L3) and three different functional zones, the CZ, the peripheral zone (PZ), and the rib zone (RZ) that harbor the organizing center (OC). (C) Conceptual summary of the regulation of stem cell activity in the SAM. The interaction between CLV and WUS forms a negative regulatory feedback loop in the meristem center, with cytokinin (CK) generating positive loops with WUS and STM to maintain SAM development, auxin inhibiting the action of CK, and gibberellins (GA) mediating the coordination of STM regulation. Feedback from the differentiated organs regulates stem cell activity through auxin transport modulation (see Shi et al., 2018 for details). Bars = 20 μm.

of stem cell activity. We will then summarize the history of research on phyllotaxis and discuss the multiple regulatory levels involved in the regulation of phyllotaxis. We will notably highlight the role of the phytohormones auxin and cytokinin, of biomechanical signals, as well as of SAM geometry and of post-meristematic growth.

2. Development of the shoot apical meristem

2.1 A brief overview of the organization and genetic regulation of shoot apical meristem activity

Numerous reviews have been written on the genes regulating the activity of the SAM (Barton, 2010; Gaillochet, Daum, & Lohmann, 2015; Galli & Gallavotti, 2016; Soyars, James, & Nimchuk, 2016; Truskina & Vernoux, 2018; Wang, Smith, & Li, 2018). Here, we will only briefly summarize the current knowledge. SAMs of dicots, such as the one of *A. thaliana*, contain three well-defined cell layers (Fig. 1B). Whereas the two outer layers (L1 and L2) contain cells with anticlinal cell division planes (new cell wall being perpendicular to the meristem surface), cells from the third layer (L3) divide in all directions. During development, the L1 forms the epidermis, while the L2 and L3 form the subepidermal and vascular tissues of aerial tissues. In monocots, such as maize and rice, the SAM consists only of two layers with the L1 producing similarly the epidermis and the L2 building the internal tissues.

The SAM can also be divided into different functional domains based on their gene expression patterns and signaling activities. The central zone (CZ) harbors the stem cells that divide slowly. The homeostasis of this population of cells is essential to maintain a stable meristem size. With division in the CZ, some of the daughter cells are moved outward from the CZ to the peripheral zone (PZ), where new organ primordia (leaves and flowers) are initiated. Underneath the CZ is the rib zone (RZ) that is responsible for the development of the internal tissues of the stem. In addition, there is a group of cells located in the upper part of the RZ, referred to as the organizing center (OC) that establishes a stem cell niche and regulates the stem cell population above it (Fig. 1C). First identified in *A. thaliana*, the transcription factor gene *WUSCHEL* (*WUS*) is expressed in the OC (Mayer et al., 1998). The WUS protein moves upward into the CZ through plasmodesmata (Daum, Medzihradszky, Suzaki, & Lohmann, 2014), activating in the stem cells the expression of the *CLAVATA3* (*CLV3*) gene, which is the founding member of the CLV3/EMBRYO SURROUNDING

REGION (CLE) peptide family and is expressed specifically in the CZ (Clark, Running, & Meyerowitz, 1995; Opsahl-Ferstad, Deunff, Dumas, & Rogowsky, 1997). Reciprocally, when secreted from the CZ, the CLV3 peptide is perceived by membrane receptors, notably the receptor-like kinase CLV1, in the OC to repress *WUS* activity (Clark, Williams, & Meyerowitz, 1997; Ottoline Leyser & Furner, 1992). This interaction between *CLV3* and *WUS* establishes a negative feedback regulatory loop that contributes to stem cell homeostasis in the SAM. Other independent regulators of stem cell niche homeostasis have been identified more recently, providing robustness to the organization of the SAM (Mandel et al., 2016; Schuster et al., 2014; Zhou et al., 2015). Numerous regulators of organogenesis are also known (reviewed in Besnard, Vernoux, & Hamant, 2011; Sassi & Vernoux, 2013; Sluis & Hake, 2015; Wang & Jiao, 2018), and we will discuss later how auxin acts as the master regulator of the organogenesis program.

2.2 Hormonal regulation of stem cell activity

Plant hormones have long been known to have an indispensable role in the regulation of stem cell activity and in self-organization of the SAM (Fig. 1C). First, cytokinin (CK) is thought to be important for SAM development because it can prevent cell differentiation and promote cell division of stem cells. Supporting this idea, a two-component sensor (TCS) that reports CK activity *in planta*, detects a maximum of CK signaling activity in the OC, overlapping with the expression of *WUS* (Gordon, Chickarmane, Ohno, & Meyerowitz, 2009; Muller & Sheen, 2008). This is consistent with the previous observation that the WUS protein inhibits transcription of two genes encoding CK signaling repressors, *ARABIDOPSIS RESPONSE REGULATOR7* (*ARR7*) and *ARR15* (Leibfried et al., 2005; Zhao et al., 2010), indicating that WUS positively regulates CK response sensitivity. Gordon and co-workers also reported that the CK signaling pathway, in turn, activates *WUS* levels and regulates stem cell number in the meristem (Gordon et al., 2009). Additionally, it was shown that a gene encoding a nucleotide sugar transporter, *REPRESSOR OF CYTOKININ DEFICIENCY1* (*ROCK1*), fine-tunes CK activity through modification of CK-degrading enzymes, the CK oxidases/dehydrogenases (CKXs), and thus regulates meristem activity (Niemann et al., 2015). On the other hand, the Class I *Knotted1-like homeobox* (KNOX1) genes, including *SHOOTMERISTEMLESS* (*STM*) in *A. thaliana* and *KNOTTED1* in maize, were shown to upregulate CK

biosynthesis and consequently the CK response in the SAM (Jasinski et al., 2005; Kerstetter, Laudencia-Chingcuanco, Smith, & Hake, 1997; Yanai et al., 2005). The KNOX1 gene family encodes a group of transcription factors and is essential for meristem development and maintenance (Hay & Tsiantis, 2010). An activating enzyme in CK biosynthesis of rice, encoded by the *LONELY GUY* (*LOG*) gene, is required for meristem maintenance, with mRNA expression levels of KNOX1 family genes in *log* mutants being dramatically decreased (Kurakawa et al., 2007). Thus, KNOX1 family genes and CK may act in a positive regulatory loop during SAM development and maintenance.

In contrast to CK, auxin has a low activity level in the OC of the SAM, as indicated by the auxin signaling sensors DR5 and DII-VENUS, and negatively regulates the stem cell population (Benkova et al., 2003; Brunoud et al., 2012; Shi et al., 2018). However, at the same time, periodic auxin maxima have been shown to be driving organ initiation in the SAM (Benkova et al., 2003; Heisler et al., 2005; Reinhardt et al., 2003). We will discuss this aspect more thoroughly in the phyllotaxis section below. Within the SAM, it is reported that auxin negatively regulates the CK signaling inhibitors *ARR7* and *ARR15* through the action of MONOPTEROS/AUXIN RESPONSE FACTOR5 (MP/ARF5) transcription factor, suggesting a cross-talk between CK and auxin in the regulation of stem cell activity and SAM development (Zhao et al., 2010).

Besides CK and auxin, gibberellins (GAs), a group of plant hormones that promote cell elongation and cell division and thus play an essential role in plant growth, are found to be regulated by KNOX genes in the SAM. In *A. thaliana*, GA levels are coordinated by STM activity in the SAM through the inhibition of expression of the GA biosynthesis gene *GA20-oxidase1*, which is highly expressed in organ primordia (Jasinski et al., 2005). However, how GAs affect SAM maintenance remains poorly understood.

2.3 Feedback from differentiated cells

In animals, stem cell proliferation is controlled not only by signals from the stem cell niche but also by those from differentiating progeny cells (Lander, Gokoffski, Wan, Nie, & Calof, 2009; Rue & Martinez Arias, 2015). In the SAM, it has long been hypothesized that signals from lateral organs (leaves, flowers, and branches) have a feedback on meristem homeostasis (for details, see Barton, 2010). For example, the two *A. thaliana* YABBY genes *FILAMENTOUS FLOWER* (*FIL*) and *YABBY3* (*YAB3*) might non-autonomously

regulate SAM activity through two putative signals originating from the meristem-primordia boundaries. Meristem size in *fil-8 yab3-2* double mutants is dramatically increased with enlarged *WUS* and *CLV3* expression domains (Goldshmidt, Alvarez, Bowman, & Eshed, 2008). It has also recently been reported that a maize CLE family gene, *ZmFCP1*, encoding a peptide secreted from leaf primordia, suppresses *WUS* expression and thus stem cell activity in the meristem (Je et al., 2016). More recently, combining biological experiments and mathematical modeling, it was found that polar auxin transport from lateral organs inhibits polar auxin transport from the SAM (including leaf primordia P_1 and incipient primordia I_1), keeping a constant low auxin level in the SAM, thereby maintaining a robust SAM stem cell activity and thus normal meristem growth and development (Shi et al., 2018). Based on this work, it was proposed that the lateral organs feedback on the growth of the SAM through an auxin transport switch mechanism (Fig. 1C). In summary, all these studies suggest that both signals emanating from the meristem-primordia boundaries and/or long-distance hormone transportation from lateral organs are responsible for a feedback regulation on stem cell proliferation and meristem development, which might balance the self-maintenance and organogenesis activities of the meristem.

3. A few words on the history of phyllotaxis research: The development of the inhibitory field concept

Phyllotaxis is a striking example of self-organized patterning in plants and, more generally, in developmental biology. Due to the unique mathematical regularities of phyllotaxis, phyllotaxis research has long been interdisciplinary and started at least as early as the 14th century (Adler, 1997). Numerous models have been proposed to explain phyllotactic patterning, and among them, the one based on the inhibitory field hypothesis is now well accepted. This hypothesis proposes that each formed organ primordium generates an inhibitory field (the inhibition could be explained non-exclusively by geometry, chemical, or mechanical signals) that prevents initiation of new primordia in its vicinity (Douady & Couder, 1996; Hofmeister, 1868; Snow & Snow, 1962). Therefore, as the SAM grows, incipient primordia can be initiated at sites where the inhibition is the lowest (Fig. 2).

As early as 1830, mathematicians discovered that in spiral phyllotaxis, the number of contact parastichies (spirals connecting two closest neighboring organs) in clockwise and counter-clockwise orientations, respectively, corresponds to two consecutive numbers of the Fibonacci series, where the first

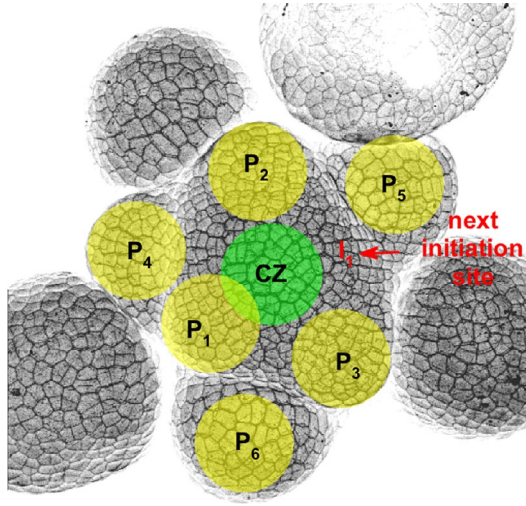

Fig. 2 Conceptual model of the inhibitory field hypothesis. Outside of the central zone (CZ), primordia initiated at the periphery produce inhibitory fields (yellow-filled circles) with the next incipient primordium (I_1) emerging at the site where the inhibitory effect is lowest.

numbers are 1 and 2, and then each number is the sum of the two previous ones. The golden angle (137.5°) is mathematically related to the Fibonacci sequence as it corresponds to the division of a circle (360°) by the value of the limit of the ratio between two consecutive numbers in the Fibonacci sequence, a ratio also called the "golden ratio." This is one of the reasons why spiral phyllotaxis has received much attention from both theoretical and experimental scientists.

One of the first models to explain phyllotaxis was put forward in the 19th century by Hofmeister (1868). He proposed that new primordia appear periodically at the apex boundary in the largest available gap left by previously formed primordia. Then, a chemical theory was put forward by Schoute (1913), stating that the placement of incipient primordium is determined by a chemical inhibitor secreted by the previously formed primordia that prevents a new primordium from emerging too close. Richard favored Schoute's hypothesis and called it a "field theory" (Richards, 1948, 1951). This inhibitory field concept also found support from microsurgical experiments conducted on meristems of *Lupinus albus* (Snow & Snow, 1932). Snows found that the position where a new leaf primordium is initiated is influenced by the previously formed primordia adjacent to the site of initiation, and thus, they proposed that "each new leaf is determined in the first space on the

growing apical cone that attains a necessary minimum size and minimum distance below the tip" (Snow & Snow, 1962). This microsurgery results were recently re-explored and further confirmed using laser-ablation approaches (Reinhardt, Frenz, Mandel, & Kuhlemeier, 2005). Wardlaw (1949) also conducted microsurgery experiments but in shoot meristems of ferns and favored an explanation of inhibition due to physical stresses. Numerical simulations were used to analyze the system dynamics emerging from inhibitory fields. In their seminal work, Douady and Couder demonstrated that an inhibitory field hypothesis can recapitulate a wide variety of phyllotactic patterns by only adjusting one geometric parameter, corresponding to the ratio between the radius of lateral inhibitory fields and that of the central zone (Douady & Couder, 1996).

Taken together, the existing evidence suggests that inhibitory fields that may arise from either chemical or physical signals or even both could be necessary and sufficient for self-organization of phyllotactic patterning in the SAM. In the following sections, we will discuss the role of chemical (auxin and cytokinin) and physical signals in phyllotaxis (Fig. 3).

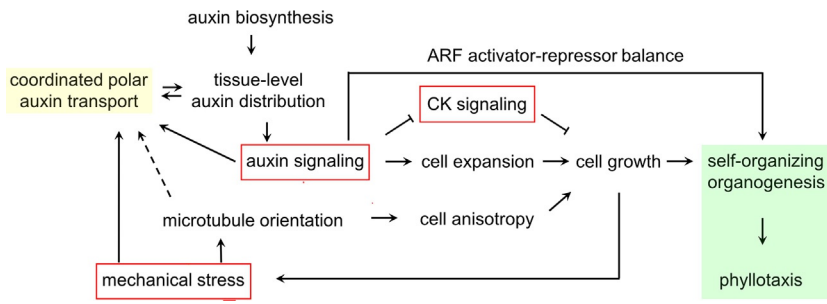

Fig. 3 Graphical summary of the regulation of chemical (auxin, CK) and mechanical signals on phyllotaxis in the SAM. First, a positive feedback loop between auxin and PIN1 polarity self-organizes the auxin distribution in the SAM. Self-organization of organogenesis driving phyllotaxis is further dependent on spatial differences in auxin signaling capacities. The signaling capacities also depend on the local balance between ARF activators and repressors. Regulation of auxin biosynthesis also contributes to the distribution of auxin. Second, CK signaling acts downstream auxin signaling in the temporal regulation of phyllotaxis. Third, polar auxin transport, primarily mediated by PIN1 in the SAM, responds directly to mechanical stress mediated by microtubule orientation. Microtubule organization also controls cell wall anisotropy, thus determining the direction of cell growth. Together with auxin that controls cell wall expansion and growth rate, this mechanism regulates cell growth. Cell growth, in turn, generates a feedback on mechanical stress, thus channeling organogenesis.

4. Phyllotaxis and chemical signals

4.1 Coordinated polar auxin transport: Tissue level auxin distribution allowing for self-organizing organ initiation

Studies over the past 20 years have identified auxin as a major actor in the molecular mechanisms of organ initiation and phyllotaxis. In contrast to that of other phytohormones, transport of auxin in plants is mainly directional, i.e., polar, involving the action of specific carriers. Among these carriers, the PIN-FORMED1 (PIN1) protein is the major regulator of polar auxin transport in the SAM. It is localized asymmetrically on plasma membranes and is thought to direct the auxin flux (Petrasek et al., 2006; Wisniewska et al., 2006). Mutants affecting *PIN1* develop almost no floral buds on the inflorescence meristem, resulting in a "pin-shaped" inflorescence, a phenotype that can be mimicked by treatment with the auxin transport inhibitor *N*-1-naphthylphthalamic acid (NPA) (Galweiler et al., 1998; Okada, 1991).

These results were the first to indicate that polar auxin transport is required for organ initiation. It was reported later that exogenous auxin treatment could rescue organogenesis of *pin1* inflorescences in *A. thaliana* or of NPA-induced pin-shaped vegetative SAMs in tomato (Reinhardt, 2000; Vernoux, Kronenberger, Grandjean, Laufs, & Traas, 2000), suggesting that auxin maxima regulate organ initiation. In addition, immunodetection and advanced live-imaging methods showed that cellular PIN1 polarities create a convergence pattern toward incipient primordia initiation sites, suggesting that polar auxin transport mediated by PIN1 forms auxin maxima in the meristem, and activates organ initiation (Heisler et al., 2005; Reinhardt et al., 2003). Using the biosensors DII-VENUS and its derivative R2D2 allowed the visualization of auxin levels in the SAM, confirming auxin accumulation at the sites where primordia initiate (Bhatia et al., 2016; Vernoux et al., 2011). Using both computer- and experiment-based analysis, the AUXIN1/LIKE AUXIN1 (AUX/LAX) family of auxin influx carriers has also been proposed to contribute significantly to auxin distribution dynamics, and thus to stabilize phyllotactic patterning (Bainbridge et al., 2008; Kramer, 2004; Reinhardt et al., 2003). Importantly, besides controlling auxin accumulation, the convergence patterns of PIN1 polarities at incipient primordia have also been proposed to deplete auxin around the primordia (Heisler et al., 2005; Reinhardt et al., 2003), a prediction that was confirmed using the DII-VENUS biosensor (Vernoux et al., 2011). Taken together, these studies indicate that depletion of

auxin, an activator of organogenesis, in the vicinity of primordia by auxin efflux transporters can generate a chemical inhibitory field.

But how is PIN1 polarity spatiotemporally regulated at the tissue level to get a coordinated auxin flux driving a self-organizing organogenesis pattern? We have extensive knowledge on the control of PIN1 polarity at the cellular level in *A. thaliana* (Friml, 2010), but our understanding at the tissue level is still limited. Different models have been proposed based on experimental observations. The concentration-based model postulates that PIN1 in the L1 of the SAM can be polarized against the auxin gradient in the tissue. For a given cell, polarity is established toward the neighboring cell that contains the highest auxin concentration, thereby resulting in auxin accumulation at the PIN1 convergence points (Jonsson, Heisler, Shapiro, Meyerowitz, & Mjolsness, 2006; Smith et al., 2006). The flux-based hypothesis, originally proposed to explain mid-vein formation (Sachs, 1969, 1981), also allows the simulation of realistic self-organization of the PIN1 network in the SAM. This hypothesis proposes that PIN1 localization at the membrane is proportional to the auxin flux through the membrane, thus stabilizing the auxin efflux (Abley, Sauret-Güeto, Marée, & Coen, 2016; Stoma et al., 2008). But, this model requires a transient auxin decrease during the formation of PIN1 convergence sites, which has not been observed to date.

A dual-polarization hypothesis has also been put forward and proposes that an up-the-gradient mechanism regulates PIN1 polarities in the epidermal cells, and that simultaneously a with-the-flux polarization acts in the internal tissues, allowing PIN1 localization to shift to the basal side of cells and to initiate venation (Bayer et al., 2009). The existence of different mechanisms of polarization is possibly supported by the analysis of a sister clade of *PIN1*, *Sister-of-PIN1* (*SoPIN1*), present in all flowering species excluding the Brassicaceae (and thus *A. thaliana*), and of two duplicated forms of *PIN1* in grasses, *PIN1a* and *PIN1b* (O'Connor et al., 2014). The spatiotemporal patterns of polarities of SoPIN1, PIN1a and PIN1b proteins in the SAM are compatible with SoPIN1 being polarized in an up-the-gradient manner in the epidermal and with PIN1a and PIN1b being localized in the inner cells as predicted by the with-the-flux mechanism (O'Connor et al., 2017, 2014).

While the assumptions are different, all models have in common the long-standing idea that auxin has a positive feedback on its transport. Taken together, they thus indicate that a regulatory loop between auxin, PIN1 protein expression, and PIN1 localization is likely responsible for the self-organization of cellular PIN1 polarities and thus of organ initiation in the

SAM. However, all models have significant limitations and further biological data and alternative mathematical models are required in the future to fully understand how polar auxin transport self-organizes the auxin distribution in the SAM (for discussion, see van Berkel, de Boer, Scheres, & ten Tusscher, 2013).

4.2 Auxin signaling: Downstream regulation of auxin distribution

Auxin signaling has also been reported more recently to play a role in phyllotaxis together with the spatial auxin distribution. Central to auxin signaling is the interaction between the AUXIN/INDOLE ACETIC ACID (AUX/IAA) transcriptional repressors and the AUXIN RESPONSE FACTOR (ARF) transcription factors. As cellular auxin levels increase, auxin promotes the association of AUX/IAA proteins with the TRANSPORT INHIBITOR RESPONSE1 (TIR1) F-box protein [or another one of three related AUXIN-RELATED F-BOX (AFB) proteins], which is part of an SCF E3 ubiquitin ligase complex. The AFBs act as co-receptors of auxin and their association with the SCF complex induces the proteolytic degradation of AUX/IAA proteins and thus releases the ARFs from the AUX/IAA repressors, allowing the ARFs to regulate transcriptional responses (Calderon Villalobos et al., 2012; Dharmasiri, Dharmasiri, & Estelle, 2005; Kepinski & Leyser, 2005; Tan et al., 2007). Some AUX/IAA family genes are also targets of ARFs, allowing for a negative feedback loop.

There are 29 AUX/IAAs and 23 ARFs in *A. thaliana*, with most ARFs being regulatory repressors and only 5 of them (ARF5 to ARF8 and ARF19) being activators (Guilfoyle & Hagen, 2007). Using in situ hybridization, Vernoux et al. (2011) have drawn a spatial regulatory map of auxin signaling in the SAM by analyzing the expression of most TIR1/AFB, AUX/IAA, and ARF family genes. This analysis showed a general trend with a low level of expression of ARF and Aux/IAA genes in the CZ and a high expression level in the PZ. Thus, there is large-scale co-expression of ARF activators and repressors in the SAM. A mathematical model of auxin signaling, based on a large-scale analysis of the AUX/IAA-ARF interaction networks, predicted that (1) the differential expression patterns between ARF activators and repressors produce a differential sensitivity to auxin between the CZ (low) and the PZ (high) and (2) the balance between ARF activators and repressors provides a buffering capacity toward input fluctuations, thereby stabilizing regulatory responses (Vernoux et al., 2011). The auxin signaling input sensor DII-Venus, and the output signaling reporter DR5::Venus,

could be used to confirm these two predictions. These results likely explain why exogenous auxin treatment cannot induce organ initiation in the CZ of the *pin* mutant (Reinhardt, 2000) and that organogenesis occurs only in the PZ. Also, it suggests that auxin signaling plays a role in the robustness of phyllotaxis.

More evidence on the role of the auxin signaling pathway comes from studies of the MP/ARF5 transcription factor, one of the ARF activators in *A. thaliana*. The *mp* mutant shows a *pin*-like inflorescence meristem phenotype, but unlike in the *pin1* mutant, exogenous auxin application is not able to rescue its flower initiation defects (Hardtke & Berleth, 1998; Reinhardt et al., 2003; Zhao et al., 2010). MP/ARF5 was further shown to regulate floral organ initiation through the direct activation of key regulators of flower development: *LEAFY* (*LFY*), *AINTEGUMENTA* (*ANT*), *AINTEGUMENTA-LIKE6/PLETHORA3* (*AIL6/PLT3*), and *FIL*, and the cytokinin response factors *ARR7*, *TARGET OF MONOPTEROS3/CYTOKININ RESPONSE FACTOR2* (Weijers & Wagner, 2016; Yamaguchi et al., 2013). This allows for a better understanding of the molecular mechanisms by which auxin directly controls organogenesis. More recently, work combining live-imaging and molecular genetics proposed that MP is necessary in the SAM to stabilize the PIN1 convergence site before primordia outgrowth (Bhatia et al., 2016). Auxin signaling would thus be directly involved in the mechanisms of PIN1 polarization, thus playing a central role alongside polar auxin transport in the regulation of phyllotaxis. Finally, a recent study found that auxin transcriptional responses are restricted to the boundary between domains of expression of dorsoventral polarity regulators, i.e., *REVOLUTA* and *KANADI* genes (Caggiano et al., 2017), suggesting that organ polarity genes can also be essential for phyllotaxis by regulating auxin signaling capacities.

4.3 Regulation of auxin biosynthesis: Upstream regulation of auxin distribution

As mentioned in Section 1, *A. thaliana* plants change their leaf phyllotactic pattern from decussate to spiral after the initiation of the first pair of true leaves; however, this shift is dramatically delayed in the *plt3 plt5 plt7* triple mutant (Prasad et al., 2011). *PLT* genes encode members of the AP2-domain transcriptional factor family. The *PLT3*, *PLT5*, and *PLT7* genes are found expressed both in the CZ and the PZ (Prasad et al., 2011). Furthermore, genetics and functional analysis revealed that the PLT proteins regulate the expression of the auxin biosynthesis genes *YUC1* and *YUC4*

(Pinon, Prasad, Grigg, Sanchez-Perez, & Scheres, 2013). It was also found that three INDETERMINATE DOMAIN (IDD) transcription factors, IDD14, IDD15, and IDD16, promote auxin accumulation by directly regulating the expression of *PIN1* and the two auxin biosynthesis genes *YUC5* and *TRYPTOPHAN AMINOTRANSFERASE of ARABIDOPSIS* (Cui et al., 2013). Thus, these results indicate a role for PLT- or IDD-dependent auxin biosynthesis in the *A. thaliana* meristem. In maize, it was reported that two auxin biosynthesis genes, *VANISHING TASSEL2* and *SPARSE INFLORESCENCE1*, act in the same pathway to regulate vegetative and reproductive meristem development and phyllotaxis, with their double mutant exhibiting a barren inflorescence meristem without lateral organs or functional spikelets (Gallavotti, Yang, Schmidt, & Jackson, 2008; Phillips et al., 2011). Taken together, all these results suggest that auxin biosynthesis is also required for phyllotaxis.

The above-mentioned findings are consistent with earlier work, which revealed that mutations affecting *YUC1* and *YUC4* enhance the *pin1* mutant phenotype, and that disruption of *AUX1* in the *yuc1 yuc2 yuc4 yuc6* quadruple mutant phenocopies the *yuc1 yuc4 pin1* triple mutant (Cheng, Dai, & Zhao, 2007). These results indicate that auxin biosynthesis and polar auxin transport contribute synergistically to phyllotaxis. However, we are still missing a clear view of the sites of auxin biosynthesis in the SAM, and auxin biosynthesis remains to be incorporated into auxin transport-based phyllotaxis models to get a more comprehensive understanding of self-organized patterning in the SAM.

4.4 Cytokinin: A secondary inhibitory field acting on the plastochrone

Given that auxin and CK signaling cross-talk during SAM development (see above), one might ask whether there is a role for CK in organ initiation and phyllotaxis? It was reported that CK, along with auxin, is required for organ formation (Yoshida, Mandel, & Kuhlemeier, 2011). In this section, we will discuss how cytokinin is involved in phyllotaxis.

A. thaliana mutants affecting the CK signaling inhibitor *ARABIDOPSIS HISTIDINE PHOSPHOTRANSFER PROTEIN6* (*AHP6*) have a phenotype of increased organ co-initiation that results in permutations of the order of siliques along the stem, while the divergence angle between organ initiation sites in the SAM is unchanged (Besnard, Rozier, & Vernoux, 2014). Further observations found that *AHP6* expression in organ primordia is directly activated by auxin through MP and appears specifically one plastochron later

than expression of the DR5 reporter (Besnard et al., 2014). More interestingly, it was discovered that the AHP6 protein can move out of the primordia where it is transcribed, establishing a differential of accumulation between successive incipient primordia: AHP6 is low in I_1 (Fig. 2), while it accumulates in I_2 where the next primordium is expected to form after I_1. Blocking AHP6 protein movement by fusing three copies of Venus to the AHP6 protein was not able to rescue *ahp6* mutants in contrast to fusions with a single copy of Venus that can move. This finding supports a scenario where low levels of AHP6 at I_1 allow for high CK signaling and organ initiation, while high levels of AHP6 at I_2 non-cell autonomously repress CK signaling and organ initiation, thereby avoiding organ co-initiation and stabilizing the plastochron (Besnard et al., 2014). Thus, in addition to the primary auxin inhibitory fields that specify the sites of organ initiation, AHP6, acting downstream of auxin, produces a CK-based secondary inhibitory field that increases the robustness of the timing of phyllotaxis patterning (Besnard et al., 2014).

These findings also indicate that AHP6 filters out noise in phyllotaxis, as co-initiation results in permutations of organ order along the stem, and thus in changes of the relative angles on the stem. Phyllotaxis disorder resulting from noise in plastochron initiation has been shown to be common in plants (Refahi et al., 2016). A modeling approach was used to further explore the origin of co-initiation. More precisely, the authors revisited the deterministic model of phyllotaxis developed by Douady and Couder (1996) and developed a stochastic model of primordia initiation at the SAM combining cell-autonomous decisions and stochastic signal perception by cells (Refahi et al., 2016). This model accurately recapitulates the classical phyllotactic patterns and, in addition, produces realistic permutation disorders as a result of stochasticity in signal perception by cells. The model thus predicts that perception and processing of the signals (among which auxin) driving phyllotaxis have stochastic properties (a prediction that remains to be proven), which can induce the co-initiation of primordia. Moreover, the CK-based fields allow to limit the propagation of noise from the cellular level to the tissue scale and thus its impact on the construction of the stem.

5. Mechanical signals: How does physics affect phyllotaxis?

While the role of chemical signals is now well established, the role of mechanical signals in phyllotaxis is still elusive; but accumulating evidence indicates that they also play a role in patterning the SAM. Using atomic force

microscopy imaging and quantitative modeling, several groups have found that the SAM shows locally distinct mechanical properties. In the L1, cell walls of the CZ are much stiffer than those of the PZ (Kierzkowski et al., 2012; Milani et al., 2011, 2014), and incipient primordia and growing primordia have an increased cell wall elasticity (Peaucelle et al., 2011). These findings suggest that organ initiation in the SAM is correlated with a change in mechanical properties (Robinson et al., 2013).

Plant cells are under turgor pressure and glued together by cell walls that contain cellulose and hemicellulose fibrils embedded in a matrix of pectin and proteins (Keegstra, 2010; Wolf, Hématy, & Höfte, 2012). Organogenesis is a process involving coordinated local cell division and directional cell growth (Cosgrove, 2005; Sablowski & Carnier Dornelas, 2014). Cell growth is, in turn, based on irreversible changes in cell wall expansion (i.e., growth rate) and cell wall anisotropy (i.e., growth direction) (Hamant & Traas, 2010).

Irreversible cell expansion induced by auxin during growth is linked to both acidic conditions in the cell wall and the activity of cell wall remodeling enzymes. First, according to the acid growth hypothesis, an auxin-induced decrease of apoplastic pH increases the activity of expansion proteins (which can release the cross-links between polysaccharides complexes), thereby resulting in cell wall loosening (Arsuffi & Braybrook, 2018; Cosgrove, 2005; Murray, Jones, Godin, & Traas, 2012; Nakayama et al., 2012). Second, pectin demethylesterification by PECTIN METHYLESTERASES (PMEs) mediates local auxin-dependent cell wall loosening and thereby organogenesis (Braybrook & Peaucelle, 2013; Peaucelle et al., 2011, 2008). The homeodomain transcription factor BELLRINGER (BLR) was found to be required for the establishment of normal phyllotaxis by restricting PME5 activity to organ primordia (Peaucelle et al., 2011). Thus, during organogenesis, auxin probably triggers cell expansion through modifications of the mechanical properties of the cell wall. Adding to the complexity, other signals, such as the phytohormones GA and brassinosteroid (BR) as well as an active regulation of turgor pressure, are also likely involved, but their precise impact on cell walls and cell expansion remains to be established.

Microtubules are important for the determination of cell wall anisotropy, which is established via the spatial organization of cellulose microfibrils in the cell wall. The cellulose microfibrils determine the direction of growth and their orientation is guided by microtubules through controlling the insertion and movement of cellulose synthase complexes in the plasma membrane (Bringmann et al., 2012; Lei, Li, Du, Bashline, & Gu, 2013; Li, Lei, Somerville, & Gu, 2012). It has been reported that cortical

microtubule orientations align parallel to the predicted mechanical stress (Hamant et al., 2008). Laser-ablation and pharmacological treatments weakening the cell wall further support a scenario where microtubules sense the mechanical stress on the SAM surface, and align accordingly to guide anisotropic cellulose deposition, thus counteracting the mechanical stress (Hamant et al., 2008). This stress-driven microtubule reorientation relies on the action of the microtubule-severing protein KATANIN (Uyttewaal et al., 2012).

In addition to microtubule arrays, mechanical stress has been proposed as a possible factor orienting cellular PIN1 polarity (Heisler et al., 2010; Nakayama et al., 2012). In the *A. thaliana* SAM, PIN1 localizes to anticlinal cell walls parallel to the main microtubule orientation (Heisler et al., 2010). Using mathematical modeling, it was shown that mechanical signals can mediate the feedback loop between auxin and the polar auxin transport system, thereby influencing phyllotaxis (Heisler et al., 2010). Further support comes from experiments in tomato where mechanical stress in the cell walls, mediated through plasma membrane properties, would influence PIN1 levels in each cell and the proportion of PIN1 localized to specific areas of the plasma membrane (Nakayama et al., 2012). Auxin was later shown to act on the organization of the cortical microtubule arrays during organ initiation to directly reduce the mechanical anisotropy of cells, thereby promoting organ initiation (together with the effects on cell wall mechanical properties) (Sassi et al., 2014). Intuitively, considering the role of MP in auxin signaling and phyllotaxis (see Section 4.2), the positive feedback loop between auxin, PIN1, and microtubule orientation is proposed to act through a localized auxin response mediated by MP activity (reviewed in Bhatia & Heisler, 2018).

6. The SAM geometry: Phyllotaxis diversity

The inhibitory field models and notably the work from Douady and Couder (1996) predict that the geometry of the SAM should determine phyllotactic patterning through potentially changing the ratio between the radius of inhibitory fields and that of the CZ of the SAM. Consistent with this idea, the analysis of all major lineages of land plants revealed that the level of phyllotactic diversity correlates with that of SAM organization (Gola & Banasiak, 2016).

Several pieces of experimental work highlight this link between SAM geometry and phyllotaxis, and identified some regulatory genes mediating it. First, mutants of maize in the cytokinin-inducible two-component

response regulator *ABERRANT PHYLLOTAXY1* (*ABPH1*) display an opposite (decussate) rather than a normal alternative (distichous) phyllotaxis as in wild-type maize and other grasses. The role of *ABPH1* in phyllotaxis regulation has been shown to correlate with an enlargement of the meristem, thought to result from changes in cytokine signaling, whereas the size of lateral organs remains unchanged (Giulini, Wang, & Jackson, 2004; Jackson & Hake, 1999). Second, a dominant maize mutant, *abph2*, has the same meristematic and phyllotactic phenotype as *abph1*. The molecular origin of the mutation is a transposition of a glutaredoxin gene, *MALE STERILE CONVERTED ANTHER1* (*MSCA1*), to another site in the genome. MSAC1 directly interacts with the bZIP transcription factor *FASCIATED EAR4* (FEA4) that regulates SAM size, suggesting that MSAC1 modifies phyllotaxis through a FEA4-mediated meristem size modification (Pautler et al., 2015; Yang et al., 2015). Similarly, a rice mutant, *decussate* (*dec*), was reported to present an enlarged meristem and an alternate-to-decussate shift in phyllotaxis. Several type A response regulator genes that act in the cytokinin signaling pathway were found to be down-regulated in the *dec* mutant, suggesting that a change in cytokinin signaling is also involved in this case (Itoh, Hibara, Kojima, Sakakibara, & Nagato, 2012). Taken together, all these findings indicate that changes in SAM size can trigger a transition in phyllotactic patterning. Future discoveries on factors influencing SAM geometry will certainly allow for a better understanding of how changes in SAM geometry during development mediate phyllotactic transitions.

7. Conclusions

In summary, the SAM, from which all above-ground organs are derived, is a self-organizing structure implicating a multilayered regulation of stem cell homeostasis and multiple factors (among which hormones and biomechanical forces) that determine phyllotactic patterning.

Since the molecular cloning of the first genes regulating the development and function of the SAM in maize (*KNOTTED1* in 1989) and *A. thaliana* (*AGAMOUS* in 1990), the past 30 years have seen a tremendous expansion of our knowledge of the underlying molecular mechanisms. Systems biology and multidisciplinary experimental approaches, such as advanced live-imaging, quantitative analysis, and computational modeling, provided a dynamic view of SAM development and phyllotaxis. Further insights into the molecular mechanisms underlying the self-organization of this unique developmental

system will certainly come in the future with the use of tools such as CRISPR-Cas gene editing and single cell genomics.

Novel experimental tools will allow the answering of many remaining questions on how hormones like auxin, cytokinin, and others establish cross-talks, and on the structure and properties of the gene networks influenced by these dynamic signals. How auxin distribution is coordinately established by the polar auxin transport system is also a key question; addressing it will certainly require an in depth analysis of the cellular polarization mechanisms in the SAM to understand its emerging properties. Furthermore, although growth is a crucial parameter in inhibitory field models that drive the dynamics of self-organization, global growth regulation in the SAM has largely been overlooked. Thus, it will be interesting to explore the contribution of growth to phyllotactic patterning. Finally, it would be interesting to know how cells sense mechanical signals, as this will likely be needed to clarify the role of these signals in meristem homeostasis and phyllotaxis.

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