From genes to plants via meristems

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Summary

The Society for Experimental Biology organised a 'Plant Frontier' meeting, which was recently held at the University of Sheffield, UK. One of the sessions of this broad meeting was on plant meristems, which covered a range of topics, including stem cells, patterning, long distance signalling and epigenetic regulation of meristem development.

Introduction

Meristems are groups of organogenic cells that are established during plant embryogenesis. There are two apical meristems that reside in the growing shoot and root tips of plants, and produce the aerial and subterranean parts of the plant body, respectively. To fulfil this function, a meristem produces daughter cells that differentiate into distinct cell types, thus producing the different tissue types that make up the organs of the plant. However, a meristem must also regenerate itself to allow organogenic processes to continue throughout the life of a plant. This dual function requires a constant flow of cells through a meristem. This flow is maintained by an autoregulatory system that ensures a constant stem cell population (Fig. 1A) and by factors that prevent the premature differentiation of meristem cells (Fig. 1B). Mechanisms that underlie and direct meristem function were the focus of this meeting session on Plant Meristems organised by Keith Lindsey (University of Durham, Durham, UK).

Meristems from past to present

Nick Battey (University of Reading, Reading, UK) appropriately opened the meeting by discussing meristem action from a historical and philosophical perspective. Meristems act to iteratively form organs and, therefore, to ultimately produce the whole plant. This behaviour, Battey argued, embodies the Aristotelian 'final cause', as it can be taken to represent the 'purpose' of meristem function. Meristem activity also represents a key difference between plant and animal development because meristematic stem cells can generate new pattern throughout the life of a plant, whereas in animals, stem cell activity largely maintains existing patterns of development.

A key problem highlighted by Battey is whether phyllotaxis – the regular pattern of organ initiation at the shoot apical meristem (SAM) – is a cause or a consequence of growth. Over 100 years ago, Church established the SAM as the origin of pattern with his equipotential theory of phyllotaxis (Church, 1904), but he failed to see that pattern could be generated merely as a consequence of regular growth at the apex. The idea that phyllotaxis is generated via the graded distribution of an inhibitor of primordium initiation at the SAM gained prominence, and, for the past 50 years, auxin has been proposed to be this inhibitor. Cris Kuhlemeier (University of Bern, Bern, Switzerland) has recently turned this theory on its head by demonstrating that auxin is not an inhibitor but an activator of primordium initiation (Reinhardt et al., 2003). As Kuhlemeier reported, another key difference from the classical inhibitor theory is the source of auxin distribution. Rather than diffusing from the meristem centre, elegant immunolocalisation experiments demonstrated that auxin is transported basipetally by the PINFORMED1 protein through the epidermal layer of the shoot up to the periphery of the SAM, where it induces primordium initiation (Fig. 1B). The scavenging of diffusible auxin by the putative auxin influx protein AUX1 confines these auxin gradients to the epidermis, and much evidence demonstrates that these gradients are not only permissive but also instructive for organ initiation (Reinhardt et al., 2000; Reinhardt et al., 2003). Kuhlemeier also highlighted several unanswered questions in this area. Is the source of auxin localised? How is PIN1 polarised in the cell? When do primordia switch from auxin sink to source? How are phyllotactic patterns first established? His group is tackling these questions using the combined approaches of computer modelling and mutagenesis.

Shoot meristems and organ growth: close connections

Organogenesis occurs at the SAM, raising the issue of how cell division, differentiation and morphogenesis are coordinated to facilitate this process. Andrew Fleming (University of Sheffield, Sheffield, UK) used an inducible expression system to show that localised induction of the cell wall-loosening protein, expansin, is sufficient to produce a leaf from the SAM (Pien et al., 2001), whereas induction of cell division or a re-orientation of the cell division plane is not (Wyrzykowska and Fleming, 2003; Wyrzykowska et al., 2002). By performing identical experiments in the margins of young leaves, Fleming has found that an inverse relationship exists between cell division, which restricts growth, and cell expansion, which promotes growth, in the generation of leaf shape. But what links the processes of cell growth, differentiation and proliferation? Fleming suggests that the retinoblastoma protein (AtRBR), which acts as a suppressor of cell proliferation (Ebel et al., 2004), provides such a link in *Arabidopsis* because transient *AtRBR* expression in the SAM suppresses growth and cell division while promoting cell differentiation.

Miltos Tsiantis (University of Oxford, Oxford, UK) also discussed the developmental transition from meristem to leaf cell fate and returned to Battey's Aristotelian view of a meristem to argue that a Heraclitian view may be more accurate – that ordered development is produced through 'conflict'. Mutual antagonism between KNOTTED1-like homeobox (KNOX) and ASYMMETRIC LEAVES1/ROUGHSHEATH2/PHANTASTICA transcription factors regulate meristem versus leaf fate (Byrne et al., 2000; Timmermans et al., 1999; Tsiantis et al., 1999; Waites et al., 1998), and Tsiantis presented evidence that auxin may act

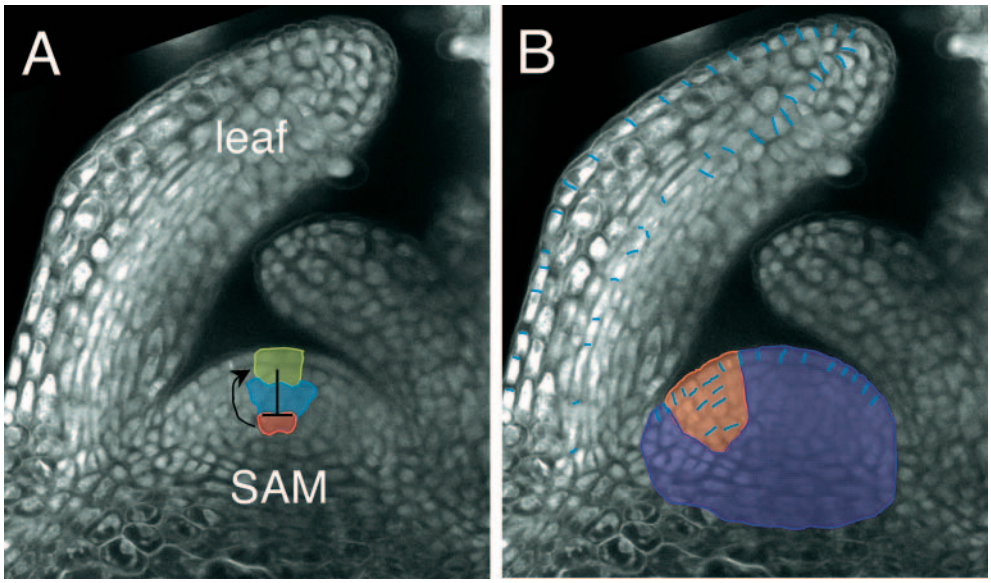

Fig. 1. Signalling processes that regulate stem cell activity and cell fate decisions at the *Arabidopsis* shoot apical meristem (SAM). (A) Stem cells in the outer layers of the central zone of the SAM express CLAVATA3 (CLV3, green) and their activity is promoted by a signal emanating from WUSCHEL-expressing cells (WUS, red). CLV3 signals through CLV1 (blue) to restrict the WUS expression domain. (B) Leaf cell fate at the flanks of the SAM is promoted by ASYMMETRIC LEAVES1 (orange) and is prevented by the activity of KNOTTED1-like homeodomain proteins (purple) in the SAM. Directional flux of auxin via the polar distribution of the PINFORMED1 protein (blue) determines sites of leaf initiation.

within this framework to repress meristem-promoting activities in the leaf. Lateral growth is also driven by antagonism between adaxial- and abaxial-promoting factors (Bowman et al., 2002), and Tsiantis proposed that gibberellin biosynthesis is confined to the leaf via the repression by KNOX transcription factors (Hay et al., 2002), where it mediates the activity of polar growth determinants.

If mutually antagonistic interactions are the key to driving shoot development, then how are the boundaries between meristems and lateral organs, such as leaves, defined, and what is the function of these boundaries? Rüdiger Simon (Heinrich-Heine University, Düsseldorf, Germany) is using several approaches to answer these questions. Stem cell number in the SAM is controlled by an autoregulatory loop between the putative ligand CLAVATA3 (CLV3) signalling through the CLV1 receptor kinase to the homeodomain protein WUSCHEL (WUS) (Fletcher et al., 1999; Schoof et al., 2000). Simon elegantly investigated the function of this feedback loop by varying CLV3 expression in the CLV3-expressing domain using an alcohol-inducible system (Deveaux et al., 2003). These experiments showed that this autoregulatory system tolerates large variability in relative levels of CLV3 and WUS expression. Simon also proposed that this feedback system shows differential sensitivity in different meristems, because although an increase in CLV3 expression was sufficient to rapidly decrease WUS expression in the shoot meristem it was not in the floral meristem. Pulsed CLV3 expression in the same domain produced an 'overshoot' effect on WUS expression and stem cell number, indicating that other targets, perhaps *WUS*-related *WOX* genes, might rapidly sense and respond to changes in WUS expression. Simon also presented results from morphometric analyses that were carried out in collaboration with Dorota Kwiatkowska (University of Wroclaw, Wroclaw, Poland) and that identified that the cells at the boundary between meristem and primordium have negative Gaussian curvature (Fig. 2), as do most cells in an arrested SAM, raising the possibility that these cells have a boundary fate. This research demonstrates how quantitative analysis of growth greatly enriches molecular genetic views of development. Simon also identified the *LATERAL ORGAN BOUNDARIES* gene family member *LOLLO* as being a novel component of the mechanisms that specify boundary fate. *LOLLO* is expressed at the meristem-leaf boundary, and its broadened expression perturbs growth patterns within the leaf and meristem, while dominant-negative *LOLLO* mutations are embryo lethal, indicating that correctly defining developmental boundaries is crucial for shoot development.

Lucy Moore (University of Oxford, Oxford, UK) presented evidence that interactions between three different families of homeodomain proteins might be important for shoot development. BELLRINGER (BLR) and class I KNOX homeodomain proteins interact with each other (Byrne et al., 2003; Smith and Hake, 2003), and Moore showed here that BLR also interacts with REVOLUTA (REV), a member of the class III homeodomain leucine zipper (HD-Zip III) family, but that REV does not interact with the KNOX proteins. This suggests that BLR may act as an intermediate between KNOX and REV proteins to promote SAM function. Keith Lindsey also discussed the possibility that HD-Zip III proteins bind sterol ligands to specify embryo polarity. Lindsey showed how sterols could affect ethylene receptors in a genetic analysis of the sterol biosynthetic mutants *hydra* and *fackel* (Schrick et al., 2000; Souter et al., 2002). He proposed that loss of sterol biosynthesis results in membrane defects that render membrane-localised ethylene receptors 'on'. His group is now using laser capture on early embryos in order to carry out whole-genome expression analysis to identify unique apically versus basally expressed genes and to assess their role in embryo polarity.

How to know how much to grow?

Delphine Fleury [Flanders Interuniversity Institute for Biotechnology (VIB), Ghent, Belgium] used mutational analyses in *Arabidopsis* to demonstrate that the 'Elongator' histone acetyl transferase transcriptional complex functions in leaf and root growth by regulating cell proliferation. Genetic epistasis and clustering of genome-wide expression analyses of *elongata* mutants indicate that the Elongator complex forms in

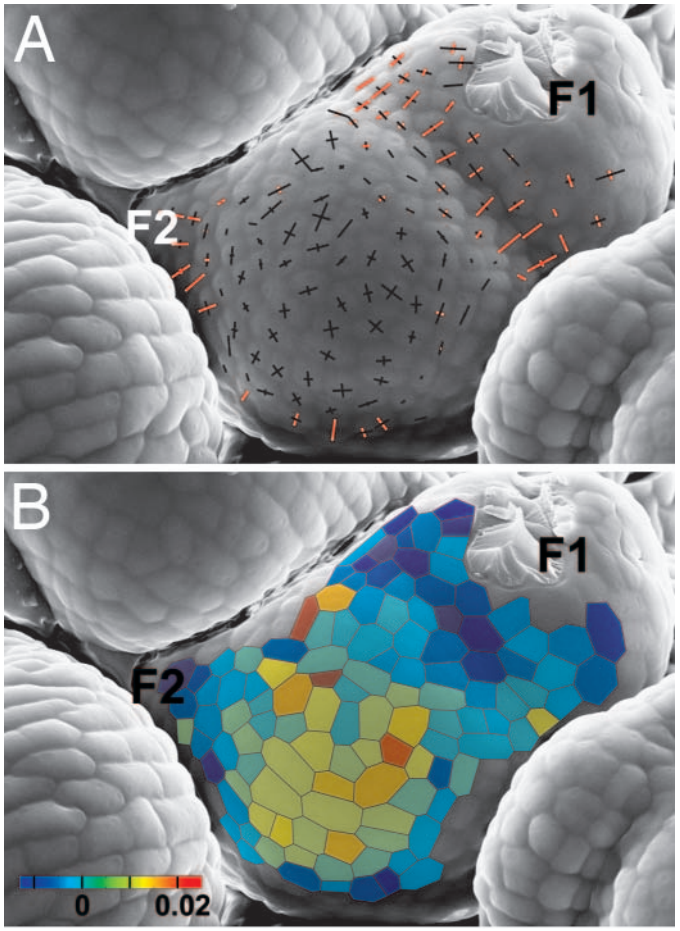

Fig. 2. Differential surface growth at meristem-lateral organ boundaries. Scanning electron micrograph of an *Arabidopsis* inflorescence, showing the meristem in the centre and floral primordia successively initiating at its flanks (F1,F2). (A) Plot crosses denote the directions in which the apex surface is either minimally or maximally curved. Black crossed arms indicate a convex surface and red crossed arms a concave one. Arm length is proportional to the curvature in these directions. (B) A colour map of the Gaussian curvature overlaid on the same micrograph. The colour scale indicates Gaussian curvature values in 10^{-1} m^{-2} (Dumais and Kwiatkowska, 2002). Where both red and black arms form a cross, the surface is saddle shaped and the Gaussian curvature is negative. This is seen at the boundaries between the meristem and floral primordia. Image courtesy of Dorota Kwiatkowska.

plants and acts in the RNA polymerase II-mediated transcriptional process downstream of the Mediator complex. This work showed that, in plants, the Elongator complex acts in meristems and that the histone code is important for regulating organ growth.

Jim Haseloff (University of Cambridge, Cambridge, UK) emphasised that the acquisition of positional information is required for organ growth and relies on feedback between gene expression and organ anatomy. He demonstrated 3D imaging techniques to model the connections between individual cells within the *Arabidopsis* root apical meristem. His accurate measurement of cell contacts highlighted that even in this relatively simple 3D system, intercellular contacts are numerous and complex. To facilitate modelling the cellular basis of plant growth, he introduced as a model species the Charophyte alga Coleochaete, which grows as a simple sheet of cells and enables growth to be modelled in two dimensions.

Manuela Costa (John Innes Centre, Norwich, UK) discussed the problem of how differential regulation of organ growth may have contributed to the evolution of floral dorsoventral asymmetry, a trait that has evolved numerous independent times in flowering plants, including *Antirrhinum.* Several *Antirrhinum* mutants show loss of dorsal petal identity, and combinations of these mutants result in symmetrical flowers (Corley et al., 2005; Galego and Almeida, 2002; Luo et al., 1999; Luo et al., 1996). These genetic interactions define a gene network that controls differential petal growth in *Antirrhinum* and functions partly via the direct transcriptional regulation of *RADIALIS* (*RAD*) by the DNA-binding protein CYCLOIDEA (CYC). Costa investigated how this gene network is configured in *Arabidopsis*, which unlike *Antirrhinum* has symmetrical flowers. In *Arabidopsis,* the *CYC* orthologue *TCP1* is also expressed in the dorsal side of flowers, but only transiently (Cubas et al., 2001). However, *RAD*-like genes are not expressed in *Arabidopsis* flowers, indicating that the function of this developmental network is at least partially diverged. Nevertheless, elements of this network are conserved because inducible CYC expression in *Arabidopsis* is sufficient to alter leaf and petal growth, and to activate the expression of a *RAD::RAD* transgene. This talk also highlighted the importance of the integrated study of developmental patterning and organ growth in understanding plant development.

Stem cells and vascular development underground

Ben Scheres (Utrecht University, Utrecht, The Netherlands) reached the heart of questions about meristem development by asking what specifies stem cells. Patterning the stem cell niche in the *Arabidopsis* root meristem requires radial coordinates from the SHORT ROOT (SHR) and SCARECROW (SCR) GRAS-type transcription factors (Di Laurenzio et al., 1996; Helariutta et al., 2000) and apical-basal coordinates from feedback between PLETHORA (PLT) AP2-type transcription factors and auxin (Aida et al., 2004; Blilou et al., 2005) (Fig. 3). But what specifies stem cells? The NAC-domain putative transcription factors FEZ and SOMBRERO (SMB) are expressed in root cap stem cells, and their loss affects stem cell number. For example, *fez* mutants initiate fewer stem cells and *smb* mutants initiate an excess. *fez* is epistatic to *smb* and *FEZ* overexpression results in extra stem cells, indicating that *SMB* acts downstream of *FEZ* to promote stem cell activity and feeds back to repress *FEZ*. Expression analysis showed that PLT proteins, but not SHR/SCR, regulate *FEZ* and *SMB* (Fig. 3). All of these patterning and stem cell-specific transcription factors are plant specific, raising the issue of whether the mechanisms that specify plant stem cells resemble those in animals. Scheres' results show that modulating the expression of G1 regulators specifically affects stem cell number, and that these genes act downstream of SCR (Fig. 3). Therefore, common cellular modules may be independently recruited to facilitate stem cell function in multicellular eukaryotes.

The *Arabidopsis* root also emerged as the model of choice for understanding the differentiation of provascular cells into the distinct phloem and xylem tissues that form the vascular system. Yka Helariutta (University of Helsinki, Helsinki,

Finland) described the isolation of suppressors of the short root mutant *wooden leg* (*wol*), providing a powerful example of how forward genetic analyses are still indispensable for dissecting development and understanding protein function. *WOL/CRE1* encodes a hybrid two-component signal transduction molecule that acts as a receptor for the hormone cytokinin and is required for provascular cell proliferation (Hwang and Sheen, 2001; Inoue et al., 2001; Mahonen et al., 2000). The *wol* mutation produces a mutant protein that abolishes cytokinin binding and prevents cell proliferation by blocking activity not only of CRE1 but also of the related and redundantly acting AHK1 and AHK2 proteins (Higuchi et al., 2004). Helariutta also described an extragenic mutant *suppressor of wol1* (*sow1*), which allows the proliferation of provascular cells and the development of phloem in *wol*. He was able to show that cytokinin is required to maintain provascular stem cell identity and prevent protoxylem differentiation, while SOW1 counteracts cytokinin activity to allow protoxylem differentiation.

Liam Dolan (John Innes Centre, Norwich, UK) discussed the transcriptional patterning system that specifies root hair cells. He introduced the roles of the ROOT HAIR DEFECTIVE6 family (RDL) of bHLH proteins in root hair development and went on to show conservation of *RDL*-like gene function in tip growth of the moss *Physcomitrella patens*, demonstrating that the genetic pathways controlling tip growth may be conserved in plant lineages that diverged 450 million years ago.

Hormonal control of meristem function

In her presentation, Ottoline Leyser (University of York, York, UK) explored the control of shoot branching. Branches form via the activity of axillary meristems, which share functional attributes with the SAM but reside in the leaf axils. The classical hormone auxin and a novel hormone provisionally named 'Mystery Compound X' (MCX) both inhibit branching. The *auxin resistant1* (*axr1*) mutant has excessive branching, while the dominant auxin over-responding mutant *axr3-1* has no branching (Lincoln et al., 1990). AXR1 and AXR3 are components of an auxin-signalling pathway in which Aux/IAA repressor proteins, such as AXR3, are targeted for proteolysis by a ubiquitin ligase SCF^{TIR1} complex (named after the components SkpI, Cullin and the F-box protein TIR1) (Gray et al., 2001). AXR3 degradation de-represses AUXIN RESPONSE FACTOR transcription factors, enabling auxin-responsive genes to be turned on. So what binds and senses auxin in this pathway? Current results indicate that SCF^{TIR1} has a key role in this process. Understanding auxin signalling is not, however, sufficient to understand shoot branching, as auxin regulates this process by acting in the stem and not the axillary bud. The key to discovering what happens in buds might lie in understanding a novel developmental pathway that is defined by the *more axillary branching* (*max*) mutants. Grafting experiments have shown that MAX1, MAX3 and MAX4 act outside of the bud, probably as biosynthetic enzymes of a carotenoid-derived signal currently called MCX, which inhibits bud growth (Booker et al., 2004; Booker et al., 2005; Sorefan et al., 2003; Stirnberg et al., 2002). Grafting experiments and clonal analysis show that MAX2 acts cell autonomously in the bud to receive the MCX signal. *MAX2* encodes an F-box protein that also forms a SCF complex, indicating that MCX and auxin signalling may both operate via regulated proteolysis. How, then, is MCX and auxin signalling integrated to control bud development? As Leyser discussed, grafting either *axr1* mutant or wild-type roots to *max3* shoots restores normal branching, indicating that the interaction between auxin and MCX occurs after MCX synthesis. One possibility being tested is whether MCX signalling regulates auxin efflux from buds.

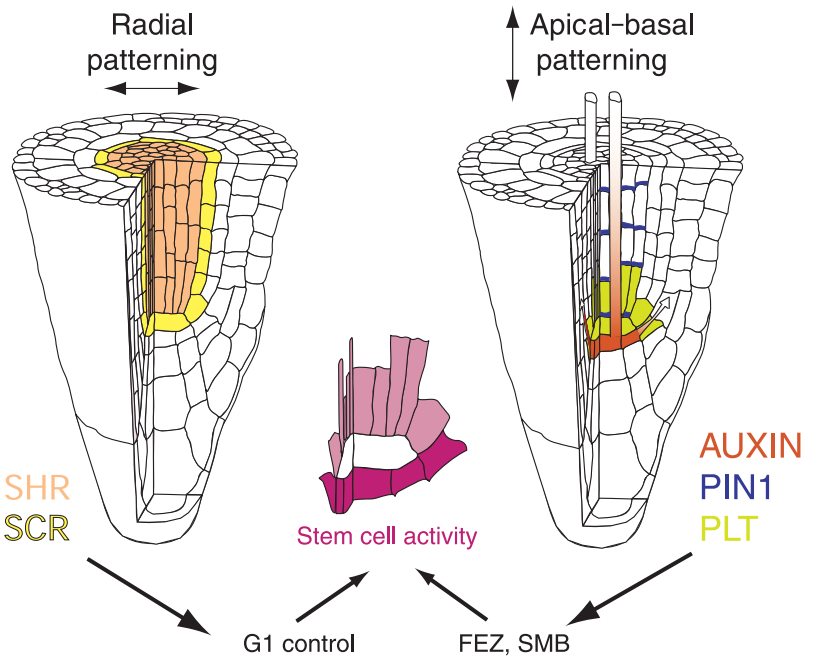

Fig. 3. Stem cell specification in the root apical meristem. Stem cell activity is regulated by both the FEZ pathway (right) acting downstream of PIN1-directed auxin flux and the PLT proteins, and by G1 regulators acting downstream of the SHR/SCR pathway (left). Stem cells are shown in pink, with the stem cell subpopulation that specifically responds to the FEZ pathway and 'G1 regulators' shown in dark pink. Image courtesy of Ben Scheres.

More mystery signals

'Florigen' is another mystery compound that is produced in the leaf and that signals long-distance to the shoot meristem to promote flowering. George Coupland (Max Planck Institute for Plant Breeding, Köln, Germany) is investigating how this elusive signal is integrated into the genetic hierarchy of known flowering time genes in *Arabidopsis*. The transcriptional regulator CONSTANS (CO) is sufficient to induce flowering when expressed in the phloem but not in the SAM, whereas the CO-activated gene *FLOWERING LOCUS T* (*FT*), encoding a phosphatidylethanolamine-binding protein, induces flowering in either tissue (An et al., 2004). This signal acts quantitatively: the specific induction of CO activity in the phloem tissue of a single leaf could activate *FT* expression but not flowering. This signal is also strictly temporally controlled: CO is only sufficient to induce *FT* expression at the end of the day because of the antagonistic effects of the photoreceptors PHYTOCHROME B (PHYB) and

PHYA/CRYPTOCHROME1/2 on CO protein stability (Valverde et al., 2004). Additionally, the bHLH protein PHYTOCHROME-INTERACTING FACTOR 4 (PIF4) is expressed at midday and represses PHYB action, potentially restricting the effect of PHYB to the morning. Nevertheless, the phloem signal that triggers flowering in the SAM in response to CO activity remains a mystery.

Epigenetic regulation of meristem development

Caroline Dean (John Innes Centre, Norwich, UK) presented a compelling framework for how plants use a 'memory' of winter to trigger flowering. Vernalization is the facilitation of flowering by prolonged cold, and it acts by establishing a mitotically stable gene expression state that is reset at meiosis and is, therefore, epigenetic in nature. Vernalization represses the MADS-box gene *FLOWERING LOCUS C* (*FLC*), which blocks flowering by inhibiting genes required to switch the meristem from vegetative to floral development (Michaels and Amasino, 1999). Many regulators of *FLC* alter chromatin structure or are involved in RNA processing (reviewed by Henderson and Dean, 2004). One unanswered question is how these chromatin marks are erased from *FLC* to allow expression again in the early embryo? Dean also highlighted the substantial natural variation in the vernalization requirement of *Arabidopsis* accessions, mostly owing to allelic variation at the *FLC* and *FRIGIDA* (*FRI*) loci (Gazzani et al., 2003). FRI is a novel nuclear protein that acts non-cell autonomously to promote *FLC* expression and thus prevent flowering (Johanson et al., 2000). Strikingly, 15 independent mutations in the *FRI* locus have been identified in rapid cycling accessions.

Conclusions

The scope and breadth of this meeting reflected how, only a few decades after plant developmental genetics emerged as a discipline, it has moved to the forefront of modern biology. Current research is not only illuminating older problems, such as the mechanisms underlying the generation of canonical patterns in nature, in the case of phyllotaxis, but is also elucidating newer ones, such as how developmental patterning mechanisms are intertwined with the cell-division machinery to specify stem-cell identity or how transcriptional states are mitotically maintained. The meeting also prefigured future research. For example, it is not clear how cell fate allocation mechanisms defined in molecular genetic frameworks are translated into precise growth patterns that generate organismal form. The use of morphometric analyses in the context of molecular genetics appears to hold a lot of promise in this direction. How the genetic hierarchies discussed in the meeting are reconfigured during evolution to produce natural variation in form will also be a major challenge for the future. Research on natural variation in flowering time has shown, for example, how the use of wild accessions of plant model systems has much to offer in this respect.

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