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MEETING REVIEW

Coordinating cell polarity: heading in the right direction?

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ABSTRACT

A diverse group of researchers working on both plant and animal systems met at a Company of Biologists workshop to discuss 'Coordinating Cell Polarity'. The meeting included considerable free discussion as well as presentations exploring the ways that groups of cells in these various systems achieve coordinated cell polarity. Here, we discuss commonalities, differences and themes that emerged from these sessions that will serve to inform ongoing studies.

KEY WORDS: Cell polarity, Auxin, Eukaryotes

Introduction

In May 2014, The Company of Biologists hosted a workshop entitled 'Coordinating Cell Polarity', which took place at Wiston House, a grand old estate in Sussex, England. Within this idyllic setting, the eclectic nature of the group, consisting of about 30 participants working across a broad range of disciplines (including experimentalists and modelers, working on both plant and animal systems), was intended to promote the goal of exploring broad themes in collective cell polarity in both plants and animals. Reflecting one of the emerging themes – the spontaneous emergence of polarity – the meeting itself was self-organizing, with the first session devoted to defining major questions in the field, from which the speaking order emerged.

Here, we review some themes of discussion, beginning with the notion of polarization within individual cells, and continuing toward increasing levels of complexity. We will attempt to point out some commonality of principles of coordinated cell polarization despite implementation with distinct molecular machineries, as well as to discuss some of the big unanswered questions.

A diversity of biological examples of polarity was represented by participants from both experimental and theoretical or modeling disciplines. Among the first order of business was to define for the group how to discuss polarity conceptually, what the premier models to study polarity are, and what the different models can teach us. Despite considerable discussion of the distinction between anisotropy and polarity, no consensus emerged. For example, some argued that anisotropy (deviation from purely symmetric or isotropic form or growth) was equivalent to what we commonly call polarity, whereas others contended that anisotropy was merely a prerequisite for polarity and that directionality was required for true polarity. In other words, the debate concerned whether a cell could have a 'front' without also defining a separate 'back'. Similarly, the group discussed whether anisotropy is a polarity if no function is attributed to it, or if it only becomes cell polarity when we are aware of some importance to the anisotropy. Finally, computational biologist Przemyslaw Prusinkiewicz (University of Calgary, Canada) pointed out that, in spite of the wide use of the term, there is no satisfactory mathematical definition of polarity. This hinders, in particular, the efforts to model polar phenomena at the scale of entire tissues.

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Common polarity models

Among the diverse audience, two central experimental systems were most highly represented in the discussions: the localization and function of the hormone auxin in plant polarity, and the collection of polarly localized transmembrane proteins that interact to constitute the *Drosophila* planar cell polarity system. Although the molecular details of these systems are distinct, these differences actually served to emphasize some of the conceptual similarities.

The PIN proteins, which made an appearance in all but one of the plant polarity talks, were introduced by Ottoline Leyser (Sainsbury Laboratory, Cambridge, UK) in connection with the grand coordinator of plant development and long-range tissue polarity, auxin. As plasma membrane auxin efflux facilitators, PIN proteins promote the movement of auxin out of cells. Their localization on one face of the cell is both a cause and consequence of auxin distribution and of tissue polarity (Fig. 1E). During the initiation of leaves in *Arabidopsis*, PIN1 protein accumulates in a polar fashion, towards the direction of highest auxin concentration (thus moving auxin against a gradient); in vein formation, however, PIN1 orients in the direction of highest flux (Bennett et al., 2014). How a single protein reads auxin information in these different ways is unclear, but turning to other plants in which these activities are under the control of different isoforms might clarify the structural and regulatory issues (O'Connor et al., 2014). From a more conceptual standpoint, Przemyslaw Prusinkiewicz used the distribution of plant PIN proteins in the shoot apical meristem during phyllotactic pattern formation in *Arabidopsis* and other plants as a motivating example to propose a mathematical definition of polarity as a combination of vector and tensor quantities.

On the majority of the adult *Drosophila* cuticle, cellular projections called trichomes show a remarkably well coordinated polarity, generally pointing toward the distal end of extremities or the posterior of the body. This polarity, which is referred to as planar cell polarity (PCP), is evident in other *Drosophila* structures, and conserved mechanisms function to regulate polarity in other organisms including vertebrates. Two molecular modules in *Drosophila* contribute to PCP signaling: the 'core' PCP module and the Fat (Ft)/Dachsous (Ds)/Four-jointed (Fj) modules (Fig. 1C,D). Each displays molecular polarity at the level of individual cells. In core PCP signaling, complexes of Frizzled (Fz) on one cell and Van Gogh (Vang; also known as Strabismus) on the neighbor, plus associated cytosolic factors, are bridged by the atypical cadherin Flamingo (Fmi; also known as Starry night). These complexes segregate into a highly asymmetric distribution with Fz predominantly on one side of the cell and Vang on the other (Strutt and Strutt, 2009). Ft and Ds are atypical cadherins that form heterodimeric bridges that couple cells to each other, and, much like the core PCP system, these proteins also achieve subcellular asymmetry (Matis and Axelrod, 2013). Intensive study has led

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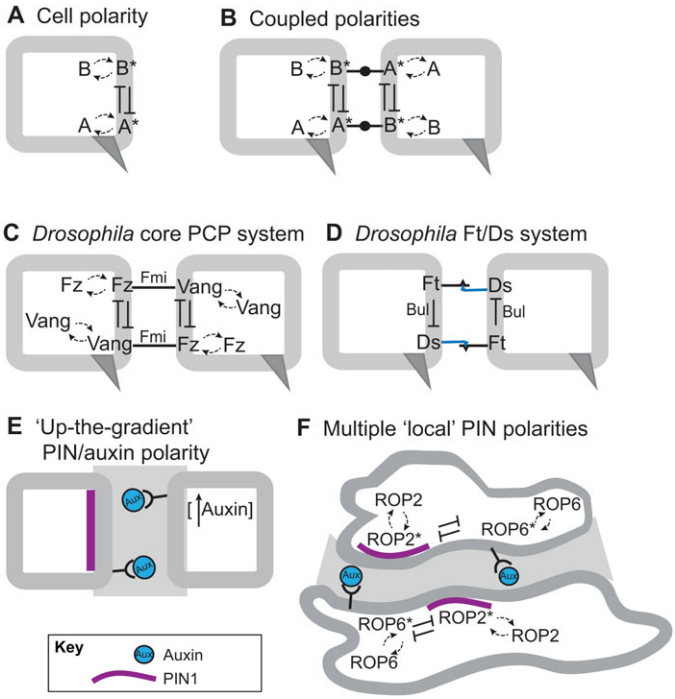

Fig. 1. Generalized model for generating coordinated cell polarity. (A) Polarity within a single cell can result from recruitment to the correct region of the membrane (or the localized activation) of two polarity proteins, A and B (where the asterisk indicates an activated and membrane-associated form and dashed arrows the cycling between forms), together with positive feedback, for example by cooperative recruitment, and with mutual inhibition. (B) If A* and B* interact across cell junctions (as indicated by linkers between cells), then this system can also couple polarity between neighboring cells. (C) Evidence exists for positive and negative feedback as well as for coupling among the core PCP proteins; for simplicity, only Fz and Vang are shown. Fz on one cell and Vang on the other are bridged by Fmi. (D) Within the Ft/Ds polarity system, weak polarization results from graded expression of Ds and Fj (not shown). Coupling between Ft and Ds in adjacent cells has been demonstrated, and evidence for intracellular mutual inhibition mediated by Bulge (Bul) was presented at the workshop. Positive feedback is inferred from observed clustering, but has not otherwise been demonstrated. These activities could amplify polarization. (E) PIN1 accumulates in membranes adjacent to cells with higher auxin concentrations, pumping additional auxin in that direction. Because of the thick cell wall (gray box) between cells, coupling between cells cannot be direct, although auxin itself has been modeled as the mobile mediator of plant cell coupling. (F) ROP2 and ROP6 show reciprocal recruitment to convex and concave regions, respectively, of opposing cell membranes in pavement cells. They mutually inhibit each other's activity indirectly via activities of their downstream cytoplasmic effectors, and their opposite effects on local expansion lead to interdigitation. The mechanism of coupling has been modeled as differential sensitivity to auxin, as well as a positive feedback through recruitment of PIN1 to ROP2 regions.

to substantial advances in understanding how they generate coordinated polarity, but much remains to be understood about their function.

Intrinsic polarity and polarity in single cells

After opening discussions that laid out the key questions, sessions were organized roughly along a gradient of developmental complexity, with auxin and PCP components making appearances throughout. A recurring discussion topic was the question of to what extent cell polarization is intrinsic in various systems. Several clear examples of single-cell polarization were discussed, beginning with a provocative hypothesis talk suggesting the possibility that cell polarization in eukaryotes might have been a natural consequence of the origins of eukaryotic cells. Buzz Baum (UCL, London, UK), working in collaboration with David Baum (University of Wisconsin, Madison, USA), suggested a dramatic rethinking of the mechanism by which archaea and eubacteria combined to form eukaryotes. Rather than the engulfment of eubacteria by archaea, as currently envisioned (Williams et al., 2013), it was suggested that archaea might have formed multiple cytoplasmic protrusions that surrounded symbiotic eubacteria in what was initially an extracellular compartment. In the model, the protrusions would have become the cytoplasm, with the invention of nuclear pore complexes separating them from the archaeal cell body, now the nucleus. Membrane fusion between cytoplasmic protrusions could then have brought the eubacteria into the cell interior, converting the nearby extracellular space into endoplasmic reticulum. Such an origin of eukaryotes would have necessarily resulted in a highly compartmentalized cytoplasm that could have been polarized by the selective distribution of mRNAs into individual compartments.

Stan Marée [John Innes Centre (JIC), Norwich, UK] discussed a well-studied example of individual polarized cells. Fish keratinocytes will migrate when plated in culture, forming distinct front and back with different cytoskeletal dynamics, and changing direction when they encounter obstacles. When keratinocytes are enucleated, they can rest in an isotropic state, but when physically prodded they polarize and initiate migration that can last for hours. Marée presented a model involving feedback loops between small GTPases in active and inactive forms that will produce spontaneous polarization (Walther et al., 2012). The introduction of communication by diffusion at appropriate scales makes the model stable in the contexts of cell migration and upon collisions that change the shape of the cell. Simulations show that the model requires only small signals to change direction, but polarization is very hard to break once initiated (Marée et al., 2012). While this model stably predicts two compartments, i.e. front and back, Veronica Grieneisen (JIC, Norwich, UK) argued that a similar mechanism operating within the confines of a highly irregularly shaped cell, such as an *Arabidopsis* pavement cell, can result in multiple front domains in protruding parts of the cell (Fig. 1F). These two examples showed high convergence in the behavior of plant and animal polarity systems at both the conceptual and physical levels, as both invoked the switch-like properties of small GTPases. Dominique Bergmann (Stanford University and HHMI, Stanford, USA) introduced a polarity-generating system in the *Arabidopsis* epidermis that relied wholly on proteins unique to plants; strikingly, however, the dynamics of these novel molecules in polarity generation could be modeled in terms of conserved positive-feedback loops or other simple motifs analogous to those used in animal or yeast cell polarity.

From single cells to tissues

As cells come into contact, they are often seen to coordinate their polarities. Two examples of coordinated migration were discussed. Tadashi Uemura (Kyoto University, Japan) described the Ds-dependent coordinated posterior migration of *Drosophila* larval epidermal cells. Although its role here is not yet known, Ds in other contexts was discussed at length, as described below. John Robert Davis (Stramer laboratory, King's College London, UK) described an 'intercellular clutch' that coordinates contact inhibition of locomotion between hemocytes in the *Drosophila* embryo (Davis et al., 2012). As two hemocytes migrate toward and contact each other, an adhesive junction is formed between them. These junctions couple to treadmilling actin, applying tension and inducing stress fibers as polarity is reversed. Both cells must be

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initially migrating toward each other or neither will respond. The signal that reverses polarity is not yet known.

Katie Abley (Coen laboratory, JIC, Norwich, UK) laid the groundwork for considering models of *Drosophila* PCP and plant auxin-mediated coordinated polarization. Inspired by and building on a mechanism of cell polarization with intercellular coupling originally proposed by Hans Meinhardt, she presented computational models showing that intracellular partitioning combined with cell-cell coupling, and with overlaid gradients or boundary conditions, can reproduce coordinated cell polarization reminiscent of that seen in *Drosophila* PCP or in a variety of auxin-mediated events in plants (Abley et al., 2013). Various modes of cell-cell coupling, sharing a similar conceptual basis, can be envisioned and, depending on how much of the intracellular partitioning mechanism is preserved, uncoupled cells may or may not retain the ability to partition (Fig. 1).

Polarity in tissues – intercellular polarity coupling and feedback

Intercellular coupling mechanisms were then extensively discussed in the contexts of *Drosophila* PCP and plant auxin signaling. Laura Brown (Jönsson laboratory, University of Cambridge, UK) showed that a model of auxin signaling in which the auxin efflux channel PIN on one cell surface repels PIN on the neighboring cell, together with the auxin-dependent regulation of PIN production, can produce realistic leaf venation patterns given an auxin source and sink. Przemyslaw Prusinkiewicz built a similar coupling model in which high auxin produces elevated PIN in the neighboring cell, inducing efflux and reinforcing the high auxin level. His model, together with growth, could replicate the beautiful spiral pattern of the shoot apical meristem. The molecular foundations of this coupling remain to be determined. Similar cell-cell coupling principles are evident in both the core and Ft/Ds/Fj systems in PCP signaling, where Fz and Vang complexes assemble on opposing membranes and oppositely oriented complexes show mutual inhibition that depends on a set of cytosolic core factors (Strutt and Strutt, 2009) (Fig. 1).

Nick Monk (University of Sheffield, UK) addressed whether the simplest forms of these coupling and feedback mechanisms, predicted to show bistability at intercellular junctions, can produce realistic tiling patterns in 2D cell arrays. In biological systems, junctions perpendicular to the direction of polarization are often seen to each accumulate intermediate levels of signaling components, a result not simply reconciled with bistability. Monk suggested that networks including both positive and negative feedback could produce tristability that is compatible with this outcome (Jaeger and Monk, 2014). This engendered discussion of a variety of underlying assumptions that could lead to additional investigation. Nonetheless, Jeff Axelrod (Stanford University, Stanford, USA) presented evidence that oppositely oriented core PCP complexes directly interact through both positive and negative feedback, with negative feedback mediated by endocytosis of the disrupted complex.

Three participants discussed aspects of the *Drosophila* Ft/Ds/Fj system, where the current model is that the phosphorylation of both Ft and Ds by Fj makes Ft a stronger ligand and Ds a weaker ligand for the other. Therefore, oppositely oriented gradients of Fj and Ds both promote asymmetric orientations of Ft-Ds heterodimers with respect to the expression gradients. An open question among experimentalists in the field is whether this simple model can produce quantitatively sufficient asymmetry. David Sprinzak (Tel Aviv University, Israel), using a synthetic approach, reconstituted vertebrate Ft-Ds interactions in cultured pairs of cells, and the measured dynamics suggested cooperativity. Furthermore, he showed dramatic increases in the stability of bound complexes as confirmed by fluorescence recovery after photobleaching (FRAP). *In vivo* FRAP experiments reported by David Strutt (University of Sheffield, UK) confirmed the effect of Fj previously measured *in vitro*. He then described a mass action model based on the mechanism outlined above that produces low-level subcellular asymmetry. Various scenarios for increasing asymmetry were examined, such as including diffusion and production/degradation dynamics, or incorporating feedback. Notably, it is challenging to incorporate feedback in a way that produces a similar response across the entire field. Mariana Rodrigues Campos (Thompson laboratory, CRUK-London Research Institute, UK) then described experimental results suggesting that a novel ubiquitin ligase is recruited by Ft and acts on Ds and the associated Dachs protein, providing a plausible feedback amplification mechanism. Substantial attention to this mechanism is likely to provide a deeper understanding in the near future.

Two talks discussed how polarity is maintained through development. Peter Lawrence (University of Cambridge, UK) described work showing that between the fly larval molts the denticle polarity patterns are stable, yet the epidermal cells rearrange substantially. To achieve this, the fates of individual cells and their polarities change between molts (Saavedra et al., 2014). Danelle Devenport (Princeton University, Princeton, USA), studying PCP in mouse skin, identified a cell cycle-dependent kinase pathway that facilitates maintenance of PCP through cell division by regulating Celsr1 (the mammalian homolog of *Drosophila* Fmi) internalization and redistribution to the membrane.

The role of forces in polarity

The interplay between mechanical forces and molecular signaling systems in shaping cell polarization was examined by numerous meeting participants (Fig. 2). In the *Drosophila* embryo, elongation of the germ band is accomplished by polarized intercalations of cells. The polarized accumulation and activation of MyoII selectively at anteroposterior cell boundaries drives intercalation by promoting shrinkage of those boundaries until they form four-cell junctions that resolve irreversibly in the opposite orientation (known as T1 transitions; Fig. 2C). Thomas Lecuit (IDBML, Marseille, France) described pulsatile apical actin flows operating during germ band elongation, similar to those reported to propel apical constriction (Martin et al., 2009) except that the flows are anisotropic, alternating between anterior and posterior cell boundaries, suggesting a model for the accumulation and/or activation of MyoII at these locations (Levayer and Lecuit, 2013). Additional evidence suggests that an activating signal is required asymmetrically at these junctions. Later in the *Drosophila* embryo, as the stripes of Wingless (Wg)-expressing and Engrailed (En)-expressing cells (which define the segments of the animal) are established, mixing between these cell populations is not seen. Bénédicte Sanson (University of Cambridge, UK) described actomyosin cables that run on either side of the Wg/En cell junctions (Monier et al., 2010). These cables are under tension, forcing the border into a straight line and presumably blocking mixing. Cell divisions at the Wg/En boundary fail to disrupt this border. Unlike the earlier case, in which MyoII enrichment causes junctional rearrangements, these junctions remain stable. The reason for the difference in junctional stability is not yet known.

Boris Shraiman (Kavli Institute, University of California at Santa Barbara, USA) presented a theoretical model of the early phase of germ band extension described by Lecuit. Assuming that junctional stress is dominated by actomyosin and is in approximate equilibrium,

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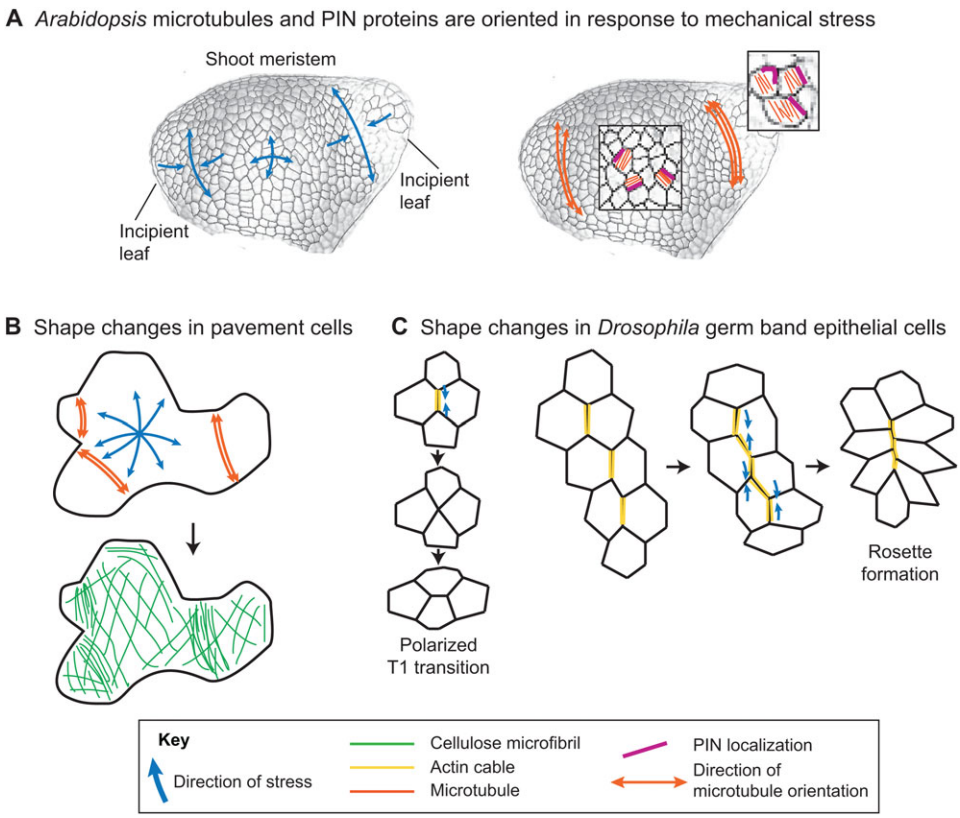

Fig. 2. Interactions between polarity and mechanics in development. (A) Within the plant shoot meristem, tissue arrangements and the turgor pressure intrinsic to each cell lead to predictable mechanical stress patterns. As new leaf primordia are formed at the flanks of the meristem, changes in tissue architecture (bends, folds, outgrowths) change the stress directions. Both cortical microtubules and PIN1 localization become aligned in response to mechanical cues within the cells. Here, the overall microtubule orientation in multiple cells is indicated (orange arrows). (B) Mechanics and morphogenesis in individual *Arabidopsis* pavement cells. A uniform outward force drives isotropic cell expansion. Microtubules guide the deposition of cellulose, which is the main force-resisting cell wall polymer, resulting in localized restriction of growth and the formation of lobes. (C) In animal cells, cytoskeletal activity both contributes to and responds to polarity. In the *Drosophila* germ band embryo, actin-dependent flows establish polarity of actomyosin activity. Contraction of the actomyosin then shrinks individual cell junctions, or groups of cell junctions, leading to polarized rearrangements of cell packing and contributing to elongation of the embryo.

and including negative tension contributions from E-cadherin bridges, he showed that mechanical stress feedback onto myosin and cadherin levels can spontaneously produce an anisotropic state, characterized by the presence of parallel myosin cables with elevated tension. This anisotropic state is unstable and progresses toward the formation of cellular 'rosettes' via unresolved T1 processes. Resolution of these four-cell (and higher) cellular junctions requires reorganization of cable structures. Further work is needed to relate the dynamics of the cables to the global structure of cell flow.

The interplay between mechanics and polarity in plant cells is dominated by the presence of a rigid cell wall that eliminates the possibility of the morphogenetic movements seen in animals. Nevertheless, membrane tension in both animal and plant cells can act as a common cue to channel cell polarity (Asnacios and Hamant, 2012). Mechanistically, this involves the cytoskeleton. As described by Olivier Hamant (INRA, Lyon, France), animal cells rely on actin to generate cortical tension and shape, whereas plants employ a microtubule-based cortical array whose dynamics and impact on cell wall synthesis allow the cell to efficiently resist mechanical forces, leading to directional growth and tissue morphogenesis (Fig. 2A,B) (Hamant et al., 2008; Sampathkumar et al., 2014). Two specific manifestations of these principles were described in the emergence of lateral roots by Amaya Vilches Barro (Maizel laboratory, University of Heidelberg, Germany) and in the generation of new organs in the shoot by Jan Traas (INRA, Lyon, France), who also integrated auxin and PIN protein localization, noting that both microtubules and PIN protein localization responded to mechanical force, but that the disassembly of highly aligned microtubule arrays was actually a requirement for symmetry breaking and the auxin-driven outgrowth of organs (Heisler et al., 2010; Burian et al., 2013).

The role of polarity in morphogenesis was further discussed in two vertebrate systems. Eleni Panousopoulou (Green laboratory, King's College London, UK) described a group of cells that delaminate from the mouse tooth bud and form arches over the apical surface of the bud. These cells appear to undergo a convergent extension. Cutting experiments demonstrate that they are under tension, thereby providing force to drive bud formation. Tadashi Uemura described studies on the mouse oviduct, which has invaginated ridges running parallel to the length of the tube. Mutations in *Celsr1* disrupt the organization of these ridges, suggesting that planar polarity might contribute to ridge formation.

Linked or independent systems

In several systems, the possible or apparent linkage between distinct signaling systems in controlling polarity was discussed. Pluripotent mouse epiblast cells differentiate in culture into a variety of cell fates and this is likely to depend on transcription factor levels, intercellular signals and cell polarity, as manipulating polarity alters differentiation. Guillaume Blin (Lowell laboratory, University of Edinburgh, UK) is investigating whether models integrating data regarding cell contacts, cell shapes and polarities can predict the differentiation pathway of individual cells in these cultures.

Claire Grierson (University of Bristol, UK) discussed the interaction of Rho of plants (ROP) and auxin in determining the subcellular localization of lateral root hair outgrowth. Root hairs normally grow laterally from the distal end of cells where subcellular auxin is expected to be highest. A patch of ROP accumulates at the site to direct growth. Ectopic auxin and changes in ROP levels can alter the number and location of outgrowths. Grierson suggested that a Turing type model can potentially account for the wild-type pattern, as well as for a number of interventions that alter root hair localization (Payne and Grierson, 2009). The model is awaiting more quantitative tests.

The anteroposterior axis of planarians depends on Wnt signaling, with high-level signaling inducing tail formation. Along the body

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length, cells also have a PCP that is evident in the orientation of the ciliary rootlets and appears to depend on conserved core PCP components. Preliminary evidence suggests that local PCP requires the Wnt signal. Sarah Mansour (Rink laboratory, MPI-CBG, Dresden, Germany) discussed the possibility of cut portions of body to 'remember' their orientation and regenerate accordingly by virtue of their planar polarity. This hypothesis remains to be tested. Suzanne Eaton (MPI-CBG, Dresden, Germany) has examined the relationship between the Ft/Ds and core PCP systems in the fly wing. By mapping their orientations throughout wing development in wild-type and mutant conditions, she concludes that at different developmental stages the systems are either coupled or uncoupled and that, when coupled, one or the other dominates to determine orientation in a stage-dependent way.

In each of these cases the level of complexity is high and, although for some, evidence of coupling is provided, the mechanisms for coupling remain to be determined.

Ideas, themes and questions

The workshop was structured in a way that was intended to foster discussion, and indeed discussions were plentiful and invigorating. One recurring theme was the extent to which the collective polarization of cells is built upon intrinsic intracellular polarization mechanisms. Modeling can produce collective polarization either with or without intrinsic cell polarization. Thinking about this problem will require consideration of hierarchies of polarizing mechanisms. For example, an intrinsic polarizing mechanism might operate strictly downstream of a system that couples the polarities of neighboring cells. However, it is possible that polarity-coupling mechanisms might also have intrinsic polarizing activities. An experimental challenge will be to identify paradigms that will determine whether such cell-intrinsic mechanisms exist in a given system, and for this Boris Shraiman proposed an experimental approach. As the various collective polarization systems are investigated further, answers to this question will begin to come into focus.

Another common theme was the potential functions and consequences of clustering of transmembrane signaling structures into discrete puncta. The formation of puncta might simply be a consequence of amplification mechanisms that use positive feedback, but one could envisage other important implications of these structures. For example, modelers tend to think of any given cell-cell interface as a homogenous structure with identical properties throughout, but the subregionalization of interfaces could challenge this view.

For the field to move forward, a number of technical advances are required, many focused on the acquisition of quantitative data in living tissues. For *Drosophila* PCP, knowing the stoichiometry of polarity complexes would enable a better evaluation of current models of activity. New imaging techniques, such as super-resolution microscopy, were frequently discussed, and new applications of fluorescence correlation spectroscopy (FCS) or iterative raster scanning, as presented by Rosangela Sozzani (North Carolina State University, Raleigh, USA) for her work following cell fates in plant stem cell niches, hold promise for determining *in vivo* protein complex dynamics. While the drive towards more definitive assignments of proteins to specific places and genes to specific networks was a goal of many participants, Eric Siggia (Rockefeller University, New York, USA) advocated instead for 'messy' genetics. Although geneticists tend to prefer fully penetrant and expressive phenotypes, he suggested that quantitative information from partially expressive and/or penetrant phenotypes is a richer source from which to derive model parameters. As an example, he pointed to the fly eye, where quantitative data about ommatidial rotation are available.

In summary, the meeting pointed to a number of commonalities among the diverse mechanisms of collective cell polarization and, perhaps more importantly, may catalyze closer dialog between the various constituencies as they work toward the common goal of a better understanding of these processes.

Competing interests

The authors declare no competing financial interests.

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