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Basic principles of polarity establishment and maintenance

Conference on Mechanisms of Cell Polarity

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See Glossary for abbreviations used in this article.

Introduction

"Consider a spherical cow." So goes the punchline of a well-known joke told by and about theoretical physicists. The concept of a completely symmetric, spherical cell is as foreign to biologists as the spherical bovine is to farmers: the establishment and maintenance of polarity has a crucial role in the correct function of numerous cell types; even spherical bacteria exhibit polarity. The Ninety-Seventh International Titisee Conference on Mechanisms of Cell Polarity brought together experts on diverse organisms and cell types to discuss general principles governing the establishment and maintenance of cell polarity.

Polarity during bacterial cell division

The mechanisms that are responsible for the localized positioning of the bacterial division machinery were discussed by J. Errington (Newcastle, UK) in *Bacillus subtilis* and by C. Jacobs-Wagner (New Haven, USA) in *Caulobacter crescentus*. During cytokinesis of *B. subtilis*, cell-wall growth is spatially restricted to a circular ring, which eventually becomes the division septum. The tubulin-like bacterial protein, FtsZ, which is usually found in helical-like structures, rearranges as a ring about the division plane where it recruits other proteins that are responsible for cell division (Cabeen & Jacobs-Wagner, 2007). After cytokinesis, rod-shaped bacteria elongate by localizing their growth either to cylindrical regions—for example, *Escherichia coli* and *B. subtilis*or—to the poles—for example, *Corynebacterium*. This polarized growth is partly regulated by the bacterial actin homologue MreB. These proteins—found only in non-spherical bacteria—form helical filamentous structures that are involved directly in the control of cell-shape. Elongation of *B. subtilis* requires the coordinated activity of MreB and its two homologues, Mbl and MreBH. MreB also has a role in establishing polarity in *C. crescentus*, where it alternates between a helical structure and a ring-like form defining the division plane. Division in *C. crescentus* is asymmetrical, yielding a swarmer daughter cell that is shorter than its stalked sister. The protein, TipN, localizes at the tip of the new pole that is created by division (Fig 1A), and is responsible for establishing and maintaining correct polarization; Δ*tipN*-mutant cells produce swarmer cells that are longer than their stalked brethren. The size of bacteria presents a considerable challenge to the understanding of the functional properties of bacterial cytoskeleton proteins such as FtsZ and MreB. M. Balasubramanian (Singapore) demonstrated that MreB function can be elucidated by expressing the bacterial protein

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Glossary

Cdc42	cell-division cycle 42
CXCR7	chemokine (C-X-C motif) receptor 7
FtsZ	Filamentous temperature-sensitive protein Z
GAP	GTPase-activating protein
GEF	guanine nucleotide-exchange factor
GFP	green fluorescent protein
GSK3	glycogen synthase kinase 3
ICR1	interactor of constitutive active Rops
MAPK	mitogen-activated protein kinase
Mbl	MreB-like
MreB	Mecillinam resistance gene B
MreBH	MreB homologue
Par	partitioning defective
PI(3)K	phosphatidylinositol-3-kinase
$PI(3,4,5)P_3$	phosphatidylinositol 3,4,5-trisphosphate
PI(4)P	phosphatidylinositol 4-phosphate
$PI(4,5)P_2$	phosphatidylinositol 4,5-bisphosphate
PKC	protein kinase C
PPK-1	PIP kinase 1
PLA2	phospholipase A2
PTEN	phosphatase and tensin homologue
Rap1	Ras-related protein 1
RFP	red fluorescent protein
RNAi	RNA interference
Rop	Rac-Rho of plant
Tiam1	T lymphoma invasion and metastasis 1
TipN	Tip of New pole
TORC2	target of rapamycin complex
Tre1	Trapped in endoderm 1
v-SNARE	vesicular soluble N-ethylmaleimide-sensitive factor attachment protein receptor

in fission yeast, *Schizosaccharomyces pombe*, where it results in a linear array extending the length of the cell, which is reminiscent of the yeast microtubules (Srinivasan *et al*, 2007).

Polarity during development

P. Martin (Bristol, UK) and P. Lawrence (Cambridge, UK) discussed polarity in the context of *Drosophila* development. Martin uses dorsal closure, which occurs late in embryogenesis, as a model of epithelial fusion. During this process, filopodia extend from approaching epithelial sheets and meet in an interdigitated pattern known as 'zippering'. By using flies that express RFP–moesin and GFP–moesin under different promoters, it is possible to establish that distinct recognition mechanisms regulate cell matching during dorsal closure (Millard & Martin, 2008). These filopodia extensions resemble the pseudopod extensions during amoeboid locomotion that were also discussed at the meeting (see below). Lawrence explored a model of planar cell polarity to explain how hair cells acquire their orientation. The consensus view is that *Dachsous* (*Ds*) and two genes, *fat* (*ft*) and *four-jointed* (*fj*), function together to read morphogen gradients, establishing a positive-feedback loop that amplifies the external asymmetrical signal. Ds and Ft then provide the polarizing signal to the Starry night (Stan) pathway, consisting of the three genes *frizzled* (*fz*), *Van Gogh* (*Vang*) and *stan*, which, in turn, signals to downstream effectors. Lawrence, however, presented evidence that excess Ft, Ds or Fj can polarize adjoining cells that have a complete block in Stan signalling (for example, fz^- mutant cells; Fig 2D), suggesting that the Ds system can generate planar cell polarity independently of the Stan system. The morphogen gradients necessary for planar cell polarity provide the spatial information that is required for hair-cell orientation and represent mechanisms that are likely to be translated into directional movement of migrating cells.

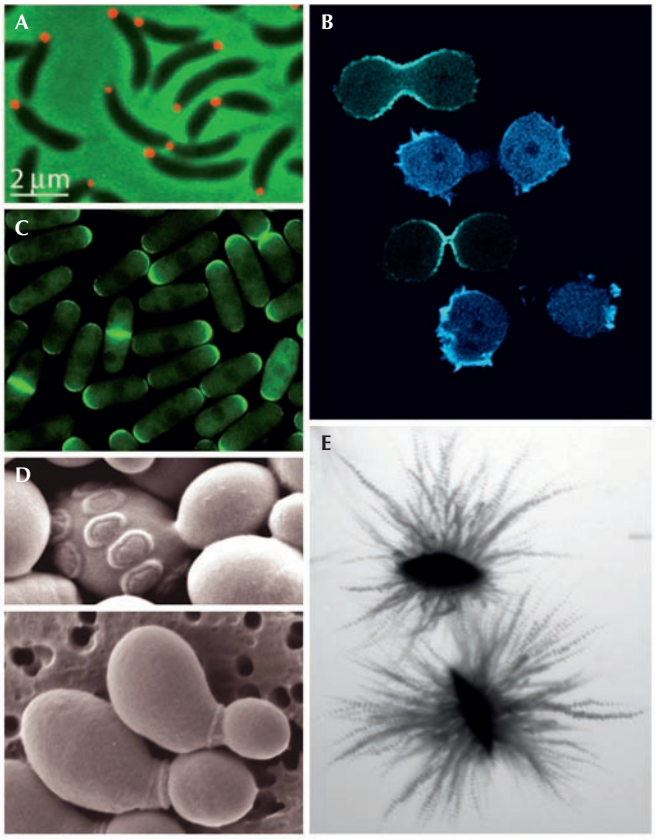

Fig 1 | Polarization during division in unicellular organisms. (**A**) In the bacterium *Caulobacter crescentus*, the cell-polarity determinant TipN (red) sets up the polarity axis of the cell by tracking the last division site. (**B**) In *Dictyostelium*, components of the PI(3)K pathway localize differentially during cytokinesis. PTEN (first and third cells from the top) localizes to the cleavage furrow, and PH domains (second and fourth cells from the top) are found preferentially at the poles. (**C**) Localization of the Rho1 GEF Rgf1–GFP in *Schizosaccharomyces pombe*. Rgf1 localizes to one or both poles during cell growth and to the septum during cytokinesis. (**D**) Haploid wild-type *Saccharomyces cerevisiae* cells form a new bud adjacent to the previous bud scar (top). In the absence of the Cdc42 GAP Rga1 activity, haploid yeast cells bud within old cell-division sites (bottom). (**E**) Filamentous *Candida albicans* colonies embedded in agar. Cdc42, cell-division cycle 42; GEF, guanine nucleotide-exchange factor; GFP, green fluorescent protein; PH, pleckstrin homology; PI(3)K, phosphatidylinositol-3-kinase; PTEN, Phosphatase and tensin homologue; TipN, Tip of New pole. Images kindly provided by C. Jacobs-Wagner (**A**), P. Devreotes (**B**), Y. Sanchéz-Martín (**C**), E. Bi (**D**), and M. Bassilana and R. Arkowitz (**E**).

Directed cell migration

For some of the cells, the initial step in the establishment of polarity is binding an external chemical, although the identity of this cue

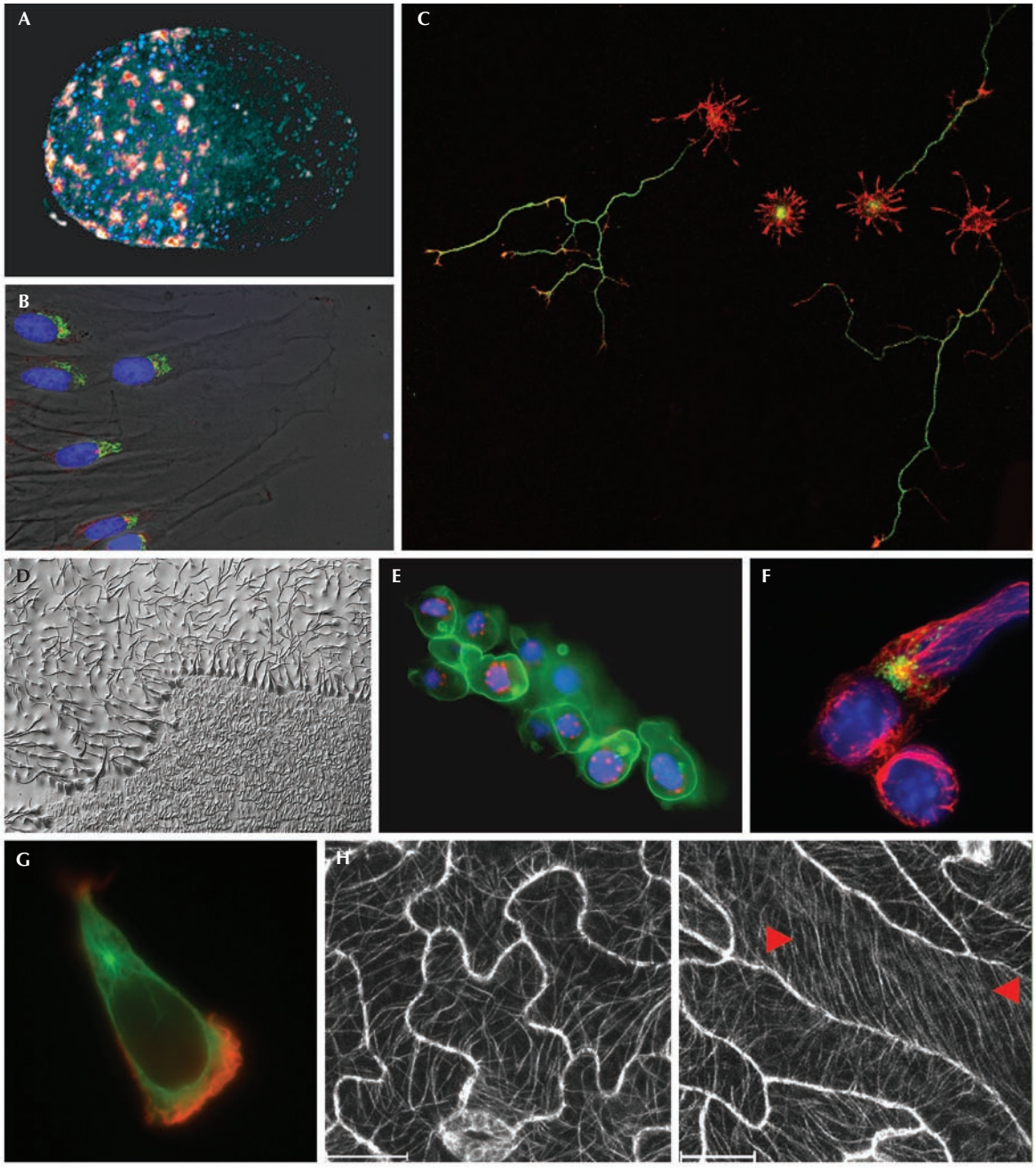

Fig 2 | Polarization in multicellular organisms. (**A**) One-cell *Caenorhabditis elegans* embryo marked with EEA1 (blue) and NMY-2 (red), both of which are enriched at the anterior cortex. (**B**) Polarized migrating astrocytes showing Golgi (green), centrosome (red) and nuclei (blue). (**C**) Polarized hippocampal neurons showing F-actin (red) and the axonal marker Tau (green). (**D**) Disrupted polarization in the *Drosophila* pleura. The cells at the bottom right (marked by the absence of hairs) overexpress FZ. Adjacent fz^- mutant cells are polarized by the over-expressing cells; however, mutant cells far from the clone have a random polarity. (**E**) Migrating zebrafish primordial germ cells. Actin is shown in green and the nucleus is shown in blue. (**F**) Cytotoxic T lymphocyte with secretory granules (green) and microtubule-organizing centre polarized towards one of two target cells. Nuclei are stained blue and microtubules are stained red. (**G**) T cell migrating on ICAM-1, stained for F-actin (red) and microtubules (green). (**H**) Leaf epidermal cells of plants that express a GFP–tubulin in a wild-type background (left) and in plants overexpressing the ROP GTPase scaffold protein ICR1 (right). In wild-type cells, the microtubules are orientated in different directions; in ICR-overexpressing cells, they are arranged in a direction transverse to the long axis of cells (arrowheads). EEA1, early endosomal autoantigen 1; FZ, Frizzled; GFP, green fluorescent protein; ICAM-1, intercellular adhesion molecule 1; ICR1, interactor of constitutive active Rops; NMY-2, non-muscle myosin type II. Images kindly provided by J. Ahringher (**A**), S. Etienne-Manneville (**B**), B. Eckholt (**C**), P. Lawrence and J. Casal (**D**), E. Raz (**E**), G. Griffiths (**F**), S. Heasman and A. Ridley (**G**), and S. Yalovsky (**H**).

and its associated receptor is not always known. One such setting is the migration of primordial germ cells in *Drosophila,* as discussed by R. Lehmann (New York, USA). Before gastrulation, these cells are found in an organized group that expresses *Drosophila* E-cadherin at its centre, and during development they dissociate and begin directional migration. A novel G-protein-coupled receptor, Tre1, the ligand of which has not yet been identified, is required for primordial germ-cell polarization and transepithelial, but not subsequent, migration. During migration along the midgut, two lipid phosphate phosphatases, Wunen and Wunen2, are expressed along the midline and act as chemorepellants. Primordial germ-cell migration in zebrafish was discussed by E. Raz (Munster, Germany). These cells are propelled by bleb-like protrusions that are generated by calcium-dependent actomyosin contraction (Fig 2E). The blebs can be either orientated in response to an external chemoattractant or uniformly distributed. This alternating pattern generates a movement that is reminiscent of bacterial runs/tumbles. Raz discussed recent evidence that an additional chemoattractant-dependent receptor, CXCR7, has an essential role during cell polarity, primarily in somatic non-migrating cells (Boldajipour *et al*, 2008).

Plasma-membrane blebbing has also been observed in amoeboid cells; however, these cells migrate primarily by the extension and retraction of pseudopods. P. van Haastert (Groningen, The Netherlands) reported on computer-aided analysis of the patterns of pseudopod extensions in *Dictyostelium*. New pseudopods are formed in two ways: the splitting of existing pseudopods, which is the predominant method, and *de novo* formation. In shallow chemical gradients, cells extend pseudopods in an alternating left–right pattern reminiscent of an ice skater. When the direction of this gradient is changed, the cells skip steps and use consecutive pseudopods on the side of the new direction (left–left or right–right) to reorientate themselves. Multiple signalling pathways control *Dictyostelium* chemotaxis and its regulation depends on the extent to which cells are polarized (Veltman *et al*, 2008). Early in their development, *Dictyostelium* chemotaxis is regulated by the PI(3)K and PLA2 pathways. Subsequently, cells become considerably more polarized. At this point, soluble guanylyl cyclase is important for orientation and directional persistence.

For an external gradient of chemoattractant to elicit intracellular polarization, cells must interpret receptor-mediated signals. *Dictyostelium* and neutrophils sense these gradients spatially: immobilized cells that are placed in a static chemoattractant gradient respond by selectively and persistently translocating intracellular markers, such as pleckstrin homology (PH) domains, to the side of the cell with the highest receptor occupancy. However, the same cells, when exposed to spatially homogeneous but persistent signals, respond transiently. A local-excitation, global-inhibition mathematical model that explains these two modes of response was presented by P. Iglesias (Baltimore, USA). In the model, receptor occupancy triggers a fast excitation, as well as a slower inhibitory response. Diffusion of the inhibitor results in loss of the local information about receptor occupancy, leading to an inhibitory signal that reflects the global level of the stimulus. Iglesias presented simulations in which the model recreates the observed behaviour for both graded and spatially homogeneous stimuli. Although originating in the observed behaviour of *Dictyostelium*, this model also seems to fit data presented by M. Peter (Zurich, Switzerland) for *Saccharomyces cerevisiae,* suggesting that an excitation–inhibition mechanism might also regulate pheromone sensing in budding yeast.

Directed motility can also have dire consequences, such as enabling tumour invasion, as discussed by P. Chavrier (Paris, France). Extensions of invadopodia require membrane-type metalloproteases (MT-MMPs) such as MT1-MMPs, and Chavrier provided evidence that the v-SNARE vesicle-associated membrane protein 7 (VAMP7), which colocalizes with MT1-MMP at the invadopodia, is required for the invasive activity of a breast cancer cell line, suggesting that exocytosis is important for such behaviour.

Roles of Rho GTPases in cell polarity

For a polarized morphology to be observed, not only must the cell have a means of sensing spatial heterogeneities through internal or external cues, but these initial cues must also be greatly amplified and spatial information subsequently transduced to the cytoskeleton and secretory apparatus. For example, during an immune response, engagement of the T-cell receptor results in the polarized secretion of lytic granules to the target cell, as discussed by G. Griffiths (Cambridge, UK). At the area of contact, concentric rings of secretion, signalling and adhesion are observed. The lytic granules travel on microtubules towards the microtubule-organizing centre, and cortical actin is then cleared away from the site of secretion (Fig 2F). In this case, polarization of the secretory apparatus and the cytoskeleton is crucial for target-cell destruction. Feedback loops involving the Rho-GTPases, Rho, Rac and Cdc42, are crucial for transduction of such spatial information and have been proposed as a means of amplifying the weak heterogeneities in receptor signalling. The role of Rho-GTPases in polarization of yeast cells, plants, keratinocytes, T cells and astrocytes was discussed at the meeting.

Temporal and spatial activation of Rho-GTPases is accomplished by tightly regulated GEFs and GAPs. Activation through GEFs was discussed by R. Arkowitz (Nice, France) in *S. cerevisiae* and *Candida albicans*, and by Y. Sánchez Martín (Salamanca, Spain) in *S. pombe*. In budding yeast, the localization of the Cdc42 GEF Cdc24 is dependent on homo-oligomerization, which might provide a means for regulating this GTPase (Mionnet *et al*, 2008). In the pathogenic yeast *C. albicans*, Rac1 activation is crucial for morphological changes in response to some signals (Fig 1E), whereas Cdc42 is required for morphological changes that occur in response to other signals. In the fission yeast, the Rho1 GEF Rgf1 is necessary for cell-wall integrity and, in particular, for glucan synthesis. This GEF localizes as a ring at the site of cytokinesis and at both cell ends, and probably specifies regions of activated Rho1 (Fig 1C). In *S. pombe*, PKC and MAPK pathways that are important for cell-wall integrity function downstream of Rgf1. E. Bi (Philadelphia, USA) presented results showing how the Cdc42 GAP Rga1 limits the region of activation of this GTPase. Surprisingly, instead of forming a bud adjacent to the previous bud site, yeast mutants lacking Rga1 form a bud at the old bud site (Fig 1D). In wild-type cells, activated Cdc42 localizes adjacent to the previous bud site, and concentric zones of the GEF Cdc24 and the GAP Rga1 are thought to restrict Cdc42 activation spatially, which could result in a gradient of activated Cdc42 (Tong *et al*, 2007).

The Rop GTPases are the main regulators of plant polarity, which is particularly evident in root hairs and pollen tubes. The main classes of animal and fungal Rho-GTPase GEFs are absent from plants, and B. Kost (Warwick, UK) discussed the role of the Rac-Rop GTPases, which are found at the apical plasma membrane of tobacco pollen tubes. The restriction of their activated form to the pollen-tube tip is crucial for polarized growth. As in yeast, the zone of the activated Rac-Rop GTPase Nt-Rac5 seems also to be restricted by Nt-RhoGAP1, which localizes to the flanks of the pollen-tube tip. Furthermore, the Rho guanine nucleotide-dissociation

inhibitor Nt-RhoGDI2 can both positively and negatively affect Nt-Rac5 activity. S. Yalovsky (Tel Aviv, Israel) discussed the roles of Rac-Rop GTPases in plant polarity during *Arabidopsis* development. One such Rho-GTPase, ATROP6, is transiently palmitoylated and stearylated (S-acylated) in its activated state, thereby promoting its partitioning into specific membrane domains that might act to amplify polarity signals (Lavy *et al*, 2007). Activated ATROPs bind to the novel effector protein, ICR1, which is a coiled-coil domain protein that also binds to itself and the exocyst complex component Sec3. This protein functions as a scaffold linking Rho-GTPase signalling to secretion and is likely to be important for amplifying signals that are crucial for polarity (Fig 2H).

The role of the Par–Tiam1 GEF complex in various cell-polarization processes was discussed by J. Collard (Amsterdam, The Netherlands). The work that Collard presented emphasized the requirement of the Par–Tiam1 complex for apical–basal polarity of contacting keratinocytes, and for the persistent—and hence chemotactic—migration of non-contacting migratory keratinocytes. The Par complex is also important during Rap1 and chemokine-induced T-cell polarization (Pegtel *et al*, 2007). The Rac1 GEF Tiam1 interacts with both the Rap1 GTPase and the Par1 complex, indicating that the association of Rac1, Tiam1 and the Par complex is likely to be important to amplify the signals necessary for persistent cell polarization. I. Macara (Charlottesville, USA) discussed the role of the Par3–Tiam1 complex in hippocampal neurons during spine morphogenesis. Neurons in which Par3 is reduced by RNAi or Tiam1 is overexpressed form multiple filopodia and lamellipodia. In Par3-knockdown cells, this phenotype can be suppressed upon expression of a constitutively active Rac.

The roles of different Rho-GTPases, and their activation in T-cell migration and cell stopping, were discussed by A. Ridley (London, UK). T cells undergo persistent migration until they are engaged and movement stops (Fig 2G). Rac1 is required for cell migration, although, surprisingly, this Rho-GTPase is activated when cell movement stops, whereas RhoA activation levels decrease. When Rac1 is activated there is a decrease in ezrin–radixin–moesin (ERM) protein phosphorylation and adhesion receptors are lost at the back of the cell. Ridley also presented results showing the importance of the microtubule cytoskeleton, which is crucial for T-cell motility and polarity. These findings highlight the fact that Rho-GTPases need to be tightly regulated for both motility and cell-contact responses. Work presented by S. Etienne-Manneville (Paris, France) illustrated the importance of cell interactions with the extracellular matrix, and especially intercellular contacts, as signals for astrocyte polarization (Fig 2B). Cell contacts—including calcium-dependent cell–cell adhesion—are transduced by *N*-cadherin to the RhoA-GTPase, which probably amplifies the spatial signals, resulting in the orientation of the microtubule-organizing centre (or centrosome)–nucleus axis, which establishes the division axis. This response requires the actin and microtubule cytoskeleton, respectively.

L. Edelstein-Keshet (Vancouver, Canada) presented a mathematical model that shows how the interactions between Rho-GTPases can lead to stable polarized movement. In this model, Cdc42 and Rho are mutually antagonistic, and Cdc42 also activates Rho through Rac. This network of interactions induces bistability, which, when coupled to diffusion, leads to a travelling wave. By adding inactive cytosolic components of the three GTPases, the wave can be made to stop, giving the cell a stable polarized form. Edelstein-Keshet presented simulations that recreate the stable migration of fish keratocytes (Fig 3B).

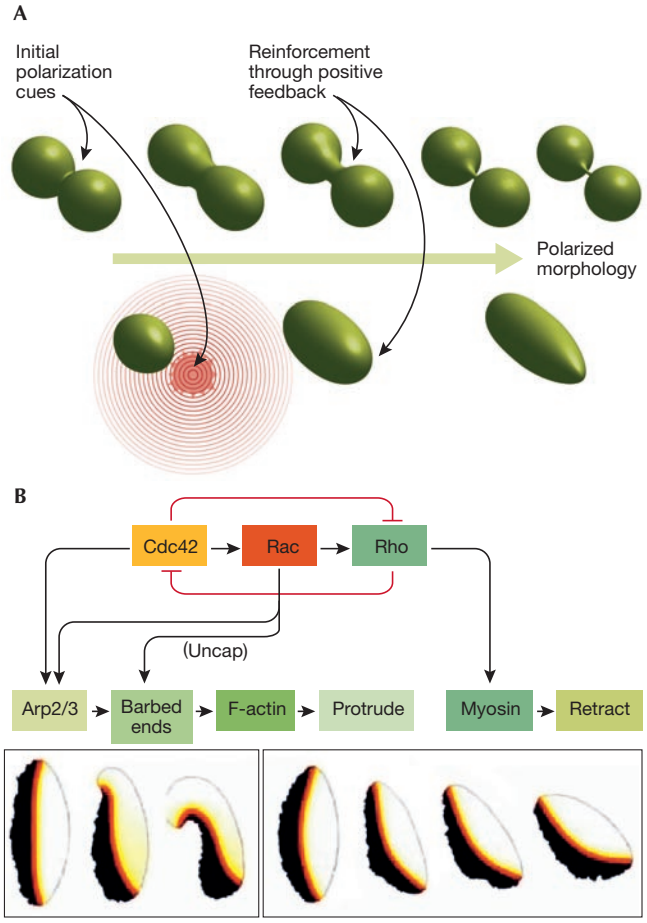

Fig 3 | Steps in polarization. (**A**) Polarization begins with an initial cue, which can be intracellular (for example, cell division; top) or extracellular (for example, chemotaxis; bottom). This cue is amplified, typically by positive-feedback loops, resulting in a polarized morphology. (**B**) Internal signalling modules (top) were combined to produce local protrusion/retraction of a two-dimensional model cell (Maree *et al*, 2006). The level of Rho is used to regulate myosin-based contraction. The cell initiates and maintains persistent motion if stimulated by a small transient gradient of Cdc42 activation. The cell turns in response to a strong (bottom left) or shallow (bottom right) gradient. Images courtesy of L. Edelstein-Keshet (**B**). Arp2/3, actin-related protein 2/3; Cdc42, cell-division cycle 42.

Role of phosphoinositides in polarization

In some cell types, subtle internal or external cues result in a pronounced spatial asymmetry of plasma-membrane lipid phosphoinositide phosphates, including $PI(4,5)P_2$ and $PI(3,4,5)P_3$. The spatial restriction of these phospholipids is likely to be one of the first manifestations of cell polarity, and the steepness of this response relative to a shallow external gradient or small signal heterogeneities indicates that substantial amplification must take place beforehand. Phosphoinositide phosphate asymmetries—which can be observed immediately following exposure to a cue—are a convenient measure of cell polarization. The requirement for $PI(4,5)P_2$ and $PI(3,4,5)P_3$ in different cell-polarization processes was the topic of several presentations. For example, $PI(4,5)P_2$ and $PI(3,4,5)P_3$ can function by

recruiting and activating a range of signalling proteins, in particular small Rho G-proteins.

In *Dictyostelium*, PI(3,4,5)P_3 is tightly restricted to the front or leading edge, as is the kinase responsible for its generation, PI(3)K. However, PTEN, which is crucial for PI(3,4,5)P_3 hydrolysis, accumulates at the rear of the cell. During cytokinesis, these enzymes also polarize to either the pole (PI(3)K) or the furrow (PTEN; Fig 1B). P. Devreotes (Baltimore, USA) reported that PI(3,4,5)P_3 induces the translocation of the PH domain containing protein kinase B (PKBA) to the front of the cell. He also showed that TORC2 activates PKBA as well as a second related kinase, PKBR1, which lacks a PH domain yet is myristylated, suggesting that its localization is not PI(3,4,5)P_3-dependent (Kamimura *et al*, 2008). Intriguingly, a PI(4)P-5-kinase homologue is a substrate for PKB, raising the possibility that PI(4,5)P_2 might also be important for chemotaxis.

Cortical polarity during asymmetrical cell division in *C. elegans* was discussed by C. Cowan (Vienna, Austria) and J. Ahringer (Cambridge, UK). Approximately 30 min after fertilization, PAR proteins segregate to two distinct cortical domains establishing an anterior–posterior axis in the one-cell embryo (Fig 2A). The initial division is asymmetrical because of higher posterior pulling forces on the mitotic spindle. Gβ subunits of heterotrimeric G-proteins and their Goloco-domain-containing non-receptor regulators GPR-1/2 control the spindle pulling forces, and PAR-directed posterior enrichment of GPR-1/2 leads to higher posterior forces. Ahringer discussed new proteins that are required for spindle positioning, as identified in an RNAi screen. After knockdown of a casein kinase homologue (CSNK-1), GPR-1/2 asymmetry is abolished, indicating that this kinase is upstream of heterotrimeric G-protein signalling. As the yeast orthologue of CSNK-1 phosphorylates PI(4)P-5-kinase, the Ahringer group studied the worm homologue PPK-1, which was found to localize to the posterior end of the embryo, and to be required for cortical GPR-1/2 association and the generation of pulling forces. These results indicate that PI(4,5)P_2 might have a role in transducing the spatial signal from PAR protein asymmetry to heterotrimeric G-protein signalling, which is crucial for asymmetrical cell division.

The PI(3)K pathway also has an important role in controlling axon specification and elongation, as discussed by B. Eckholt (London, UK). Hippocampal neurons extend several short processes (neurites) of equal length after being plated. Polarity is achieved through the restriction of PI(3)K activation to one of these neurites, leading to its lengthening and rapid growth (Fig 2C). PI(3)K regulation is achieved through two pathways: PI(3)K activates Rho GEFs, leading to the activation of the Rho-GTPases that regulate the actin cytoskeleton, and it also activates AKT, leading to the downstream inhibition of GSK3, which, in turn, controls microtubule dynamics.

Conclusion and perspectives

A forte of this meeting brought together participants with a wide range of scientific backgrounds to examine the broad array of molecules and mechanisms that govern the establishment and maintenance of cell polarity, and to compare them in model systems ranging from unicellular bacteria to complex multicellular organisms. Owing to the diverse nature of the topics considered, it is not surprising that a consensus was not reached as to where the polarity field is headed. Nevertheless, some common themes emerged from the meeting. In most cases, the establishment of polarity requires the initial sensing of subtle spatial heterogeneities (internal or external), their subsequent amplification and stabilization, and the eventual transduction of this spatial information to various outputs; for example, cytoskeleton and secretory apparatus. The presence of positive-feedback loops—in particular those involving small GTPases and phosphoinositides—as a means of amplifying signals was reported in a range of systems. Another common feature was the highly redundant nature of the systems, with multiple pathways cooperating to achieve their function. The inherent beauty of polarized cells and organisms merged with that of Lake Titisee and the Black Forest. The winds over the lake that prevent the surface from freezing in the winter time are reminiscent of the continued excitement and movement in the cell-polarity field and of the discoveries that lie ahead.

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