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CELL SCIENCE AT A GLANCE

Development and dynamics of cell polarity at a glance

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ABSTRACT

Cells exhibit morphological and molecular asymmetries that are broadly categorized as cell polarity. The cell polarity established in early embryos prefigures the macroscopic anatomical asymmetries characteristic of adult animals. For example, eggs and early embryos have polarized distributions of RNAs and proteins that generate global anterior/posterior and dorsal/ventral axes. The molecular programs that polarize embryos are subsequently reused in multiple contexts. Epithelial cells require apical/basal polarity to establish their barrier function. Migrating cells polarize in the direction of movement, creating distinct leading and trailing structures. Asymmetrically dividing stem cells partition different molecules between themselves and their daughter cells. Cell polarity can develop *de novo*, be maintained through rounds of cell division and be dynamically remodeled. In this Cell Science at a Glance review and poster, we describe molecular asymmetries that underlie cell polarity in several cellular contexts. We highlight multiple developmental systems that first establish cell/developmental polarity, and then maintain it. Our poster showcases repeated use of the Par, Scribble and Crumbs polarity complexes, which drive the development of cell polarity in many cell types and organisms. We then briefly discuss the diverse and dynamic changes in cell polarity that occur during cell migration, asymmetric cell division and in planar polarized tissues.

KEY WORDS: Cell polarity complexes, Par complex, Scribble complex, Crumbs complex, Axis specification, Asymmetric cell division, Planar cell polarity, Apical basal polarity, Cell migration, Cell polarity signaling

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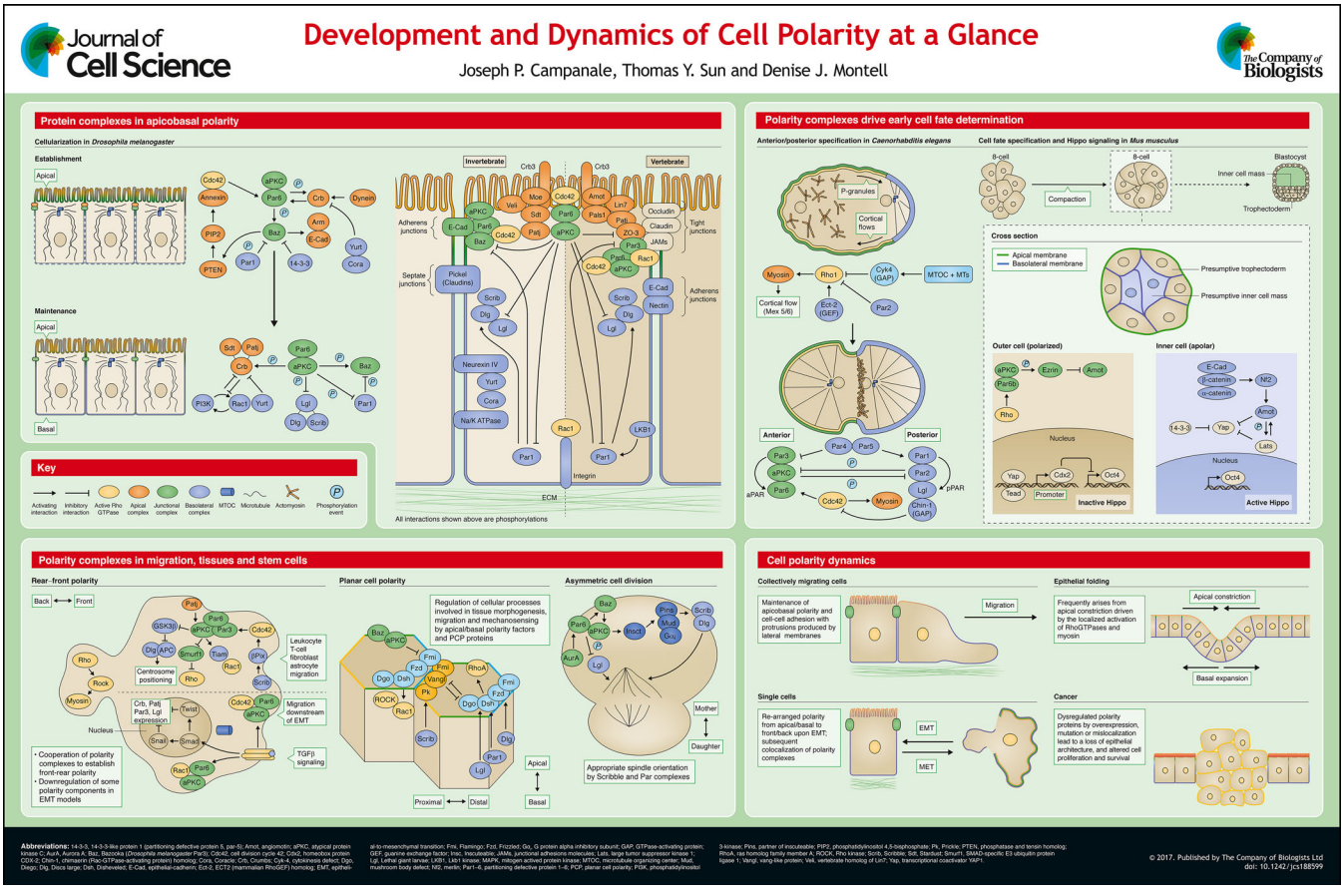
Introduction

Cells are polarized biochemically and morphologically, which allows them to produce diverse cell shapes optimized for equally varied functions. For example, epithelial cells have apical membranes contacting the environment, lateral membranes sealing paracellular spaces, and basal membranes anchored to extracellular matrices. In contrast, migrating cells extend highly dynamic lamellipodia and filopodia primarily from leading edges to



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drive forward protrusion, while the rear retracts resulting in net movement. Remarkably, the establishment and maintenance of such diverse cell shapes requires a common set of molecules. The Par, Crumbs, and Scribble complexes, originally identified in *Drosophila melanogaster* and *Caenorhabditis elegans* (reviewed in Assémat et al., 2008, discussed in Box 1), are now well-known components of polarity-generating signaling networks underlying the development of diverse cell shapes and function in nearly all animals (Nance and Zallen, 2011; St Johnston and Ahringer, 2010; Thompson, 2013; Wodarz, 2002). Interestingly, not all cellular contexts require all three complexes; rather, they are deployed in different combinations to produce distinct morphologies. In this Cell Science at a glance review and the accompanying poster, we highlight how these complexes pattern early development of diverse animal embryos, and drive asymmetries in cell shape and division.

The subcellular machinery dictating cell polarity has long fascinated cell biologists. Genetic screens in yeast identified the core polarity-generating Rho GTPase family member Cdc42 (reviewed in Chant, 1999; Drubin, 1991; Johnson, 1999). In yeast, Cdc42 activity regulates many cellular processes including polarized vesicle trafficking, cytoskeletal architecture, bud site selection and activation of signaling cascades, including MAPK. Yeast polarity is the subject of a previous Cell Science at a glance article (Irazoqui and Lew, 2004). Like yeast, animal cells use Rho family GTPases for cell polarization. However, as described below, more elaborate regulatory mechanisms evolved, including multiple GTPases as well as upstream regulation by Par, Crumbs, and Scribble polarity protein complexes (Box 1). Ultimately, polarity complexes build signaling centers that scaffold Rho GTPases to specific membrane domains. This in turn controls cell shape and function by regulating the actomyosin cytoskeleton (Etienne-Manneville and Hall, 2003; Ngok et al., 2014), directing recycling endosome traffic (Harris and Tepass, 2010a; Shivas et al., 2010), and controlling E-cadherin distribution and stability in adherens junctions (Bilder et al., 2000; Harris and Tepass, 2010b; Rodriguez-Boulan and Macara, 2014).

In this article, we provide a brief primer describing how these protein complexes first establish and then maintain cell polarity during development. We highlight examples from animal models that showcase how cell polarity in eggs and early embryos is translated into tissue, organ and organismal polarity. Embryos deploy polarity complex proteins to control axis specification and morphogenesis as well as cell fate, division, shape and dynamic behaviors. Compared to studies of cultured cells, embryos offer the advantage of *in vivo* observations. Here, we expand on an earlier Cell Science at a glance article that illustrated polarity complexes and the role of their domain architecture in apicobasal polarity (Margolis and Borg, 2005). We summarize how these proteins interact to produce cell polarity in multiple biological contexts. We briefly highlight the development of apicobasal polarity in the *Drosophila* embryo, axis specification in *C. elegans* and early cell fate decisions in mammalian embryos. We also describe contexts in which polarity proteins control migratory, tissue and stem cell polarity. Due to space constraints, we limit our analyses to polarity protein complexes and their regulation of RhoGTPase localization. We cite additional reviews that provide greater depth. Table S1 lists all polarity proteins described in the poster and text, while Box 2 provides a brief summary of the roles of polarity proteins in health and disease, including cancer.

Modular protein complexes establish apical/basal polarity

A defining feature of epithelial cells is polarization along the apicobasal axis. The *Drosophila* embryonic epithelium is an

Box 1. Core polarity proteins

The Crumbs complex includes the integral membrane protein, Crumbs (Crb), as well as PALS1 (*Drosophila* Stardust), and the PALS1-associated tight junction homologue (Patj). The apical/junctional Par complex comprises Par3 (*Drosophila* Bazooka), Par6 and atypical protein kinase C (aPKC). The basolateral Scribble complex consists of the proteins Scribble (Scrib), Discs Large (Dlg) and Lethal Giant Larva (Lgl). The Scribble complex is distinct from the Par and Crumbs complexes in that, although there are clearly strong genetic interactions, there is limited evidence for physical interactions. One study shows binding of Dlg to phosphorylated Lgl (Zhu et al., 2014), another shows that the adapter protein GUK-holder is required for interaction between Scrib and Dlg (Mathew et al., 2002). Recent evidence indicates that an additional basolateral complex consists of yurt, coracle, neurexin IV and the Na^+/K^+ ATPase (Laprise et al., 2009). Table S1 lists the protein components of the primary, polarity-generating signaling networks. All proteins in the Par, Crumbs and Scribble complexes are primarily composed of protein–protein interaction domains that scaffold distinct signaling centers in apical, lateral and basal domains. For instance, many polarity proteins contain multiple PSD95–Dlg–ZO1 (PDZ) domains, which bring together proteins that then become tethered to cortical F-actin (Bilder, 2001; Bilder et al., 2003). One output of polarized membrane domains is spatially regulated Rho GTPase signaling.

Box 2. Cell polarity in birth defects and disease

For vertebrates, as for invertebrates, polarity complex proteins are essential for life. Homozygous mouse knockouts of many polarity genes are lethal (see Table S1). Interestingly, several mutations cause the same lethal neural tube defect called craniorachischisis. In mouse, null mutations of *Scrib* – resulting in the *circletail* mouse mutant – cause craniorachischisis (Murdoch et al., 2003), as do mutations of the core PCP genes *Celsr1* and *Vangl2*. Strikingly, mice heterozygous for these mutations – alone or in combination – also exhibit craniorachischisis (Murdoch et al., 2014). The human genetics of neural tube defects is complex and poorly understood, and the mouse studies reveal that both genetic background and environmental effects lead to complexities, such as phenotypes that are incompletely penetrant or variably expressive. Whole-exome and whole-genome sequencing will undoubtedly be important tools in revealing the precise genetic interactions that underlie this common group of birth defects and the roles that are played by polarity genes. Additional human birth defects attributed to alterations in the Scrib protein include coloboma, microcephaly, short stature, as well as craniofacial, cardiac and renal defects (Dauber et al., 2013). Mutations in CRB1 cause retinitis pigmentosa and Leber congenital amaurosis (Mehalow et al., 2003). Mutations in *DLG5* contribute to inflammatory bowel disease (Stoll et al., 2004), whereas truncated DLG3 causes severe mental retardation (Tarpey et al., 2004). Polarity proteins are also implicated in cancer. An early hallmark of cancers derived from epithelial tissues is loss of apicobasal polarity. Genetic studies in *Drosophila* support the idea that loss of polarity is tumorigenic (Bilder, 2004; Bilder et al., 2000; Gateff, 1978). Moreover, Zen and colleagues found that the *PARD3* gene is homozygously deleted in human esophageal squamous cell carcinoma cell lines (Zen et al., 2009). However, deletions and mutations of polarity genes are rare in human cancers, and the genes encoding aPKCζ, Par3, Dlg and Scribble can be amplified or overexpressed, suggesting they may also have pro-tumorigenic roles (Halaoui and McCaffrey, 2014; Huang and Muthuswamy, 2010; Lin et al., 2015; Rothenberg et al., 2010). Therefore, deciphering precisely how cell polarity is rewired and contributes to tumor progression in diverse types of cancer is a key open question. Equally important is to elucidate how polarity proteins function in collectively migrating cells that maintain both apicobasal and leading/lagging polarity, because this form of motility renders cancer cells more efficient at metastasis than single cells (Cheung and Ewald, 2016; Cheung et al., 2016; Fischer et al., 2015; Zheng et al., 2015).

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excellent model for understanding the *de novo* development of apicobasal polarity (Jiang et al., 2015; Mazumdar and Mazumdar, 2002; Tepass, 1997, 2012; Thompson, 2013). Following fertilization, the early *Drosophila* embryo undergoes thirteen rounds of nuclear division, to produce a syncytium composed of ∼6000 nuclei enclosed in a single plasma membrane. During cellularization, the plasma membrane simultaneously encapsulates all nuclei, thus forming the embryonic epithelium (Foe and Alberts, 1983; Mavrakis et al., 2009). As cellularization progresses, specialized zonula adherens junctions (hereafter referred to as adherens junctions), form on lateral membranes just below the apical surfaces (see poster). Adherens junctions generate a belt-like band of F-actin and connect adjacent cells through cell adhesion proteins, such as E-cadherin (reviewed in Harris and Tepass, 2010b). Invertebrate cells develop septate junctions that form immediately basal to the adherens junctions, and prohibit paracellular diffusion of ions and small organic molecules. Vertebrate epithelia also form adherens junctions but, instead of septate junctions, vertebrate cell–cell interfaces include tight junctions and desmosomes. Tight junctions are composed of claudins, occludins and junctional adhesion molecules (JAMs) (see poster) (Rodriguez-Boulan and Macara, 2014), while desmosomes contain desmosomal cadherin linked to cytokeratin filaments.

An essential cue driving the establishment of apicobasal polarity is the dynein-dependent transport of the Par complex protein Bazooka (Baz; also known as Par3 in vertebrates) to adherens junctions (Harris and Peifer, 2005). Diffusion of Baz onto the basolateral membrane is restricted by Par1-kinase-mediated phosphorylation of two conserved Ser residues and subsequent binding to members of the 14-3-3 protein family (Benton and Johnston, 2003). Phosphorylation of Ser151 prohibits Baz oligomerization, and phosphorylation at Ser1085 prevents the binding of aPKC, thus blocking the Par complex from forming on basolateral membranes (Jiang et al., 2015). Apically, phosphorylation of Baz by aPKC at Ser980 releases the Par6–aPKC cassette to bind Crb, and frees Baz so it can bind the lipid phosphatase PTEN, which produces phosphatidylinositol 4,5-bisphosphate (PIP2) from phosphatidylinositol (3,4,5)-trisphosphate (PIP3) (Stein, 2005). In mammals, Cdc42 can then bind annexin, which is localized to PIP2-rich membranes (Martin-Belmonte et al., 2007). Work in Madin-Darby canine kidney (MDCK) cells indicates that the Cdc42 guanine nucleotide exchange factor (Cdc42GEF) protein Tuba then locally activates Cdc42 (Bryant et al., 2010; Cestra et al., 2005). This promotes apical accumulation of the Par6–aPKC complex in a feedback loop (Hutterer et al., 2004) (see poster). Dynein, a minus-end-directed microtubule motor, also aids in Crb accumulation by transporting Crb proteins and transcripts apically (Li et al., 2008). Kinesins, which are plus-end-directed microtubule motors, might also aid in apical transport of polarity proteins, which would require a subset of microtubules to orient their plus-ends apically. Kinesins drive the apical delivery of Crb in adult eyes, but it is not yet known whether this is also true in other epithelia (League and Nam, 2011). In addition to the positive regulators of Crb localization, basolaterally localized yurt and coracle prevent basolateral diffusion of Crb, thus stabilizing basolateral identity (Laprise et al., 2006, 2009). In polarizing MDCK cysts, attachment to extracellular matrix through integrin/FAK defines the basal side, thus establishing polarity (Bryant et al., 2014).

Once established, apicobasal polarity is maintained through mutual antagonism or negative feedback regulation between the apical and basolateral complexes (Benton and Johnston, 2003; Bilder et al., 2003; Tanentzapf and Tepass, 2002). For instance, aPKC-mediated phosphorylation of Lgl and Par1 prevents their accumulation at the apical cell surface. Par1 continues to inhibit basolateral localization of Baz, whereas Lgl excludes Par6 from basolateral domains (Doerflinger et al., 2010; Hutterer et al., 2004). The precise mechanism of Lgl–Par6 antagonism remains unclear. Additionally, a feedback loop between Rac1 and PI3K antagonizes basolateral diffusion of Crumbs (Chartier et al., 2011a). These interactions, together with other antagonistic relationships, thus establish distinct apical and basal membrane domains, and promote domain-specific signaling by scaffolding signaling molecules, including regulators of Rho GTPases.

Polarity proteins simultaneously drive asymmetric cell division and axis specification in *C. elegans*

The Par proteins were originally identified in a genetic screen for maternal-effect lethal mutations that disrupt early asymmetries in the *C. elegans* embryo (Kemphues et al., 1988). Here, the one-celled zygote simultaneously segregates the somatic and germ cell lineages (future AB and P1 cells, respectively) and specifies the anterior-posterior axis (see poster). In this system, dense cytoplasmic RNA-protein granules called P-granules are initially distributed symmetrically throughout the egg. After fertilization, polarity proteins establish distinct anterior and posterior domains at the cell cortex. The core anterior Par (aPar) complex is composed of Par3, Par6 and protein kinase C-like 3 (PKC-3; hereafter referred to as aPKC), whereas the core posterior Par (pPar) complex consists of Par1, Par2 and Lgl (Motegi and Seydoux, 2013; Nance, 2005; Noatynska and Gotta, 2012). The mutually antagonistic interactions of these complexes are reinforced by the Par regulators, Par4, Par5, non-muscle myosin and the Rho GTPase regulators Cyk-4, Chin-1 and Ect-2 (Munro and Bowerman, 2009). Par4 is a homolog of the liver kinase B1 (LKB1) and regulates myosin activity at the aPar and pPar boundary. Par4 controls myosin activity through phosphorylation of anilin, a non-muscle myosin regulator (Chartier et al., 2011b; Pacquelet et al., 2015). Par5 belongs to the family of 14-3-3 regulatory proteins, and binds and inhibits cortical localization of aPars in the posterior of the embryo (Morton et al., 2002). Myosin contractions promote cortical flow of the aPar complex, as well as Mex5 and Mex6 in the anterior direction (Cuenca et al., 2003; Munro et al., 2004). The accumulation of Mex5 and Mex6 specifies somatic fate in the anterior AB cell. P-granules segregate to the P1 germline progenitor cell in *C. elegans*, yet interestingly, their segregation is driven by asymmetric assembly and disassembly in a manner that directs their enrichment in P1 cells, rather than by active transport or myosin-generated flows (Brangwynne et al., 2009; Gallo et al., 2010).

The process of aPar and pPar complex segregation occurs in two phases: establishment and maintenance. Symmetry is initially broken upon fertilization by delivery of the sperm-derived MTOC to the future posterior pole (Motegi et al., 2011). During polarity establishment, the MTOC and/or the microtubules it spawns, recruit Par2 and Par1 from the cytoplasm to the posterior cortex where, together with several Rho GTPase-activating proteins (GAPs) (Anderson et al., 2008; Cuenca et al., 2003; Jenkins et al., 2006), they antagonize the anterior Par proteins, limiting them to the anterior cortical domain of the zygote. This polarization is reinforced by anteriorly-directed, myosin-dependent cortical flows. During maintenance, the aPars enter a feedback loop such that Cdc42, not Rho1, promotes Par6 localization (Aceto et al., 2006), while the pPar domain is maintained by Par2 recruitment of

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Par1 and Lgl (Beatty et al., 2010; Hoege et al., 2010). Par4 and Par5 continue to maintain the boundary between the aPar and pPar complexes (see poster).

Polarity protein signaling determines trophectoderm and inner cell mass fates in vertebrate embryos

Like *C. elegans*, *Mus musculus* embryos use the Par complex to regulate an early asymmetric cell fate decision (Motosugi et al., 2005; Rossant, 2004) (see poster). Mouse embryos segregate the placenta-forming trophectoderm cells from the inner cell mass (ICM), which will form the embryo proper. This segregation begins in the 8-cell embryo and continues to the 32-cell stage. In the 1980s, ideas backed by limited molecular evidence predicted that cell polarity, specifically the amount of apical cell membrane, would dictate the fates of trophectoderm and ICM (Johnson, 2009; Yamanaka et al., 2006). It is now clear that activation of the apical polarity complex specifies trophectoderm cell fate and that suppression of aPKC by basolateral Par1 specifies ICM cell fate (Alarcon, 2010; Dard et al., 2009; Plusa et al., 2005; Vinot et al., 2005).

Unlike in *C. elegans*, the downstream effects of polarity in vertebrate embryos are to inactivate Hippo signaling in the trophectoderm and activate it in the ICM (Hirate and Sasaki, 2014). The Par6–Par3–aPKC complex in trophectoderm acts to silence the Hippo signaling protein angiomotin (Amot) by phosphorylating ezrin, thus allowing Yap to activate transcription of Cdx2, which in turn suppresses the pluripotency gene Oct4. In contrast, ICM cells lack apical membrane and retain active Amot, which suppresses nuclear Yap localization. Preventing translocation of Yap into the nucleus suppresses expression of Cdx2, de-represses Oct4 and maintains pluripotency of the ICM. Knockdown of either aPKC or loss of cell junctions is sufficient to activate Hippo signaling and drive cells to an ICM fate, whereas inactivation of the Hippo signal transducer Amot is sufficient to drive cells towards a trophectoderm fate (Hirate et al., 2013).

Cell polarity complexes organize the polarity of migrating cells, planar polarization of epithelial cells and asymmetric cell division

Migrating cells

Migrating cells interact with their environment differently than epithelial cells by adopting a back–front polarity in response to chemotactic signals (Ridley et al., 2003). Precisely how, and the extent to which, migrating cells reorganize and employ epithelial polarity complex proteins remains an active area of research. One mechanism of producing migratory cells from epithelial cells is through epithelial-to-mesenchymal transitions (EMTs). EMTs are a general mechanism to redistribute cells during morphogenesis (Lim and Thiery, 2012). The transcription factor Snail, among others, drives EMT and downregulates some polarity complex components, including Crb and Lgl (Moreno-Bueno et al., 2008). Yet migratory cells do not completely dispense with polarity protein signaling, and polarity complexes are not always lost during cell migration. Rather, at least in some cell types, their antagonistic interactions cease and they promote one another's localization at the leading edge, while antagonizing rear-promoting signals (Etienne-Manneville, 2008; Nelson, 2009). For example, in primary rat astrocytes, Scribble and disks large homolog 1 (Dlg) regulate cell direction by controlling the spatial pattern of Cdc42 activity and microtubule orientation (Etienne-Manneville et al., 2005; Osmani et al., 2006). In this case, formation of lamellipodia and filopodia is dependent on Scrib binding the Cdc42GEF βPix (also known as ARHGEF7) at the leading edge. Together, Scrib and βPix locally activate Cdc42 to promote recruitment of the aPKC–Par6–Par3 complex, and the Rac1GEF Tiam1 (Etienne-Manneville and Hall, 2003; Pegtel et al., 2007) (see poster). The leading edge signaling, through aPKC-mediated recruitment of the E3 ubiquitin ligase Smurf1, removes the protrusion-inhibiting Rho GTPase RhoA, (Wang et al., 2003). Epithelial polarity protein complexes also contribute to collectively migrating cells as they maintain junctions and coordinate their behaviors (Mayor and Etienne-Manneville, 2016; Montell et al., 2012). Although the detailed mechanisms may differ from one cell type to another or from individual to collectively migrating cells, taken together, the simplest – and likely to be oversimplified – view is that polarity complexes facilitate migration by organizing signaling networks that localize the activation of the RhoGTPases Cdc42 and Rac to the leading edge, and thus drive forward directed protrusions and RhoA to the rear in order to mediate retraction (Iden and Collard, 2008).

Planar cell polarity

In addition to apicobasal polarity, epithelial cells display polarization along the orthogonal axis within the plane of the epithelium. This is called planar cell polarity (PCP). Core PCP genes were first discovered through genetic screens for mutant insects exhibiting retina patterning and cuticle defects (Gubb and García-Bellido, 1982; Lawrence and Shelton, 1975). Subsequent studies showed that PCP proteins represent a core, evolutionarily conserved, polarization mechanism in animal tissues (Devenport, 2014). PCP is important during development. Many core PCP genes are required for viability (Table S1 and Box 2), while conditional knock-outs reveal defects in tissues with organized cilia such as the cochlea, and in patterning of epidermal appendages such as hair follicles.

Planar polarity derives from the mutual antagonism between proximal and distal protein complexes. The proximal cassette includes vang-like protein (Vangl) and Prickle (pk) (see poster), whereas the distal complex includes Frizzled (Fz), Dishevelled (Dsh), and Diego (Dgo). Flamingo (Fmi, vertebrate Celsr) associates with both complexes and serves to connect adjacent cells via homophilic interactions. Apicobasal polarity feeds into PCP, as members of the Scribble and Par complex physically bind core PCP components (Humbert et al., 2015; Wu and Mlodzik, 2009). For instance, Scribble stabilizes proximal Vangl localization. Scrib mutants display PCP defects in diverse tissues, including in mouse neural tube and lung, *Drosophila* larval eye and wing discs, and impaired wound healing in mammalian skin (Humbert et al., 2015).

The functional output of PCP signaling is typically a polarized organization of the actomyosin cytoskeleton. During the development of *Drosophila* eye, for example, Fz/Dsh signaling acts via downstream effectors including RhoA and *Drosophila* Rho-associated kinase (Rok) to cause directional rotation of functional groups of cells so they achieve the correct orientation within the mature eye (Winter et al., 2001). In the wing, the same pathway controls localization of F-actin polymerization and bundling to the distal side of each cell so that wing hairs all point in the same direction (Winter et al., 2001). In vertebrate neural tube closure, Fmi recruits Fz/Dsh, which activates PDZ-RhoGEF and, therefore, RhoA, which then activates Rok (Nishimura et al., 2012). This process orients apical actomyosin contractility along the medial −lateral axis, which provides directionality to apical constrictions; this then causes the neural plate to bend and, subsequently, fold to form the neural tube (Nishimura et al., 2012).

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Asymmetric stem cell division

Stem cells can undergo asymmetric cell divisions that result simultaneously in self-renewal and production of a daughter cell that can differentiate. This process is, therefore, crucial for tissue development and homeostasis across the animal kingdom (Knoblich, 2001). Both cell-extrinsic and cell-intrinsic fate determinants promote asymmetric cell division (Chen et al., 2016). A classic model that has led to the identification of cell-intrinsic determinants is that of *Drosophila* neuroblasts. In developing embryos, neuroblasts inherit the apical Par complex from the epithelial cells in the neuroectoderm from which they derive. At the onset of asymmetric division, the mitotic kinase Aurora-A phosphorylates Par6, which activates aPKC and allows Baz to form a complex with aPKC and Par6 (Wirtz-Peitz et al., 2008). Baz then anchors the adaptor protein Inscuteable (Insc), which recruits the $G\alpha_i$–Pins–Mud complex in order to orient the mitotic spindle (Homem and Knoblich, 2012) (see poster). The Scribble complex is transiently polarized during asymmetric cell division and serves two important functions. First, Dlg, together with Scrib, can bind to Pins and orient the spindle in the so-called 'telophase rescue' process (Albertson and Doe, 2003; Albertson et al., 2004; Morin and Bellaiche, 2011). Second, aPKC-dependent phosphorylation of Lgl prevents Lgl from localizing to membrane regions that are enriched in aPKC and Par6 (Betschinger et al., 2003). Ultimately, this cascade serves to segregate mother and daughter cell determinants in the developing *Drosophila* nervous system.

The molecular underpinning of polarity-driven orientation of the mitotic division plane in *Drosophila* neuroblasts is conserved during vertebrate stem cell divisions, albeit with tissue-specific differences (reviewed in Gönczy, 2008; Lu and Johnston, 2013). Work on mouse skin shows that the polarity regulators aPKC and Par3, together with Insc and the vertebrate homolog of Pins, LGN (also known as GPSM3), set the balance for symmetric and asymmetric stem cell divisions (Lechler and Fuchs, 2005; Poulson and Lechler, 2010). Recent evidence from retinal progenitors suggests similar mechanisms of polarity- and LGN-assisted asymmetric divisions during eye development (Lacomme et al., 2016).

Perspectives

In virtually all animals, cell polarity complexes are deployed for a great variety of purposes during development and homeostasis. We have highlighted the conserved protein interactions that establish and maintain cell polarity during embryonic development, and their effects on morphogenesis and cell fate specification. These examples represent the best-studied models to date, but the full complement of cellular contexts and developmental circumstances in which these proteins operate remains to be explored. For instance, epithelial tissues are diverse in their function and morphology. Lung or gill epithelia are highly specialized, containing exaggerated apical membranes to enable gas exchange. Do these or other cells require additional, cell-type-specific components that are yet to be identified, or is it sufficient to tweak the relative concentrations or affinities of the known proteins and interactions? Our current understanding of the precise interactions and signaling roles of polarity proteins derives primarily from studying the models outlined in the poster. Clearly, many components and interactions are highly conserved. However, variations are also likely to exist on this theme, perhaps even apicobasal and planar polarization mechanisms that are completely different in nature. A recent review on this topic raises the question as to how these complexes are deployed in a cell-type or stage-specific way (Flores-Benitez and Knust, 2016). One of the great potential benefits of CRISPR/Cas9 gene-editing techniques is that they stand to expand dramatically the repertoire of model organisms under investigation. The careful study of additional cell types and organisms will perhaps reveal unexpected diversity in cell and embryo polarization mechanisms. Moreover, sophisticated modeling approaches seek to extract and formalize the design principles of polarity-generating networks in a variety of contexts (Chau et al., 2012; Wu and Lew, 2013). These approaches can reveal the minimal molecular features and interactions that are required to polarize cells and tissues.

Many open questions also remain concerning the detailed mechanisms of regulation of these complexes in diverse cellular contexts, such as during cell migration or epithelial morphogenesis. Moreover, polarity proteins seem to possess both polarity-dependent and -independent roles. The Scribble complex, for example, antagonizes the apical complexes and also interfaces with the Ras/MAPK and JNK pathways that drive oncogenic transformation (Etienne-Manneville, 2009). It will be increasingly important to disentangle the polarity-dependent and -independent roles for a better understanding of how these proteins contribute to both homeostasis and disease (Box 2).

Acknowledgements

We thank the entire D.J.M. lab for critical feedback on this poster article. We acknowledge the authors of many primary works that could not be referenced due to space limitations.

Competing interests

The authors declare no competing or financial interests.

Funding

Support to complete this poster and short review was provided by the National Institutes of Health to D.J.M. [grant number: GM46425-22]. Deposited in PMC for release after 12 months.

Supplementary information

Supplementary information available online at
http://jcs.biologists.org/lookup/doi/10.1242/jcs.188599.supplemental

References

Aceto, D., Beers, M. and Kemphues, K. J. (2006). Interaction of PAR-6 with CDC-42 is required for maintenance but not establishment of PAR asymmetry in C. elegans. *Dev. Biol.* **299**, 386-397.

Alarcon, V. B. (2010). Cell Polarity Regulator PARD6B Is Essential for Trophectoderm Formation in the Preimplantation Mouse Embryo. *Biol. Reprod.* **83**, 347-358.

Albertson, R. and Doe, C. Q. (2003). Dlg, Scrib and Lgl regulate neuroblast cell size and mitotic spindle asymmetry. *Nat. Cell Biol.* **5**, 166-170.

Albertson, R., Chabu, C., Sheehan, A. and Doe, C. Q. (2004). Scribble protein domain mapping reveals a multistep localization mechanism and domains necessary for establishing cortical polarity. *J. Cell Sci.* **117**, 6061-6070.

Anderson, D. C., Gill, J. S., Cinalli, R. M. and Nance, J. (2008). Polarization of the C. elegans embryo by RhoGAP-mediated exclusion of PAR-6 from cell contacts. *Science* **320**, 1771-1774.

Assémat, E., Bazellières, E., Pallesi-Pocachard, E., Le Bivic, A. and Massey-Harroche, D. (2008). Polarity complex proteins. *Biochim. Biophys. Acta.* **1778**, 614-630.

Beatty, A., Morton, D. and Kemphues, K. (2010). The C. elegans homolog of Drosophila Lethal giant larvae functions redundantly with PAR-2 to maintain polarity in the early embryo. *Development* **137**, 3995-4004.

Benton, R. and Johnston, D. S. (2003). Drosophila PAR-1 and 14-3-3 inhibit Bazooka/PAR-3 to establish complementary cortical domains in polarized cells. *Cell* **116**, 139.

Betschinger, J., Mechtler, K. and Knoblich, J. A. (2003). The Par complex directs asymmetric cell division by phosphorylating the cytoskeletal protein Lgl. *Nature* **422**, 326-330.

Bilder, D. (2001). PDZ proteins and polarity: functions from the fly. *Trends Genet.* **17**, 511-519.

Bilder, D. (2004). Epithelial polarity and proliferation control: links from the Drosophila neoplastic tumor suppressors. *Gene Dev* **18**, 1909-1925.

Bilder, D., Li, M. and Perrimon, N. (2000). Cooperative regulation of cell polarity and growth by Drosophila tumor suppressors. *Science* **289**, 113-116.
Bilder, D., Schober, M. and Perrimon, N. (2003). Integrated activity of PDZ protein complexes regulates epithelial polarity. *Nat. Cell Biol.* **5**, 53-58.
Brangwynne, C. P., Eckmann, C. R., Courson, D. S., Rybarska, A., Hoege, C., Gharakhani, J., Juelicher, F. and Hyman, A. A. (2009). Germline P granules are liquid droplets that localize by controlled dissolution/condensation. *Science* **324**, 1729-1732.
Bryant, D. M., Datta, A., Rodríguez-Fraticelli, A. E., Peränen, J., Martín-Belmonte, F. and Mostov, K. E. (2010). A molecular network for de novo generation of the apical surface and lumen. *Nat. Cell Biol.* **12**, 1035-1U24.
Bryant, D. M., Roignot, J., Datta, A., Overeem, A. W. and Kim, M., Yu, W., Peng, X., Eastburn, D. J., Ewald, A. J., Werb, Z. et al. (2014). A molecular switch for the orientation of epithelial cell polarization. *Dev. Cell.* **31**, 171-187.
Cestra, G., Kwiatkowski, A., Salazar, M., Gertler, F. and De, and Camilli, P. (2005). Tuba, a GEF for CDC42, links dynamin to actin regulatory proteins. In *GTPases Regulating Membrane Dynamics*, (eds Balch, W. E., Der, C. J. Hall, A.), Vol. 404 pp. 537-545. Elsevier.
Chant, J. (1999). Cell polarity in yeast. *Annu. Rev. Cell Dev. Biol.* **15**, 365-391.
Chartier, F. J.-M., Hardy, É. J.-L. and Laprise, P. (2011a). Crumbs controls epithelial integrity by inhibiting Rac1 and PI3K. *J. Cell Sci.* **124**, 3393-3398.
Chartier, N. T., Salazar Ospina, D. P., Benkemoun, L., Mayer, M., Grill, S. W., Maddox, A. S. and Labbé, J.-C. (2011b). PAR-4/LKB1 mobilizes nonmuscle myosin through anillin to regulate C. elegans embryonic polarization and cytokinesis. *Curr. Biol.* **21**, 259-269.
Chau, A. H., Walter, J. M., Gerardin, J., Tang, C. and Lim, W. A. (2012). Designing synthetic regulatory networks capable of self-organizing cell polarization. *Cell* **151**, 320-332.
Chen, C., Fingerhut, J. M. and Yamashita, Y. M. (2016). The ins(ide) and outs(ide) of asymmetric stem cell division. *Curr. Opin. Cell Biol.* **43**, 1-6.
Cheung, K. J. and Ewald, A. J. (2016). A collective route to metastasis: seeding by tumor cell clusters. *Science* **352**, 167-169.
Cheung, K. J., Padmanaban, V., Silvestri, V., Schipper, K., Cohen, J. D., Fairchild, A. N., Gorin, M. A., Verdone, J. E., Pienta, K. J., Bader, J. S. et al. (2016). Polyclonal breast cancer metastases arise from collective dissemination of keratin 14-expressing tumor cell clusters. *Proc. Natl Acad. Sci. USA* **113**, E854-E863.
Cuenca, A. A., Schetter, A., Aceto, D., Kemphues, K. and Seydoux, G. (2003). Polarization of the C. elegans zygote proceeds via distinct establishment and maintenance phases. *Development* **130**, 1255-1265.
Dard, N., Le, T., Maro, B. and Louvet-Vallée, S. (2009). Inactivation of aPKClambda reveals a context dependent allocation of cell lineages in preimplantation mouse embryos. *PLoS ONE* **4**, e7117.
Dauber, A., Golzio, C., Guenot, C., Jodelka, F. M., Kibaek, M., Kjaergaard, S., Leheup, B., Martinet, D., Nowaczyk, M. J. M., Rosenfeld, J. A. et al. (2013). SCRIB and PUF60 are primary drivers of the multisystemic phenotypes of the 8q24.3 copy-number variant. *Am. J. Hum.Genet.* **93**, 798-811.
Devenport, D. (2014). Cell biology in development: the cell biology of planar cell polarity. *J. Cell Biol.* **207**, 171-179.
Doerflinger, H., Vogt, N., Torres, I. L., Mirouse, V., Koch, I., Nüsslein-Volhard, C. and St Johnston, D. (2010). Bazooka is required for polarisation of the Drosophila anterior-posterior axis. *Development* **137**, 1765-1773.
Drubin, D. G. (1991). Development of cell polarity in budding yeast. *Cell* **65**, 1093-1096.
Etienne-Manneville, S., Manneville, J.-B., Nicholls, S., Ferenczi, M. A. and Hall, A. (2005). Cdc42 and Par6-PKCzeta regulate the spatially localized association of Dlg1 and APC to control cell polarization. *J. Cell Biol.* **170**, 895-901.
Etienne-Manneville, S. (2008). Polarity proteins in migration and invasion. *Oncogene* **27**, 6970-6980.
Etienne-Manneville, S. (2009). Scribble at the crossroads. *J. Biol.* **8**, 104.
Etienne-Manneville, S. and Hall, A. (2003). Cell polarity: Par6, aPKC and cytoskeletal crosstalk. *Curr. Opin. Cell Biol.* **15**, 67-72.
Fischer, K. R., Durrans, A., Lee, S., Sheng, J., Li, F., Wong, S. T. C., Choi, H., El Rayes, T., Ryu, S., Troeger, J. et al. (2015). Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. *Nature* **527**, 472-476.
Flores-Benitez, D. and Knust, E. (2016). Dynamics of epithelial cell polarity in Drosophila: how to regulate the regulators? *Curr. Opin. Cell Biol.* **42**, 13-21.
Foe, V. E. and Alberts, B. M. (1983). Studies of nuclear and cytoplasmic behaviour during the five mitotic cycles that precede gastrulation in *Drosophila* embryogenesis. *J. Cell Sci.* **61**, 31-70.
Gallo, C. M., Wang, J. T., Motegi, F. and Seydoux, G. (2010). Cytoplasmic partitioning of P granule components is not required to specify the germline in C. elegans. *Science* **330**, 1685-1689.
Gateff, E. (1978). Malignant neoplasms of genetic origin in Drosophila melanogaster. *Science* **200**, 1448-1459.
Gönczy, P. (2008). Mechanisms of asymmetric cell division: flies and worms pave the way. *Nat. Rev. Mol. Cell Bio.* **9**, 355-366.
Gubb, D. and García-Bellido, A. (1982). A genetic analysis of the determination of cuticular polarity during development in Drosophila melanogaster. *Development* **68**, 37-57.
Halaoui, R. and McCaffrey, L. (2014). Rewiring cell polarity signaling in cancer. **34**, 939-950.
Harris, T. J. C. and Peifer, M. (2005). The positioning and segregation of apical cues during epithelial polarity establishment in Drosophila. *J. Cell Biol.* **170**, 813-823.
Harris, K. P. and Tepass, U. (2010a). Cdc42 and vesicle trafficking in polarized cells. *Traffic* **11**, 1272-1279.
Harris, T. J. C. and Tepass, U. (2010b). Adherens junctions: from molecules to morphogenesis. *Nat. Rev. Mol. Cell Bio.* **11**, 502-514.
Hirate, Y. and Sasaki, H. (2014). The role of angiomotin phosphorylation in the Hippo pathway during preimplantation mouse development. *Tissue Barriers* **2**, e28127.
Hirate, Y., Hirahara, S., Inoue, K.-i., Suzuki, A., Alarcon, V. B., Akimoto, K., Hirai, T., Hara, T., Adachi, M., Chida, K. et al. (2013). Polarity-dependent distribution of angiomotin localizes hippo signaling in preimplantation embryos. *Curr. Biol.* **23**, 1181-1194.
Hoege, C., Constantinescu, A.-T., Schwager, A., Goehring, N. W., Kumar, P. and Hyman, A. A. (2010). LGL can partition the cortex of one-cell caenorhabditis elegans embryos into two domains. *Curr. Biol.* **20**, 1296-1303.
Homem, C. C. F. and Knoblich, J. A. (2012). Drosophila neuroblasts: a model for stem cell biology. *Development* **139**, 4297-4310.
Huang, L. and Muthuswamy, S. K. (2010). Polarity protein alterations in carcinoma: a focus on emerging roles for polarity regulators. *Curr. Opin. Genet. Dev.* **20**, 41-50.
Humbert, P. O., Russell, S. M., Smith, L. and Richardson, H. E. (2015). The scribble–Dlg–Lgl module in cell polarity regulation. In *Cell Polarity*, Vol. 1 (ed. K. Ebnet), pp. 65-111. Springer International Publishing.
Hutterer, A., Betschinger, J., Petronczki, M. and Knoblich, J. A. (2004). Sequential roles of Cdc42, Par-6, aPKC, and Lgl in the establishment of epithelial polarity during Drosophila embryogenesis. *Dev. Cell* **6**, 845-854.
Iden, S. and Collard, J. G. (2008). Crosstalk between small GTPases and polarity proteins in cell polarization. *Nat. Rev. Mol. Cell Bio.* **9**, 846-859.
Irazoqui, J. E. and Lew, D. J. (2004). Polarity establishment in yeast. *J. Cell Sci.* **117**, 2169-2171.
Jenkins, N., Saam, J. R. and Mango, S. E. (2006). CYK-4/GAP provides a localized cue to initiate anteroposterior polarity upon fertilization. *Science* **313**, 1298-1301.
Jiang, T., David, D. J. V. and Harris, T. J. C. (2015). Epithelial apicobasal polarity in the drosophila embryo. In *Cell Polarity* Vol. 1 (ed. K. Ebnet), pp. 167-187. Springer International Publishing.
Johnson, D. I. (1999). Cdc42: an essential rho-type GTPase controlling eukaryotic cell polarity. *Microbiol. Mol. Biol. Rev.* **63**, 54-105.
Johnson, M. H. (2009). From mouse egg to mouse embryo: polarities, axes, and tissues. *Annu. Rev. Cell Dev. Biol.* **25**, 483-512.
Kemphues, K. J., Priess, J. R., Morton, D. G. and Cheng, N. (1988). Identification of genes required for cytoplasmic localization in early C-elegans embryos. *Cell* **52**, 311-320.
Knoblich, J. A. (2001). Asymmetric cell division during animal development. *Nat. Rev. Mol. Cell Bio.* **2**, 11-20.
Lacomme, M., Tarchini, B., Boudreau-Pinsonneault, C., Monat, C. and Cayouette, M. (2016). The LGN protein promotes planar proliferative divisions in the neocortex but apicobasal asymmetric terminal divisions in the retina. *Development* **143**, 575-581.
Laprise, P., Beronja, S., Silva-Gagliardi, N. F., Pellikka, M., Jensen, A. M., McGlade, C. J. and Tepass, U. (2006). The FERM protein yurt is a negative regulatory component of the crumbs complex that controls epithelial polarity and apical membrane size. *Dev. Cell* **11**, 363-374.
Laprise, P., Lau, K. M., Harris, K. P., Silva-Gagliardi, N. F., Paul, S. M., Beronja, S., Beitel, G. J., McGlade, C. J. and Tepass, U. (2009). Yurt, Coracle, Neurexin IV and the Na+,K+-ATPase form a novel group of epithelial polarity proteins. *Nature* **459**, 1141-1145.
Lawrence, P. A. and Shelton, P. M. J. (1975). The determination of polarity in the developing insect retina. *Development* **33**, 471-486.
League, G. P. and Nam, S.-C. (2011). Role of kinesin heavy chain in crumbs localization along the rhabdomere elongation in drosophila photoreceptor. *PLoS ONE* **6**, e21218.
Lechler, T. and Fuchs, E. (2005). Asymmetric cell divisions promote stratification and differentiation of mammalian skin. *Nature* **437**, 275-280.
Li, Z., Wang, L., Hays, T. S. and Cai, Y. (2008). Dynein-mediated apical localization of crumbs transcripts is required for Crumbs activity in epithelial polarity. *J. Cell Biol.* **180**, 31-38.
Lim, J. and Thiery, J. P. (2012). Epithelial-mesenchymal transitions: insights from development. *Development* **139**, 3471-3486.
Lin, W.-H., Asmann, Y. W. and Anastasiadis, P. Z. (2015). Expression of polarity genes in human cancer. *Cancer Inform* **14**, 15-28.
Lu, M. S. and Johnston, C. A. (2013). Molecular pathways regulating mitotic spindle orientation in animal cells. *Development* **140**, 1843-1856.

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Margolis, B. and Borg, J.-P. (2005). Apicobasal polarity complexes. *J. Cell Sci.* **118**, 5157-5159.
Martin-Belmonte, F., Gassama, A., Datta, A., Yu, W., Rescher, U., Gerke, V. and Mostov, K. (2007). PTEN-mediated apical segregation of phosphoinositides controls epithelial morphogenesis through Cdc42. *Cell* **128**, 383-397.
Mathew, D., Gramates, L. S., Packard, M., Thomas, U., Bilder, D., Perrimon, N., Gorczyca, M. and Budnik, V. (2002). Recruitment of scribble to the synaptic scaffolding complex requires GUK-holder, a novel DLG binding protein. *Curr. Biol.* **12**, 531-539.
Mavrakis, M., Rikhy, R. and Lippincott-Schwartz, J. (2009). Plasma membrane polarity and compartmentalization are established before cellularization in the fly embryo. *Dev. Cell* **16**, 93-104.
Mayor, R. and Etienne-Manneville, S. (2016). The front and rear of collective cell migration. *Nat. Rev. Mol. Cell Bio.* **17**, 97-109.
Mazumdar, A. and Mazumdar, M. (2002). How one becomes many: blastoderm cellularization in Drosophila melanogaster. *Bioessays* **24**, 1012-1022.
Mehalow, A. K., Kameya, S., Smith, R. S., Hawes, N. L., Denegre, J. M., Young, J. A., Bechtold, L., Haider, N. B., Tepass, U., Heckenlively, J. R. et al. (2003). CRB1 is essential for external limiting membrane integrity and photoreceptor morphogenesis in the mammalian retina. *Hum. Mol. Genet.* **12**, 2179-2189.
Montell, D. J., Yoon, W. H. and Starz-Gaiano, M. (2012). Group choreography: mechanisms orchestrating the collective movement of border cells. *Nat. Rev. Mol. Cell Bio.* **13**, 631-645.
Moreno-Bueno, G., Portillo, F. and Cano, A. (2008). Transcriptional regulation of cell polarity in EMT and cancer. *Oncogene* **27**, 6958-6969.
Morin, X. and Bellaïche, Y. (2011). Mitotic spindle orientation in asymmetric and symmetric cell divisions during animal development. *Dev. Cell* **21**, 102-119.
Morton, D. G., Shakes, D. C., Nugent, S., Dichoso, D., Wang, W., Golden, A. and Kemphues, K. J. (2002). The Caenorhabditis elegans par-5 gene encodes a 14-3-3 protein required for cellular asymmetry in the early embryo. *Dev. Biol.* **241**, 47-58.
Motegi, F. and Seydoux, G. (2013). The PAR network: redundancy and robustness in a symmetry-breaking system. *Philos. Trans. R. Soc. Lond., B Biol. Sci.* **368** 20130010
Motegi, F., Zonies, S., Hao, Y., Cuenca, A. A., Griffin, E. and Seydoux, G. (2011). Microtubules induce self-organization of polarized PAR domains in Caenorhabditis elegans zygotes. *Nat. Cell Biol.* **13**, 1361-1367.
Motosugi, N., Bauer, T., Polanski, Z., Solter, D. and Hiiragi, T. (2005). Polarity of the mouse embryo is established at blastocyst and is not prepatterned. *Gene Dev* **19**, 1081-1092.
Munro, E. and Bowerman, B. (2009). Cellular symmetry breaking during Caenorhabditis elegans development. *Cold Spring Harb. Perspect. Biol.* **1**, a003400.
Munro, E., Nance, J. and Priess, J. R. (2004). Cortical flows powered by asymmetrical contraction transport PAR proteins to establish and maintain anterior-posterior polarity in the early C-elegans embryo. *Dev. Cell* **7**, 413-424.
Murdoch, J. N., Henderson, D. J., Doudney, K., Gaston-Massuet, C., Phillips, H. M., Paternotte, C., Arkell, R., Stanier, P. and Copp, A. J. (2003). Disruption of scribble (Scrb1) causes severe neural tube defects in the circletail mouse. *Hum. Mol. Genet.* **12**, 87-98.
Murdoch, J. N., Damrau, C., Paudyal, A., Bogani, D., Wells, S., Greene, N. D. E., Stanier, P. and Copp, A. J. (2014). Genetic interactions between planar cell polarity genes cause diverse neural tube defects in mice. *Dis. Model Mech.* **7**, 1153-1163.
Nance, J. (2005). PAR proteins and the establishment of cell polarity duringC. elegans development. *Bioessays* **27**, 126-135
Nance, J. and Zallen, J. A. (2011). Elaborating polarity: PAR proteins and the cytoskeleton. *Development* **138**, 799-809.
Nelson, W. J. (2009). Remodeling epithelial cell organization: transitions between front-rear and apical-basal polarity. *Cold Spring Harb. Perspect. Biol.* **1**, a000513-a000513.
Ngok, S. P., Lin, W.-H. and Anastasiadis, P. Z. (2014). Establishment of epithelial polarity - GEF who's minding the GAP? *J. Cell Sci.* **127**, 3205-3215.
Nishimura, T., Honda, H. and Takeichi, M. (2012). Planar cell polarity links axes of spatial dynamics in neural-tube closure. *Cell* **149**, 1084-1097.
Noatynska, A. and Gotta, M. (2012). Cell polarity and asymmetric cell division: the C. elegans early embryo. *Essays Biochem.* **53**, 1-14.
Osmani, N., Vitale, N., Borg, J.-P. and Etienne-Manneville, S. (2006). Scrib controls Cdc42 localization and activity to promote cell polarization during astrocyte migration. *Curr. Biol.* **16**, 2395-2405.
Pacquelet, A., Uhart, P., Tassan, J.-P. and Michaux, G. (2015). PAR-4 and anillin regulate myosin to coordinate spindle and furrow position during asymmetric division. *J. Cell Biol.* **210**, 1085-1099.
Pegtel, D. M., Ellenbroek, S. I. J., Mertens, A. E. E., van der Kammen, R. A., de Rooij, J. and Collard, J. G. (2007). The Par-Tiam1 complex controls persistent migration by stabilizing microtubule-dependent front-rear polarity. *Curr. Biol.* **17**, 1623-1634.
Plusa, B., Frankenberg, S., Chalmers, A., Hadjantonakis, A.-K., Moore, C. A., Papalopulu, N., Papaioannou, V. E., Glover, D. M. and Zernicka-Goetz, M. (2005). Downregulation of Par3 and aPKC function directs cells towards the ICM in the preimplantation mouse embryo. *J. Cell Sci.* **118**, 505-515.
Poulson, N. D. and Lechler, T. (2010). Robust control of mitotic spindle orientation in the developing epidermis. *J. Cell Biol.* **191**, 915-922.
Ridley, A. J., Schwartz, M. A., Burridge, K., Firtel, R. A., Ginsberg, M. H., Borisy, G., Parsons, J. T. and Horwitz, A. R. (2003). Cell migration: integrating signals from front to back. *Science* **302**, 1704-1709.
Rodriguez-Boulan, E. and Macara, I. G. (2014). Organization and execution of the epithelial polarity programme. *Nat. Rev. Mol. Cell Bio.* **15**, 225-242.
Rossant, J. (2004). Lineage development and polar asymmetries in the peri-implantation mouse blastocyst. *Semin. Cell Dev. Biol.* **15**, 573-581.
Rothenberg, S. M., Mohapatra, G., Rivera, M. N., Winokur, D., Greninger, P., Nitta, M., Sadow, P. M., Sooriyakumar, G., Brannigan, B. W., Ulman, M. J. et al. (2010). A genome-wide screen for microdeletions reveals disruption of polarity complex genes in diverse human cancers. *Cancer Res.* **70**, 2158-2164.
Shivas, J. M., Morrison, H. A., Bilder, D. and Skop, A. R. (2010). Polarity and endocytosis: reciprocal regulation. *Trends Cell Biol.* **20**, 445-452.
St Johnston, D. and Ahringer, J. (2010). Cell polarity in eggs and epithelia: parallels and diversity. *Cell* **141**, 757-774.
Stein, von, W. (2005). Direct association of Bazooka/PAR-3 with the lipid phosphatase PTEN reveals a link between the PAR/aPKC complex and phosphoinositide signaling. *Development* **132**, 1675-1686.
Stoll, M., Corneliussen, B., Costello, C. M., Waetzig, G. H., Mellgard, B., Koch, W. A., Rosenstiel, P., Albrecht, M., Croucher, P. J. P., Seegert, D. et al. (2004). Genetic variation in DLG5 is associated with inflammatory bowel disease. *Nat. Genet.* **36**, 476-480.
Tanentzapf, G. and Tepass, U. (2002). Interactions between the crumbs, lethal giant larvae and bazooka pathways in epithelial polarization. *Nat. Cell Biol.* **5**, 46-52.
Tarpey, P., Parnau, J., Blow, M., Woffendin, H., Bignell, G., Cox, C., Cox, J., Davies, H., Edkins, S., Holden, S. et al. (2004). Mutations in the DLG3 gene cause nonsyndromic X-linked mental retardation. *Am. J. Hum. Genet.* **75**, 318-324.
Tepass, U. (1997). Epithelial differentiation in *Drosophila*. *Bioessays* **19**, 673-682.
Tepass, U. (2012). The apical polarity protein network in Drosophila epithelial cells: regulation of polarity, junctions, morphogenesis, cell growth, and survival. *Annu. Rev. Cell Dev. Biol.* **28**, 655-685.
Thompson, B. J. (2013). Cell polarity: models and mechanisms from yeast, worms and flies. *Development* **140**, 13-21.
Vinot, S., Le, T., Ohno, S., Pawson, T., Maro, B. and Louvet-Vallée, S. (2005). Asymmetric distribution of PAR proteins in the mouse embryo begins at the 8-cell stage during compaction. *Dev. Biol.* **282**, 307-319.
Wang, H. R., Zhang, Y., Ozdamar, B. and Ogunjimi, A. A., Alexandrova, E., Thomsen, G. H. and Wrana, J. L. (2003). Regulation of cell polarity and protrusion formation by targeting RhoA for degradation. *Science*. Vol. 302, pp. 1775-1779.
Winter, C. G., Wang, B., Ballew, A., Royou, A., Karess, R., Axelrod, J. D. and Luo, L. (2001). Drosophila Rho-Associated Kinase (Drok) links frizzled-mediated planar cell polarity signaling to the actin cytoskeleton. *Cell* **105**, 81-91.
Wirtz-Peitz, F., Nishimura, T. and Knoblich, J. A. (2008). Linking cell cycle to asymmetric division: aurora-A phosphorylates the par complex to regulate numb localization. *Cell* **135**, 161-173.
Wodarz, A. (2002). Establishing cell polarity in development. *Nat. Cell Biol.* **4**, E39-E44.
Wu, C.-F. and Lew, D. J. (2013). Beyond symmetry-breaking: competition and negative feedback in GTPase regulation. *Trends Cell Biol.* **23**, 476-483.
Wu, J. and Mlodzik, M. (2009). A quest for the mechanism regulating global planar cell polarity of tissues. *Trends Cell Biol.* **19**, 295-305.
Yamanaka, Y., Ralston, A., Stephenson, R. O. and Rossant, J. (2006). Cell and molecular regulation of the mouse blastocyst. *Dev. Dyn.* **235**, 2301-2314.
Zen, K., Yasui, K., Gen, Y., Dohi, O., Wakabayashi, N., Mitsufuji, S., Itoh, Y., Zen, Y., Nakanuma, Y., Taniwaki, M. et al. (2009). Defective expression of polarity protein PAR-3 gene (PARD3) in esophageal squamous cell carcinoma. *Oncogene* **28**, 2910-2918.
Zheng, X., Carstens, J. L., Kim, J., Scheible, M., Kaye, J., Sugimoto, H., Wu, C.-C., LeBleu, V. S. and Kalluri, R. (2015). Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. *Nature* **527**, 525-530.
Zhu, J., Shang, Y., Wan, Q., Xia, Y., Chen, J., Du, Q. and Zhang, M. (2014). Phosphorylation-dependent interaction between tumor suppressors Dlg and Lgl. *Cell Res.* **24**, 451-463.