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PERSPECTIVE

SPECIAL ISSUE: CELL AND TISSUE POLARITY

Perspectives on polarity – exploring biological asymmetry across scales

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ABSTRACT

In this Perspective, Journal of Cell Science invited researchers working on cell and tissue polarity to share their thoughts on unique, emerging or open questions relating to their field. The goal of this article is to feature 'voices' from scientists around the world and at various career stages, to bring attention to innovative and thought-provoking topics of interest to the cell biology community. These voices discuss intriguing questions that consider polarity across scales, evolution, development and disease. What can yeast and protists tell us about the evolution of cell and tissue polarity in animals? How are cell fate and development influenced by emerging dynamics in cell polarity? What can we learn from atypical and extreme polarity systems? How can we arrive at a more unified biophysical understanding of polarity? Taken together, these pieces demonstrate the broad relevance of the fascinating phenomenon of cell polarization to diverse fundamental biological questions.

KEY WORDS: Cell polarity, Tissue polarity, Evolution, Self-organization, Epithelia

Cell polarity networks as a window into self-organization in evolution

Marieke Glazenburg, Nynke Marije Hettema and Liedewij Laan

Cell polarization is an evolutionarily highly conserved mechanism that is present throughout the tree of life from simple unicellular life forms to complex multicellular organisms. Remarkably, despite the strong phenotypic conservation, the molecular composition of polarity protein networks can vary massively, even between closely related species (Diepeveen et al., 2018). This observation is not limited to polarization networks alone; genetic variability under phenotypic stability has been observed across many different systems and scales (Kops et al., 2020; Laan et al., 2015; Shen et al., 2018). How is it possible that robust protein networks are so diversified during evolution, even in their essential components? We believe this to be rooted in a cell's capacity to buffer its phenotype through self-organization.

Polarization is, in essence, a symmetry-breaking process. Biological systems continuously rely on forming and maintaining these asymmetries to avoid them deteriorating into a state of pure homogeneity, which would be equivalent to cell death. Like many other cellular processes, cell polarity is not a static equilibrium but instead requires constant dissipation of energy. Systems like these, where interactions at a microscopic level cause emergent macroscopic patterns under the consumption of energy, are often referred to as self-organizing (Halatek et al., 2018). The ability to self-organize allows cells to construct robust patterns 'bottom-up' from transient protein–protein interactions, instead of relying on external cues or fixed templates.

It therefore seems plausible that the variance and flexibility of protein networks over the course of evolution is promoted by a cell's self-organizing capacity (Johnson and Lam, 2010). Proteins in a self-organizing network act as a collective rather than as independent individuals, implying that networks respond to perturbations and evolving circumstances as a connected whole. For instance, experimentally evolved budding yeast cells show many changes in the functional importance of genes across the entire genome after being perturbed in a major polarity component (Kingma and Laan, 2024 preprint). Thus, internal relationships and functional importance of proteins might shift over the course of evolution, while the resulting macroscopic pattern or phenotype remains unperturbed. Indeed, there is increasing evidence suggesting that phenotypic similarity of related species does not immediately imply genetic or molecular similarity (Glazenburg and Laan, 2023; True and Haag, 2001). These observations seem to indicate that protein 'functions' might be much more fluid than traditionally assumed.

The range of possible protein functions can be conveniently probed in the isolated environment of *in vitro* studies (Vendel et al., 2019). *In vitro* experiments can reveal new, unexpected and seemingly unrelated properties that are not directly observed in the context of a living cell. These so-called hidden protein functions are often disregarded as physiologically irrelevant, but could be key in the evolutionary adaptivity of organisms. Hidden functions can accommodate fast adaptation to changing environments or could rescue the functioning of failing cellular machinery (Schwille and Frohn, 2022). Many key polarity proteins are part of complex networks with multiple binding partners, have diverse functional domains and have large disordered

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domains (Tschirpke et al., 2023 preprint), indicating a high likelihood of hidden multifunctionality (Zanzoni et al., 2019).

Hidden functions of polarity proteins could play an essential role in the self-organizational buffering capacity of cells over the course of evolution. By studying yeast cell polarity *in vivo* and *in vitro*, we aim to get a full picture of the molecular mechanisms behind the self-organizational buffering we suspect can explain the massive diversity of molecular networks between species. With modern experimental and analytical techniques, we expect more evidence of genotypic variability and flexible protein functionality to emerge in the upcoming years. Ultimately, our hope is that this approach will get us closer to understanding the molecular dynamics of evolution and the fascinating complexity of life.

Rethinking polarity – the challenge of non-binary division in bacterial cells

Ophélie Remy and Géraldine Laloux

Bacteria were originally perceived as simplistic organisms that are far less complex than eukaryotic cells. Fortunately, this view has undergone a profound volte-face as our understanding of the astounding intricacies of bacterial cells has expanded. To proliferate, each bacterium coordinates vital functions, including DNA replication, growth and division, ensuring they occur at the right time and subcellular location. External factors, such as inter-species interactions or nutrient availability, fine-tune this orchestration, resulting in highly diverse growth and development processes, such as predation and sporulation. Remarkably, bacteria typically achieve these feats without the well-defined membrane-bound compartments characteristic of eukaryotic cells. The question thus arises: how do bacteria effectively organize their cellular processes in space and time? The answer lies in polarity.

Cell polarity is defined as the asymmetric distribution of cellular components, such as proteins, signalling networks and genetic loci, in restricted areas typically located at one or both cellular pole(s) (Nelson, 2003). However, proteins confined at cell poles can change position as the cell cycle proceeds or in response to stimuli (Laloux and Jacobs-Wagner, 2014). Identifying the mechanisms that establish and regulate cell polarity remains a critical focus in bacterial cell biology. To achieve asymmetric distribution of their cellular content, bacteria rely on ‘hub’ proteins, which exhibit the unique ability to accumulate at the cell pole(s) at specific times by various mechanisms, including phase separation (Azaldegui et al., 2021) and membrane curvature-sensing (Ramamurthi, 2010). The interaction of these proteins with multiple partners facilitates the assembly of polarized protein networks. Hub proteins and their networks have been extensively studied in model organisms, for example, PopZ in *Caulobacter crescentus* and HubP in *Vibrio cholerae* (Laloux and Jacobs-Wagner, 2014). These bacterial models divide classically into two daughter cells through ‘binary division’. In this case, division generates an inherent asymmetry in the distribution of cellular components – each daughter cell necessarily inherits one ‘old’ pole from the mother cell and one ‘new’ pole from the division site.

Polarization without organelles becomes even more challenging when daughter cells inherit only new poles, which occurs when one mother cell produces more than two progenies through ‘non-binary division’ (Eswara and Ramamurthi, 2017). This is exemplified by *Bdellovibrio bacteriovorus*, known for its predatory behaviour against other bacteria. *B. bacteriovorus* employs polarized structures for predation – a flagellum at the posterior pole, for swimming towards prey, and pili at the anterior pole for invasion (Kaplan et al., 2023). The predator’s chromosome is also polarized, with its origin of replication strictly positioned near the piliated pole. Once inside its prey, *B. bacteriovorus* elongates, replicates its genetic material many times and progressively distributes all copies of the chromosome along the filamentous cell (Kaljević et al., 2021). Upon non-binary division of the filamentous mother cell, the flagellum, pili and chromosome are again precisely polarized in all new daughter predators.

How the future poles are distinguished within the mother cell just prior to or soon after division represents an unsolved puzzle. The polarized orientation of newly segregated chromosomes might serve as a cue to set the polarity of future daughter cells along the filamentous mother cell. Additionally, establishing polarity likely involves a specific assortment of proteins, such as the polar multiprotein complex found in *Streptomyces coelicolor* (Holmes et al., 2013), another bacterium that uses non-binary division. In *B. bacteriovorus* cells, several proteins localize exclusively to the anterior pole (Milner et al., 2014; Remy et al., 2023 preprint), where they might serve as polar hubs. Uncovering the protein networks and subcellular dynamics of these proteins will be crucial to determining their function as ‘polar organizers’. Thus, expanding bacterial cell biology models beyond the textbook classics promises to offer fresh insights into the diverse mechanisms that bacteria utilize to establish cell polarity.

The pre-metazoan roots of epithelial polarity and the modular nature of cell evolution

Thibaut Brunet

In Edwin Abbott’s 1884 novel ‘Flatland’, the characters are polygons living in a strictly hierarchical society. Their social class is determined by a mathematical rule – the more sides they have, the higher their status. Triangles are at the bottom, whereas circles – with their infinite number of sides – are aristocrats (Abbott, 1884). If cells were ranked according to Flatland’s system, the process of cell differentiation would be one of slow decadence – as cells differentiate from the spherical zygote, they tend to become less symmetrical, sprout protrusions and appendages, and acquire polarities. One of the most iconic examples of this is the apicobasal polarity of epithelial cells, which is universally conserved across animals (Buckley and St Johnston, 2022).

How did epithelial polarity evolve? An early hypothesis from Ernst Haeckel (1834–1919) assumed that development recapitulated evolution. Haeckel hypothesized that the single-celled ancestor of animals resembled the single-celled apolar stage of embryonic development; he reconstructed that ancestor as an amoeba without clear polarity that would have undergone serial cell divisions to develop into a sphere of cells, the Blastaea. Only then would these cells have polarized by developing outward-projecting cilia (reviewed in Brunet and King, 2022).

However, some biologists, like Elie Metchnikoff (1845–1916), pointed out that many unicellular eukaryotes swim with apical flagella or cilia similar to those of epithelial cells or sperm. In that view, animals had likely evolved from flagellates rather than amoebae, and a form of apicobasal cell polarity thus preceded multicellularity. In the 20th century, the homology of flagella across eukaryotes was confirmed based on cytoskeletal ultrastructure and protein composition (Carvalho-Santos et al., 2011). Moreover, molecular phylogenies revealed the closest relatives of animals to be the choanoflagellates – aquatic microeukaryotes with facultative multicellularity that display an apical flagellum surrounded by microvilli (Leadbeater, 2014).

Although Metchnikoff was right about the pre-metazoan ancestry of apicobasal polarity, Haeckel might not have been fully wrong

either. First, rising evidence suggests that unicellular ancestors of animals might not have been flagellated over their full life cycle, but might have been able to shape-shift into an amoeboid form in certain conditions (Brunet et al., 2021; Ros-Rocher et al., 2021). Second, Haeckel's idea of *de novo* acquisition of epithelial polarity in development has been largely confirmed. In mouse and nematode embryos, apicobasal polarity is defined by the geometric arrangement of cells – the cellular pole most distant from cell–cell junctions is specified as apical (Anderson et al., 2008; Korotkevich et al., 2017). In three-dimensional cell culture systems, such as cysts of Madin–Darby canine kidney cells, the basal pole of the cell is defined by contact with the surrounding extracellular matrix (Wang et al., 1990). Thus, even though epithelial cell apicobasal polarity echoes that of ancient flagellates, it is now deployed under the control of self-organized interactions within embryonic tissues.

The evolution of epithelial cell polarity thus showcases the modular nature of evolution. Ancient eukaryotic organelles – such as the polarized cilium and flagellum – are assembled and positioned, within epithelia, under the control of animal-specific mechanisms for intercellular coordination (Brunet and Booth, 2023). More generally, the evolution of cellular phenotypes might often have involved differential temporal and spatial deployment of conserved, self-contained cellular modules such as cilia, lamellipodia and vesicles (Achim and Arendt, 2014). Interestingly, one of Haeckel's other contributions was to recognize such temporal and spatial shifts in the evolution of embryonic development, which he termed heterochrony and heterotopy. As evolutionary cell biology crystallizes into a coherent and mature field, the concepts of its older sister, evolutionary developmental biology, might eventually help provide a coherent framework to understand the evolution of features such as cell and tissue polarity.

Breaking symmetry: asymmetric histone inheritance

Xin Chen

For single-cell organisms, DNA replication and mitosis result in daughter cells that share identical genetic information and cell fates. However, in multicellular organisms, development, tissue homeostasis and regeneration warrant far more divergent outcomes. In metazoan development, a fertilized egg embarks on a journey of divisions and lineage specification, eventually giving rise to a diverse array of cell types. What molecular and cellular mechanisms underlie this initial symmetry breaking? This intriguing query has lingered within the realm of developmental biology for decades. The morphogen gradient model offers a valuable framework for understanding how extrinsic cues influence symmetry-breaking processes (Wolpert, 1969; Rogers and Schier, 2011). Yet, the question of how individual cells are primed to make the crucial choices that will determine their fate persists.

A crucial part of the answer might lie in the complexities of chromatin structure, which is influenced by factors such as the composition, position, density and covalent modifications of nucleosomes and their associated DNA. These features shape the epigenome and govern whether a specific genomic region is active, silenced or poised for future alterations. As the foundational elements of nucleosomes, histone proteins and their modifications thus play a pivotal role in the astonishingly precise regulation of cell fate. In recent years, the study of asymmetric division of adult stem cells, which produces one self-renewing stem cell and one differentiating cell, has unveiled two related modes of histone protein partitioning underlying this process.

First, pre-existing 'old' histones are preferentially retained within the self-renewing stem cell, whereas newly synthesized histones become enriched in the differentiating cell. This phenomenon has been observed genome-wide in *Drosophila* male germline stem cells (Tran et al., 2012) and intestinal stem cells (Zion et al., 2023). It can also be detected in a gene-specific manner in *Drosophila* female germline stem cells (Kahney et al., 2021) and induced asymmetrically dividing mouse embryonic stem cells (Ma et al., 2020; Sun et al., 2021). Second, genetically identical sister chromatids exhibit various nucleosomal densities, differing accessibility to trans-acting factors and differential condensation during mitosis (Ranjan et al., 2022). Notably, these unique properties render the sister chromatids distinct substrates for interaction with the polarized mitotic machinery. This interaction unfolds along an axis of asymmetric cellular components, including centrosomes (Yamashita et al., 2007), microtubules, nuclear envelope, kinetochores and centromeres (Ranjan et al., 2019).

Delving into these mechanisms offers profound insight into under-appreciated roles of DNA replication. Although replication has the remarkable ability to faithfully duplicate genetic sequences, its unequal selectivity in arranging histones between the two sister chromatids results in controlled asymmetric inheritance. This process appears to leverage the inherent asymmetry between the continuous synthesis of the leading strand and the discontinuous synthesis of the lagging strand. The differential incorporation of histones between these two strands showcases the multifaceted nature of DNA replication and a highly nuanced function in orchestrating cellular asymmetry (Wooten et al., 2019). Remarkably, molecular asymmetries observed within a single cell during DNA replication or mitosis appear to deviate from the typical influence exerted by morphogen gradients, which traditionally operate in a concentration-dependent manner across distances. These observations thus challenge conventional paradigms and beckon us to reconsider the mechanisms governing intracellular asymmetry.

The mis-regulation of asymmetric histone inheritance can yield stem cell loss and progenitor cell over-proliferation, which can lead to tumorigenesis. This underscores the significance of histone inheritance in maintaining tissue homeostasis. That the precise orchestration of histone inheritance is a linchpin in preserving cellular health and function (Xie et al., 2015; Zion et al., 2023) is a testament to the delicate balance that exists within multicellular life. The fascinating complexities of histone dynamics in the context of asymmetric cell division thus shed light on the intricate interplay of molecular processes and cellular components in cell fate determination, maintenance, and reprogramming in multicellular organisms.

Chiral self-organization of the actin cytoskeleton – how do cells tell left from right?

Yee Han Tee

Outwardly, our bodies show reflective symmetry. However, our internal organs show left-right asymmetry in their morphogenesis and function. Intriguingly, there is a consistent left-right bias: for example, most of us have our heart oriented toward the left side. This has inspired the hypothesis that left-right asymmetry might emerge from underlying mechanisms arising from special chiral molecules (Brown and Wolpert, 1990). Because the left-right axis is defined by the posterior-anterior and dorsal-ventral axes, these proposed chiral molecules should have properties reflecting all three axes. In other words, left-right asymmetry establishment is intimately associated with cell and tissue polarity.

Cytoskeletal fibres have been implicated as these special chiral molecules (Henley, 2012). The asymmetric morphogenesis of

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visceral organs has been attributed to primary motile cilia, microtubule-based cellular projections found in specialized cells in the embryonic node (Nonaka et al., 1998, 2002). Filopodia (actin-rich cellular projections) also exhibit chiral behaviour driven by the interaction between actin filaments and associated myosin motors (Li et al., 2023). Further, non-conventional myosins are known to control chirality in *Drosophila* organs (Hozumi et al., 2006; Lebreton et al., 2018). Thus, how the actin cytoskeleton might drive chiral processes is of immense interest to researchers.

Self-organization of the actin cytoskeleton demonstrates chirality (Tee et al., 2015). Bundles of filaments are bound by crosslinking proteins to form linear arrays of fibres, including radial, transverse and stress fibres. Actin filaments in radial fibres grow from peripheral focal adhesions via a formin-dependent mechanism (Tee et al., 2015, 2023; Jalal et al., 2019). The barbed ends of the filaments are directed towards the adhesions, whereas the pointed ends extend in a centripetal direction towards the dorsal surface of the cell. As the membrane-anchored formin adds new actin monomers, the growing filament spirals around its axis due to its handed-helical nature (Mizuno et al., 2011). This biased rotational torque potentially creates the chiral cellular actin pattern, characterized by unidirectionally tilted radial fibres and anti-clockwise rotational flow of centripetally moving transverse fibres, as has been observed in human fibroblasts confined on circular micropatterns (Tee et al., 2015, 2023). Similarly, unidirectional tilting of radial fibres found at apices of elliptically shaped cells also leads to bias in the formation and orientation of actin stress fibres, which deviate from the long axis of the cell (Tee et al., 2023). Perturbing regulators of actin polymerization or crosslinking can induce, suppress or even reverse chirality (Tee et al., 2015, 2023; Jalal et al., 2019). These actin regulators correspondingly can suppress or reverse chirality of collective cell alignment in cell groups confined on large rectangular micropatterns, demonstrating a definite link between single-cell and tissue-scale chirality (Tee et al., 2023; Wan et al., 2011).

Explaining how various actin regulators coordinate to organize left from right and vice versa remains challenging. The actin cytoarchitecture is built by many competing processes fighting for the finite pool of intracellular actin monomers. Thus, experimental strategies to perturb actin processes in isolation, such as *in vitro* reconstitution, are needed to decipher the key mechanisms that regulate chirality. Left–right asymmetry is a phenomenon that spans scales from molecules to organisms. Are chiralities across scales related? If so, how is chirality translated across scales? The exciting observation that cells can exhibit different chiral states influenced by actin polymerization and filament crosslinking suggests that chirality might be a tuneable cellular property that can be regulated by modulating the actin cytoarchitecture. If so, what mechanochemical pathways participate in this process, and what are their functional impacts on cells or tissues? To understand the morphogenetic events that give form and function to healthy organs and humans, it is important to understand the emergence of left–right asymmetry of cells and tissues. After all, no one wants to dance with two left feet.

Condensates – new regulators of cell polarity in neuronal development

Wenyu Wen

The differentiation, development and function of neurons require extensive cell polarization, a process involving spatiotemporal localization of certain proteins at specific subcompartments. These proteins often organize into dense but dynamic networks that form boundary-less compartments that are attached to plasma membranes on one side and face the cytoplasm on the other side. How these protein networks are assembled and disassembled had been a mystery until the recent emergence of the concept of biomolecular condensates. Biomolecular condensates are formed via multivalent molecular interactions between selected biomolecules, including proteins and nucleic acids, through a process referred to as phase separation. Phase separation can be associated with percolation, a phenomenon in which, above a certain threshold concentration, a group of molecules transitions from disconnected clusters into an interconnected network (Mittag and Pappu, 2022).

During metaphase in the asymmetric division of *Drosophila* neuroblasts, a transient apical-basal polarity is established, with the Par3–Par6–aPKC polarity complex and cell fate determinants enriched at the apical and basal cortices, respectively. This leads to unequal segregation of these factors into the two daughter cells. Par3 and Par6 form a complex with a K_d of ∼1 µM. However, the estimated average concentration of Par3 in neuroblasts has been shown to be ∼0.1 µM (Liu et al., 2020), arguing against productive complex formation. This conundrum was resolved with the discovery that Par3 and Par6 phase separate to form condensates at the apical membrane (Liu et al., 2020), allowing the local concentration of Par3 to reach ∼1.3 µM and thus form complexes with Par6. In line with this, both knockdown and exogenous overexpression of Par3 cause defects of polarity establishment in various cellular contexts (Liu et al., 2020). Notably, membrane attachment of these low-abundance proteins lowers the threshold concentration for phase separation to occur, as the frequency of multivalent interactions increases at a two-dimensional membrane surface compared to in the three-dimensional bulky cytoplasm (Liu et al., 2020; Shan et al., 2018).

Therefore, the oscillation of levels of proteins that drive phase separation acts as an important regulator of cell polarity by modulating condensate formation and dispersion. This mechanism might also extend to other cell polarity systems, such as those found in epithelial cells, where cell–cell junctions are composed of diverse junctional and signalling proteins assembled by multi-domain scaffold proteins through multivalent interactions with moderate affinities. Assembly of these junctional machineries might also be regulated by formation and dispersion of membrane-anchored condensates organized by proteins such as Par3 (Liu et al., 2020) and the tight junction protein ZO1 (also known as TJP1) (Beutel et al., 2019; Schwayer et al., 2019).

After asymmetric neuroblast division, the daughter cell inheriting the apically localized Par3 condensates obtains a stem-cell fate. A recent study using mouse radial glia cells (RGCs), progenitor cells which give rise to glial and neuronal lineages, has shed light on how this stemness transmission might be achieved (Xu et al., 2023). Par3 forms condensates with its activator Ccdc85c at the polarized cell terminals, termed endfeet, where Numb (a Notch inhibitor) is efficiently recruited and sequestered. Notch signalling is then enhanced in the soma, resulting in maintenance of stemness (Xu et al., 2023). Defects in Par3 condensate formation result in failure to sequester Numb at the endfeet, leading to inhibition of Notch signalling and consequent differentiation of RGCs into neurons. Again, the direct Par3–Numb interaction is too weak to efficiently sequester cytoplasmic Numb. In this case, Par3 condensates act as local compartments for storing cellular signalling regulators to control neuronal differentiation (Xu et al., 2023).

Condensates enable efficient local enrichment of selected low-abundance biomolecules for specific cellular reactions and signalling. Going forward, more condensates are expected to be implicated in regulating cell polarity and the development and function of neurons.

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Computational modelling of collective dynamics of planar cell polarity

Mohd Suhail Rizvi and Mohit Kumar Jolly

Planar cell polarity (PCP) is characterized by coordinated orientation of cells in the plane of epithelial tissues, enabled by asymmetric subcellular localization of proteins (Axelrod and Tomlin, 2011; Lawrence and Casal, 2018). Defects in PCP lead to developmental abnormalities such as open neural tube defects, skeletal dysplasia and hearing loss. Inter- and intra-cellular protein–protein interactions at the local level (via proteins of the 'core' module of PCP) give rise to this polarity, which is coordinated with the tissue axis via a global (tissue scale) orientation signal in the form of expression gradients of proteins of the 'global' module of PCP. Beyond experimental work to identify the proteins and their interactions responsible for establishing and maintaining PCP, computational modelling has also been used extensively to understand the physical principles of PCP (Amonlirdviman et al., 2005; Burak and Shraiman, 2009; Mani et al., 2013; Shadkhoo and Mani, 2019; Fisher and Strutt, 2019).

Existing computational models of PCP usually adopt one of two approaches – detailed models incorporating mechanistic information about protein–protein interactions (Amonlirdviman et al., 2005; Strutt et al., 2023), or phenomenological models, which represent system dynamics without including molecular specifics (Burak and Shraiman, 2009). These models have unravelled the roles of diverse variables on PCP dynamics, including protein-level gradients (Mani et al., 2013), stochasticity (Burak and Shraiman, 2009), cell shapes and mechanics (Shadkhoo and Mani, 2019), specific intra- and inter-cellular protein–protein interactions, and genetic perturbations (Amonlirdviman et al., 2005; Burak and Shraiman, 2009). Taken together, these models suggest that intercellular interactions in the core and global modules are sufficient to establish coordinated polarity in two neighbouring cells (local order), which is amplified by intracellular interactions. During this process, cell shapes (via non-local interactions of proteins and cytoskeleton), protein expression gradients and the presence of stochasticity affect the cell polarity in different ways, resulting in the rich dynamics of PCP.

These diverse approaches have produced several computational models of PCP, but we currently lack a unified modelling framework that can either establish commonalities or identify differences among all the proposed models. For example, based on experimental evidence, one of the most common assumptions in these models is the formation of intercellular dimers between molecules of the transmembrane Flamingo family (a Fmi–Fmi homodimer) or members of the atypical cadherin Fat (Ft) and Dachsous (Ds) family (a Ft–Ds heterodimer) at the membranes of two adjacent cells. The mechanistic details of these interactions, however, differ significantly among PCP models. For instance, in one approach, the rate of heterodimer formation is estimated using the law of mass action (Fisher and Strutt, 2019) with no feedback, whereas in another approach the feedback on dimer formation by dimers that are already present is considered (Burak and Shraiman, 2009; Mani et al., 2013). These differences can be further accentuated between models of differing dimensionalities, and it is not always trivial to extend the results from a one-dimensional PCP model to two dimensions. Another challenge in arriving at a unified model is understanding the context-specific nature and diversity of experimentally identified mechanisms in different tissue types and organisms; for instance, there is ongoing debate on the nature of interaction between the core and global modules of proteins in these varying contexts (Lawrence and Casal, 2018; Brittle et al., 2022).

Given this diversity in both experimental and computational model systems for PCP, the formulation of a unified theory that can explain PCP dynamics in all tissues and organisms remains a challenge for mathematical biophysicists. Such a mathematical theory will not only be valuable for understanding PCP itself but will also help unravel the relationship of PCP with other complex systems, such as magnetization, pattern formation and collective behaviour phenomena in active matter (Bowick et al., 2022).

Take a walk on the wild side – cell polarity regulation in the human placental epithelium

Meghan Riddell

Trophoblasts, the epithelial cells of the placenta, are the most important cell type you no longer have. Derived from the trophectoderm at the earliest stages of development, trophoblasts form the primary exchange interface and barrier between the mother and the embryo or fetus. In humans, this essential function is almost entirely carried out by a single cell type – the syncytiotrophoblast (ST). The ST is an unparalleled cell in human biology – it is in fact a giant multinucleate syncytium. The maternal blood-facing surface of the placenta comprises a single ST, which is estimated to be ∼12 m^2 in size and contains 64 billion nuclei by the third trimester of pregnancy (Benirschke, 2000; Simpson et al., 1992).

As an epithelial cell with a crucial role in maternal–fetal transport, the ST displays clear features of apicobasal cell polarity. Namely, it has a highly microvilliated apical surface bathed in maternal blood and displays differential expression of proteins at its apical versus basal membranes (Jansson et al., 2002; Mando et al., 2011). However, the classical definitions of apical and basal surfaces that rely on the position of cell–cell junctions cannot be applied to this behemoth, as it lacks lateral membranes and expresses junctional proteins at both surfaces (Lecuit et al., 2004; Marzioni et al., 2001). Because this cell lies on the extremes of human biology and resides in one of the body's most understudied organs (Mercuri and Cox, 2022), almost nothing is known about the molecular mechanisms governing ST polarity.

The limited work that has been done on ST polarity regulation suggests that this cell type represents a unique opportunity to identify polarity regulating factors and pathways that deviate from those characterized in classical models of cell polarity and well-studied epithelial cell beds. For example, our research group recently discovered that the ST and other trophoblasts express an additional isoform of atypical protein kinase C (aPKC), the evolutionarily conserved polarity-regulating kinase. aPKC-ζ ɯ is encoded by the *PRKCZ* gene and its sequence suggests it is an endogenously encoded dominant-negative isoform, although its function is still being elucidated (Shaha et al., 2022). Our work has shown that aPKCs in the ST regulate the induction of pyroptosis, a form of programmed necrosis, in a regionalized manner (Patel et al., 2023). This suggests that within this single cell, aPKCs most likely play multiple spatially restricted roles and that there are additional signalling networks sustaining apicobasal polarity in the ST that remain to be identified.

Despite its seemingly wild and weird cell biology, the ST is ultimately an essential piece of human biology. Placental pathologies significantly contribute to nearly every common pregnancy complication and are associated with lifelong health consequences for both the birthing parent and the child (Burton et al., 2016). This includes increased risk of cardiovascular disease, neurological pathologies and metabolic alterations (Burton et al., 2016). Therefore, pregnancy presents a crucial window where therapies to correct placental dysfunction would improve lifelong health outcomes

of two individuals and substantially contribute to the health of future generations. However, there are presently no treatments for placental dysfunction, partly due to a lack of fundamental knowledge about the biology of placental cells. So, by embracing the weird and understanding the unique cell biology of placental cells like the ST, we are beginning to fill this substantial knowledge gap to give future generations their best chance for a healthy start to life.

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All authors contributed equally; author names are shown in the order in which their contributions appear.

Competing interests

The authors declare no competing or financial interests.

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