# Cell polarity inside-out

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Robert Arkowitz is a CNRS researcher and Group Leader in the Institute of Biology Valrose at the University of Côte d'Azur (France). His research investigates morpho- genesis in fungi, focusing on cell polarity, membrane traffic, and mechanical forces during growth of the human fungal pathogen *Candida albicans.*

Cell Polarity is defined as the structural, morphological, and functional asymmetry along an axis. This fundamental process can be separated into initiation or establishment, commonly referred to as symmetry breaking, and maintenance. For both steps, tight spatial and temporal control of signaling and cellular organization is critical and can be observed at sub-cellular, cellular, multicellular, and organismal scales. Cell polarity estab- lishment is directed by intracellular and/or extracellular polarity cues, which eventually lead to a polarity signaling asymmetry *via* conserved proteins that control the dynamic organization of a range of intracellular components and processes, including cytoskeletal structures, organelles, and membrane trafficking. In addition, a variety of feedback loops play crucial roles in amplifying and strengthening small asymmetries both in space and time, which ultimately lead to robust polarity at subcellular to organismal scales.

Riga et al. summarize recent advances with respect to the molecular mechanisms governing polarity protein interactions and signaling during apical-basal epithelial polarity. Although it is abundantly clear that the localization of polarity signaling is crucial to induce cell polarization, a major question in the field is what initially controls the recruitment of these fundamental, and often evolutionary conserved, polarity complexes to specific subcellular locations. The review by R. Illukkumbura et al. shows how intracellular fluid flows participate in the intracellular patterning of polarity signaling. The interplay between polarity signaling and intracellular structures, in particular the cytoskeleton, is further illustrated in the review of J.C.M. Meiring et al. showing not only how intrinsically polarized microtubules contribute to a fundamentally polarized cell organization but also how their mechanical properties contribute to and enforce asymmetry. Together with microtubules and actin, the Golgi apparatus also appears to act as a key regulator of cell polarity both by controlling directed vesicular traffic and functioning as a localized signaling platform increasing the effective concentrations of key proteins (Y. Ravichandran et al.). Highly polarized plant and fungal cells develop in the absence of complex tissue-scale signaling and provide excellent models to study diverse cell polarity outcomes. With the example of polarized growth in filamentous fungi, M. Bassilana et al. illustrate the impact of vesicular traffic and lipid membrane composition on the generation of discrete regions of signaling proteins, which together contribute to polarity. Together with recent observations made in plant cells (R.G. Orr et al.), showing that the coordination between the cytoskeleton and vesicular traffic controls the directional persistence during growth, these model systems implicate feedback mechanisms that reinforce region-specific signaling to stabilize cell polarity both during establishment and maintenance of this process. In addition, in many circumstances, cell polarity must be a dynamic process to accommodate cell adaption to their environment. J. Herrou et al. describe how a biochemical oscillator regulates a *Myxococcus xanthus* polarity switch by controlling the asymmetric distribution of a polarity protein over time. This leaves us to ponder whether polarity signaling precedes intracellular polarization or if an intrinsically asymmetric cell organization can be the trigger for oriented polarity signaling.

A second goal of this cell polarity issue is to expose the functional implications of single cell polarity in multi- cellular organisms through tissue organization and organ structure. In single cell organisms, polarity is crucial for a number of major cellular functions starting with directed cell growth,

oriented cell division, and cell migration. In multicellular organisms, polarity signaling remains essential at the single cell scale but is also crucial at the tissue scale. Although intrinsic polarity continues to be essential, cell-to-cell communication also provides major polarity cues, which coordinate polarity axes across tissues and organs. During asymmetric cell division of *Drosophila* neuroblasts, it is an intrinsic polarity signal that results in the asymmetrical segregation of cell fate determining molecules and thereby directly contributes to the organization of tissues (N. Loyer et al.). Recent evidence also points to the role of an established apico-basal polarity in the control of cell fate and lineage specification during early embryogenesis and throughout development (F. Motegi et al.). However, as observed in single-cell organisms, many non-autonomous cell factors also contribute to the polarization of cells. Within tissues, external polarity cues provided by the surrounding cells and intercellular communication allow for coordi- nated polarization and behavior of cell collectives. Polarized organization of immune cells orient signal relays and contribute to neutrophil NETosis and migration (C.A. Saunders et al.). At a larger scale, cell interactions through large atypical cadherins organize the cytoskeleton and the adherens junctions to control planar cell polarity (A.D. Fulford et al.). Adherens junctions also contribute to the transmission of polarity; in addition to biochemical signals associated with cell adhesion, they can also transduce mechanical cues. The review by E.V. van Leen et al. discusses how cell shape and local or global tissue tension influence orientation of symmetric divisions in epithelia during morphogenesis. More generally, intercellular interactions through soluble factors or direct cell-cell contacts allow the transmission of biochemical and biophysical polarity cues to the generation of a collective control of polarity. L. Capuana's et al. review points to the idea that by transmitting po- larity cues between cells, multicellular assembly can both ensure the coordination of polarity of cell groups and promote collective polarization when polarity signals are too small to be sensed and interpreted by single cells. Finally, cell polarity transmitted between cells, at the tissue level, eventually support the global organization of tissues and organs, depending on their size. J. Cravo et al. illustrate that in *C. elegans* epithelial organization is not dependent on planar polarity cell-cell communication. However in *Drosophila*, J.D. Axelrod explains how planar polarity signals can initiate lateralization and asymmetric morphogenesis of larger organs such as the heart and the gut. In the liver, the polarized transmission of Wnt sig- nals promotes liver zonation along the central vein portal triad axis (E. Valle-Encinas et al.). Finally at the level of the mammalian embryo, the generation of a polarity pattern, delineated by the presence (basal domain) or absence (apical domain) of cell contacts is critical for ensuing morphogenesis (M. Zhu et al.).

The fundamental role of cell polarity at the tissue and organ levels hints at the likely impact on human health of an alteration of polarity signaling. The interplay between mechanics and polarity at the tissue scale is critical during tissue repair (A. Guzmán-Herrer et al.), which relies on the collective control of cell proliferation and migration. Recent observations, summarized by M. Fomicheva et al., point to the role of polarity proteins and homeostasis in cancer. More generally, a better understanding of the mechanisms controlling the organi- zation of polarized organs is likely to provide insights into the pathogenesis, as exemplified in the review by P. Caceres et al., who summarize the influence of the polarized organization of the retina in blinding diseases.

Together these reviews highlight the diversity of systems and approaches to study cell polarity and provide an overview of recent findings in this exciting area of research.