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Review

Front–Rear Polarization by Mechanical Cues: From Single Cells to Tissues

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Directed cell migration is a complex process that involves front–rear polarization, characterized by cell adhesion and cytoskeleton-based protrusion, retraction, and contraction of either a single cell or a cell collective. Single cell polarization depends on a variety of mechanochemical signals including external adhesive cues, substrate stiffness, and confinement. In cell ensembles, coordinated polarization of migrating tissues results not only from the application of traction forces on the extracellular matrix but also from the transmission of mechanical stress through intercellular junctions. We focus here on the impact of mechanical cues on the establishment and maintenance of front–rear polarization from single cell to collective cell behaviors through local or large-scale mechanisms.

Front–Rear Polarity in Single Cells and Cell Ensembles

One of the most striking features of animal cells is their ability to acquire and sustain an asymmetric shape in response to environmental cues. This cellular property, called cell polarization, is fundamental to the function of most eukaryotic cells, and it is particularly relevant for shaping tissues during development. Cell polarization also plays a pivotal role in intracellular transport, cell division, differentiation, and directional cell movement. Front–rear cell polarity occurs in both single cells and cell collectives. Front–rear cell polarity is spontaneously acquired by migrating isolated cells as well as by cohesive cells during wound healing, epithelial gap closure [1–3], development, and cancer invasion [4,5]. During migration a single cell must first polarize and form its front or leading edge, which is characterized by cytoskeleton assemblies that produce a protrusion. At the leading edge, actin projections known as **lamellipodia** (see Glossary) form associated to nascent cell–**extracellular matrix (ECM)** contacts, which leads to the stabilization of an oriented internal actin rearward flow and ultimately cell protrusion [6]. At the rear of lamellipodia, anchoring of mature cell–ECM contacts to **actomyosin** allows the formation of longitudinal stress fibers. Consequently, the rear, or uropod, is established under strong tension and adhesion sites are disassembled [7], leading to cell retraction. Cell polarity is thus associated with a particular organization and orientation of the cytoskeleton and adhesive structures.

Front–rear polarization of single cells can be elicited by chemical signals such as chemokines and morphogens [8]. For instance, reaction–diffusion processes can lead to pattern formation and trigger cell polarity as described by the pioneering work from Alan Turing [9]. However, it can also be acquired constitutively by isolated fibroblasts or keratocytes likely as a result of spontaneous changes in intracellular biochemical signaling and/or mechanics [10,11]. Indeed, many biochemical cues are involved in the establishment of cell polarity: diffusing factors such as

Trends

Physical properties of the environment have functional roles in cell polarization.

Rigidity sensing is not only governed by local dynamics of focal adhesions but also by large-scale actin cytoskeleton polarization.

Matrix stiffness regulates the internal rheological properties of the cytoskeleton.

Single cell polarization depends on the coupling between actin and microtubule cytoskeletons.

Polarization within multicellular assemblies is regulated by a crosstalk between cell–matrix and cell–cell adhesions.

Large-scale coordinated movements within epithelial cell sheets depend on external physical constraints.

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morphogens and chemokines, Rho family GTPases, as well as plasma membrane determinants such as par complex proteins, as reviewed in [12]. Front–rear polarization has also recently been shown to be elicited by external force application [13], indicating that mechanical cues control at least some aspects of the establishment of front–rear polarization. This could be achieved through changes in the cytoskeleton, **focal adhesions (FAs)**, and contractility [6,14–16]. As opposed to passive materials, living cells actively respond to mechanical perturbations occurring in their environment. Cell adhesion to the surrounding ECM is an example of a mechanical process whose cell-generated forces adapt to the mechanical properties of their microenvironment [17]. Accordingly, front–rear polarity can emerge from a symmetry breaking mechanism whose origin can be determined by the mechanochemical properties of the ECM and the preferential orientation of adhesion complexes, cytoskeletal structures, and traction forces.

Motile clusters of cells have additional strategies over single cells to polarize and migrate. In some processes, such as vascular sprouting, only the front cell of the cluster shows clear front–rear polarity [18]. By contrast, in other processes all cells within the motile group exhibit front–rear polarization, even if they retain stable cell–cell junctions [19–22]. This is the case of cell monolayers invading a free space, a process in which nearly every cell is able to extend lamellipodia and generate traction forces on its underlying substrate [23]. Polarity in cell collectives can also involve the appearance of highly motile cells at the front of the tissue called leader cells [1,24], followed by the organization of small cohorts of cells locally guided by these leaders [25]. Importantly, bulk cellular motions also display large-scale coordinated movements of cell clusters that can be seen as the emergence of large-scale polarization within the tissues [1,26]. This type of organization allows cell clusters to act as multifunctional entities in which some cells are specialized in migration while others carry out distinct functions such as differentiation or division [19]. Thus, polarized and unpolarized cells may coexist during collective cell migration.

Despite these differences, some features of collective cell polarization can be understood using the same framework as single cell polarization. For example, the emergence of large-scale polarized movements within epithelial cell sheets largely depends on external geometrical and mechanical constraints [21,27–30]. In analogy with single cells, cell polarization can be defined by cytoskeleton ordering [30,31], as well as correlated orientation over multiple cells [32]. However, the transmission of stresses through cell–cell junctions and its propagation through cellular assemblies provides an additional layer of regulation that is absent in single cells [23,26,30,33]. The present review focuses on this novel paradigm: the influence of the mechanical environment on the acquisition of polarization. In line with current understanding of active matter physics, polarization can be defined as the emergence of order and quantified by different order parameters, such as cytoskeleton organization [30,34,35], velocity correlation [26,36], cellular forces [21,34], and cell shape [37], at various length scales from the single cell [38] to multicellular assemblies [39].

Single Cell Polarization by Mechanical Cues

We first discuss how mechanical cues may direct front–rear polarization and migration of single cells (Figures 1 and 2). Cell adhesion and migration of an isolated cell on a rigid ECM revealed an intrinsic capacity of cell–ECM adhesion sites and cytoskeleton to self-polarize, that is, spontaneously organize in an anisotropic manner in the absence of external biochemical or mechanical cues [38,40]. Fibroblasts spreading on ECM-coated rigid surfaces are initially isotropic, surrounded by a circular lamellipodium in the absence of polarization [41]. Over time the evolution of isotropic radial self-organized F-actin leads, by a symmetry breaking process, to the orientation of actin fibers along a preferential direction of the lamellipodium–uropod axis [38]. This process of polarization requires cell contraction [42], FA proteins such as talin [43] and α-actinin [44], and depends on substrate compliance [34,42].