Review

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Collective cell migration: guidance principles and hierarchies

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Collective cell migration results from the establishment and maintenance of collective polarization, mechanocoupling, and cytoskeletal kinetics. The guidance of collective cell migration depends on a reciprocal process between cell-intrinsic multicellular organization with leader–follower cell behavior and results in mechanosensory integration of extracellular guidance cues. Important guidance mechanisms include chemotaxis, haptotaxis, durotaxis, and strain-induced mechanosensing to move cell groups along interfaces and paths of least resistance. Additional guidance mechanisms steering cell groups during specialized conditions comprise electrotaxis and passive drift. To form higher-order cell and tissue structures during morphogenesis and cancer invasion, these guidance principles act in parallel and are integrated for collective adaptation to and shaping of varying tissue environments. We review mechanochemical and electrical inputs and multiparameter signal integration underlying collective guidance, decision making, and outcome.

Moving cell groups

Collective cell migration is a fundamental process that enables the coordinated movement of groups of cells that remain connected via cell–cell junctions [1–3]. Collective cell movements support the formation and morphological reshaping of larger tissue structures during the morphogenesis of ducts, glands, and vessels, as well as epithelial homeostasis and regeneration [2,4,5]. In addition, when reinitiated in mature tissue during neoplasia, collective movements contribute to cancer invasion and, probably, metastasis [1,6–9].

During collective migration, cell–cell junctions secure supracellular adhesion, polarization, and mechanocoupling required to sense and integrate external guidance cues and further share signal processing and force transmission across the migrating collective (Box 1). By connecting the actin cytoskeleton across multiple cell bodies, cell–cell junctions form the basis for integrating the forces generated by individual cells within groups and their supracellular front–rear polarity [10]. Furthermore, cell–cell coupling determines collective functions beyond migration, such as 'purse-string' contraction and closure of epithelial gaps and tissue folding [11].

The mechanisms guiding individually migrating cells are well understood and include both chemical guidance by chemotactic soluble factors or haptotactic tissue-anchored factors and physical guidance [12–14]. These guidance mechanisms apply in principle also to collective movements. However, in addition to single-cell migration, which results from processing of extracellular input within a single cell body, collective movement also involves intercellular integration of guiding signals to steer and maintain the migration of a cohesive cell group [15]. This includes cell-intrinsic prerequisites like the establishment of leader–follower polarization, supracellular mechanocoupling, and external mechanical, chemical, and/or electrical stimuli to steer collective movements (Table 1). Here, we summarize cell-intrinsic and extracellular mechanisms of polarity and guidance in collective cell migration. The astounding variability of how different cell groups integrate converging and/or opposing guidance inputs in complex environments reveals collective cell migration as a versatile and adaptive example of multicellular decision making and plasticity.

Collective polarity by leader–follower behaviors

The guidance of collective migration often involves the coordination between two functionally distinct populations, leader and follower cells. Leader cells localize at the front of a moving group, where they receive guidance signals and instruct, with cell–cell junctions at their rear, follower cells into directional migration through chemical and/or mechanical signaling [16,17] (Figure 1A). By acquiring a leading edge toward the substrate, including protruding actin-based structures like lamellipodia or filopodia, and specialized gene expression and signaling programs [17,18], leader cells secure front–rear polarity and guidance along or into tissue structures. Examples of well-defined leader cells are tip cells in the developing insect trachea and mammalian sprouting vessels [18]. As a mechanism underlying tip cell selection and collective sprouting, extracellular guidance signals by morphogens and chemokines induce receptor tyrosine kinase signaling. This causes tip cell selection in cell subsets and inhibits tip cell fate in adjacent cells, then called followers, by

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Box 1. Mechanocoupling along cell–cell junctions

Cell–cell connections in collectively migrating cell groups involve homophilic interactions mediated by cadherin adhesion receptors (adherens junctions) together with desmosomal proteins, tight junction constituents, gap junctions, and homophilic or heterophilic interactions between immunoglobulin family members, including activated leukocyte adhesion molecule (ALCAM), neural CAM (N-CAM), or L1-CAM, and ephrins/Eph receptors [25,114,126–128]. Most, if not all, adhesion receptors contribute to cell–cell contact-mediated signaling (e.g., PI3K/Akt, FAK, ERK, Rho GTPases) [129–132]. Cadherins and desmosomal and tight junction proteins additionally provide stabilization of cell–cell connectivity [133]. In particular, these junctions form a mechanotransducing bridge to neighboring cells via cytoskeletal linkages at their cytoplasmic site, which underlies the supracellular organization of the actin cytoskeleton and actomyosin cables that bridge across junctions [10,134]. It is likely that multiple adhesion mechanisms cooperate in a hierarchical manner to process guidance information and provide mechanosensory integration and force coupling during collective migration. In addition, although cell–cell junctions provide mechanically stable connections, at the molecular level adhesion sites and cytoskeletal connections are dynamic and are constantly remodeled to secure both mechanical connection as well as junctional flexibility [135].

negative feedback signaling through a Delta–Notch interaction [18]. Similar leader–follower segregation can be achieved in 2D cell sheets, where mechanical signals induce leaders cells at the front, which through subsequent Delta-dependent negative feedback signaling inhibit leader formation in neighboring cells [17]. Leader cell functions may also be adopted transiently, with yet-to-be-defined characteristics, such as in the developing mammary gland, where multicellular leaders rapidly exchange position [4].

The extracellular inputs and downstream intracellular signals that define and maintain leader cells are probably cell-type and tissue-context specific (Table 1). These include mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), focal adhesion kinase (FAK), phosphoinositide-3-kinase (PI3K)/Akt, Src kinases, Notch, and Rho GTPases. The early activation of these pathways contributes to the intrinsic bipolarity in leader cells [3,19–23]. As an example, the activation of Rho GTPases (mainly Rac) at the anterior cell part regulates actin polymerization, actomyosin-based contractility, coupling, and force transmission to stabilize integrin-mediated focal adhesions and thus defines leader cell motility [20,24,25]. Conversely, the rear of the leader cell retains cell–cell junctions and junction-derived signals, which locally silence Rho/Rock signaling and downregulate actomyosin contractility [26–29]. Compared with the formation of protrusions at the leader cell, near cell–cell junctions protrusions are usually minimized and mechanical coupling is secured in a process termed contact inhibition of locomotion (CIL) [3,30] (Table 1).

Principles of force generation in collective guidance

The anterior traction forces generated by the leader cell toward the substrate are balanced by tensile forces at the cell–cell junctions with follower cells at the rear. Follower cells can also engage in cell–substrate traction forces, possibly as consequence of 'cryptic lamellipodia' that protrude underneath the neighboring cell [31] and transmit forces across a longer distance and multiple cell bodies within moving cell sheets [32,33] (Figure 1A). However, to what extent cryptic lamellipodia generate force to propel collective movement remains under debate [33,34]. Thus, both leader and, to a lesser extent, follower cells generate traction force toward the substrate, which is balanced with the forces extending across cell–cell bodies. Collectively, an integrated mechanocoupling program within the leader cell reinforces outward polarization, cyclic actomyosin coupling, force transmission, and negative feedback signaling to follower cells to guide the cell group.

Beyond active pulling toward the substrate, mechanical pushing may be imposed by neighboring cells, either by volume increase after mitosis or when cells become jammed in a confined environment [9,35] (Figure 1B). Together, pushing from the rear and pulling from the front synergize and contribute to collective coordination and displacement.

Alongside collective front–rear force transmission, moving cell groups process directional information by intra- and intercellular signaling. Along cell–cell junctions, signaling is exerted by the adhesion molecules themselves, including mainly cadherins [32,36,37] (Box 1). In addition, forces transmitted at cell–cell junctions may induce conformational changes in mechanoresponsive molecules including vinculin or filamin and thereby trigger signaling events [38–40]. Lastly, moving cell groups maintain cell–cell communication via gap junction proteins (connexins); however, how signaling propagation via gap junctions contributes to polarity and the mechanical connection between moving cells remains unclear [41].

Consequently, beyond leader–follower behavior, collective migration relies on integrated mechanocoupling and guidance throughout the cell group.

Topographic guidance

The structural and molecular organization of tissue provides important cues for collective guidance. Cell groups interact with the extracellular matrix (ECM) and molecules bound by the ECM and/or resident cells; thereby they sense, interpret, and follow the topography of their environment, termed contact guidance, or, when mediated by specific adhesion receptors, haptokinesis [42]. In the event that these physical and/or molecular cues are inhomogeneous and act as a gradient, directional sensing causes intracellular signal polarity and movement along the gradient, termed duro- and haptotaxis, respectively [43].

Contact guidance/haptokinesis

Contact guidance and haptokinesis result from cells orienting their length axis and movement along topographic cues provided by the anisotropy of the encountered environment [44,45]. To enable haptokinesis, adhesion receptors engage with the substrate and thereby 'sense' and mechanically couple to topographic cues [42,46]. These can be ECM components, including collagen fibers or basement membrane, or complex tissue structures such as nerve tracks, muscle fibers, or fat cells. To a varying degree, these structures are respected by moving cells and cell groups and therefore serve both a guiding and a barrier function shielding adjacent environments from moving cells [47–50]. Given the complexity of moving cell groups,