JCB Journal of Cell Biology

PERSPECTIVE

Patterning in motion: Cell interfaces guide mesenchymal collective migration and morphogenesis

Maik C. Bischoff[1] and Roberto Mayor[2,3]

Collective cell migration is a fundamental process in development, wound healing, and cancer. The best-characterized modes of collective migration typically involve cells that retain an epithelial architecture. However, in this review, we explore less well-understood modes of migration driven by cells with a more mesenchymal phenotype. To better understand and compare contact-dependent collective cell behaviors, we propose envisioning each cell as a structure made up of smaller dynamic parts and inferring how these parts behave to understand the overall collective behavior. By examining how local cell shapes influence single-cell behaviors, we can gain insight into how swarm-like behaviors emerge through cell–cell contact. Through this lens, we compare key processes such as contact inhibition of locomotion, mesenchymal cell intercalation, and more complex heterotypic swarm behaviors. Finally, we discuss the emerging concept of contact-mediated rules that regulate motility and have the potential to encode blueprints for complex patterns and even organ shapes.

Introduction

Collective cell migration is a fundamental process essential for the development of multicellular animals and fungi. It plays a central role in tissue repair and serves as a hallmark of cancer progression and metastasis (Friedl and Gilmour, 2009). Even facultative multicellular organisms, such as *Dictyostelium*, utilize very similar cytoskeletal architectures, chemokine signaling pathways, and even collective dynamics when compared to animals, highlighting their evolutionary conservation (Fritz-Laylin and Titus, 2023; Stuelten et al., 2018). In the 1950s, Michael Abercrombie and Joan Heaysman observed that fibroblasts repel each other, coining this phenomenon the "*social behavior of cells*" (Abercrombie and Heaysman, 1953). Since then, the definitions of collective cell migration have varied among researchers. This review adopts the broad definition proposed by Mayor and Etienne-Manneville (2016), who argue that the defining feature of collectively migrating cell groups is their enhanced efficiency compared with isolated cells (Mayor and Etienne-Manneville, 2016). As a result, collective cell migration requires coordination and cooperation among migrating cells (Scarpa and Mayor, 2016). This definition encompasses not only tightly connected epithelial cells but also more individual mesenchymal cells, which may be only transiently connected and influence each other's migratory behavior (Theveneau and Mayor, 2011).

Here, we introduce a framework that allows one to apply the terms "epithelial" and "mesenchymal" to local cellular properties, allowing a single cell to simultaneously exhibit both. This approach is not intended to replace current categorizations, but to offer additional resolution when considering contact-dependent swarm behaviors. For example, even when migrating epithelia display some local mesenchymal traits in this model, their overall architecture—including stereotypical apicobasal polarity and more stable cell–cell adhesion—remains predominantly epithelial, making the term "epithelial collective cell migration" both accurate and useful. Here, our focus will be on more "individual" collective cell behaviors such as mesenchymal collective cell migration and crawling-based intercalation, which exhibit less stable adhesions. We also explore novel roles of such modes of collective cell motility as drivers of morphogenesis and pattern formation during development.

Morphodynamic building blocks: Diverse architectures drive single-cell shape and behavior

In addition to their pioneering description of collective dynamics, Michael Abercrombie and Joan Heaysman and their colleagues uncovered the architectural complexity within a single cell that enables cell migration (Abercrombie et al., 1970a; Abercrombie et al., 1970b; Abercrombie et al., 1970c; Abercrombie et al., 1971). They were the first to describe key

[1]Institute of Integrative Cell Biology and Physiology, Cells in Motion (CiM) Interfaculty Center, University of Münster, Münster, Germany; [2]Department of Cell and Developmental Biology, University College London, London, UK; [3]Center for Integrative Biology, Faculty of Sciences, Universidad Mayor, Santiago, Chile.

Correspondence to Maik C. Bischoff: maik.bischoff@uni-muenster.de.

© 2025 Bischoff and Mayor. This article is distributed under the terms as described at https://rupress.org/pages/terms102024/.

Check for updates

https://doi.org/10.1083/jcb.202505198

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

cellular structures involved in mesenchymal motility: an advancing and sometimes retracting front protrusion they named the lamellipodium, followed by a more steadily moving region called the lamella, and finally, a trailing edge that undergoes retraction. This revealed that different regions of a cell must build different structures and that their precise spatial organization determines migration speed, directionality, and overall behavior. As a result, we can think of cells as complex patchworks of morphodynamic building blocks, with internal coordination (Fig. 1 A).

How exactly this coordination is achieved remains a matter of ongoing research and is described in detail elsewhere (Ghose et al., 2022; Peglion and Etienne-Manneville, 2023). At its core, small Rho family GTPases—Rac, Cdc42, and Rho—play pivotal roles (Lawson and Ridley, 2018; Ridley, 2003; Zegers and Friedl, 2014) as molecular switches that can be turned on and off. Upon activation, they regulate a wide array of effectors controlling the cytoskeleton and cell shape. An intricate interplay of GTPases and their regulators enables the self-organization of simple front-rear gradients in highly persistent and fast-migrating cell types, as well as in more complex exploratory cell types that lack a single dominant protrusion (Nalbant and Dehmelt, 2018; Nanda et al., 2023). In addition, the distribution of phosphoinositides, notably phosphatidylinositol (3,4,5)-trisphosphate and phosphatidylinositol (4,5)-bisphosphate, plays a crucial role (Wu et al., 2014). These two systems are closely linked, working together as a part of a larger self-regulating network. This network can respond to diverse stimuli—such as chemoattractants, cell–cell contact, and the physical properties of the environment—as well as other key regulators that control how cells move alone or in groups. In response, it builds the right structures inside cells to support processes like migration (Llense and Etienne-Manneville, 2015). Aside from "Abercrombie"-type fibroblast-like migration, in vitro and vivo research has demonstrated that cells employ many other migration strategies depending on the dimensionality and the curvature of the substrate, and the specific microenvironment, accompanied by multiple protrusion types and different global cell shapes (Balaghi et al., 2023; Bodor et al., 2020; Chen et al., 2019; Lämmermann and Sixt, 2009; Madsen et al., 2014; Roca-Cusachs et al., 2013; SenGupta et al., 2021; Ullo and Logue, 2021; Yamada and Sixt, 2019).

For this review, however, our key point is not how specific structures, like lamellipodia, blebs, or actomyosin cables, work, for which we refer to excellent recent reviews (Chastney et al., 2025; Fritz-Laylin and Titus, 2023; Merino-Casallo et al., 2022; SenGupta et al., 2021; Yamada and Sixt, 2019). Instead, we aim to highlight that a single cell can be envisioned as a patchwork of multiple local architectures, which can be sorted and grouped within a conceptual map where proximity reflects similarity (Fig. 1 A; a speculative representation). Importantly, such local architectures do not rely on single regulators; instead, they arise from the activation of a wide array of factors. For example, Arp2/3-based actin branching comes to mind when thinking about lamellipodia. However, in melanoma cells and fibroblasts, the actin bundling formin FMNL has been shown to increase force generation inside lamellipodia (Kage et al., 2017). This, and many other examples, reveals that multiple regulators in specific combinations give rise to the emergent architectures that we mean when we use words like "lamellipodium". Thus, each such local architecture can be imagined as occupying a position within our conceptual map (Fig. 1 A). More accurately, our semantics probably reflect an *area* of very similar structures, not a single point on this map. This is especially true when taking many cell types or even many species into account. For example, the Arp2/3/FMNL ratio probably differs from cell type to cell type, and a lamellipodium is not *exactly* the same "thing" in all model systems. The number of dimensions of this purely hypothetical map reflects not only the sum of all structural proteins and their regulators (with dimensions for their concentrations) but also additional dimensions, for example, representing diverse activation states of different proteins. This vast range of potential architectures represents the complexity observed in cell shape.

Crowd control: Cell–cell contact as a driver of many emergent behaviors

A single cell can be envisioned as a patchwork of various morphodynamic building blocks, all coexisting and organized in a specific spatial pattern (Fig. 1, A1 and A2). This spatial and temporal organization dictates the cell's behavior. For instance, keratocytes maintaining almost the same protrusion shape over time may migrate quickly and persistently, while an exploratory fibroblast with numerous dynamic protrusions may exhibit more erratic behavior, frequently changing direction (Nalbant and Dehmelt, 2018). In general, localized modifications to subcellular architecture can lead to dramatic shifts in behavior (Wang et al., 2010). In some modes of epithelial collective cell migration, leader cells exhibit a "mixed" morphology, characterized by a mesenchymal/lamellipodial front and an epithelial backside, which creates a dynamic interface with the epithelial sheet in epithelial migration, as reviewed recently (Stehbens et al., 2024). This specific combination of architectures drives their characteristic behavior: migrating away from the epithelial sheet and thereby introducing a break of symmetry. In our conceptual map, each individual region of the cell occupies a distinct position, and it is their combined interactions that produce emergent behavior (Fig. 1 B). Thus, to understand single or collective cell behavior, it can be useful to apply terms like mesenchymal and epithelial to specific subcellular rather than to the entire cell, as many collectively migrating cell types are hypothesized to combine features of both (Campbell and Casanova, 2016). Within the conceptual map presented above, these terms do not represent fixed, well-defined states but larger areas containing groups of local architecture regions (Fig. 1 A, green for more mesenchymal, purple for more epithelial). In this model, many cell types can be viewed as a mosaic of mesenchymal and epithelial architectures or activate protrusive dynamics under specific conditions, such as during wound closure (Brugués et al., 2014) and extrusion (Le et al., 2021), or to stabilize junctions against constriction forces (Li et al., 2020). Thus, viewing a cell as an architectural patchwork—and extrapolating collective dynamics from individual components rather than from simplified single-cell behavior—provides an alternative

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

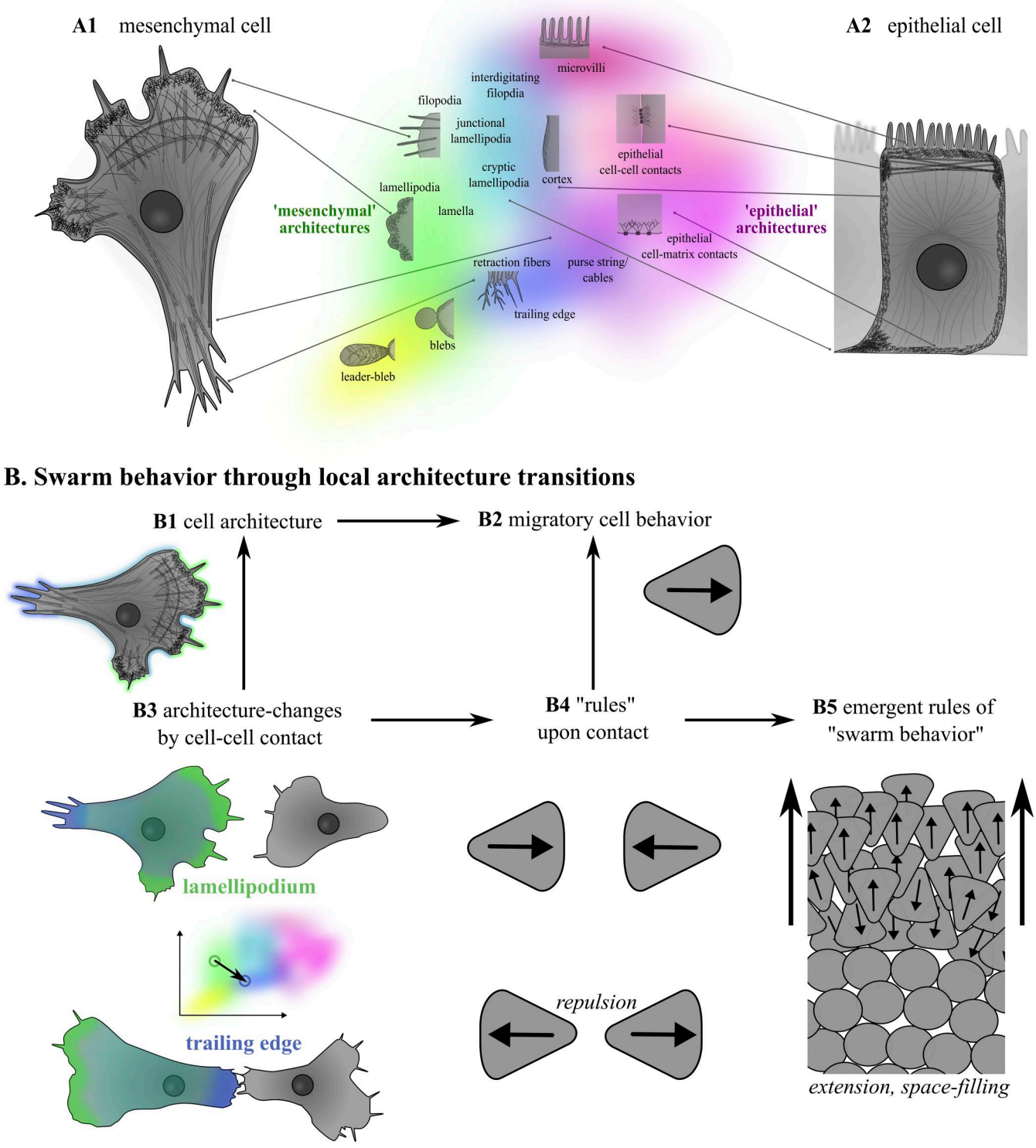

Figure 1. **Local architecture changes give rise to collective cell behaviors. (A)** Graphical representation of a speculative conceptual map of morphodynamic building blocks. Each position represents a distinct local cell architecture within a high-dimensional space, here reduced to two dimensions, where spatial proximity reflects architectural similarity. Green and blue hues represent more mesenchymal architectures, while purple hues indicate structures considered epithelial. Yellow denotes architectures typical of amoeboid cells. **(A1)** Mesenchymal cells typically exhibit combinations of features found on the left side of the map. **(A2)** Epithelial cells generally exhibit combinations of features restricted to the right side, although they can exhibit mesenchymal-like traits such as cryptic lamellipodia. **(B)** Schematic representation of how local cell architectures influence collective behavior. Colors match those in A. **(B1 and B2)** Composition of local architectures determines single-cell migration behaviors (B2), such as directionality (top row). **(B3)** Cell–cell contact-based reorganizations—such as CIL—induce local architectural changes (arrow to B1). **(B4)** These changes generate specific contact-mediated rules, such as retraction upon contact, which in turn modulate individual migration behavior, such as directionality (arrow to B2). **(B5)** Cumulative effect of these interactions gives rise to characteristic group behaviors, such as space-filling dynamics observed in CIL-driven collectives.

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

framework for understanding individual and collective cell migration.

The cell–cell contact acts as a critical leverage point, converting local architectural changes into emergent collective behaviors (Fig. 1, B1–B3). Typically, interactions via cadherin-based adherens junctions allow cells to influence one another's behavior by modifying these localized structures. Cell–cell adhesions serve as essential hubs for signaling, physically linking the junction to the cytoskeleton and driving structural modifications. The diverse roles of cell–cell adhesions in cytoskeletal remodeling have been reviewed extensively (Campàs et al., 2024). Beyond adhesions, transmembrane receptor couples such as EGFR-cadherin (Ramírez Moreno and Bulgakova, 2022) or FGFR-cadherin (Nguyen and Mège, 2016) also detect direct cell–cell contacts and can trigger localized architectural changes. Receptors traditionally known as contact-dependent "axon guidance factors" also act in nonneuronal tissues and regulate cytoskeletal dynamics upon binding to their transmembrane ligands. Examples are the Eph/ephrin (Taylor et al., 2017) system or the semaphorin/plexin (Worzfeld and Offermanns, 2014) system.

The Wnt-PCP pathway is one of the most crucial regulators of collective polarity in epithelial and mesenchymal tissues (Butler and Wallingford, 2017; Devenport, 2016; Strutt, 2008). Across animal species, the Wnt-PCP pathway is a common pathway to introduce planar polarity to epithelial tissues (Devenport, 2016). However, Wnt/PCP is also employed during mesenchymal intercalation of frog mesoderm, ensuring cell alignment by defining the position of growth cone–like lamellipodia (Keller and Sutherland, 2020; Wallingford et al., 2000). Furthermore, it is one of the main drivers of contact inhibition of locomotion (CIL) in neural crest cells (Mayor and Carmona-Fontaine, 2010). In addition to cell contact–based regulation, cell collectives can also follow noncellular cues, including chemical gradients, for example, secreted factors, or physical gradients, for example, extracellular matrix (ECM) stiffness. Such properties can also be self-regulated (Wong and Gilmour, 2021). For example, the zebrafish lateral line primordium self-generates a chemokine gradient, using polarized receptor-mediated internalization (Donà et al., 2013). However, here, we will focus on self-regulation based on cell–cell contact, rather than by protein secretion or scaffold remodeling.

At the subcellular level, contact-driven modifications influence individual cell behaviors (Fig. 1, B1–B3). When scaled to the multicellular context, such interactions can give rise to specific swarm behaviors, exemplifying how local architecture drives collective dynamics (Fig. 1, B4 and B5). A quintessential example to explain how local modification introduces a specific swarm behavior is CIL (Theveneau and Mayor, 2012a; Theveneau and Mayor, 2012b; Theveneau and Mayor, 2013). During vertebrate development, neural crest cells migrate in characteristic streams to positions where they later differentiate into a variety of cell types contributing to several organs, such as the skull, aortic outflow tract of the heart, enteric nervous system, dorsal root ganglia, adrenal gland, and melanocytes (Szabó and Mayor, 2018). When two neural crest cells make contact, the initial response is a change in architecture (Fig. 1 B2, top versus bottom). N-cadherin and Wnt/PCP signaling pathways reconfigure the contacting regions of the cells into a "trailing-edge" architecture, leading to complete repolarization away from the point of contact (Carmona-Fontaine et al., 2008). The phenomenon of CIL enforces a behavioral rule: *"walk away when you touch another cell"*! It was first observed by Abercrombie and Heaysman (1953), and dissected over many years by the Mayor Group and others, and illustrates how molecular changes in architecture underpin behavior. Zooming further out, this simple rule of contact-induced repulsion generates a specific swarm behavior, causing even cell distribution across a surface (Stramer and Mayor, 2017) (Fig. 1 B5). This example highlights how collective emergent behaviors originate from molecular-level changes that influence cell shape and architecture. Just as there is a diversity of cellular architectures and thus architectural transitions, there is a corresponding landscape of swarm behaviors, in our model defined by specific architectural transitions, that remains to be explored and understood (Fig. 2 A).

Beyond CIL: Exploring other contact-dependent rules of collective migration

Cell–cell adhesions play a crucial role in many examples of self-regulation during collective cell migration. Remarkably, even cells that lack cell–cell adhesions can still alter each other's morphology, resulting in specific swarm behaviors as a purely passive physical process. For example, spindle-shaped cells in high density can passively align with one another, leading to liquid crystal-like behavior (Duclos et al., 2017) (Fig. 2 A1). However, active restructuring near cell–cell adhesions allows for much more complexity in cell behavior. For example, fibroblasts also use an active mechanism to align. In contrast to CIL (which they can also perform), this involves down-regulation of actomyosin contraction at contact sites. This contact-dependent mode was termed collision guidance (Park et al., 2020) (Fig. 2 A1).

In some epithelial modes of collective migration, the entire sheet behaves like a single unit, with a division of labor between rows of phenotypically more mesenchymal cells at the front and rear cells phenotypically epithelial. These dynamics are also partially directly regulated by cell–cell contact (Campàs et al., 2024) and have been extensively reviewed in recent literature (Gupta and Yap, 2021; Stock and Pauli, 2021; Vishwakarma et al., 2020). Even in epithelial collectives, there are instances of "mesenchymal dynamics" outside the front edge. Cryptic lamellipodia from follower cells can support sheet migration from within the sheet (Gupta and Yap, 2021). Such structures are directly promoted by E-cadherin in flat adenocarcinoma-derived epithelial cells, where cryptic lamellipodia are located directly adjacent to adherens junctions (Ozawa et al., 2020), fitting well with the general notion that cellular interfaces directly influence emergent cell behaviors via local restructuring. However, it remains unclear whether this mechanism would also function in more columnar epithelia, where cryptic lamellipodia are located spatially much farther from adherens junctions. Meanwhile, in mammary epithelia, cryptic lamellipodium formation requires the MYO6-DOCK7 axis to spatially restrict Rac activation (Menin et al., 2023). The idea of a transition between epithelial and

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

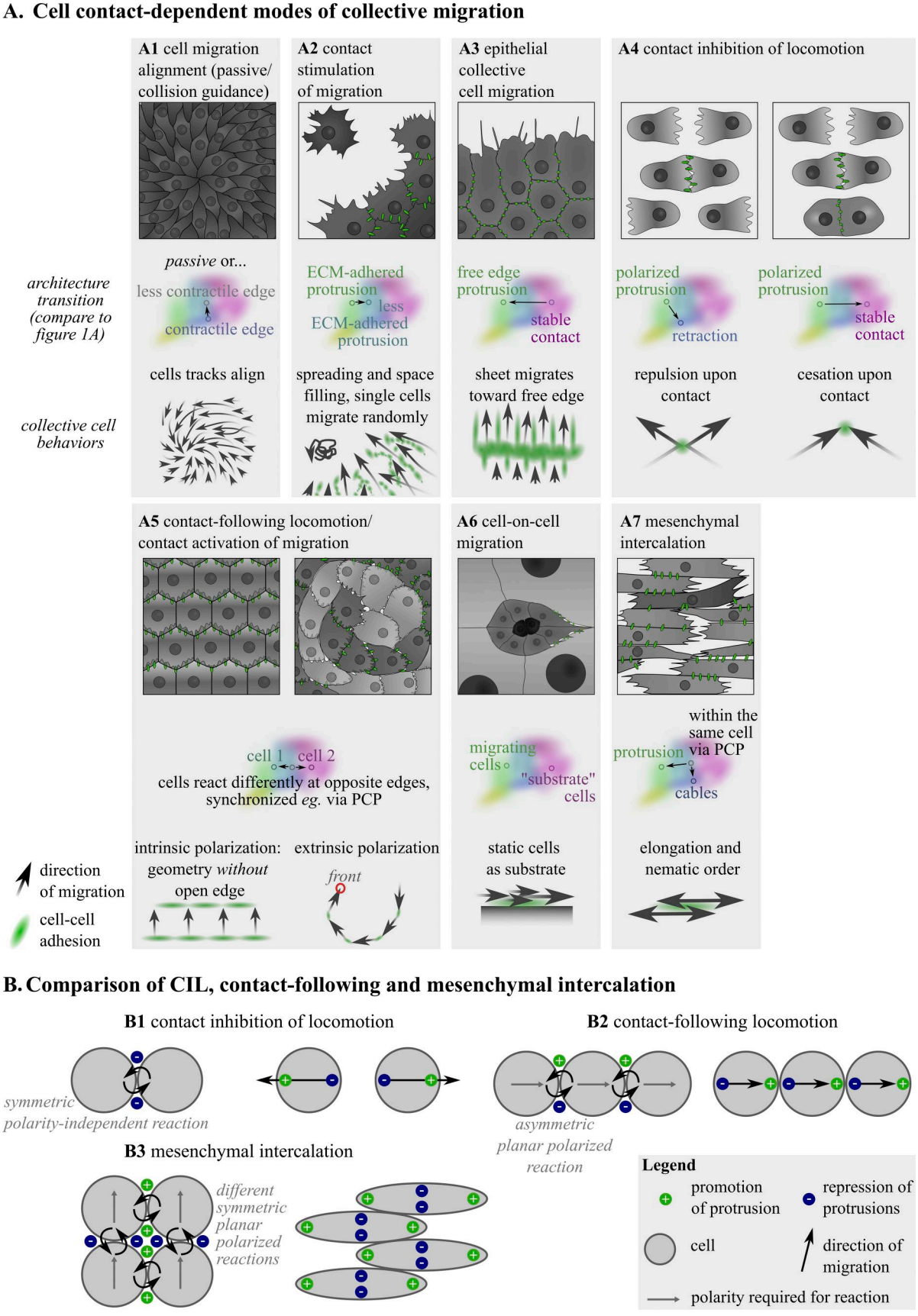

Figure 2. **Mesenchymal cells can perform diverse modes of contact-dependent collective cell migration. (A)** Diverse modes by which cell–cell contact gives rise to specific swarm behaviors. Architectural transitions are depicted using the conceptual map from Fig. 1. **(A1)** Cells can align with respect to migration

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

trajectories either passively, due to their shape, or actively through collision guidance, which involves contact-dependent downregulation of actomyosin contractility. **(A2)** In contact-stimulated migration, as observed in *Drosophila* testis myotubes, all cells remain protrusive but downregulate matrix adhesion at cell–cell interfaces. This allows individual cells to spread, while the entire sheet expands collectively—resulting in space-filling behavior without cell dissociation. **(A3)** In epithelial collective cell migration, cells exhibit apical–basal polarity, where cell–cell contact induces epithelial junctions and free edges become protrusive, enabling division of labor and coordinated space filling. **(A4)** In CIL, cells migrate individually but undergo transformation upon contact, resulting in either repolarization or cessation of migration. **(A5)** In contact-following migration, as seen in the *Drosophila* follicle cell epithelium (left), each cell must autonomously polarize, but this needs to be synchronized in the collective. Each cell becomes directionally protrusive, using PCP without a polarizing free edge. In contrast, in systems like *Dictyostelium* fruiting body development (right), contact following can be extrinsically polarized due to the presence of a defined front (the first cell in a strand). **(A6)** Cells may also use other cells as migratory substrates, as observed in the *Drosophila* border cell cluster. **(A7)** During mesenchymal intercalation, such as in frog mesoderm, cells use interface-guided protrusiveness not for migration but for tissue deformation. As in contact following, this requires internal polarization to differentially respond at different interfaces. **(B)** Comparison of CIL, contact following, and mesenchymal intercalation, deconstructing these modes into local effects on protrusion—either induction (+) or repression (-) (using the color code of the map in Fig. 1 A). **(B1)** In CIL, both cells respond symmetrically by retracting upon contact. The contact site itself induces a new polarity, overwriting the cell's previous orientation. **(B2)** In contrast, during contact following, one cell at the interface induces protrusion, while the other retracts. This asymmetric response requires synchronization and preestablished polarity, enabling cells to react differently at specific interfaces—for example, via PCP signaling modules. **(B3)** In mesenchymal intercalation, protrusions are repressed at junctions along one axis and induced along the perpendicular axis. This necessitates two predefined polarity axes, often established through PCP signaling. PCP, planar cell polarity.

mesenchymal modes of collective migration or "hybrid/partial EMT" has been discussed in the field for some time (Campbell and Casanova, 2016; Peglion and Etienne-Manneville, 2023; Revenu and Gilmour, 2009; Theveneau and Mayor, 2013; Weijer, 2009). In our opinion, the existence of cryptic lamellipodia nicely demonstrates this notion, especially as it allows modes of migration in which every cell within the sheet can be protrusive itself.

Here, we focus on modes of collective cell migration described by the term "mesenchymal collective cell migration." This refers to migration modes in which each cell migrates largely independently. Sometimes, like in CIL, contact is only transient. Mesenchymal testis nascent myotubes (TNMs), muscle precursors, are needed to cover and shape the *Drosophila* testis during pupal development, while maintaining active protrusions even at cell–cell edges (Fig. 2 A2). To do this, upon contact they use plexin A (PlexA) signaling to maintain protrusions at cell–cell interfaces, allowing each cell to spread (Bischoff et al., 2025a). This is crucial, as cells must remain flat to migrate under confinement, sandwiched between two cell layers on top of an ECM. Thus, cells project filopodial protrusions in all directions; protrusions near contacts have integrin adhesions with a shorter lifetime than those at the free edges. This causes cells to move toward open space and fill the finite area of an ellipsoid testis surface—rendering them an example of contact stimulation of migration (Fig. 2 A2) (Bischoff et al., 2021; Yamada and Sixt, 2019). Like CIL, this also causes space filling, with the critical difference that cells remain in contact with each other, which is crucial for morphogenesis. However, this contact lacks apical–basal polarity and is much more dynamic than in epithelial modes of collective cell migration (Fig. 2 A3).

CIL, contact stimulation of migration, and collision guidance all represent symmetric interactions, as both contacting cells react with identical architectural transitions (e.g., retraction in CIL, Fig. 2, A4 and B1). In contrast, some cells exhibit asymmetric interactions at cell–cell interfaces, where one cell forms protrusions and the other develops a trailing-edge architecture. This asymmetry can result in contact-following behavior, as observed in the rotational follicle cell migration during *Drosophila* egg chamber development (Cetera and Horne-Badovinac, 2015) (Fig. 2 A5, left, Fig. 2 B2). Interestingly, while follicle cells are part of a highly epithelial tissue, every cell generates planar polarized cryptic lamellipodia. Unlike most migratory tissues, there is no free edge to define directionality. Instead, these cells form a closed epithelial ellipsoid that migrates collectively on a surrounding ECM layer. Lacking external open edge–derived polarity, these cells must self-regulate planar polarity to synchronize their directionality (Fig. 2 A5, left, bottom). This coordination is achieved through the action of several key molecules, including the nonconventional cadherin Fat2 together with the receptor tyrosine kinase Lar (Barlan et al., 2017), along with PlexA/semaphorin signaling (Stedden et al., 2019). Fat2 locally promotes protrusions by activating Arp2/3-mediated actin branching through the WAVE complex (Williams et al., 2022), consistent with the broader principle that localized changes in protrusion dynamics act as drivers of self-regulation in collective migration.

Contact-following behavior is not limited to epithelial systems. For example, *Dictyostelium* cells exhibit contact following within swirling streams during fruit body formation (Fig. 2 A5, right). Unlike in follicle cell migration, there is a "front" of individual cell strands, and therefore no need to synchronize directionality "everywhere at once," but instead front-to-back (Fig. 2 A5, right, bottom). The following-behavior behavior is mediated by heterophilic adhesion molecules TgrB1/TgrC1, which locally activate the SCAR/WAVE complex to drive protrusions (Fujimori et al., 2019). Similar behaviors have also been observed in macrophage–tumor cell interactions, further highlighting the conservation of this behavior across diverse biological systems (Miskolci et al., 2021).

All of these examples are based on the concept of cells migrating within or on an ECM environment, with integrins providing linkage to the substratum and cadherins serving as mediators of cell–cell adhesion and signaling hubs. In the early 1990s, Ray Keller observed something different in *Xenopus* mesodermal explants. During mediolateral intercalation, cells exert traction forces directly on each other, resulting in cell-on-cell crawling that drives cell elongation (Shih and Keller, 1992). In *Drosophila* border cell migration, cells also use neighboring nurse cells as a substrate (Montell, 2003) (Fig. 2 A6). This

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

represents another way to utilize cell–cell interfaces to guide migration. In this context, cadherins take on a role akin to that of integrins in mesenchymal migration, providing the necessary anchorage for the actin cytoskeleton to generate force and propel movement. Other cells can provide more than just anchorage; in the fly ovary, nurse cell topography also directs the border cell cluster during migration, as it consistently follows the path with the most cell contacts, since this path is geometrically the widest (Dai et al., 2020). Only a few in vitro studies have examined the use of cadherin-based substrates in cell migration (Collins et al., 2017; Dehli et al., 2019; Li et al., 2019; Suh et al., 2024). Recently, the Cohen group tested this by placing MDCK cells on a split substrate: one half integrin-based and the other cadherin-based (Suh et al., 2024). The results were striking, with cells drastically slowing down on the cadherin-based substrate, showing reduced fluidity and dynamics and cell division. These experiments demonstrated significantly altered collective cell migration dynamics, with sharp borders forming at the split substrate boundary. As cadherin-based substrates might be used by many migratory cells in vivo, such as cancer cells, it is crucial to consider similar approaches across diverse cell types and cadherin variants to better understand the distinct architectures and behaviors at cell–cell interfaces. The fascinating phenomenon of cell-on-cell migration was reviewed recently (Le and Mayor, 2025).

Mesenchymal intercalation, whether cell-on-cell or cell-on-matrix, represents its own type of mesenchymal collective motility (Fig. 2 A7). Epithelial intercalation often relies on T1 transitions—a stereotyped sequence of cell shape changes involving junctional constriction, formation of a transient four-cell vertex, and subsequent neighbor exchange through elongation of the newly formed interface (Butler et al., 2009; Fernandez-Gonzalez and Zallen, 2011; Sawyer et al., 2011). However, mesenchymal cells can use another form of intercalation, driven by cell elongation through two opposing growth cone–like protrusions (Devenport, 2016; Keller et al., 1992; Shih and Keller, 1992). Interestingly, work by John Wallingford and others suggests that many processes likely employ a combination of both approaches (Huebner and Wallingford, 2018). By analyzing each individual cell's architectural components, it becomes evident that mesenchymal intercalation shares similarities to CIL and contact following. At some cellular interfaces, protrusions are symmetrically inhibited and local constriction–enforced, reminiscent of CIL dynamics, while at others, protrusions are reinforced, all together resulting in cell elongation (Fig. 2 B3). To define the two axes that specify which edges respond to cell–cell contact, polarity is established in a collective self-organized process which is often based on Wnt/PCP (Wallingford et al., 2000), reminiscent of contact following (Fig. 2 B2 versus Fig. 2 B3). Wnt/PCP in epithelial tissues can create distinct anterior and posterior edges. High-resolution live-cell imaging in elongating *Xenopus* mesoderm cells recently led to the identification of architectural asymmetries between the anterior and the posterior interfaces. PCP signaling, mediated by Vangl2 and Prickle2, not only establishes mediolateral symmetry but also generates a cryptic anterobasal polarity, characterized by a denser contractile actin cytoskeleton at the anterior edge. This is mediated by septins downstream of Wnt/PCP (Devitt et al., 2024).

This diverse array of contact-based interactions in mesenchymal cell migration underscores the versatility of collective migration mechanisms, where cells can adapt their behavior based on context. This enables mesenchymal cells to exhibit a broad range of migration strategies similar in complexity to epithelia but often employing more individual and fluid strategies when it comes to emergent behaviors. Next, we will explore how such dynamics can shape tissue patterning and morphogenesis.

Dynamic blueprints: Mesenchymal collective behaviors can encode complex patterns

In his pioneering work, Eric Davidson distinguished between two fundamental modes of cell specification: *autonomous* and *conditional* (Davidson, 1990). Autonomous specification depends on intrinsic, lineage-based factors, while conditional specification relies on extrinsic cues such as morphogens or the surrounding cellular environment. Thus, in conditional specification the logic is "location first, identity second," with a cell's identity determined by its position relative to its neighbors. In tissues with minimal cell rearrangement, it is helpful to think of them as static grids of cellular automata, where information flows between cells—for example, via morphogenetic gradients—in a manner similar to *Conway's Game of Life*. These concepts build on the foundational ideas of Alan Turing and Lewis Wolpert. In the groundbreaking Heidelberg screen 40 years ago, Christiane Nüsslein-Volhard, Eric Wieschaus, and colleagues discovered that similar complex interactions in an epithelial grid drive patterning in fly development, and many of the basic principles they identified hold true in vertebrates as well (Jürgens et al., 1984; Nüsslein-Volhard et al., 1984; Peifer, 2024; Wieschaus et al., 1984).

However, in some systems, a cell's identity is specified first—whether by autonomous or conditional mechanisms—and its relative position within the tissue emerges from this identity through guided motility, for example, collective cell migration. It is well established that complex epithelial rearrangements can drive morphogenetic processes, with portions of an epithelial sheet moving relative to others—as seen, for example, in kidney development (Vasilyev et al., 2009), or during *Drosophila* dorsal closure (Kiehart et al., 2017) and many more examples. However, such rearrangements can also occur at the level of individual cells, giving rise to more complex and individual swarm behaviors in which each cell acts as an autonomous agent, responding to local cues through context-dependent rules.

An example of this is the long-known ability of cells to self-sort according to the specific cadherins they express (Moscona and Moscona, 1952; Nose et al., 1988). Recently, cadherin-mediated self-sorting has been proposed as a robust mechanism that operates in concert with morphogen gradient–based patterning (Tsai et al., 2020). Differential adhesion can not only organize epithelial sheets by cadherin type but also drive more complex tissue rearrangements, particularly through the interplay between cell–cell and cell–matrix adhesion. For example, during budding morphogenesis in the stratified epithelium of

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

the developing mouse salivary gland, cells with low E-cadherin expression—regardless of their initial position—reliably sort into the surrounding basal basement membrane–contacting layer. This directed sorting behavior promotes tissue buckling and exemplifies how adhesive differences can be harnessed to coordinate patterning and morphogenesis (Wang et al., 2021).

Active protrusive dynamics are well known to change rheological properties in tissues (Hannezo and Heisenberg, 2022). This notion is based on the finding that cell behavior can resemble atoms in different states of matter—solid-, fluid-, or gas-like. Protrusive/mesenchymal dynamics typically cause cells to behave like particles in a fluid or, when interactions are minimal, like a gas (Lenne and Trivedi, 2022). Such dynamic tissues can cause collectives to respond passively in a stereotypical way to physical cues—which can be used to direct morphogenesis and form patterns. Jamming and unjamming transitions—shifts between fluid-like and solid-like states—have thus been proposed as key mechanisms in shaping tissues (Angelini et al., 2011; Hannezo and Heisenberg, 2022). We propose the term mesenchymal self-patterning to describe the process by which mesenchymal cells use motility to self-regulate cell rearrangement and generate spatial patterns. This complements the diverse and essential ways in which epithelia can self-organize, reshape, and rearrange. Mesenchymal self-patterning can occur either through general fluid- or gas-like behaviors—driven by random single-cell motility and shaped by environmental cues—or through directed interactions mediated by cell–cell contact, as discussed next.

Phenomena like CIL, contact following, or contact-stimulated migration and many more demonstrate that cells—typically those on the mesenchymal end of the spectrum—can display individual highly directed movements governed by complex, rule-based behaviors. These dynamics, often contact-dependent, allow for intricate, self-organized rearrangements that generate patterns on their own. During this, there are only a limited number of ways in which two cells can alter each other's protrusive behavior resulting in directionality or shape changes. We began assembling a list of known and potential modes of contact-dependent behavior changes, affecting either migration directionality or cell shape (Fig. 3 A). In tissues composed of multiple cell types (Fig. 3 B1), diverse heterotypic interactions can generate the complexity needed for more intricate patterns to emerge from contact-dependent changes in cell behavior (Fig. 3 B2). Rules such as CIL, contact following, or co-attraction can be specific to particular combinations of cell types—meaning a given cell might respond one way to one cell type and differently to another (Fig. 3 B2). These rules can be symmetric (both cells reacting the same) or asymmetric (each cell reacting individually), depending on the cell-type pairing. Expanding the landscape of possible interactions even further, some rules may shift based on context—such as the physical environment—or change over time. Such mechanisms could, for example, be used to generate pattern variations along body axes (Fig. 3 B4). In this view, the rules underlying mesenchymal collective cell migration themselves encode the blueprint for tissue patterning. We propose the term *directed* mesenchymal self-patterning to describe this form of dynamic, rule-based pattern formation. Next, we will present examples of directed mesenchymal self-patterning, as well as mesenchymal self-patterning more broadly.

A ballet of cells: Vignettes on directed mesenchymal self-patterning

Although these phenomena have not previously been unified under a single conceptual framework, a diverse array of biological systems display features consistent with our definition of directed mesenchymal self-patterning. In this section, we highlight representative examples—pigment cells and neural crest cells—that illustrate how contact-mediated behavioral rules in mesenchymal cells can self-generate spatial patterns. We also briefly summarize key conceptual connections and contributing mechanisms, including parallels to axon guidance, the importance of cytonemes for long-range signaling, and insights from computational modeling that help to understand directed mesenchymal self-patterning.

Pigment cells in fish

The development of fish coloration has revealed a striking example of directed mesenchymal self-patterning. Adult fish have very diverse colorful patterns, created by different types of pigment cells (Irion and Nüsslein-Volhard, 2019) (Fig. 4, A and A1). Most of them do not adopt a fixed identity based on position. Instead, they actively migrate and self-organize, and then either settle or proliferate (Irion and Nüsslein-Volhard, 2019). One might argue that such migration is guided by a morphogen prepatterned epithelium. However, in *Danio rerio* it has been shown that while the underlying horizontal myotome establishes a primary axis, everything beyond this initial cue is a self-organized, pigment cell-autonomous process (Frohnhöfer et al., 2013). During this, both homotypic and heterotypic interaction rules play essential roles. Yellow xanthophores that have a dense configuration in interstripe and a loose configuration in stripe regions (Mahalwar et al., 2014) (Fig. 4 A1) migrate as an interconnected network, extending and filling space (Walderich et al., 2016), likely using homotypic CIL or contact-stimulated migration. Meanwhile, black melanophores also exhibit homotypic repulsion, which generates free edge–based directionality and prevents clustering except when influenced by heterotypic interactions (Takahashi and Kondo, 2008).

Pattern formation in pigment cells relies on multiple heterotypic interaction rules: reflective iridophores attract xanthophores, while xanthophores repel melanophores (Frohnhöfer et al., 2013). Intriguingly, xanthophores extend long cytoneme-like protrusions that repel melanophores (Inaba et al., 2012) (Fig. 4 A2). Further, xanthophores get "dragged" by melanophores via stable cell–connecting protrusions (Yamanaka and Kondo, 2014)—resulting in "chase-and-run"/contact-following dynamics (Theveneau et al., 2013) (Fig. 4 A3, compare with Fig. 2 B2). Together, these findings illustrate that cells integrate multiple forms of contact-dependent interactions to self-regulate and harness these interactions to generate complex patterns. However, one notable exception to this is the two types of iridophores (dense interstripe and loose stripe, Fig. 4 A) that differentiate into their respective form, based on the

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

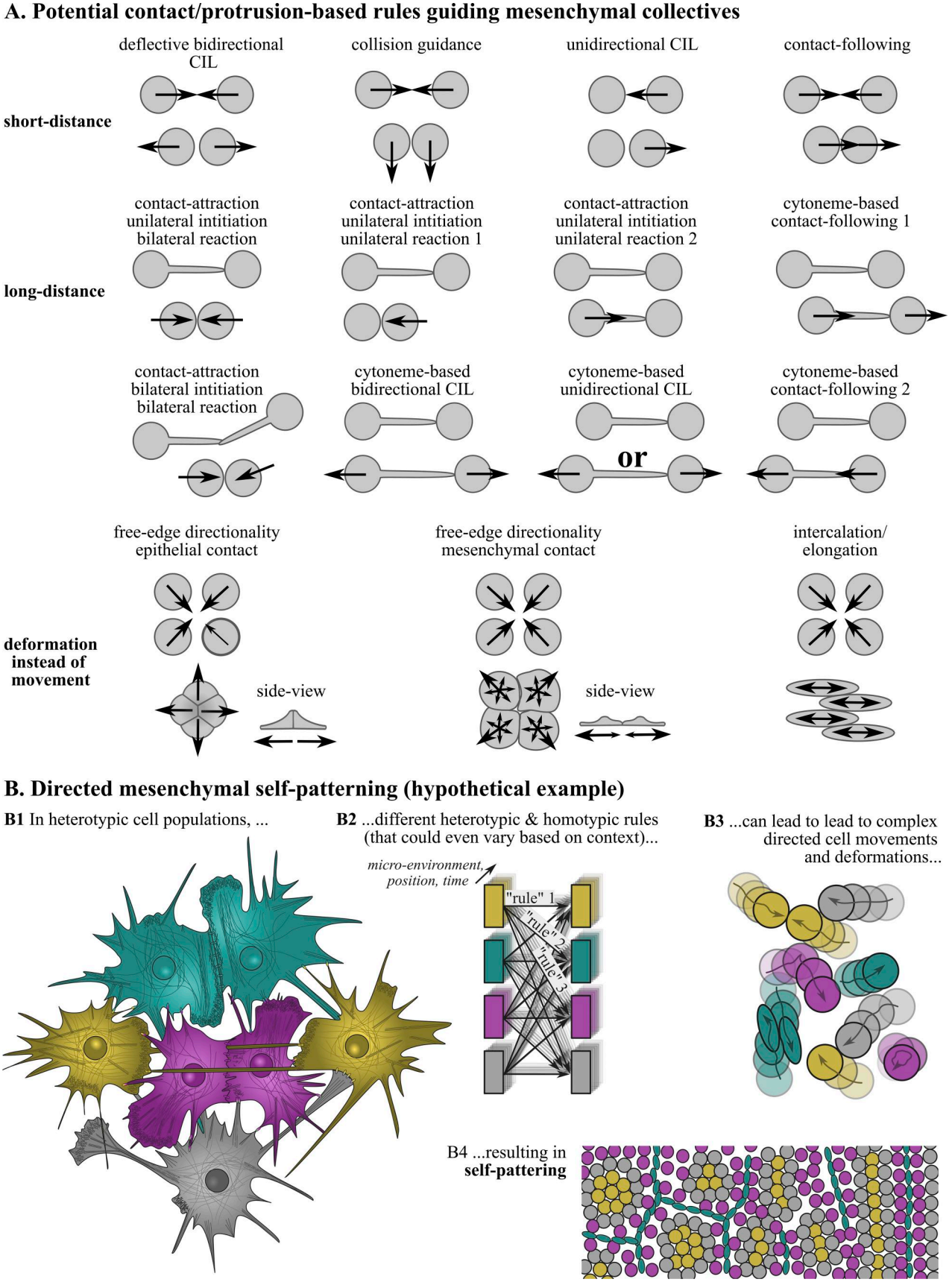

Figure 3. **Complex migration rules upon contact can lead to directed mesenchymal self-patterning. (A)** Different interaction modes—some speculative—by which two mesenchymal cells may respond to cell–cell contact through localized modulation of protrusion and retraction dynamics. These responses

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

can be broadly categorized into *short-range* modes, such as CIL, collision guidance, and contact following, and *long-range* modes involving cytonemes or cytoneme-like structures such as airinemes, which also allow contact-based *attraction*. Each mode can operate symmetrically or asymmetrically, or even as hybrid combinations. The examples presented here illustrate the basic principles, but many additional interaction rules are conceivable. Further, regulation of mesenchymal and epithelial local properties can, instead of driving migration, also affect cell shape. **(B)** Conceptual model of how defined homo- and heterotypic interaction rules can give rise to complex patterns in the absence of external cues—a process we term directed mesenchymal self-patterning. **(B1)** In heterotypic cell populations, **(B2)** different cell pairings may engage in specific combinations of the contact responses summarized in (A). These interaction "rules" may vary depending on position, microenvironment, or developmental time. **(B3)** Such rules can generate complex, directed swarm-like behaviors, **(B4)** which in turn can drive stereotyped rearrangements and the emergence of specific spatial patterns. Spatial variation in these rules could also account for regional pattern differences.

presence or absence of migration patterned melanophores (Gur et al., 2020). This demonstrates that patterns formed by directed mesenchymal self-patterning can themselves be instructive for further conditional specification.

Color patterns change throughout evolution. *Danio rerio* displays a striped pattern, whereas other *Danio* species exhibit dotted patterns. If these patterns arise through directed mesenchymal self-patterning, this raises the question of how one pattern can evolve into another. Evolutionary developmental studies using interspecies chimeric genetics have identified regulatory genes that were modified in the transition from stripes to dots. Fittingly, these genes are not signaling molecules, but proteins involved in cell–cell contact, such as tight junction and gap junction molecules (Fadeev et al., 2015; Irion et al., 2014). This suggests that evolutionary changes in patterning can arise through the modulation of direct cell–cell interactions—consistent with the central principle of directed mesenchymal self-patterning.

Cephalic neural crest migration

Neural crest cells in the head migrate collectively in stereotyped streams (Fig. 4 B). Until recently, this stream migration was thought to be guided by a preexisting pattern of inhibitory signals located at the borders of each stream. According to this view, migratory neural crest cells followed this pattern, avoiding the interstream regions due to the presence of inhibitory molecules such as ephrins, semaphorins, and Slit/Robo (Szabó and Mayor, 2018). However, recent findings show that no such inhibitory pattern exists before migration. Instead, cells expressing these inhibitory molecules are uniformly distributed adjacent to the neural crest. The initial patterning arises from mutual cell repulsion between neural crest cells and inhibitory cells (Szabó et al., 2019) (Fig. 4 B). Importantly, these inhibitory cells also express a chemoattractant for neural crest cells, which reinforces the emerging pattern. Thus, neural crest cells "push" inhibitory cells away, while inhibitory cells simultaneously attract neural crest cells, together generating the stream migration pattern. Mathematical simulations have successfully reproduced this behavior, identifying the speed difference between neural crest and inhibitory cells as a key parameter: neural crest cells migrate faster than inhibitory cells (Szabó et al., 2019).

Self-generated mechanical gradients

Neural crest cells migrate directionally by integrating both chemical and mechanical cues (Shellard and Mayor, 2019) (Fig. 4 C). One key mechanical cue is tissue stiffness (Barriga et al., 2018), which exists in the form of a gradient that neural crest cells sense and follow—a process known as durotaxis (Shellard and Mayor, 2021). Interestingly, this stiffness gradient is not present before migration begins; instead, it is generated by the neural crest cells themselves, which actively modify the mechanical properties of their environment (Fig. 4 C, compare panels). Neural crest cells migrate using other cells as substrates (compare Fig. 2 A6, cell-on-cell migration), engaging with them via N-cadherin–mediated adhesion. This adhesion alters the actin cortex of the substrate cells, resulting in reduced mechanical stiffness. The duration of N-cadherin engagement determines the degree of stiffness modulation, creating a gradient that increases with distance from the neural crest. This self-generated mechanical gradient helps direct neural crest migration.

Modeling

One crucial way to decode mesenchymal self-patterning is through mathematical modeling. For example, Painter and colleagues introduced a system that allowed modeling responses such as attraction and repulsion with interactions over variable spatial ranges within a homo- or heterogeneous cell population. They used this framework to model both neural crest–like dispersal driven by CIL and some aspects of homotypic pigment cell dynamics (Painter et al., 2015). Volkening and Sandstede took this further by creating stripe patterns from a two-population model that recapitulates stripe formation and regeneration (Volkening and Sandstede, 2015). They extended this model to include a third pigment cell type (Volkening and Sandstede, 2018) and even simulated fin stripes in a fin-shaped environment, providing an excellent example of how modeling can capture the complexity of biological systems (Volkening et al., 2020). These and many other advances are reviewed comprehensively elsewhere (Volkening, 2020). Currently, a number of groups are approaching self-patterning based on cell migration and sorting through diverse modeling strategies, as highlighted in several recent preprints (Garner et al., 2025, *Preprint*; Uçar et al., 2024; Weninger et al., 2025, *Preprint*; Yu et al., 2025, *Preprint*).

Parallels to axon guidance and neuronal migration

Contact-dependent axonal pathfinding can be viewed as a type of directed mesenchymal self-patterning. Driven by diverse cell–cell interactions, they at least share many parallels (Raper and Mason, 2010), involving a similar challenge: coordinating the movements of individual cells or growth cones to establish a precisely organized pattern. It is therefore not surprising that many proteins traditionally classified as "axon guidance factors"

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

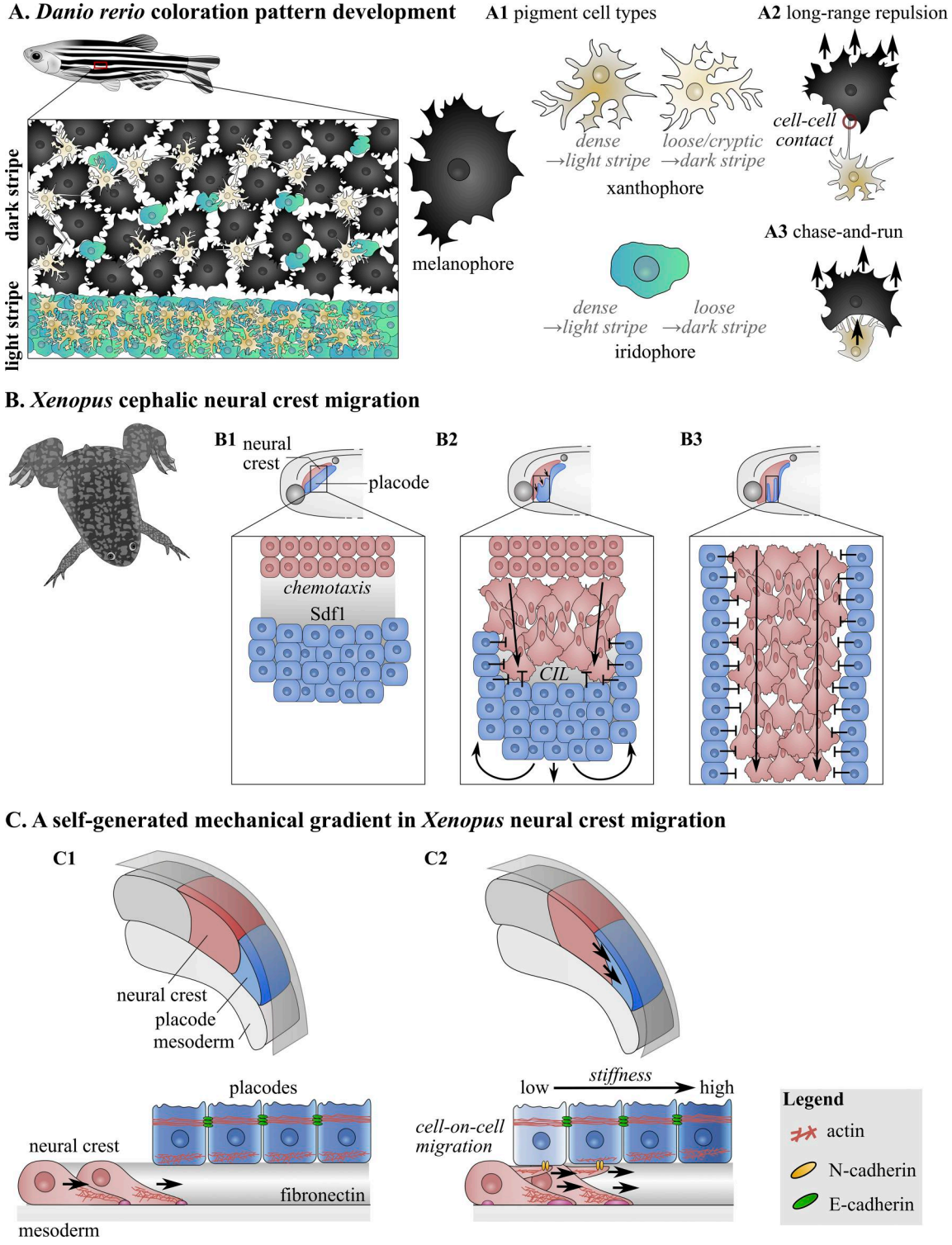

Figure 4. **Examples of mesenchymal pattering during development. (A)** During coloration pattern formation in *Danio rerio*, different pigment cell types self-organize into a characteristic striped pattern. **(A1)** Three main pigment cell types are involved: melanophores, xanthophores, and iridophores. These cells exhibit a variety of homotypic and heterotypic mesenchymal collective migration modes. **(A2)** For instance, long-range repulsion has been observed between xanthophores and melanophores, **(A3)** as well as chase-and-run interactions. These dynamic interactions are critical for maintaining boundaries—such as ensuring melanophores remain confined to the stripe regions and do not invade the interstripe zones. **(B)** *Xenopus* cephalic neural crest migration. **(B1)** Before migration, neural crest cells are located near placode cells, which produce the neural crest chemoattractant Sdf1. Very short-range chemotaxis drives the initial migration of neural crest cells toward the placodes. **(B2)** Upon reaching the placodes, mutual repulsion is established between the two cell populations, corresponding to CIL (red symbols). Despite this, placodes continue to produce Sdf1, attracting neural crest cells toward them. Meanwhile, placodes move away, resulting in a chase-and-run behavior that leads to the directional migration of placodes (straight arrows) followed by neural crest cells. As placodes migrate more slowly, they are overtaken by the neural crest, eventually being displaced to the sides of the neural crest stream (curved arrows). **(B3)** Final

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

outcome is a stream of neural crest cells flanked by placodes, which express repulsive signals toward the neural crest. **(C)** Self-generated mechanical gradients in neural crest cells. **(C1)** Placodes are positioned in front of the neural crest before the onset of migration. **(C2)** As the neural crest migrates toward the placodes, it engages in N-cadherin–mediated interactions that modify the cortical actin cytoskeleton of the placodes, softening them. Placodes in closer contact with the neural crest experience longer interactions and become softer than those farther away, creating a stiffness gradient. This gradient guides the directional cell-on-cell migration of neural crest cells through durotaxis.

are now recognized as crucial regulators of mesenchymal migration. For instance, semaphorins, ephrins, and Slit/Robo play essential roles in neural crest CIL (Szabó and Mayor, 2018); plexins and semaphorins are involved in follicle cell and testis myotube migration in *Drosophila* (Bischoff et al., 2025a; Stedden et al., 2019); and Slit/Robo guides myotube elongation during muscle development (Johnson, 2024; Schnorrer and Dickson, 2004). Interestingly, neuronal cells can also undergo migration with net translocation, exhibiting mesenchymal self-patterning dynamics. Work from the Norden laboratory has recently found that during retinal growth, photoreceptors must migrate both apically and basally. These two directions of movement are governed by distinctly different cytoskeletal architectures: apical migration depends on actin dynamics, while basal migration relies on microtubule-based mechanisms (Rocha-Martins et al., 2023).

Long-range cell–cell contact

Cytonemes—long and thin cellular protrusions interconnecting cells—were originally described in *Drosophila* imaginal disks and mouse limb buds (Ramírez-Weber and Kornberg, 1999). In principle, these structures also enable migrating cells to maintain cell–cell interfaces over long distances. This allows long-range interactions independent of diffusible gradients (Fig. 2 A and Fig. 3 A). Cytoneme-like structures have, for example, been identified in cancer cells, guiding them to osteoblasts (Muscarella et al., 2020). In development, cells might use numerous cytonemes to probe their environment, responding selectively to specific cell types with tailored reactions or causing reactions in specific other cells (Fig. 3 A). Fittingly, specialized cytoneme-like structures with membrane vesicles at the front, named airinemes, have been observed protruding from fish xanthophores (Eom et al., 2015). Such airinemes have been shown to be important for melanophore/xanthophore crosstalk via Delta/Notch (Eom, 2020; Eom et al., 2015). Intriguingly, they do not find their way to melanocytes by themselves but get dragged by migratory macrophages (Eom and Parichy, 2017). Cytoneme-like structures linking the same two cell types have also been shown to cause the aforementioned pigment cell-repulsion process (Inaba et al., 2012). Independent of migration, the importance of cytonemes in development, often replacing morphogenetic gradients, is increasingly evident. New work by the Stern Group on chick embryos revealed that cytonemes can transmit BMP signals over long distances, bypassing intermediate cells to create a kind of the developmental "nervous system" (Lee et al., 2024). In developing mouse neural tubes, sonic hedgehog is delivered to target cells via cytonemes, as well (Hall et al., 2024). Similarly, the Scholpp Group elucidated Wnt signaling mediated by cytonemes (Brunt et al., 2021; Stanganello and Scholpp, 2016; Zhang et al., 2024)—a finding that might have implications for Wnt/PCP in the light of mesenchymal self-patterning. These results demonstrate that in the context of cell–cell interactions, "neighbors" are not necessarily defined by physical proximity, which may be a crucial factor in directed mesenchymal self-patterning.

Active material: Mesenchymal collectives as organ sculptors

Mesenchymal cells, such as smooth muscle cells, surround many organs (Jaslove and Nelson, 2018). Significant research over the years has taught us how epithelial tissues bend and reshape to give organs their characteristic shapes (Moon and Xiong, 2022). Convergent extension based on cell intercalation is the best-understood example of cell redistribution–based morphogenesis (Perez-Vale and Peifer, 2020). However, mesenchymal cells—which can perform many more forms of highly stereotyped directed redistributions—are often overlooked as active participants of organogenesis. There is a growing body of evidence—such as work from Celeste Nelson's, Zev Gartner's, Sebastian Streichan laboratories, and others—indicating that mesenchymal cells actively sculpt organs. For instance, pulmonary smooth muscle cells play a role in shaping vertebrate lungs (Goodwin et al., 2023; Goodwin et al., 2019), airway muscles shape the airways (Paramore et al., 2024a), while visceral musculature contributes to the formation of gut villi (villification) (Hughes et al., 2018; Huycke et al., 2024; Shyer et al., 2013) and gut looping in *Drosophila* (Aghajanian et al., 2016; Mitchell et al., 2022) (Fig. 5 A).

Mesenchymal layers can influence organogenesis through general tissue properties such as elasticity. Seminal work in the chick gut showed that the formation of villi depends on the elastic properties of the muscle layers and the endoderm, which together lead to endodermal buckling (Shyer et al., 2013) (Fig. 5 A1). However, a recent study by the Gartner laboratory demonstrated that mesenchymal self-patterning also contributes to gut villification in mammals (Hughes et al., 2018; Huycke et al., 2024) (Fig. 5 A1). They found that within the mesenchymal layer, located between the endoderm and muscle layers, cohesive aggregates form that, in turn, cause the epithelium to buckle. These aggregates arise through a process called *dewetting*, reminiscent of fluid droplets forming on a hydrophobic surface (Fig. 5 A1). A crucial step in their formation is fluidization of mesenchymal cells, mediated by matrix metalloprotease activity. This work illustrates that fluid cells with random single-cell motility can nonetheless self-organize into complex structures—providing an example of mesenchymal self-patterning in the absence of contact-directed motility.

Recent work from the Nelson group revealed that mesenchymal motility of lung mesenchyme mediated by the Wnt/PCP component Vangl1/2 plays a crucial role in lung sculpting (Fig. 5

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

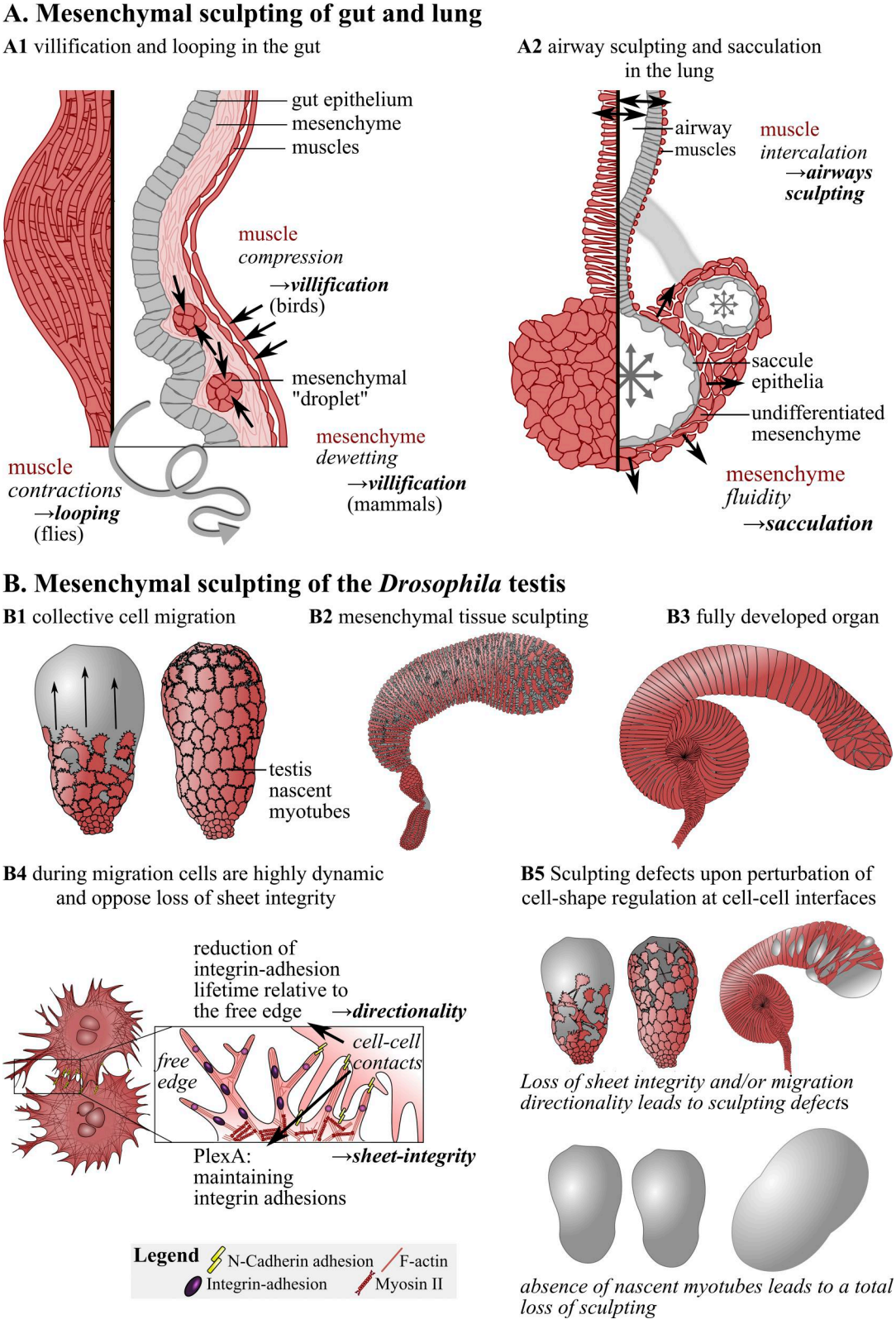

Figure 5. **Mesenchymal sculpting is a major driver of organogenesis. (A)** Mesenchymal sculpting in gut and lung. **(A1)** In the developing gut, tissue shape emerges through coordinated interactions between the muscle and epithelium. In birds, muscle compression, combined with the elasticity of the epithelium, is essential for vilification (the formation of villi). In mice, active mesenchymal migration and dewetting behavior drive the formation of droplet-like mesenchymal aggregates. In *Drosophila*, muscle contractions steer gut looping by inducing epithelial shape changes in the underlying endoderm. **(A2)** In the lung, airway smooth muscle cells undergo intercalation to sculpt the branching airways. In the distal lung, the undifferentiated mesenchyme surrounding the developing saccules must remain fluid-like, providing the compressibility required for proper sacculation. **(B)** Mesenchymal sculpting of the *Drosophila* testis. **(B1)** Unlike

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

other internal organs, the *Drosophila* testis is initially free of muscles. TNMs migrate collectively from the genital disk onto the testis surface beneath a layer of motile and squamous pigment cells (not depicted for simplicity). **(B2 and B3)** As the testis grows and loops into a spiral, TNMs undergo mesenchymal intercalation, reshaping the tissue. **(B4)** During migration, TNMs extend protrusions in all directions, but protrusions at cell–cell contacts exhibit reduced matrix adhesion, promoting expansion toward free edges. Simultaneously, PlexA maintains some matrix adhesion at contacts, enabling cells to spread dynamically during migration—an essential feature for sheet integrity. **(B5)** Disruption of migration or sheet integrity during migration impairs testis morphogenesis: the muscle layer fails to sculpt the organ, resulting in characteristic defects. In the complete absence of TNMs, the testis fails to coil and instead remains an ellipsoid.

A2). Vangl acts downstream of Wnt5 to induce a more motile and protrusive architecture in mesenchymal cells surrounding lung epithelia, leading to cell elongation and increased tissue fluidization. This transition enables proper epithelial sacculation (Paramore et al., 2024b). These findings not only reinforce the idea that mesenchymal motility and dynamic cell behaviors are key regulators of morphogenesis, but also highlight the recurring involvement of PCP components in cell-elongation processes—even within mesenchymal contexts (Devitt et al., 2024; Huebner and Wallingford, 2018; Wallingford et al., 2000). Remarkably, this holds true even in a 3D environment lacking clear apicobasal or dorsoventral polarity. This is more evidence that permutations of Wnt/PCP signaling appear to be a recurring feature of contact-based mesenchymal motility (Carmona-Fontaine et al., 2008; Wallingford et al., 2000). Paramore and colleagues (2024b) note that it remains unclear whether the observed motility is random or directionally guided, which opens an important avenue for further exploration with regard to directed mesenchymal self-patterning.

Mesenchymal cells can also directly drive morphogenesis without relying on epithelial intermediates. Recent studies in the *Drosophila* testis highlight how flat mesenchymal cells can elongate and even bend organs (Bischoff et al., 2021; Bischoff et al., 2025a; Bischoff et al., 2025b). The *Drosophila* testis is covered and shaped by migrating mesenchymal muscle precursor cells, known as TNMs, that move toward the testis tip (Fig. 5 A1) (Kozopas et al., 1998; Kuckwa et al., 2016; Rothenbusch-Fender et al., 2017; Susic-Jung et al., 2012). Testes lack a surrounding epithelium (Stern, 1941). TNMs must evenly fill the finite surface of the testis while migrating beneath a layer of large squamous and motile pigment cells (Bischoff et al., 2021; Kozopas et al., 1998). Unlike neural crest cells, TNMs must remain continuously connected, probably to compress the underlying ellipsoid testis (Bischoff and Bogdan, 2021). This demonstrates that supporting organ shape and migration can occur at the same time. When migration works, and the sheet retains integrity, the testis forms an intricate spiral structure (Bischoff et al., 2021; Bischoff et al., 2025b; Rothenbusch-Fender et al., 2017). We suspect this occurs by a subsequent step of mesenchymal intercalation (Bischoff and Bogdan, 2023), in which muscle precursors probably act as a hydrostatic skeleton "directing" germ cell expansion (Fig. 5, A2 and A3, compare with Fig. 5 A5). Migratory directionality is achieved by downregulating matrix adhesions at cell–cell interface protrusions, enabling a free edge–based migration (Bischoff et al., 2021) (Fig. 5 A4). To maintain sheet integrity, PlexA ensures that cellular interfaces remain protrusive and dynamically linked to the ECM (Fig. 5 A4). Disruptions in this delicate fine-tuning—such as those caused by PlexA knockdown—lead to more epithelial-looking cell–cell interfaces and taller cells, with strongly reduced integrin adhesions, resulting in gaps that compromise collective migration and sculpting (Bischoff et al., 2025a). Retaining ECM-tethered filopodia close to cell–cell contacts in wild type might also be important for the sculpting role TNMs take—parallel to migration. This demonstrates how the fine-tuning of local cell architecture directly influences morphogenesis.

Interestingly, the protrusive activity at cell–cell edges observed in TNMs (characterized by bilateral protrusions rather than unilateral cryptic lamellipodia) bears some similarities to interdigitating polarized filopodia (cadherin fingers) and lamellipodia near junctions in migrating endothelia, needed for directionality and tissue integrity (Cao et al., 2017; Hayer et al., 2016). Protrusive forces can stabilize junctions, as shown by Li and colleagues in MDCK cells, where filopodia-like microspikes at cell–cell adhesions counteract contractile forces—preventing them from tearing E-cadherin junctions (Li et al., 2020). After PlexA knockdown, the near-absence of ECM-tethered filopodia at cell–cell interfaces causes cells to elongate and adopt highly irregular shapes, suggesting that protrusion at "all edges" is required for spread. Future work will show whether local activation of protrusive activity is an ancestral function of plexins, for example, in wound closure or extrusion—which involves plexin activity (Yoo et al., 2016).

Conclusion

The findings and perspectives presented here underscore the intricate interplay between local cell shape and emergent cell behaviors. A conceptual map of subcellular architectures such as protrusions, adhesions, and contractile units scales up to a landscape of collective behaviors through interactions between cells. A key requirement for this mechanism to function is a spatially restricted cytoskeletal response to cell–cell contact. It is therefore not surprising that components of the Wnt/PCP pathway and various axon guidance factors emerge as recurring themes. Emergent collective behaviors can encode the blueprints for complex patterns. This capacity of self-organization of mesenchymal cells can also be used to drive morphogenesis. What the cell and developmental biology communities need—moving forward—are new model systems and innovative computational cell migration–based modeling approaches to uncover the organizational principles and molecular underpinnings of mesenchymal collective migration, self-patterning, and morphogenesis.

Acknowledgments

We are grateful to Uwe Irion and Alexandria Volkening for their valuable input on the manuscript, and to Christiane Nüsslein-

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

Volhard for extensive discussions with Maik C. Bischoff that initially inspired its conception. We thank Mark Peifer and Roland Wedlich-Söldner for their critical reading of the manuscript and the Peifer laboratory for their ongoing feedback throughout its development. We also sincerely thank the reviewers for their great suggestions, which significantly improved the manuscript, and for coining the term *"morphodynamic building block"* that perfectly captures the concept we aimed to articulate.

Maik C. Bischoff is supported by Mark Peifer's NIH grant (NIH R35 GM118096). Work in the laboratory of Roberto Mayor is supported by grants from the Medical Research Council (MR/S007792/1), Biotechnology and Biological Sciences Research Council (M008517; BB/T013044), and Wellcome Trust (102489/Z/13/Z).

Author contributions: Maik C. Bischoff: conceptualization, investigation, project administration, visualization, and writing—original draft, review, and editing. Roberto Mayor: funding acquisition and writing—review and editing.

Disclosures: The authors declare no competing interests exist.

Submitted: 30 May 2025
Revised: 9 August 2025
Accepted: 3 September 2025

References

Abercrombie, M., and J.E. Heaysman. 1953. Observations on the social behaviour of cells in tissue culture. I. Speed of movement of chick heart fibroblasts in relation to their mutual contacts. *Exp. Cell Res.* 5:111–131. https://doi.org/10.1016/0014-4827(53)90098-6

Abercrombie, M., J.E. Heaysman, and S.M. Pegrum. 1970a. The locomotion of fibroblasts in culture. *Exp. Cell Res.* 62:389–398. https://doi.org/10.1016/0014-4827(70)90570-7

Abercrombie, M., J.E. Heaysman, and S.M. Pegrum. 1970b. The locomotion of fibroblasts in culture. III. Movements of particles on the dorsal surface of the leading lamella. *Exp. Cell Res.* 62:389–398. https://doi.org/10.1016/0014-4827(70)90570-7

Abercrombie, M., J.E. Heaysman, and S.M. Pegrum. 1970c. The locomotion of fibroblasts in culture. II. "RRuffling". *Exp. Cell Res.* 60:437–444. https://doi.org/10.1016/0014-4827(70)90537-9

Abercrombie, M., J.E. Heaysman, and S.M. Pegrum. 1971. The locomotion of fibroblasts in culture. IV. Electron microscopy of the leading lamella. *Exp. Cell Res.* 67:359–367. https://doi.org/10.1016/0014-4827(71)90420-4

Aghajanian, P., S. Takashima, M. Paul, A. Younossi-Hartenstein, and V. Hartenstein. 2016. Metamorphosis of the Drosophila visceral musculature and its role in intestinal morphogenesis and stem cell formation. *Dev. Biol.* 420:43–59. https://doi.org/10.1016/j.ydbio.2016.10.011

Angelini, T.E., E. Hannezo, X. Trepat, M. Marquez, J.J. Fredberg, and D.A. Weitz. 2011. Glass-like dynamics of collective cell migration. *Proc. Natl. Acad. Sci. USA.* 108:4714–4719. https://doi.org/10.1073/pnas.1010059108

Balaghi, N., G. Erdemci-Tandogan, C. McFaul, and R. Fernandez-Gonzalez. 2023. Myosin waves and a mechanical asymmetry guide the oscillatory migration of Drosophila cardiac progenitors. *Dev. Cell.* 58:1299–1313.e5. https://doi.org/10.1016/j.devcel.2023.05.005

Barlan, K., M. Cetera, and S. Horne-Badovinac. 2017. Fat2 and lar define a basally localized planar signaling system controlling collective cell migration. *Dev. Cell.* 40:467–477.e5. https://doi.org/10.1016/j.devcel.2017.02.003

Barriga, E.H., K. Franze, G. Charras, and R. Mayor. 2018. Tissue stiffening coordinates morphogenesis by triggering collective cell migration in vivo. *Nature.* 554:523–527. https://doi.org/10.1038/nature25742

Bischoff, M.C., and S. Bogdan. 2021. Collective cell migration driven by filopodia-New insights from the social behavior of myotubes. *Bioessays.* 43:e2100124. https://doi.org/10.1002/bies.202100124

Bischoff, M.C., and S. Bogdan. 2023. Dissecting collective cell behavior in migrating testis myotubes in Drosophila. *In* Cell Migration in Three Dimensions. Vol. 2608. First edition. C. Margadant, editor. Springer US, New York. 117–129.

Bischoff, M.C., S. Lieb, R. Renkawitz-Pohl, and S. Bogdan. 2021. Filopodia-based contact stimulation of cell migration drives tissue morphogenesis. *Nat. Commun.* 12:791. https://doi.org/10.1038/s41467-020-20362-2

Bischoff, M.C., J.E. Norton, S.E. Clark, and M. Peifer. 2025a. Plexin/Semaphorin antagonism orchestrates collective cell migration and organ sculpting by regulating epithelial-mesenchymal balance. *Sci. Adv.* 11: eadu3741. https://doi.org/10.1126/sciadv.adu3741

Bischoff, M.C., J.E. Norton, E.A. Munguia, S.E. Clark, N.J. Gurley, R. Korankye, E.A. Gyabaah, T. Encarnacion, C.J. Serody, and C.D. Jones. 2025b. A large reverse-genetic screen identifies numerous regulators of testis nascent myotube collective cell migration and collective organ sculpting. *Mol. Biol. Cell.* 36:ar21. https://doi.org/10.1091/mbc.E24-10-0456

Bodor, D.L., W. Pönisch, R.G. Endres, and E.K. Paluch. 2020. Of cell shapes and motion: The physical basis of animal cell migration. *Dev. Cell.* 52: 550–562. https://doi.org/10.1016/j.devcel.2020.02.013

Brugués, A., E. Anon, V. Conte, J.H. Veldhuis, M. Gupta, J. Colombelli, J.J. Muñoz, G.W. Brodland, B. Ladoux, and X. Trepat. 2014. Forces driving epithelial wound healing. *Nat. Phys.* 10:683–690. https://doi.org/10.1038/nphys3040

Brunt, L., G. Greicius, S. Rogers, B.D. Evans, D.M. Virshup, K.C.A. Wedgwood, and S. Scholpp. 2021. Vangl2 promotes the formation of long cytonemes to enable distant Wnt/β-catenin signaling. *Nat. Commun.* 12:2058. https://doi.org/10.1038/s41467-021-22393-9

Butler, L.C., G.B. Blanchard, A.J. Kabla, N.J. Lawrence, D.P. Welchman, L. Mahadevan, R.J. Adams, and B. Sanson. 2009. Cell shape changes indicate a role for extrinsic tensile forces in Drosophila germ-band extension. *Nat. Cell Biol.* 11:859–864. https://doi.org/10.1038/ncb1894

Butler, M.T., and J.B. Wallingford. 2017. Planar cell polarity in development and disease. *Nat. Rev. Mol. Cell Biol.* 18:375–388. https://doi.org/10.1038/nrm.2017.11

Campàs, O., I. Noordstra, and A.S. Yap. 2024. Adherens junctions as molecular regulators of emergent tissue mechanics. *Nat. Rev. Mol. Cell Biol.* 25: 252–269. https://doi.org/10.1038/s41580-023-00688-7

Campbell, K., and J. Casanova. 2016. A common framework for EMT and collective cell migration. *Development.* 143:4291–4300. https://doi.org/10.1242/dev.139071

Cao, J., M. Ehling, S. März, J. Seebach, K. Tarbashevich, T. Sixta, M.E. Pitulescu, A.-C. Werner, B. Flach, E. Montanez, et al. 2017. Polarized actin and VE-cadherin dynamics regulate junctional remodelling and cell migration during sprouting angiogenesis. *Nat. Commun.* 8:2210. https://doi.org/10.1038/s41467-017-02373-8

Carmona-Fontaine, C., H.K. Matthews, S. Kuriyama, M. Moreno, G.A. Dunn, M. Parsons, C.D. Stern, and R. Mayor. 2008. Contact inhibition of locomotion in vivo controls neural crest directional migration. *Nature.* 456:957–961. https://doi.org/10.1038/nature07441

Cetera, M., and S. Horne-Badovinac. 2015. Round and round gets you somewhere: Collective cell migration and planar polarity in elongating Drosophila egg chambers. *Curr. Opin. Genet. Dev.* 32:10–15. https://doi.org/10.1016/j.gde.2015.01.003

Chastney, M.R., J. Kaivola, V.-M. Leppänen, and J. Ivaska. 2025. The role and regulation of integrins in cell migration and invasion. *Nat. Rev. Mol. Cell Biol.* 26:147–167. https://doi.org/10.1038/s41580-024-00777-1

Chen, T., A. Callan-Jones, E. Fedorov, A. Ravasio, A. Brugués, H.T. Ong, Y. Toyama, B.C. Low, X. Trepat, T. Shemesh, et al. 2019. Large-scale curvature sensing by directional actin flow drives cellular migration mode switching. *Nat. Phys.* 15:393–402. https://doi.org/10.1038/s41567-018-0383-6

Collins, C., A.K. Denisin, B.L. Pruitt, and W.J. Nelson. Changes in E-cadherin rigidity sensing regulate cell adhesion. 2017. *Proc. Natl. Acad. Sci. USA.* 114:E5835–E5844. https://doi.org/10.1073/pnas.1618676114

Dai, W., X. Guo, Y. Cao, J.A. Mondo, J.P. Campanale, B.J. Montell, H. Burrous, S. Streichan, N. Gov, W.J. Rappel, and D.J. Montell. 2020. Tissue topography steers migrating Drosophila border cells. *Science.* 370: 987–990. https://doi.org/10.1126/science.aaz4741

Davidson, E.H. 1990. How embryos work: A comparative view of diverse modes of cell fate specification. *Development.* 108:365–389. https://doi.org/10.1242/dev.108.3.365

Dehli, J., C. Karlsson, C. Bizelli-Silveira, X. Jiang, D. Kraft, and M. Foss. 2019. E-cadherin mediated cell-biomaterial interaction reduces migration of keratinocytes in-vitro. *Colloids Surf. B Biointerfaces.* 180:326–333. https://doi.org/10.1016/j.colsurfb.2019.04.010

Devenport, D. 2016. Tissue morphodynamics: Translating planar polarity cues into polarized cell behaviors. *Semin. Cell Dev. Biol.* 55:99–110. https://doi.org/10.1016/j.semcdb.2016.03.012

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

Devitt, C.C., S. Weng, V.D. Bejar-Padilla, J. Alvarado, and J.B. Wallingford. 2024. PCP and Septins govern the polarized organization of the actin cytoskeleton during convergent extension. *Curr. Biol.* 34:615–622.e4. https://doi.org/10.1016/j.cub.2023.12.025

Donà, E., J.D. Barry, G. Valentin, C. Quirin, A. Khmelinskii, A. Kunze, S. Durdu, L.R. Newton, A. Fernandez-Minan, W. Huber, et al. 2013. Directional tissue migration through a self-generated chemokine gradient. *Nature*. 503:285–289. https://doi.org/10.1038/nature12635

Duclos, G., C. Erlenkämper, J.-F. Joanny, and P. Silberzan. 2017. Topological defects in confined populations of spindle-shaped cells. *Nat. Phys.* 13: 58–62. https://doi.org/10.1038/nphys3876

Eom, D.S. 2020. Airinemes: Thin cellular protrusions mediate long-distance signalling guided by macrophages. *Open Biol.* 10:200039. https://doi.org/10.1098/rsob.200039

Eom, D.S., E.J. Bain, L.B. Patterson, M.E. Grout, and D.M. Parichy. 2015. Long-distance communication by specialized cellular projections during pigment pattern development and evolution. *Elife*. 4:e12401. https://doi.org/10.7554/eLife.12401

Eom, D.S., and D.M. Parichy. 2017. A macrophage relay for long-distance signaling during postembryonic tissue remodeling. *Science*. 355:1317–1320. https://doi.org/10.1126/science.aal2745

Fadeev, A., J. Krauss, H.G. Frohnhöfer, U. Irion, and C. Nüsslein-Volhard. 2015. Tight junction protein 1a regulates pigment cell organisation during zebrafish colour patterning. *Elife*. 4:e06545. https://doi.org/10.7554/eLife.06545

Fernandez-Gonzalez, R., and J.A. Zallen. 2011. Oscillatory behaviors and hierarchical assembly of contractile structures in intercalating cells. *Phys. Biol.* 8:045005. https://doi.org/10.1088/1478-3975/8/4/045005

Friedl, P., and D. Gilmour. 2009. Collective cell migration in morphogenesis, regeneration and cancer. *Nat. Rev. Mol. Cell Biol.* 10:445–457. https://doi.org/10.1038/nrm2720

Fritz-Laylin, L.K., and M.A. Titus. 2023. The evolution and diversity of actin-dependent cell migration. *Mol. Biol. Cell*. 34:pe6. https://doi.org/10.1091/mbc.E22-08-0358

Frohnhöfer, H.G., J. Krauss, H.-M. Maischein, and C. Nüsslein-Volhard. 2013. Iridophores and their interactions with other chromatophores are required for stripe formation in zebrafish. *Development*. 140:2997–3007. https://doi.org/10.1242/dev.096719

Fujimori, T., A. Nakajima, N. Shimada, and S. Sawai. 2019. Tissue self-organization based on collective cell migration by contact activation of locomotion and chemotaxis. *Proc. Natl. Acad. Sci. USA*. 116:4291–4296. https://doi.org/10.1073/pnas.1815063116

Garner, R.M., S.E. McGeary, A.M. Klein, and S.G. Megason. 2025. Tissue fluidity: A double-edged sword for multicellular patterning. *bioRxiv*. https://doi.org/10.1101/2025.03.01.640992 (Preprint posted March 05, 2025).

Ghose, D., T. Elston, and D. Lew. 2022. Orientation of cell polarity by chemical gradients. *Annu. Rev. Biophys.* 51:431–451. https://doi.org/10.1146/annurev-biophys-110821-071250

Goodwin, K., B. Lemma, P. Zhang, A. Boukind, and C.M. Nelson. 2023. Plasticity in airway smooth muscle differentiation during mouse lung development. *Dev. Cell*. 58:338–347.e4. https://doi.org/10.1016/j.devcel.2023.02.002

Goodwin, K., S. Mao, T. Guyomar, E. Miller, D.C. Radisky, A. Košmrlj, and C.M. Nelson. 2019. Smooth muscle differentiation shapes domain branches during mouse lung development. *Development*. 146:dev181172. https://doi.org/10.1242/dev.181172

Gupta, S., and A.S. Yap. 2021. How adherens junctions move cells during collective migration. *Fac. Rev.* 10:56. https://doi.org/10.12703/r/10-56

Gur, D., E.J. Bain, K.R. Johnson, A.J. Aman, H.A. Pasolli, J.D. Flynn, M.C. Allen, D.D. Deheyn, J.C. Lee, J. Lippincott-Schwartz, and D.M. Parichy. 2020. In situ differentiation of iridophore crystallotypes underlies zebrafish stripe patterning. *Nat. Commun.* 11:6391. https://doi.org/10.1038/s41467-020-20088-1

Hall, E.T., M.E. Dillard, E.R. Cleverdon, Y. Zhang, C.A. Daly, S.S. Ansari, R. Wakefield, D.P. Stewart, S.M. Pruett-Miller, A. Lavado, et al. 2024. Cytoneme signaling provides essential contributions to mammalian tissue patterning. *Cell*. 187:276–293.e23. https://doi.org/10.1016/j.cell.2023.12.003

Hannezo, E., and C.-P. Heisenberg. 2022. Rigidity transitions in development and disease. *Trends Cell Biol.* 32:433–444. https://doi.org/10.1016/j.tcb.2021.12.006

Hayer, A., L. Shao, M. Chung, L.M. Joubert, H.W. Yang, F.C. Tsai, A. Bisaria, E. Betzig, and T. Meyer. 2016. Engulfed cadherin fingers are polarized junctional structures between collectively migrating endothelial cells. *Nat. Cell Biol.* 18:1311–1323. https://doi.org/10.1038/ncb3438

Huebner, R.J., and J.B. Wallingford. 2018. Coming to consensus: A unifying model emerges for convergent extension. *Dev. Cell*. 46:389–396. https://doi.org/10.1016/j.devcel.2018.08.003

Hughes, A.J., H. Miyazaki, M.C. Coyle, J. Zhang, M.T. Laurie, D. Chu, Z. Vavrušová, R.A. Schneider, O.D. Klein, and Z.J. Gartner. 2018. Engineered tissue folding by mechanical compaction of the mesenchyme. *Dev. Cell*. 44:165–178.e6. https://doi.org/10.1016/j.devcel.2017.12.004

Huycke, T.R., T.J. Häkkinen, H. Miyazaki, V. Srivastava, E. Barruet, C.S. McGinnis, A. Kalantari, J. Cornwall-Scoones, D. Vaka, Q. Zhu, et al. 2024. Patterning and folding of intestinal villi by active mesenchymal dewetting. *Cell*. 187:3072–3089.e20. https://doi.org/10.1016/j.cell.2024.04.039

Inaba, M., H. Yamanaka, and S. Kondo. 2012. Pigment pattern formation by contact-dependent depolarization. *Science*. 335:677. https://doi.org/10.1126/science.1212821

Irion, U., H.G. Frohnhöfer, J. Krauss, T. Çolak Champollion, H.-M. Maischein, S. Geiger-Rudolph, C. Weiler, and C. Nüsslein-Volhard. 2014. Gap junctions composed of connexins 41.8 and 39.4 are essential for colour pattern formation in zebrafish. *Elife*. 3:e05125. https://doi.org/10.7554/eLife.05125

Irion, U., and C. Nüsslein-Volhard. 2019. The identification of genes involved in the evolution of color patterns in fish. *Curr. Opin. Genet. Dev.* 57:31–38. https://doi.org/10.1016/j.gde.2019.07.002

Jaslove, J.M., and C.M. Nelson. 2018. Smooth muscle: A stiff sculptor of epithelial shapes. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 373:20170318. https://doi.org/10.1098/rstb.2017.0318

Johnson, A.N. 2024. Myotube guidance: Shaping up the musculoskeletal system. *J. Dev. Biol.* 12:25. https://doi.org/10.3390/jdb12030025

Jürgens, G., E. Wieschaus, C. Nüsslein-Volhard, and H. Kluding. 1984. Mutations affecting the pattern of the larval cuticle inDrosophila melanogaster. *Wilhelm Roux's Arch. Dev. Biol.* 193:283–295. https://doi.org/10.1007/bf00848157

Kage, F., M. Winterhoff, V. Dimchev, J. Mueller, T. Thalheim, A. Freise, S. Brühmann, J. Kollasser, J. Block, G. Dimchev, et al. 2017. FMNL formins boost lamellipodial force generation. *Nat. Commun.* 8:14832. https://doi.org/10.1038/ncomms14832

Keller, R., J. Shih, and C. Domingo. 1992. The patterning and functioning of protrusive activity during convergence and extension of the Xenopus organiser. *Dev. Suppl.* 116:81–91.

Keller, R., and A. Sutherland. 2020. Convergent extension in the amphibian, Xenopus laevis. *Curr. Top. Dev. Biol.* 136:271–317. https://doi.org/10.1016/bs.ctdb.2019.11.013

Kiehart, D.P., J.M. Crawford, A. Aristotelous, S. Venakides, and G.S. Edwards. 2017. Cell sheet morphogenesis: Dorsal closure in Drosophila melanogaster as a model system. *Annu. Rev. Cell Dev. Biol.* 33:169–202. https://doi.org/10.1146/annurev-cellbio-111315-125357

Kozopas, K.M., C.H. Samos, and R. Nusse. 1998. DWnt-2, a Drosophila Wnt gene required for the development of the male reproductive tract, specifies a sexually dimorphic cell fate. *Genes Dev.* 12:1155–1165. https://doi.org/10.1101/gad.12.8.1155

Kuckwa, J., K. Fritzen, D. Buttgereit, S. Rothenbusch-Fender, and R. Renkawitz-Pohl. 2016. A new level of plasticity: Drosophila smooth-like testes muscles compensate failure of myoblast fusion. *Development*. 143: 329–338. https://doi.org/10.1242/dev.126730

Lämmermann, T., and M. Sixt. 2009. Mechanical modes of "amoeboid" cell migration. *Curr. Opin. Cell Biol.* 21:636–644. https://doi.org/10.1016/j.ceb.2009.05.003

Lawson, C.D., and A.J. Ridley. 2018. Rho GTPase signaling complexes in cell migration and invasion. *J. Cell Biol.* 217:447–457. https://doi.org/10.1083/jcb.201612069

Le, A.P., J.F. Rupprecht, R.-M. Mège, Y. Toyama, C.T. Lim, and B. Ladoux. 2021. Adhesion-mediated heterogeneous actin organization governs apoptotic cell extrusion. *Nat. Commun.* 12:397. https://doi.org/10.1038/s41467-020-20563-9

Le, H.A., and R. Mayor. 2025. Neighboring cells as living substrates for guiding collective cell migration during development. *Cold Spring Harb Perspect. Biol.*:a041741. https://doi.org/10.1101/cshperspect.a041741

Lee, H.C., N.M.M. Oliveira, C. Hastings, P. Baillie-Benson, A.A. Moverley, H.C. Lu, Y. Zheng, E.L. Wilby, T.T. Weil, K.M. Page, et al. 2024. Regulation of long-range BMP gradients and embryonic polarity by propagation of local calcium-firing activity. *Nat. Commun.* 15:1463. https://doi.org/10.1038/s41467-024-45772-4

Lenne, P.F., and V. Trivedi. 2022. Sculpting tissues by phase transitions. *Nat. Commun.* 13:664. https://doi.org/10.1038/s41467-022-28151-9

Li, J., J. Di Russo, X. Hua, Z. Chu, J.P. Spatz, and Q. Wei. 2019. Surface immobilized E-cadherin mimetic peptide regulates the adhesion and

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

clustering of epithelial cells. *Adv. Healthc. Mater.* 8:1801384. https://doi.org/10.1002/adhm.201801384
Li, J.X.H., V.W. Tang, and W.M. Brieher. 2020. Actin protrusions push at apical junctions to maintain E-cadherin adhesion. *Proc. Natl. Acad. Sci. USA*. 117:432–438. https://doi.org/10.1073/pnas.1908654117
Llense, F., and S. Etienne-Manneville. 2015. Front-to-rear polarity in migrating cells. *Cell Polarity 1: Biol. Role Basic Mech.*:115–146. https://doi.org/10.1007/978-3-319-14463-4_5
Madsen, C.D., S. Hooper, M. Tozluoglu, A. Bruckbauer, G. Fletcher, J.T. Erler, P.A. Bates, B. Thompson, and E. Sahai. 2015. STRIPAK components determine mode of cancer cell migration and metastasis. *Nat. Cell Biol.* 17:68–80. https://doi.org/10.1038/ncb3083
Mahalwar, P., B. Walderich, A.P. Singh, and C. Nüsslein-Volhard. 2014. Local reorganization of xanthophores fine-tunes and colors the striped pattern of zebrafish. *Science*. 345:1362–1364. https://doi.org/10.1126/science.1254837
Mayor, R., and C. Carmona-Fontaine. 2010. Keeping in touch with contact inhibition of locomotion. *Trends Cell Biol.* 20:319–328. https://doi.org/10.1016/j.tcb.2010.03.005
Mayor, R., and S. Etienne-Manneville. 2016. The front and rear of collective cell migration. *Nat. Rev. Mol. Cell Biol.* 17:97–109. https://doi.org/10.1038/nrm.2015.14
Menin, L., J. Weber, S. Villa, E. Martini, E. Maspero, C.A. Niño, V. Cancila, A. Poli, P. Maiuri, A. Palamidessi, et al. 2023. A planar polarized MYO6-DOCK7-RAC1 axis promotes tissue fluidification in mammary epithelia. *Cell Rep.* 42:113001. https://doi.org/10.1016/j.celrep.2023.113001
Merino-Casallo, F., M.J. Gomez-Benito, S. Hervas-Raluy, and J.M. Garcia-Aznar. 2022. Unravelling cell migration: Defining movement from the cell surface. *Cell Adh. Migr.* 16:25–64. https://doi.org/10.1080/19336918.2022.2055520
Miskolci, V., L.C. Klemm, and A. Huttenlocher. 2021. Cell migration guided by cell-cell contacts in innate immunity. *Trends Cell Biol.* 31:86–94. https://doi.org/10.1016/j.tcb.2020.11.002
Mitchell, N.P., D.J. Cislo, S. Shankar, Y. Lin, B.I. Shraiman, and S.J. Streichan. 2022. Visceral organ morphogenesis via calcium-patterned muscle constrictions. *Elife*. 11:e77355. https://doi.org/10.7554/eLife.77355
Montell, D.J. 2003. Border-cell migration: The race is on. *Nat. Rev. Mol. Cell Biol.* 4:13–24. https://doi.org/10.1038/nrm1006
Moon, L.D., and F. Xiong. 2022. Mechanics of neural tube morphogenesis. *Semin. Cell Dev. Biol.* 130:56–69. https://doi.org/10.1016/j.semcdb.2021.09.009
Moscona, A., and H. Moscona. 1952. The dissociation and aggregation of cells from organ rudiments of the early chick embryo. *J. Anat.* 86:287–301.
Muscarella, A.M., W. Dai, P.G. Mitchell, W. Zhang, H. Wang, L. Jia, F. Stossi, M.A. Mancini, W. Chiu, and X.H.F. Zhang. 2020. Unique cellular protrusions mediate breast cancer cell migration by tethering to osteogenic cells. *npj Breast Cancer*. 6:42. https://doi.org/10.1038/s41523-020-00183-8
Nalbant, P., and L. Dehmelt. 2018. Exploratory cell dynamics: A sense of touch for cells? *Biol. Chem.* 399:809–819. https://doi.org/10.1515/hsz-2017-0341
Nanda, S., A. Calderon, A. Sachan, T.-T. Duong, J. Koch, X. Xin, D. Solouk-Stahlberg, Y.-W. Wu, P. Nalbant, and L. Dehmelt. 2023. Rho GTPase activity crosstalk mediated by Arhgef11 and Arhgef12 coordinates cell protrusion-retraction cycles. *Nat. Commun.* 14:8356. https://doi.org/10.1038/s41467-023-43875-y
Nguyen, T., and R.M. Mège. 2016. N-Cadherin and Fibroblast Growth Factor Receptors crosstalk in the control of developmental and cancer cell migrations. *Eur. J. Cell Biol.* 95:415–426. https://doi.org/10.1016/j.ejcb.2016.05.002
Nose, A., A. Nagafuchi, and M. Takeichi. 1988. Expressed recombinant cadherins mediate cell sorting in model systems. *Cell*. 54:993–1001. https://doi.org/10.1016/0092-8674(88)90114-6
Nüsslein-Volhard, C., E. Wieschaus, and H. Kluding. 1984. Mutations affecting the pattern of the larval cuticle in Drosophila melanogaster. *Wilhelm Roux's Arch. Dev. Biol.* 193:267–282. https://doi.org/10.1007/bf00848156
Ozawa, M., S. Hiver, T. Yamamoto, T. Shibata, S. Upadhyayula, Y. Mimori-Kiyosue, and M. Takeichi. 2020. Adherens junction regulates cryptic lamellipodia formation for epithelial cell migration. *J. Cell Biol.* 219:e202006196. https://doi.org/10.1083/jcb.202006196
Painter, K.J., J.M. Bloomfield, J.A. Sherratt, and A. Gerisch. 2015. A nonlocal model for contact attraction and repulsion in heterogeneous cell populations. *Bull. Math. Biol.* 77:1132–1165. https://doi.org/10.1007/s11538-015-0080-x
Paramore, S.V., K. Goodwin, E.W. Fowler, D. Devenport, and C.M. Nelson. 2024a. Mesenchymal Vangl1 and Vangl2 facilitate airway elongation and widening independently of the planar cell polarity complex. *Development*. 151:dev202692. https://doi.org/10.1242/dev.202692
Paramore, S.V., C. Trenado-Yuste, R. Sharan, C.M. Nelson, and D. Devenport. 2024b. Vangl-dependent mesenchymal thinning shapes the distal lung during murine sacculation. *Dev. Cell*. 59:1302–1316.e5. https://doi.org/10.1016/j.devcel.2024.03.010
Park, D., E. Wershof, S. Boeing, A. Labernadie, R.P. Jenkins, S. George, X. Trepat, P.A. Bates, and E. Sahai. 2020. Extracellular matrix anisotropy is determined by TFAP2C-dependent regulation of cell collisions. *Nat. Mater.* 19:227–238. https://doi.org/10.1038/s41563-019-0504-3
Peglion, F., and S. Etienne-Manneville. 2024. Cell polarity changes in cancer initiation and progression. *J. Cell Biol.* 223:e202308069. https://doi.org/10.1083/jcb.202308069
Peifer, M. 2024. 40 years since the Heidelberg genetic screen that revolutionized developmental and cell biology. *Development*. 151:dev204433. https://doi.org/10.1242/dev.204433
Perez-Vale, K.Z., and M. Peifer. 2020. Orchestrating morphogenesis: Building the body plan by cell shape changes and movements. *Development*. 147:dev191049. https://doi.org/10.1242/dev.191049
Ramírez-Weber, F.A., and T.B. Kornberg. 1999. Cytonemes: Cellular processes that project to the principal signaling center in Drosophila imaginal discs. *Cell*. 97:599–607. https://doi.org/10.1016/s0092-8674(00)80771-0
Ramírez Moreno, M., and N.A. Bulgakova. 2022. The cross-talk between EGFR and E-cadherin. *Front. Cell Dev. Biol.* 9:828673. https://doi.org/10.3389/fcell.2021.828673
Raper, J., and C. Mason. 2010. Cellular strategies of axonal pathfinding. *Cold Spring Harb. Perspect. Biol.* 2:a001933. https://doi.org/10.1101/cshperspect.a001933
Revenu, C., and D. Gilmour. 2009. Emt 2.0: Shaping epithelia through collective migration. *Curr. Opin. Genet. Dev.* 19:338–342. https://doi.org/10.1016/j.gde.2009.04.007
Ridley, A.J., M.A. Schwartz, K. Burridge, R.A. Firtel, M.H. Ginsberg, G. Borisy, J.T. Parsons, and A.R. Horwitz. 2003. Cell migration: Integrating signals from front to back. *Science*. 302:1704–1709. https://doi.org/10.1126/science.1092053
Roca-Cusachs, P., R. Sunyer, and X. Trepat. 2013. Mechanical guidance of cell migration: Lessons from chemotaxis. *Curr. Opin. Cell Biol.* 25:543–549. https://doi.org/10.1016/j.ceb.2013.04.010
Rocha-Martins, M., E. Nerli, J. Kretzschmar, M. Weigert, J. Icha, E.W. Myers, and C. Norden. 2023. Neuronal migration prevents spatial competition in retinal morphogenesis. *Nature*. 620:615–624. https://doi.org/10.1038/s41586-023-06392-y
Rothenbusch-Fender, S., K. Fritzen, M.C. Bischoff, D. Buttgereit, S.F. Oenel, and R. Renkawitz-Pohl. 2017. Myotube migration to cover and shape the testis of Drosophila depends on Heartless, Cadherin/Catenin, and myosin II. *Biol. Open*. 6:1876–1888. https://doi.org/10.1242/bio.025940
Sawyer, J.K., W. Choi, K.C. Jung, L. He, N.J. Harris, and M. Peifer. 2011. A contractile actomyosin network linked to adherens junctions by Canoe/afadin helps drive convergent extension. *Mol. Biol. Cell*. 22:2491–2508. https://doi.org/10.1091/mbc.E11-05-0411
Scarpa, E., and R. Mayor. 2016. Collective cell migration in development. *J. Cell Biol.* 212:143–155. https://doi.org/10.1083/jcb.201508047
Schnorrer, F., and B.J. Dickson. 2004. Muscle building mechanisms of myotube guidance and attachment site selection. *Dev. Cell*. 7:9–20. https://doi.org/10.1016/j.devcel.2004.06.010
SenGupta, S., C.A. Parent, and J.E. Bear. 2021. The principles of directed cell migration. *Nat. Rev. Mol. Cell Biol.* 22:529–547. https://doi.org/10.1038/s41580-021-00366-6
Shellard, A., and R. Mayor. 2019. Integrating chemical and mechanical signals in neural crest cell migration. *Curr. Opin. Genet. Dev.* 57:16–24. https://doi.org/10.1016/j.gde.2019.06.004
Shellard, A., and R. Mayor. 2021. Collective durotaxis along a self-generated stiffness gradient in vivo. *Nature*. 600:690–694. https://doi.org/10.1038/s41586-021-04210-x
Shih, J., and R. Keller. 1992. Cell motility driving mediolateral intercalation in explants of Xenopus laevis. *Development*. 116:901–914. https://doi.org/10.1242/dev.116.4.901
Shyer, A.E., T. Tallinen, N.L. Nerurkar, Z. Wei, E.S. Gil, D.L. Kaplan, C.J. Tabin, and L. Mahadevan. 2013. Villification: How the gut gets its villi. *Science*. 342:212–218. https://doi.org/10.1126/science.1238842
Stanganello, E., and S. Scholpp. 2016. Role of cytonemes in Wnt transport. *J. Cell Sci.* 129:665–672. https://doi.org/10.1242/jcs.182469
Stedden, C.G., W. Menegas, A.L. Zajac, A.M. Williams, S. Cheng, E. Özkan, and S. Horne-Badovinac. 2019. Planar-polarized semaphorin-5c and Plexin

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026

A promote the collective migration of epithelial cells in Drosophila. *Curr. Biol.* 29:908–920.e6. https://doi.org/10.1016/j.cub.2019.01.049
Stehbens, S.J., E. Scarpa, and M.D. White. 2024. Perspectives in collective cell migration – moving forward. *J. Cell Sci.* 137:jcs261549. https://doi.org/10.1242/jcs.261549
Stern, C. 1941. The growth of testes in Drosophila. I. The relation between vas deferens and testis within various species. *J. Exp. Zoolog.* 87:113–158. https://doi.org/10.1002/jez.1400870109
Stock, J., and A. Pauli. 2021. Self-organized cell migration across scales – from single cell movement to tissue formation. *Development*. 148:dev191767. https://doi.org/10.1242/dev.191767
Stramer, B., and R. Mayor. 2017. Mechanisms and in vivo functions of contact inhibition of locomotion. *Nat. Rev. Mol. Cell Biol.* 18:43–55. https://doi.org/10.1038/nrm.2016.118
Strutt, D. 2008. The planar polarity pathway. *Curr. Biol.* 18:R898–R902. https://doi.org/10.1016/j.cub.2008.07.055
Stuelten, C.H., C.A. Parent, and D.J. Montell. 2018. Cell motility in cancer invasion and metastasis: Insights from simple model organisms. *Nat. Rev. Cancer*. 18:296–312. https://doi.org/10.1038/nrc.2018.15
Suh, K., Y.K. Cho, I.B. Breinyn, and D.J. Cohen. 2024. E-cadherin biomaterials reprogram collective cell migration and cell cycling by forcing homeostatic conditions. *Cell Rep.* 43:113743. https://doi.org/10.1016/j.celrep.2024.113743
Susic-Jung, L., C. Hornbruch-Freitag, J. Kuckwa, K.H. Rexer, U. Lammel, and R. Renkawitz-Pohl. 2012. Multinucleated smooth muscles and mononucleated as well as multinucleated striated muscles develop during establishment of the male reproductive organs of Drosophila melanogaster. *Dev. Biol.* 370:86–97. https://doi.org/10.1016/j.ydbio.2012.07.022
Szabó, A., and R. Mayor. 2018. Mechanisms of neural crest migration. *Annu. Rev. Genet.* 52:43–63. https://doi.org/10.1146/annurev-genet-120417-031559
Szabó, A., E. Theveneau, M. Turan, and R. Mayor. 2019. Neural crest streaming as an emergent property of tissue interactions during morphogenesis. *PLOS Comput. Biol.* 15:e1007002. https://doi.org/10.1371/journal.pcbi.1007002
Takahashi, G., and S. Kondo. 2008. Melanophores in the stripes of adult zebrafish do not have the nature to gather, but disperse when they have the space to move. *Pigment Cell Melanoma Res.* 21:677–686. https://doi.org/10.1111/j.1755-148X.2008.00504.x
Taylor, H., J. Campbell, and C.D. Nobes. 2017. Ephs and ephrins. *Curr. Biol.* 27:R90–R95. https://doi.org/10.1016/j.cub.2017.01.003
Theveneau, E., and R. Mayor. 2011. Can mesenchymal cells undergo collective cell migration? The case of the neural crest. *Cell Adh. Migr.* 5:490–498, https://doi.org/10.4161/cam.5.6.18623
Theveneau, E., and R. Mayor. 2012a. Cadherins in collective cell migration of mesenchymal cells. *Curr. Opin. Cell Biol.* 24:677–684. https://doi.org/10.1016/j.ceb.2012.08.002
Theveneau, E., and R. Mayor. 2012b. Neural crest delamination and migration: From epithelium-to-mesenchyme transition to collective cell migration. *Dev. Biol.* 366:34–54. https://doi.org/10.1016/j.ydbio.2011.12.041
Theveneau, E., and R. Mayor. 2013. Collective cell migration of epithelial and mesenchymal Cells. *Cell Mol. Life Sci.* 70:3481–3492. https://doi.org/10.1007/s00018-012-1251-7
Theveneau, E., B. Steventon, E. Scarpa, S. Garcia, X. Trepat, A. Streit, and R. Mayor. 2013. Chase-and-run between adjacent cell populations promotes directional collective migration. *Nat. Cell Biol.* 15:763–772. https://doi.org/10.1038/ncb2772
Tsai, T.Y.-C., M. Sikora, P. Xia, T. Colak-Champollion, H. Knaut, C.-P. Heisenberg, and S.G. Megason. 2020. An adhesion code ensures robust pattern formation during tissue morphogenesis. *Science*. 370:113–116. https://doi.org/10.1126/science.aba6637
Uçar, M.C., Z. Alsberga, J. Alanko, M. Sixt, and E. Hannezo. 2024. Self-generated chemotaxis of mixed cell populations. *Proc. Natl. Acad. Sci. USA*. 122:e2504064122. https://doi.org/10.1073/pnas.2504064122
Ullo, M.F., and J.S. Logue. 2021. ADF and cofilin-1 collaborate to promote cortical actin flow and the leader bleb-based migration of confined cells. *Elife*. 10:e67856. https://doi.org/10.7554/eLife.67856
Vasilyev, A., Y. Liu, S. Mudumana, S. Mangos, P.-Y. Lam, A. Majumdar, J. Zhao, K.-L. Poon, I. Kondrychyn, V. Korzh, and I.A. Drummond. 2009. Collective cell migration drives morphogenesis of the kidney nephron. *PLoS Biol.* 7:e1000009. https://doi.org/10.1371/journal.pbio.1000009
Vishwakarma, M., J.P. Spatz, and T. Das. 2020. Mechanobiology of leader-follower dynamics in epithelial cell migration. *Curr. Opin. Cell Biol.* 66:97–103. https://doi.org/10.1016/j.ceb.2020.05.007
Volkening, A. 2020. Linking genotype, cell behavior, and phenotype: Multidisciplinary perspectives with a basis in zebrafish patterns. *Curr. Opin. Genet. Dev.* 63:78–85. https://doi.org/10.1016/j.gde.2020.05.010
Volkening, A., M.R. Abbott, N. Chandra, B. Dubois, F. Lim, D. Sexton, and B. Sandstede. 2020. Modeling stripe formation on growing zebrafish tailfins. *Bull. Math. Biol.* 82:56. https://doi.org/10.1007/s11538-020-00731-0
Volkening, A., and B. Sandstede. 2015. Modelling stripe formation in zebrafish: An agent-based approach. *J. R. Soc. Interf.* 12:20150812. https://doi.org/10.1098/rsif.2015.0812
Volkening, A., and B. Sandstede. 2018. Iridophores as a source of robustness in zebrafish stripes and variability in Danio patterns. *Nat. Commun.* 9:3231. https://doi.org/10.1038/s41467-018-05629-z
Walderich, B., A.P. Singh, P. Mahalwar, and C. Nüsslein-Volhard. 2016. Homotypic cell competition regulates proliferation and tiling of zebrafish pigment cells during colour pattern formation. *Nat. Commun.* 7:11462. https://doi.org/10.1038/ncomms11462
Wallingford, J.B., B.A. Rowning, K.M. Vogeli, U. Rothbächer, S.E. Fraser, and R.M. Harland. 2000. Dishevelled controls cell polarity during Xenopus gastrulation. *Nature*. 405:81–85. https://doi.org/10.1038/35011077
Wang, S., K. Matsumoto, S.R. Lish, A.X. Cartagena-Rivera, and K.M. Yamada. 2021. Budding epithelial morphogenesis driven by cell-matrix versus cell-cell adhesion. *Cell*. 184:3702–3716.e30. https://doi.org/10.1016/j.cell.2021.05.015
Wang, X., L. He, Y.I. Wu, K.M. Hahn, and D.J. Montell. 2010. Light-mediated activation reveals a key role for Rac in collective guidance of cell movement in vivo. *Nat. Cell Biol.* 12:591–597. https://doi.org/10.1038/ncb2061
Weijer, C.J. 2009. Collective cell migration in development. *J. Cell Sci.* 122:3215–3223. https://doi.org/10.1242/jcs.036517
Weninger, J., A. Prakash, S. Raman, R. Ladher, M. Rao, and K. Kruse. 2025. Force patterning drives cell flows and 3D spatial order in auditory epithelia. *bioRxiv*. https://doi.org/10.1101/2025.06.26.661757 (Preprint posted June 28, 2025).
Wieschaus, E., C. Nüsslein-Volhard, and G. Jürgens. 1984. Mutations affecting the pattern of the larval cuticle inDrosophila melanogaster. *Wilhelm Roux's Arch. Dev. Biol.* 193:296–307. https://doi.org/10.1007/bf00848158
Williams, A.M., S. Donoughe, E. Munro, and S. Horne-Badovinac. 2022. Fat2 polarizes the WAVE complex in trans to align cell protrusions for collective migration. *Elife*. 11:e78343. https://doi.org/10.7554/eLife.78343
Wong, M., and D. Gilmour. 2021. Going your own way: Self-guidance mechanisms in cell migration. *Curr. Opin. Cell Biol.* 72:116–123. https://doi.org/10.1016/j.ceb.2021.07.004
Worzfeld, T., and S. Offermanns. 2014. Semaphorins and plexins as therapeutic targets. *Nat. Rev. Drug Discov.* 13:603–621. https://doi.org/10.1038/nrd4337
Wu, C.-Y., M.-W. Lin, D.-C. Wu, Y.-B. Huang, H.-T. Huang, and C.-L. Chen. 2014. The role of phosphoinositide-regulated actin reorganization in chemotaxis and cell migration. *Br. J. Pharmacol.* 171:5541–5554. https://doi.org/10.1111/bph.12777
Yamada, K.M., and M. Sixt. 2019. Mechanisms of 3D cell migration. *Nat. Rev. Mol. Cell Biol.* 20:738–752. https://doi.org/10.1038/s41580-019-0172-9
Yamanaka, H., and S. Kondo. 2014. In vitro analysis suggests that difference in cell movement during direct interaction can generate various pigment patterns in vivo. *Proc. Natl. Acad. Sci. USA*. 111:1867–1872. https://doi.org/10.1073/pnas.1315416111
Yoo, S.K., H.G. Pascoe, T. Pereira, S. Kondo, A. Jacinto, X. Zhang, and I.K. Hariharan. 2016. Plexins function in epithelial repair in both Drosophila and zebrafish. *Nat. Commun.* 7:12282. https://doi.org/10.1038/ncomms12282
Yu, C., M. Mederacke, R. Vetter, and D. Iber. 2025. Directed cell migration is a versatile mechanism for rapid developmental pattern formation. *bioRxiv*. https://doi.org/10.1101/2025.07.24.666657 (Preprint posted July 29, 2025).
Zegers, M.M., and P. Friedl. 2014. Rho GTPases in collective cell migration.
Zhang, C., L. Brunt, Y. Ono, S. Rogers, and S. Scholpp. 2024. Cytoneme-mediated transport of active Wnt5b–Ror2 complexes in zebrafish. *Nature*. 625:126–133. https://doi.org/10.1038/s41586-023-06850-7

Downloaded from http://rupress.org/jcb/article-pdf/224/11/e202505198/1950542/jcb_202505198.pdf by guest on 09 August 2026