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SPOTLIGHT

Two ways to move together: Force coordination in collective chemotaxis

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Collective chemotaxis is often viewed through a mesenchymal lens, emphasizing peripheral polarity and force generation. In this issue, Diaz and Mayor (https://doi.org/10.1083/jcb.202507211) reveal that epithelial-like neural crest clusters achieve directed chemotaxis through a junction-centered strategy that redistributes polarity, contractility, and traction forces internally.

Many of the most complex tissue behaviors in development and disease depend on cells migrating not alone, but together. From embryonic development to wound repair, collective cell migration drives coordinated cell movements across diverse biological contexts, including cancer (1, 2, 3). This mode of migration involves cells moving as adhesive clusters, strands, or sheets, guided by mechanical cues and chemotactic signals. It is observed across numerous cell types, in which cells migrate in close association to maintain physical contact and coordinated movement. During collective migration, cells often preserve cell–cell junctions, establish supracellular polarity of the actin cytoskeleton to generate traction, and actively remodel the extracellular environment along their migratory path (4). Often, mesenchymal cells exhibit greater motility and flexibility in their organization, whereas epithelial cells migrate as more rigid, stable sheets. Although the structural organization of these collectives differs, their coordinated behavior enables efficient group movement that supports both tissue morphogenesis and cancer invasion.

The work by Diaz and Mayor addresses a key gap in our understanding of how epithelial organization influences collective chemotaxis (5). They compare stage-matched neural crest clusters with elevated E-cadherin expression (epithelial-like) to mesenchymal neural crest clusters to determine how cell–cell adhesion affects polarity, directional migration, and force transmission during chemotaxis. The cephalic neural crest is a well-established model for studying collective migration, in which cells normally undergo an epithelial-to-mesenchymal transition (EMT), a process involving the disruption of epithelial adhesion and the acquisition of mesenchymal characteristics (6). Using neural crest explants and live imaging, both epithelial-like and mesenchymal neural crest clusters responded to chemotactic cues; however, epithelial-like clusters remained cohesive and nondispersive and displayed more uniform, internally coordinated trajectories during chemotaxis. Moreover, epithelial-like clusters exhibited more persistent and coordinated internal cell movements than mesenchymal clusters, suggesting that E-cadherin–mediated cell–cell adhesion promotes internal coordination during collective chemotaxis.

Previous work has shown that mesenchymal neural crest cells form supracellular actomyosin cables at their periphery during migration (7, 8). This so-called "rear-wheel drive" organization promotes directed chemotaxis in mesenchymal neural crest clusters. Diaz and Mayor asked whether a similar supracellular organization operates in other collective contexts during chemotaxis toward SDF1, a chemokine that guides directional migration (9). To address this, they examined actomyosin organization in epithelial-like and mesenchymal clusters during SDF1-driven chemotaxis. Whereas mesenchymal clusters displayed peripheral actomyosin cables, epithelial-like clusters accumulated phosphorylated myosin light chain, a marker of actomyosin contractility, within cryptic protrusions near E-cadherin–mediated cell–cell junctions. These findings reveal distinct actomyosin architectures in epithelial and mesenchymal neural crest clusters (Fig. 1) and demonstrate that supracellular contractility is not the sole organization capable of supporting collective chemotaxis.

A key feature of collective migration is the formation of dynamic cellular protrusions, which can emerge at the periphery or within migrating cell groups. These protrusions are critical for environmental sensing and migratory activity and are typically concentrated at the leading edge of polarized mesenchymal neural crest cells. Actin-based protrusions are regulated by the small GTPase Rac1, which promotes actin polymerization (10). Diaz and Mayor examined how protrusions, polarity, and Rac1 activity differ between epithelial-like and mesenchymal neural crest clusters during SDF1-driven chemotaxis. Whereas mesenchymal clusters formed large, directed protrusions at the leading edge with less

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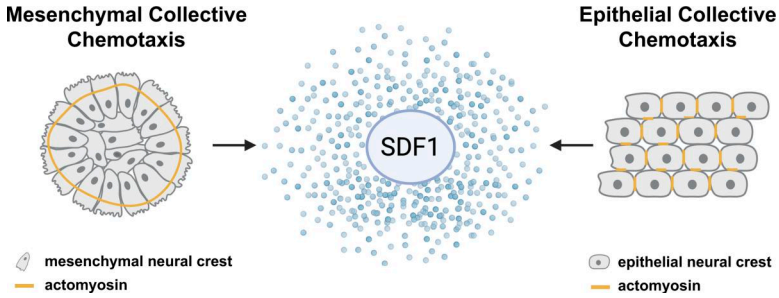

Figure 1. **Distinct force architectures drive epithelial and mesenchymal collective chemotaxis.** Mesenchymal and epithelial-like neural crest clusters achieve directed migration toward SDF1 through different organizational principles. Mesenchymal clusters rely on peripheral supracellular actomyosin cables to generate traction and polarized protrusions, whereas epithelial-like clusters redistribute traction forces toward E-cadherin–mediated cell–cell junctions, enabling coordinated, junction-centered force transmission. Yellow denotes actomyosin organization. Model adapted from Diaz and Mayor (Fig. 8) (5).

organized internal protrusions, epithelial-like clusters generated prominent, chemotactically aligned protrusions within the cluster interior. Consistent with this organization, Rac1 activity was detected at the periphery but also tended to accumulate internally in epithelial-like clusters, while remaining strongly enriched at the periphery in mesenchymal clusters. These findings indicate that epithelial-like clusters redistribute protrusive activity and polarity internally, potentially through E-cadherin–mediated cell–cell adhesion, to support directional collective migration.

In line with this redistribution of polarity and contractility, focal adhesions and traction forces were also reorganized between cluster types. Epithelial-like clusters enriched focal adhesions and traction forces near cell–cell junctions, whereas mesenchymal clusters generated strong traction forces at edge protrusions, consistent with peripheral force transmission. These results indicate that epithelial-like collectives transmit forces through junction-centered networks rather than edge-based protrusions, revealing a distinct mechanical strategy for collective chemotaxis.

Diaz and Mayor identify an alternative mode of collective chemotaxis operating in epithelial-like clusters. This mode is distinguished by differences in actomyosin organization, polarity, and traction force distribution compared with mesenchymal neural crest clusters. Despite maintaining tight cell–cell adhesion, epithelial-like neural crest cells undergo directed migration through coordinated internal cell movements, polarized internal protrusions, and stabilized actomyosin contractility associated with Rac1 activity within the cluster interior. In contrast, mesenchymal neural crest clusters rely on supracellular contractility, leading-edge polarization, and Rac1 activity concentrated in peripheral protrusions. Although key components of adhesion and contractility have been implicated previously in collective migration (6, 7), this work demonstrates that they can be organized into distinct mechanical strategies to support chemotaxis. More broadly, these findings highlight the plasticity of neural crest migration, revealing how cells adopt varying epithelial or mesenchymal characteristics as they move along embryonic streams. Such flexibility may extend to other developmental and disease contexts in which cell–cell junctions help shape migratory behavior before or during EMTs.

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