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DEVELOPMENT AT A GLANCE

Cell interactions in collective cell migration

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ABSTRACT

Collective cell migration is the coordinated movement of a physically connected group of cells and is a prominent driver of development and metastasis. Interactions between cells within migrating collectives, and between migrating cells and other cells in the environment, play key roles in stimulating motility, steering and sometimes promoting cell survival. Similarly, diverse heterotypic interactions and collective behaviors likely contribute to tumor metastasis. Here, we describe a sampling of cells that migrate collectively *in vivo*, including well-established and newer examples. We focus on the under-appreciated property that many – perhaps most – collectively migrating cells move as cooperating groups of distinct cell types.

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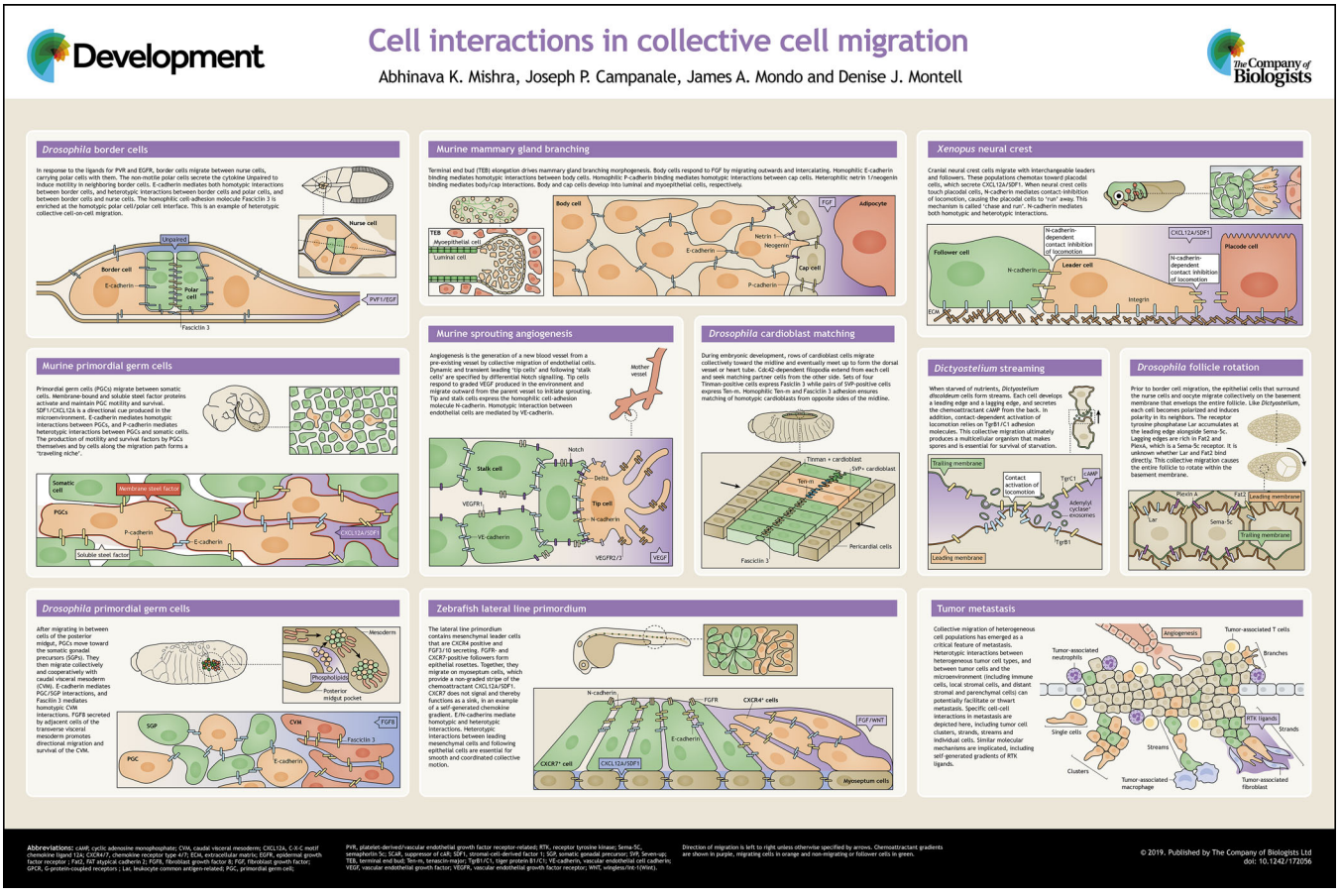
Introduction

The ability to move is a fundamental property of animal cells. Mechanistic studies of cell migration initially focused on single cells crawling on extracellular matrix-coated coverslips *in vitro*. Advances in live imaging have led to an appreciation that cells within developing embryos, forming organs and healing wounds, often migrate in groups and communicate as they move. As previously reviewed (Friedl and Mayor, 2017; Montell et al., 2012; Norden and Lecaudey, 2019; Scarpa and Mayor, 2016; Shellard and Mayor, 2019), such collectives vary in cell number, cohesiveness, epithelial versus mesenchymal characteristics and guidance mechanisms.

By definition, collectively migrating cells exhibit homotypic interactions (between the same types of cells), but a less-appreciated characteristic is engagement in important heterotypic interactions (between different cell types). These interactions are mediated by homophilic (binding of the same type of protein expressed on two



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different cells) or heterophilic (binding of different molecules such as a ligand/receptor) interactions. Some interactions occur within the migrating cohort while others involve cells in the micro-environment. Even cells that are not thought to move collectively, such as primordial germ cells (PGCs), require dynamic and regulated interactions with each other and with cells they encounter during migration.

Homotypic and heterotypic cell-cell interactions are prevalent in cancer. As cancer cells tend to hijack developmental processes, diverse heterotypic cell-cell interactions appear during metastasis. Although cancer research has historically focused on mechanisms autonomous to individual tumor cells, or between tumor cells and the extracellular matrix, the current focus is on understanding the full range of cell-cell interactions within tumors and between tumor cells and cell types encountered during metastasis. As with the study of cell proliferation, fate and survival, cross-fertilization between developmental biology and cancer biology should accelerate progress in both fields. Here, we present selected examples, focusing on the adhesion and signaling molecules that promote motility, direction sensing and, in some cases, survival.

Border cell migration

One of the earliest identified examples of heterotypic cell-cell interactions during collective cell migration is that of the *Drosophila* border cells, a group of four to six epithelial cells that delaminate and migrate in tight association with a pair of non-motile polar cells during ovarian development (Montell, 2003; Montell et al., 2012). Neither polar cells nor border cells can move without the other, a recurring theme in this article. Border cells require polar cells to secrete a cytokine that activates Jak/STAT signaling, which stimulates the motility of neighboring border cells (Silver and Montell, 2001). Polar cells never acquire the autonomous ability to move and need border cells to carry them.

Rather than migrating on extracellular matrix, border cells engage in a second heterotypic interaction as they squeeze in between nurse cells on their way to the oocyte. The nurse cells and oocyte secrete chemoattractants that bind to the receptor tyrosine kinases (RTKs) PVR and EGFR to stimulate migration speed and provide direction. A key downstream RTK effector is the small GTPase Rac, the role of which in cell migration *in vivo* was first identified in the border cells (Murphy and Montell, 1996).

The cell-cell adhesion molecule E-cadherin is crucial in border cells (Cai et al., 2014; Niewiadomska et al., 1999). Polar cells express the highest level of E-cadherin in the egg chamber, which is crucial to maintain cluster cohesion and collective migration (Cai et al., 2014). Adhesion between individual outer border cells via E-cadherin is essential for collective direction sensing. E-cadherin-mediated cell-cell adhesion between border cells mechanically couples them, enabling leader cells to direct follower cells. This has emerged as a common principle in the guidance of collective cell migration during development and in cancer (Khalil and de Rooij, 2019; Ladoux et al., 2016). Every outer border cell is competent to lead, although at any given moment only one cell is typically in that position. For coordinated collective movement, the lead border cell suppresses outward-directed protrusions in the followers, which is observed in a variety of collective migrations (Ladoux and Mège, 2017). E-cadherin also mediates the essential and dynamic interaction between border cells and nurse cells. Thus, border cells engage in homotypic cell-cell interactions as well as in heterotypic interactions with polar cells within the migrating group and with nurse cells in the microenvironment. The themes of interdependent, heterotypic cell subpopulations, cell-on-cell migration and the roles of classical cadherins, RTK and Rac signaling reappear in multiple examples of collective migration during development, as described below, as well as in tumor cell invasion and migration (Khalil and de Rooij, 2019; Labernadie et al., 2017; Richardson et al., 2018).

Primordial germ cell migration

Primordial germ cells (PGCs) are the precursors of sperm and egg cells. In most organisms, specification of PGCs occurs at sites distant from the eventual gonads, so PGCs must migrate significant distances through the embryo (Richardson and Lehmann, 2010). Although PGCs do not adhere tightly to one another as they move and so are not usually described as migrating collectively, evidence suggests that dynamic homotypic and heterotypic cell-cell interactions are essential.

The specification process and migratory routes of PGCs vary from one organism to another, yet share many conserved principles (Barton et al., 2016; DeFalco and Capel, 2009). In mice, PGCs are specified at the extreme posterior end of the epiblast, near extra-embryonic ectoderm. They then travel through the gut and dorsal mesentery to reach the incipient somatic gonads called genital ridges. In zebrafish, four clusters of PGCs develop in different locations in the embryo and take initially distinct routes, before converging on the gut and mesentery to travel to the gonads. Although PGCs migrate from the gut to the gonad in mouse, fish and fly (described below), in chick, PGCs cluster in the extra-embryonic region anterior to the head before entering and traveling within the bloodstream. They then extravasate and migrate in clusters and streams to the genital ridges (Hen et al., 2014). Therefore, avian PGC migration may represent an underappreciated model for intra- and extra-vasation, crucial steps in metastasis.

In several organisms, the molecular signals that promote motility of PGCs are required for their survival. In mouse, such factors include SDF1 (stromal cell-derived factor 1, also known as CXCL12) (Molyneaux et al., 2003) and steel factor (Gu et al., 2009). SDF1 binds and activates the GPCR (G-protein-coupled receptor) CXCR4, whereas steel factor binds and activates the RTK Kit. First discovered in zebrafish (Doitsidou et al., 2002), the chemokine SDF1 provides a directional cue for PGCs. CXCR4 transduces SDF1 guidance information, causing PGCs to form filopodia, then blebs, towards increasing SDF1 levels (Meyen et al., 2015). A second receptor, CXCR7, acts as a sink for SDF1, creating an optimal migratory path (Valentin et al., 2007). In mice too, SDF1 and CXCR4 probably direct migration (Molyneaux et al., 2003). In contrast, steel factor expression in both PGCs and adjacent somatic cells creates a 'traveling niche', supporting motility and survival rather than guidance (Gu et al., 2009). Steel factor is expressed in a pattern that allows the migrating cells continuous exposure to it throughout their migration, akin to Jak/STAT signaling between polar cells and border cells.

Depending on the organism and location along the migration path, PGCs can be found squeezing between other cells, migrating on or through matrix and/or engaging in homotypic cell-cell interactions. In mice, E-cadherin expression is downregulated prior to migration, to permit cell separation and movement into the hindgut. Subsequently, E-cadherin is re-expressed to promote homotypic PGC-PGC interactions throughout the rest of their migration (De Felici et al., 2005). Heterotypic interactions between PGCs and somatic cells along the path are enhanced by P-cadherin expression on both cell types. N-cadherin expression is limited to the post-migratory phase and mediates heterotypic interactions between germ cells and the somatic gonad. Kit and a membrane-bound isoform of steel factor are both expressed on the surfaces of mouse PGCs during migration and facilitate homotypic interactions (De Felici et al., 2005, Gu et al., 2009). Thus, homotypic and

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heterotypic cell-cell interactions are vital to PGC migration and survival.

In *Drosophila*, similar to mouse, PGCs develop at the extreme posterior end of the embryo, immediately outside of the embryo proper, and migrate through the developing gut to reach somatic gonadal precursors. Migration of fly PGCs through endoderm requires the GPCR Tre1 (Richardson and Lehmann, 2010). The lipid phosphate phosphatases Wunen and Wunen2 serve multiple functions: autonomous Wunen/Wunen2 expression within PGCs is required for uptake of an essential phospholipid and for PGC survival, while expression in somatic tissues serves as a sink, thereby sculpting a path that is rich in the chemoattractant/survival factor for the PGCs to follow. First discovered in flies, the importance of lipid signals to PGC migration is conserved in other organisms, including mice, and may prove to be general (Barton et al., 2016).

An intriguing heterotypic cell-cell interaction has been discovered in flies, after the PGCs cross the posterior midgut epithelium. Interactions between PGCs and collectively migrating muscle precursor cells referred to as caudal visceral mesoderm (CVM) are essential for both migrations (Broihier et al., 1998; Stepanik et al., 2016). As PGCs move from endoderm to mesoderm, they attract the CVM cells via an as-yet-unidentified cue. PGCs then require CVM for migration – another example of mutual dependence of several cell types (Broihier et al., 1998; Ismat et al., 2010). Once CVM cells migrate past the PGCs, however, the CVM cells follow FGF (fibroblast growth factor) secreted by the ectoderm (Bae et al., 2012; Reim et al., 2012).

As in mouse, fly PGCs adhere to one another via E-cadherin prior to migration, then downregulate E-cadherin to individualize and cross the gut epithelium. PGCs require E-cadherin to interact with the gut, and later with the somatic gonadal precursors. CVM expresses high levels of the homphilic cell-adhesion molecule fasciclin 3 (Fas3), but the adhesive molecules that regulate heterotypic interactions between CVM and PGCs – if any – are not known.

Mammary gland branching

In mammals, puberty stimulates mammary gland development (Shamir and Ewald, 2015). Immature mammary ducts contain a bilayer of inner luminal epithelial cells and outer myoepithelial cells (Friedl and Gilmour, 2009). During puberty, steroid hormone and RTK signaling stimulate ducts to elongate into the surrounding adipose tissue and undergo branching morphogenesis. At the tips of elongating branches, cells lose apicobasal polarity, proliferate and become motile, thereby converting a bilayered structure into a multilayered terminal end bud (TEB). Cells crawl over one another within the TEB, in another example of E-cadherin mediated cell-on-cell migration. Cells exchange positions dynamically, similar to border cells, without leader/follower distinctions. FGF signaling through its RTK receptor FGFR2 is essential for branch outgrowth. The most motile cells at branch tips, exhibit high levels of phosphorylated ERK1/2, which is sufficient for cell motility and branch elongation (Huebner et al., 2016).

Homotypic and heterotypic cell-cell interactions are important in breast cancer. During branching morphogenesis, the outer layer of cap cells confines the migratory population within TEBs, preventing their escape into the surrounding tissue. Netrin/neogenin interactions (expressed by the inner cells and cap cells, respectively) hold the TEB together; in their absence, the TEBs fall apart (Srinivasan et al., 2003). In addition, homophilic P-cadherin interactions between cap cells are essential; in P-cadherin knockout mice, luminal epithelial cells prematurely differentiate, and exhibit hyperplasia and dysplasia with age (Radice et al., 1997), suggesting that the myoepithelium inhibits luminal epithelial proliferation and promotes its organization. Therefore, in this tissue, cell-cell junctions, rather than the basement membrane, appear to be the most important line of defense.

The presence of tumor cells beyond the myoepithelial layer is the key histological hallmark of invasive cancer. Consistent with a barrier function of the myoepithelium, the myoepithelial layer can prevent cancer cells from disseminating (Sirka et al., 2018). In an organotypic culture model of luminal breast cancer, P-cadherin expression in the myoepithelium restrains invasive luminal cells. Myoepithelial cells can even ‘recapture’ escaping luminal cells. Thus, normal developmental processes probably limit breast cancer metastasis.

Sprouting angiogenesis

New blood vessels form from pre-existing vessels through spouting angiogenesis, which is crucial during development, wound healing, and tumor metastasis (Ausprunk and Folkman, 1977; Chung and Ferrara, 2011). *In vivo* and *in vitro* models for angiogenesis include the developing mouse retina, rabbit cornea, quail and chicken embryos, and intersegmental vessel growth in zebrafish (Betz et al., 2016; Ribatti and Crivellato, 2012). Sprouting angiogenesis occurs when endothelial cells acquire transient and reversible ‘tip’ and ‘stalk’ fates with distinct morphologies and functions (reviewed by Betz et al., 2016; Kolte et al., 2016; Ribatti and Crivellato, 2012; Siekmann et al., 2013). Tip cells are highly polarized, sprout multiple filopodia and migrate, whereas stalk cells line the lumen and proliferate (Gerhardt et al., 2003). Homotypic interactions between endothelial cells are mediated by vascular endothelial cadherin (VE-cadherin) (Dejana, 1996; Lampugnani et al., 1995).

Tip cells express high levels of vascular endothelial growth factor receptors 2 and 3 (VEGFR2, VEGFR3/Flt-4), platelet-derived growth factor B (PDGFB) and unc-5 homolog B (UNC5B), and low levels of VEGFR1 (Claxton and Fruttiger, 2004; Gerhardt et al., 2003; Jakobsson et al., 2010; Lu et al., 2004; Siekmann and Lawson, 2007; Suchting et al., 2007). Tip cells acquire their unique morphology and migratory behavior in response to VEGF acting on VEGFR-2/3 (De Smet et al., 2009; Gerhardt et al., 2003), which triggers high levels of delta-like ligand 4 (Dll4) expression. Dll4 stimulates Notch activity in stalk, thus spacing tip cells by lateral inhibition.

Stalk cells express JAG-1, which inhibits Notch in tip cells, and VEGFR-1, which binds but poorly activates VEGFRs and thereby blocks stalk cell sprouting (Benedito et al., 2009; Chappell et al., 2009). Endothelial cells dynamically compete for the tip cell position. Cells with higher VEGFR signaling increase Dll4 expression, which activates Notch in neighboring cells to inhibit tip cell fate. Higher Dll4 in tip cells further increases the sensitivity of cells to VEGF. Thus, a fine-tuned feedback between VEGF and Notch/Dll4 is established and ensures adequate spacing between sprouts (Holderfield and Hughes, 2008; Jakobsson et al., 2010). Non-canonical Wnt5A/Ror signaling stabilizes junctions between endothelial cells to keep migrating endothelial cells moving collectively in the same direction (Carvalho et al., 2019).

Further steps in vessel maturation include: bridging of filopodia from nearby tip cells to form a new vessel; transitioning of bridged tip cells from sprouting to quiescence, which includes increased cell-cell adhesion and low VEGF responsiveness; and vasculature stabilization (Ruhrberg et al., 2002; Bentley et al., 2009; Bautch, 2009; Mazzone et al., 2009). Meanwhile, stalk cells create a lumen and synthesize basement membrane. Pruning removes excess endothelial cells and redundant channels (Ashton, 1966).

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Semaphorin 3E and netrin-UNC5B signaling also guide developing vessels (Adams and Eichmann, 2010).

Drosophila cardioblast matching

A recent study describes collective cell migration during *Drosophila* cardiogenesis (Zhang et al., 2018). Cardioblasts develop in two symmetric rows ∼100 µm apart. During the process of dorsal closure, dorsal epidermal cells migrate toward one another and replace the extra-embryonic tissue (amnioserosa). Beneath the epidermis, cardioblasts migrate towards the midline, establishing one-to-one connections with their corresponding partners. Although the cardioblasts appear superficially to be a uniform population, molecular differences ensure proper matching of cells from different sides of the embryo. There is a '4/2/4/2/4' pattern, in which four cells express the homeobox gene *tinman* (*tin*) and higher levels of the adhesion molecule Fas3, while the next two cells express the orphan nuclear receptor gene *seven-up* (*svp*) and elevated Teneurin adhesion protein Ten-m. These distinct cell types form distinct functional structures: Svp-positive cells form the inflow tracts, whereas Tin-positive cells line the dorsal vessel and form cardiac valves.

As the rows of cardioblasts converge, heterotypic cells sort from one another and homotypic cells adhere preferentially to one another. When the rows are ∼15-20 µm apart, cardioblasts extend filopodia, which physically contact those from cells migrating from the other side. Contact areas of homotypic interactions enlarge, ensuring accurate cell matching. A similar filopodia-mediated matching mechanism occurs in the overlying epidermis during dorsal closure (Millard and Martin, 2008), although the adhesion receptors remain unknown.

Zebrafish lateral line primordium

The bilateral lateral line primordia (LLP) are cohesive cohorts of ∼140 cells that migrate from head to tail, near the surface – just under the skin of zebrafish embryos (Dalle Nogare and Chitnis, 2017; Friedl and Gilmour, 2009; Olson and Nechiporuk, 2018). About 12 mesenchymal cells lead the epithelial cohort. All cells move at approximately the same speed in a smooth coordinated fashion. As it travels, the rear of the LLP deposits a series of rosette-like mechanosensory structures (neuromasts). All LLP cells express E-cadherin and N-cadherin (Dalle Nogare et al., 2014). N-cadherin stabilizes apical junctions in followers (Revenu et al., 2014). Leading cells lack apical/basal polarity and exchange positions frequently, extending and retracting dynamic lamellipodia and filopodia.

The LLP interacts with cells in the environment. It migrates on the surface of horizontal myoseptum cells, expressing the chemokine SDF1a (or CXCL12). The chemokine receptor CXCR4B is expressed at higher levels in the leading zone, whereas trailing cells express CXCR7B (Dambly-Chaudière et al., 2007; Haas and Gilmour, 2006; Valentin et al., 2007). CXCR7B acts as a sink for SDF1, converting an initially ungraded distribution into a local gradient (Dalle Nogare et al., 2014). Thus, heterotypic interactions between leader and followers result in a self-generated chemokine gradient; such gradients also promote melanoma cell invasion (Muinonen-Martin et al., 2014).

Leading cells in the LLP secrete FGF3 and FGF10 to induce epithelial character in the followers. FGF signaling is essential for coordination of the collective movement (Lecaudey et al., 2008). In FGF3/10 double mutants, the lead cells migrate faster and followers slower, disrupting the coordinated behavior and slowing the LLP two-fold.

Neural crest

Neural crest cells (NCCs) are multipotent, migratory cell populations that arise in vertebrates during late gastrula/early neurula stages at the interface between neural and non-neural ectoderm. The neural crest (NC) gives rise to diverse derivatives, including neurons of the peripheral nervous system, smooth muscles, glia and melanocytes – to name a few (Shellard and Mayor, 2019; Simões-Costa and Bronner, 2015; Szabó and Mayor, 2018). Migration involves delamination via complete or partial epithelial-to-mesenchymal transition (EMT), depending on the organism and cranial versus caudal location (Theveneau and Mayor, 2012). NCCs show dynamic leader-follower behavior as they migrate in diverse streams. Early NCCs migrate ventrally alongside the neural tube, then split along a variety of paths, later contributing to organs including the sympathetic and parasympathetic nervous systems, heart valves and craniofacial structures. Late NCCs stay on a more dorsal path and spread throughout the epidermal ectoderm, eventually populating it with melanocytes (pigment cells).

In *Xenopus* cephalic NC, the pre-migratory population expresses E-cadherin like the adjacent epidermal ectoderm, whereas migratory NCCs switch to N-cadherin expression (Scarpa et al., 2015). In different organisms, distinct patterns of cadherin expression are observed (Gouignard et al., 2018). In *Xenopus*, the chemokine Sdf1 stabilizes Rac-dependent protrusions at the free edges of leader cells. N-cadherin suppresses protrusion and Rac activity at cell-cell contacts in follower cells by a process called contact inhibition of locomotion (CIL) (Theveneau et al., 2010). Regulated internalization of N-cadherin enables dynamic adhesion with the surrounding tissue while maintaining homotypic adhesions necessary for collective behavior (Kuriyama et al., 2014). Remarkably *Xenopus* NCCs can only chemotax collectively; when cells are dissociated, they fail to migrate up an Sdf1 gradient. For these cells then, homotypic cell-cell interactions are essential for directional migration (Theveneau et al., 2010).

In addition to homotypic interactions between NCCs, they form heterotypic interactions with adjacent placodal cells; NCCs express the receptor Cxcr4 and initially migrate towards Sdf-expressing placodal cells. Upon contact, a repulsive N-cadherin-dependent CIL response occurs. This 'chase and run' behavior coordinates movement of NCCs and placodal cells (Theveneau et al., 2013).

Dictyostelium streaming

When growing in a nutrient-rich vegetative state, the social amoebae *Dictyostelium discoideum* remain largely free living. However, in response to starvation they activate expression of cyclic AMP (cAMP) receptors. Although capable of chemotaxis as isolated individual cells toward a pipette of cAMP, they naturally tend to migrate towards one another, exhibiting a collective behavior called streaming that eventually forms aggregates of hundreds to millions of cells. Streaming is achieved by chemotaxis within self-organized cAMP gradients. Here, each cell is both a leader and a follower. The enzyme adenylyl cyclase (ACA), which converts ATP into cAMP, is distributed in two pools. One fraction is localized at the plasma membrane, and the other in multivesicular bodies enriched at the trailing edge. The ACA-containing MVBs are released as exosomes, creating a local source of cAMP from the back of each cell that serves as a chemoattractant for the following cell. The deposition of MVBs synthesizing cAMP, rather than direct release of cAMP itself probably creates a longer-lasting source. cAMP binds the cell-surface GPCR (cAMP receptor 1), leading to cell polarization, cytoskeletal rearrangement and migration (Das et al., 2017; Nichols

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et al., 2015). Intriguingly, an analogous mechanism is used during neutrophil chemotaxis (Majumdar et al., 2016).

Contrary to CIL described above, a recent study describes a 'contact activation of locomotion' phenomenon. Heterophilic binding between transmembrane proteins TgrB1 and TgrC1 recruits the SCAR complex, resulting in Arp2/3 activation and F-actin polymerization to promote protrusions at the leading edge of follower cells. This contact-dependent activity drives mobility in follower cells, even when the leader is immobilized by UV irradiation (Fujimori et al., 2019).

Once aggregated, cells differentiate into either prespore or prestalk cells, both competent to engage in cell contact-dependent protrusion and chemoattractant-guided migration. However, when challenged with both a chemoattractant and a contact signal, prestalk cells prioritize chemotaxis, whereas prespore cells favor contact-dependent collective migration (Fujimori et al., 2019).

Drosophila follicle rotation

Returning to *Drosophila*, the egg chamber exhibits a second collective cell movement that is distinct from border cell migration. Remarkably, the entire follicular epithelium migrates upon laminin- and collagen-rich basement membranes that surround the egg chamber. Like hamsters running on a wheel, these cells drive rotation of the follicle relative to the basement membrane, a phenomenon that is impossible to capture in fixed tissue. Recent work has shown that ∼850 cells coordinate their leading and trailing edges to move in the same direction. Similar to the contact-dependent locomotion in *Dictyostelium*, each follicle cell stimulates the cell directly behind it to protrude (Barlan et al., 2017; Stedden et al., 2019). The receptor tyrosine phosphatase Lar accumulates at the leading edge of each cell, alongside Sema-5c. PlexA (a Sema-5c receptor) and Fat2 (an atypical cadherin) are enriched at lagging cell edges. The precise mechanism that breaks symmetry in this system is under investigation.

Tumor metastasis

Tumor metastasis remains an intractable cause of cancer deaths and is extensively reviewed elsewhere (Lambert et al., 2017; Massagué and Obenauf, 2016; Peinado et al., 2017; Turajlic and Swanton, 2016; Welch and Hurst, 2019). Efforts to identify genes that promote or suppress tumor metastasis have had limited success and therapeutic benefits remain elusive. The most significant improvement in treatment of metastatic disease is the development of immune checkpoint inhibitors, highlighting the importance of heterotypic cell-cell interactions between T cells and tumor cells in metastasis. Still, most tumors do not respond to current treatments, and those that do inevitably evolve resistance. Therefore, new strategies to prevent and combat metastasis are needed. Although historically cancer research has focused on cell autonomous properties of tumor cells (Nieto et al., 2016; Vogelstein et al., 2013), it is clear that homotypic and heterotypic cell-cell interactions are important regulators of disease progression (Steeg, 2016). T-cell migration into tumors might be a key limiting factor for immunotherapy (Melero et al., 2014). Interactions between tumor cells and tumor-associated macrophages and fibroblasts, endothelia of blood and lymphatic vessels, and resident cells of the stroma and parenchyma of distant colonization sites are all likely to participate in disease evolution (Lambert et al., 2017; Motz and Coukos, 2013). Single-cell sequencing has revealed extensive intratumor heterogeneity, indicating that heterotypic cell-cell interactions occur between divergent tumor cells. One example is the emergence of leader (or 'trailblazer') and follower cells in lung and breast cancers (Haney et al., 2018; Westcott et al., 2015). Several studies suggest that tumor cell groups are more effective at metastasis than individual cells (Aceto et al., 2014; Cheung et al., 2016; Elisha et al., 2018; Padmanaban et al., 2019), and some metastases are seeded by polyclonal cell groups. An under-appreciated principle is that, in advanced disease, only surviving cells are detected, not necessarily the cells that facilitated movement and survival beforehand. Metastasis prevention requires a deeper understanding of key cell-cell interactions at every step.

Metastasis proceeds, like developmental cell migrations, by a series of cell-cell interactions mediated by adhesion molecules, RTKs, GPCRs and cytokine receptors, activated by ligands supplied by the microenvironments through which the cells move and/or by 'traveling niches' (Massagué and Obenauf, 2016; Stuellton et al., 2017). Although the details remain to be elucidated rough analogies exist between the types of homotypic and heterotypic cell-cell interactions that have been well characterized during development and those that are, or are likely to, facilitate or thwart tumor metastasis. As cancer hijacks developmental mechanisms, continued interactions between these two fields will provide important insights.

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Competing interests

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References

Aceto, N., Bardia, A., Miyamoto, D. T., Donaldson, M. C., Wittner, B. S., Spencer, J. A., Yu, M., Pely, A., Engstrom, A., Zhu, H. et al. (2014). Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. *Cell* **158**, 1110-1122. doi:10.1016/j.cell.2014.07.013

Adams, R. H. and Eichmann, A. (2010). Axon guidance molecules in vascular patterning. *Cold Spring Harb. Perspect. Biol.* **2**, a001875. doi:10.1101/cshperspect.a001875

Ashton, N. (1966). Oxygen and the growth and development of retinal vessels. In vivo and in vitro studies. The XX Francis I. Proctor Lecture. *Am. J. Ophthalmol.* **62**, 412-435. doi:10.1016/0002-9394(66)91322-5

Ausprunk, D. H. and Folkman, J. (1977). Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis. *Microvasc. Res.* **14**, 53-65. doi:10.1016/0026-2862(77)90141-8

Bae, Y.-K., Trisnadi, N., Kadam, S. and Stathopoulos, A. (2012). The role of FGF signaling in guiding coordinate movement of cell groups: guidance cue and cell adhesion regulator? *Cell Adh. Migr.* **6**, 397-403. doi:10.4161/cam.21103

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

Barton, L. J., LeBlanc, M. G. and Lehmann, R. (2016). Finding their way: themes in germ cell migration. *Curr. Opin. Cell Biol.* **42**, 128-137. doi:10.1016/j.ceb.2016.07.007

Bautch, V. L. (2009). Endothelial cells form a phalanx to block tumor metastasis. *Cell* **136**, 810-812. doi:10.1016/j.cell.2009.02.021

Benedito, R., Roca, C., Sörensen, I., Adams, S., Gossler, A., Fruttiger, M. and Adams, R. H. (2009). The notch ligands Dll4 and Jagged1 have opposing effects on angiogenesis. *Cell* **137**, 1124-1135. doi:10.1016/j.cell.2009.03.025

Bentley, K., Mariggi, G., Gerhardt, H. and Bates, P. A. (2009). Tipping the balance: robustness of tip cell selection, migration and fusion in angiogenesis. *PLoS Comput. Biol.* **5**, e1000549. doi:10.1371/journal.pcbi.1000549

Betz, C., Lenard, A., Belting, H.-G. and Affolter, M. (2016). Cell behaviors and dynamics during angiogenesis. *Development* **143**, 2249-2260. doi:10.1242/dev.135616

Broihier, H. T., Moore, L. A., Van Doren, M., Newman, S. and Lehmann, R. (1998). zfh-1 is required for germ cell migration and gonadal mesoderm development in Drosophila. *Development* **125**, 655-666.

Cai, D., Chen, S.-C., Prasad, M., He, L., Wang, X., Choesmel-Cadamuro, V., Sawyer, J. K., Danuser, G. and Montell, D. J. (2014). Mechanical feedback through E-cadherin promotes direction sensing during collective cell migration. *Cell* **157**, 1146-1159. doi:10.1016/j.cell.2014.03.045

Carvalho, J. R., Fortunato, I. C., Fonseca, C. G., Pezzarossa, A., Barbacena, P., Dominguez-Cejudo, M. A., Vasconcelos, F. F., Santos, N. C., Carvalho, F. A. and Franco, C. A. (2019). Non-canonical Wnt signaling regulates junctional mechanocoupling during angiogenic collective cell migration. *eLife* **8**, e45853. doi:10.7554/eLife.45853

Chappell, J. C., Taylor, S. M., Ferrara, N. and Bautch, V. L. (2009). Local guidance of emerging vessel sprouts requires soluble Flt-1. *Dev. Cell* **17**, 377-386. doi:10.1016/j.devcel.2009.07.011

Cheung, K. J., Padmanaban, V., Silvestri, V., Schipper, K., Cohen, J. D., Fairchild, A. N., Gorin, M. A., Verdone, J. E., Pienta, K. J., Bader, J. S. et al. (2016). Polyclonal breast cancer metastases arise from collective dissemination of keratin 14-expressing tumor cell clusters. *Proc. Natl. Acad. Sci. USA* **113**, E854-E863. doi:10.1073/pnas.1508541113

Chung, A. S. and Ferrara, N. (2011). Developmental and pathological angiogenesis. *Annu. Rev. Cell Dev. Biol.* **27**, 563-584. doi:10.1146/annurev-cellbio-092910-154002

Claxton, S. and Fruttiger, M. (2004). Periodic Delta-like 4 expression in developing retinal arteries. *Gene Expr. Patterns* **5**, 123-127. doi:10.1016/j.modgep.2004.05.004

Dalle Nogare, D. and Chitnis, A. B. (2017). A framework for understanding morphogenesis and migration of the zebrafish posterior Lateral Line primordium. *Mech. Dev.* **148**, 69-78. doi:10.1016/j.mod.2017.04.005

Dalle Nogare, D., Somers, K., Rao, S., Matsuda, M., Reichman-Fried, M., Raz, E. and Chitnis, A. B. (2014). Leading and trailing cells cooperate in collective migration of the zebrafish posterior lateral line primordium. *Development* **141**, 3188-3196. doi:10.1242/dev.106690

Dambly-Chaudière, C., Cubedo, N. and Ghysen, A. (2007). Control of cell migration in the development of the posterior lateral line: antagonistic interactions between the chemokine receptors CXCR4 and CXCR7/RDC1. *BMC Dev. Biol.* **7**, 23. doi:10.1186/1471-213X-7-23

Das, S., Parker, J. M., Guven, C., Wang, W., Kriebel, P. W., Losert, W., Larson, D. R. and Parent, C. A. (2017). Adenylyl cyclase mRNA localizes to the posterior of polarized DICTYOSTELIUM cells during chemotaxis. *BMC Cell Biol.* **18**, 23. doi:10.1186/s12860-017-0139-7

De Felici, M., Scaldaferri, M. L. and Farini, D. (2005). Adhesion molecules for mouse primordial germ cells. *Front. Biosci.* **10**, 542-551. doi:10.2741/1550

De Smet, F., Segura, I., De Bock, K., Hohensinner, P. J. and Carmeliet, P. (2009). Mechanisms of vessel branching: filopodia on endothelial tip cells lead the way. *Arterioscler. Thromb. Vasc. Biol.* **29**, 639-649. doi:10.1161/ATVBAHA.109.185165

DeFalco, T. and Capel, B. (2009). Gonad morphogenesis in vertebrates: divergent means to a convergent end. *Annu. Rev. Cell Dev. Biol.* **25**, 457-482. doi:10.1146/annurev.cellbio.042308.13350

Dejana, E. (1996). Endothelial adherens junctions: implications in the control of vascular permeability and angiogenesis. *J. Clin. Invest.* **98**, 1949-1953. doi:10.1172/JCI118997

Doitsidou, M., Reichman-Fried, M., Stebler, J., Köprunner, M., Dörries, J., Meyer, D., Esguerra, C. V., Leung, T. C. and Raz, E. (2002). Guidance of primordial germ cell migration by the chemokine SDF-1. *Cell* **111**, 647-659. doi:10.1016/S0092-8674(02)01135-2

Elisha, Y., Kalchenko, V., Kuznetsov, Y. and Geiger, B. (2018). Dual role of E-cadherin in the regulation of invasive collective migration of mammary carcinoma cells. *Sci. Rep.* **8**, 4986. doi:10.1038/s41598-018-22940-3

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

Friedl, P. and Mayor, R. (2017). Tuning collective cell migration by cell–cell junction regulation. *Cold Spring Harb. Perspect. Biol.* **9**, a029199. doi:10.1101/cshperspect.a029199

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

Gerhardt, H., Golding, M., Fruttiger, M., Ruhrberg, C., Lundkvist, A., Abramsson, A., Jeltsch, M., Mitchell, C., Alitalo, K., Shima, D. et al. (2003). VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J. Cell Biol.* **161**, 1163-1177. doi:10.1083/jcb.200302047

Gouignard, N., Andrieu, C. and Theveneau, E. (2018). Neural crest delamination and migration: Looking forward to the next 150 years. *Genesis* **56**, e23107. doi:10.1002/dvg.23107

Gu, Y., Runyan, C., Shoemaker, A., Surani, A. and Wylie, C. (2009). Steel factor controls primordial germ cell survival and motility from the time of their specification in the allantois, and provides a continuous niche throughout their migration. *Development* **136**, 1295-1303. doi:10.1242/dev.030619

Haas, P. and Gilmour, D. (2006). Chemokine signaling mediates self-organizing tissue migration in the zebrafish lateral line. *Dev. Cell* **10**, 673-680. doi:10.1016/j.devcel.2006.02.019

Haney, S., Konen, J., Marcus, A. I. and Bazhenov, M. (2018). The complex ecosystem in non small cell lung cancer invasion. *PLoS Comput. Biol.* **14**, e1006131. doi:10.1371/journal.pcbi.1006131

Hen, G., Friedman-Einat, M. and Sela-Donenfeld, D. (2014). Primordial germ cells in the dorsal mesentery of the chicken embryo demonstrate left-right asymmetry and polarized distribution of the EMA1 epitope. *J. Anat.* **224**, 556-563. doi:10.1111/joa.12163

Holderfield, M. T. and Hughes, C. C. W. (2008). Crosstalk between vascular endothelial growth factor, notch, and transforming growth factor-beta in vascular morphogenesis. *Circ. Res.* **102**, 637-652. doi:10.1161/CIRCRESAHA.107.167171

Huebner, R. J., Neumann, N. M. and Ewald, A. J. (2016). Mammary epithelial tubes elongate through MAPK-dependent coordination of cell migration. *Development* **143**, 983-993. doi:10.1242/dev.127944

Ismat, A., Schaub, C., Reim, I., Kirchner, K., Schultheis, D. and Frasch, M. (2010). HLH54F is required for the specification and migration of longitudinal gut muscle founders from the caudal mesoderm of Drosophila. *Development* **137**, 3107-3117. doi:10.1242/dev.046573

Jakobsson, L., Franco, C. A., Bentley, K., Collins, R. T., Ponsioen, B., Aspalter, I. M., Rosewell, I., Busse, M., Thurston, G., Medvinsky, A. et al. (2010). Endothelial cells dynamically compete for the tip cell position during angiogenic sprouting. *Nat. Cell Biol.* **12**, 943-953. doi:10.1038/ncb2103

Khalil, A. A. and de Rooij, J. (2019). Cadherin mechanotransduction in leader-follower cell specification during collective migration. *Exp. Cell Res.* **376**, 86-91. doi:10.1016/j.yexcr.2019.01.006

Kolte, D., McClung, J. A. and Aronow, W. S. (2016). Vasculogenesis and angiogenesis. In *Translational Research in Coronary Artery Disease* (ed. W. Aronow and J. A. McClung), pp. 49-65. Elsevier.

Kuriyama, S., Theveneau, E., Benedetto, A., Parsons, M., Tanaka, M., Charras, G., Kabla, A. and Mayor, R. (2014). In vivo collective cell migration requires an LPAR2-dependent increase in tissue fluidity. *J. Cell Biol.* **206**, 113-127. doi:10.1083/jcb.201402093

Labernadie, A., Kato, T., Brugués, A., Serra-Picamal, X., Derzsi, S., Arwert, E., Weston, A., González-Tarragó, V., Elosegui-Artola, A., Albertazzi, L. et al. (2017). A mechanically active heterotypic E-cadherin/N-cadherin adhesion enables fibroblasts to drive cancer cell invasion. *Nat. Cell Biol.* **19**, 224-237. doi:10.1038/ncb3478

Ladoux, B. and Mège, R.-M. (2017). Mechanobiology of collective cell behaviours. *Nat. Rev. Mol. Cell Biol.* **18**, 743-757. doi:10.1038/nrm.2017.98

Ladoux, B., Mège, R.-M. and Trepat, X. (2016). Front-rear polarization by mechanical cues: from single cells to tissues. *Trends Cell Biol.* **26**, 420-433. doi:10.1016/j.tcb.2016.02.002

Lambert, A. W., Pattabiraman, D. R. and Weinberg, R. A. (2017). Emerging biological principles of metastasis. *Cell* **168**, 670-691. doi:10.1016/j.cell.2016.11.037

Lampugnani, M. G., Corada, M., Caveda, L., Breviario, F., Ayalon, O., Geiger, B. and Dejana, E. (1995). The molecular organization of endothelial cell to cell junctions: differential association of plakoglobin, beta-catenin, and alpha-catenin with vascular endothelial cadherin (VE-cadherin). *J. Cell Biol.* **129**, 203-217. doi:10.1083/jcb.129.1.203

Lecaudey, V., Cakan-Akdogan, G., Norton, W. H. J. and Gilmour, D. (2008). Dynamic Fgf signaling couples morphogenesis and migration in the zebrafish lateral line primordium. *Development* **135**, 2695-2705. doi:10.1242/dev.025981

Lu, X., Le Noble, F., Yuan, L., Jiang, Q., De Lafarge, B., Sugiyama, D., Bréant, C., Claes, F., De Smet, F., Thomas, J.-L. et al. (2004). The netrin receptor UNC5B mediates guidance events controlling morphogenesis of the vascular system. *Nature* **432**, 179-186. doi:10.1038/nature03080

Majumdar, R., Tavakoli Tameh, A. and Parent, C. A. (2016). Exosomes mediate LTB4 release during neutrophil chemotaxis. *PLoS Biol.* **14**, e1002336. doi:10.1371/journal.pbio.1002336

Massagué, J. and Obenauf, A. C. (2016). Metastatic colonization by circulating tumour cells. *Nature* **529**, 298-306. doi:10.1038/nature17038

Mazzone, M., Dettori, D., de Oliveira, R. L., Loges, S., Schmidt, T., Jonckx, B., Tian, Y.-M., Lanahan, A. A., Pollard, P., de Almodovar, C. R. et al. (2009). Heterozygous deficiency of PHD2 restores tumor oxygenation and inhibits metastasis via endothelial normalization. *Cell* **136**, 839-851. doi:10.1016/j.cell.2009.01.020

Melero, I., Rouzaut, A., Motz, G. T. and Coukos, G. (2014). T-cell and NK-cell infiltration into solid tumors: a key limiting factor for efficacious cancer immunotherapy. *Cancer Discov.* **4**, 522-526. doi:10.1158/2159-8290.CD-13-0985

Meyen, D., Tarbashevich, K., Banisch, T. U., Wittwer, C., Reichman-Fried, M., Maugis, B., Grimaldi, C., Messerschmidt, E.-M. and Raz, E. (2015). Dynamic

filopodia are required for chemokine-dependent intracellular polarization during guided cell migration in vivo. *eLife* **4**, e05279. doi:10.7554/eLife.05279
Millard, T. H. and Martin, P. (2008). Dynamic analysis of filopodial interactions during the zippering phase of Drosophila dorsal closure. *Development* **135**, 621-626. doi:10.1242/dev.014001
Molyneaux, K. A., Zinszner, H., Kunwar, P. S., Schaible, K., Stebler, J., Sunshine, M. J., O'Brien, W., Raz, E., Littman, D., Wylie, C. et al. (2003). The chemokine SDF1/CXCL12 and its receptor CXCR4 regulate mouse germ cell migration and survival. *Development* **130**, 4279-4286. doi:10.1242/dev.00640
Montell, D. J. (2003). Border-cell migration: the race is on. *Nat. Rev. Mol. Cell Biol.* **4**, 13-24. doi:10.1038/nrm1006
Montell, D. J., Yoon, W. H. and Starz-Gaiano, M. (2012). Group choreography: mechanisms orchestrating the collective movement of border cells. *Nat. Rev. Mol. Cell Biol.* **13**, 631-645. doi:10.1038/nrm3433
Motz, G. T. and Coukos, G. (2013). Deciphering and reversing tumor immune suppression. *Immunity* **39**, 61-73. doi:10.1016/j.immuni.2013.07.005
Muinonen-Martin, A. J., Susanto, O., Zhang, Q., Smethurst, E., Faller, W. J., Veltman, D. M., Kalna, G., Lindsay, C., Bennett, D. C., Sansom, O. J. et al. (2014). Melanoma cells break down LPA to establish local gradients that drive chemotactic dispersal. *PLoS Biol.* **12**, e1001966. doi:10.1371/journal.pbio.1001966
Murphy, A. M. and Montell, D. J. (1996). Cell type-specific roles for Cdc42, Rac, and RhoL in Drosophila oogenesis. *J. Cell Biol.* **133**, 617-630. doi:10.1083/jcb.133.3.617
Nichols, J. M. E., Veltman, D. and Kay, R. R. (2015). Chemotaxis of a model organism: progress with Dictyostelium. *Curr. Opin. Cell Biol.* **36**, 7-12. doi:10.1016/j.ceb.2015.06.005
Nieto, M. A., Huang, R. Y.-J., Jackson, R. A. and Thiery, J. P. (2016). EMT: 2016. *Cell* **166**, 21-45. doi:10.1016/j.cell.2016.06.028
Niewiadomska, P., Godt, D. and Tepass, U. (1999). DE-Cadherin is required for intercellular motility during Drosophila oogenesis. *J. Cell Biol.* **144**, 533-547. doi:10.1083/jcb.144.3.533
Norden, C. and Lecaudey, V. (2019). Collective cell migration: general themes and new paradigms. *Curr. Opin. Genet. Dev.* **57**, 54-60. doi:10.1016/j.gde.2019.06.013
Olson, H. M. and Nechiporuk, A. V. (2018). Using zebrafish to study collective cell migration in development and disease. *Front. Cell Dev. Biol.* **6**, 83. doi:10.3389/fcell.2018.00083
Padmanaban, V., Krol, I., Suhail, Y., Szczerba, B. M., Aceto, N., Bader, J. S. and Ewald, A. J. (2019). E-cadherin is required for metastasis in multiple models of breast cancer. *Nature* **573**, 439-444. doi:10.1038/s41586-019-1526-3
Peinado, H., Zhang, H., Matei, I. R., Costa-Silva, B., Hoshino, A., Rodrigues, G., Psaila, B., Kaplan, R. N., Bromberg, J. F., Kang, Y. et al. (2017). Pre-metastatic niches: organ-specific homes for metastases. *Nat. Rev. Cancer* **17**, 302-317. doi:10.1038/nrc.2017.6
Radice, G. L., Ferreira-Cornwell, M. C., Robinson, S. D., Rayburn, H., Chodosh, L. A., Takeichi, M. and Hynes, R. O. (1997). Precocious mammary gland development in P-cadherin-deficient mice. *J. Cell Biol.* **139**, 1025-1032. doi:10.1083/jcb.139.4.1025
Reim, I., Hollfelder, D., Ismat, A. and Frasch, M. (2012). The FGF8-related signals Pyramus and Thisbe promote pathfinding, substrate adhesion, and survival of migrating longitudinal gut muscle founder cells. *Dev. Biol.* **368**, 28-43. doi:10.1016/j.ydbio.2012.05.010
Revenu, C., Streichan, S., Donà, E., Lecaudey, V., Hufnagel, L. and Gilmour, D. (2014). Quantitative cell polarity imaging defines leader-to-follower transitions during collective migration and the key role of microtubule-dependent adherens junction formation. *Development* **141**, 1282-1291. doi:10.1242/dev.101675
Ribatti, D. and Crivellato, E. (2012). "Sprouting angiogenesis", a reappraisal. *Dev. Biol.* **372**, 157-165. doi:10.1016/j.ydbio.2012.09.018
Richardson, B. E. and Lehmann, R. (2010). Mechanisms guiding primordial germ cell migration: strategies from different organisms. *Nat. Rev. Mol. Cell Biol.* **11**, 37-49. doi:10.1038/nrm2815
Richardson, A. M., Havel, L. S., Koyen, A. E., Konen, J. M., Shupe, J., Wiles, W. G., Martin, W. D., Grossniklaus, H. E., Sica, G., Gilbert-Ross, M. et al. (2018). Vimentin is required for lung adenocarcinoma metastasis via heterotypic tumor cell-cancer-associated fibroblast interactions during collective invasion. *Clin. Cancer Res.* **24**, 420-432. doi:10.1158/1078-0432.CCR-17-1776
Ruhrberg, C., Gerhardt, H., Golding, M., Watson, R., Ioannidou, S., Fujisawa, H., Betsholtz, C. and Shima, D. T. (2002). Spatially restricted patterning cues provided by heparin-binding VEGF-A control blood vessel branching morphogenesis. *Genes Dev.* **16**, 2684-2698. doi:10.1101/gad.242002
Scarpa, E. and Mayor, R. (2016). Collective cell migration in development. *J. Cell Biol.* **212**, 143-155. doi:10.1083/jcb.201508047
Scarpa, E., Szabó, A., Bibonne, A., Theveneau, E., Parsons, M. and Mayor, R. (2015). Cadherin switch during EMT in neural crest cells leads to contact inhibition of locomotion via repolarization of forces. *Dev. Cell* **34**, 421-434. doi:10.1016/j.devcel.2015.06.012
Shamir, E. R. and Ewald, A. J. (2015). Adhesion in mammary development: novel roles for E-cadherin in individual and collective cell migration. *Curr. Top. Dev. Biol.* **112**, 353-382. doi:10.1016/bs.ctdb.2014.12.001
Shellard, A. and Mayor, R. (2019). Integrating chemical and mechanical signals in neural crest cell migration. *Curr. Opin. Genet. Dev.* **57**, 16-24. doi:10.1016/j.gde.2019.06.004
Siekmann, A. F. and Lawson, N. D. (2007). Notch signalling limits angiogenic cell behaviour in developing zebrafish arteries. *Nature* **445**, 781-784. doi:10.1038/nature05577
Siekmann, A. F., Affolter, M. and Belting, H.-G. (2013). The tip cell concept 10 years after: new players tune in for a common theme. *Exp. Cell Res.* **319**, 1255-1263. doi:10.1016/j.yexcr.2013.01.019
Silver, D. L. and Montell, D. J. (2001). Paracrine signaling through the JAK/STAT pathway activates invasive behavior of ovarian epithelial cells in Drosophila. *Cell* **107**, 831-841. doi:10.1016/S0092-8674(01)00607-9
Simões-Costa, M. and Bronner, M. E. (2015). Establishing neural crest identity: a gene regulatory recipe. *Development* **142**, 242-257. doi:10.1242/dev.105445
Sirka, O. K., Shamir, E. R. and Ewald, A. J. (2018). Myoepithelial cells are a dynamic barrier to epithelial dissemination. *J. Cell Biol.* **217**, 3368-3381. doi:10.1083/jcb.201802144
Srinivasan, K., Strickland, P., Valdes, A., Shin, G. C. and Hinck, L. (2003). Netrin-1/neogenin interaction stabilizes multipotent progenitor cap cells during mammary gland morphogenesis. *Dev. Cell* **4**, 371-382. doi:10.1016/S1534-5807(03)00054-6
Stedden, C. G., Menegas, W., Zajac, A. L., Williams, A. M., Cheng, S., Özkan, E. and Horne-Badovinac, S. (2019). Planar-polarized semaphorin-5c and plexin A promote the collective migration of epithelial cells in Drosophila. *Curr. Biol.* **29**, 908-920. doi:10.1016/j.cub.2019.01.049
Steeg, P. S. (2016). Targeting metastasis. *Nat. Rev. Cancer* **16**, 201-218. doi:10.1038/nrc.2016.25
Stepanik, V., Dunipace, L., Bae, Y.-K., Macabenta, F., Sun, J., Trisnadi, N. and Stathopoulos, A. (2016). The migrations of Drosophila muscle founders and primordial germ cells are interdependent. *Development* **143**, 3206-3215. doi:10.1242/dev.134346
Stuellton, C., Parent, C. A. and Montell, D. J. (2017). Cell motility in cancer metastasis: mechanistic insights from simple model organisms. *Nat. Rev. Cancer* **18**, 296-312. doi: 10.1038/nrc.2018.15
Suchting, S., Freitas, C., le Noble, F., Benedito, R., Bréant, C., Duarte, A. and Eichmann, A. (2007). The Notch ligand Delta-like 4 negatively regulates endothelial tip cell formation and vessel branching. *Proc. Natl. Acad. Sci. USA* **104**, 3225-3230. doi:10.1073/pnas.0611177104
Szabó, A. and Mayor, R. (2018). Mechanisms of neural crest migration. *Annu. Rev. Genet.* **52**, 43-63. doi:10.1146/annurev-genet-120417-031559
Theveneau, E. and Mayor, R. (2012). Neural crest delamination and migration: from epithelium-to-mesenchyme transition to collective cell migration. *Dev. Biol.* **366**, 34-54. doi:10.1016/j.ydbio.2011.12.041
Theveneau, E., Marchant, L., Kuriyama, S., Gull, M., Moepps, B., Parsons, M. and Mayor, R. (2010). Collective chemotaxis requires contact-dependent cell polarity. *Dev. Cell* **19**, 39-53. doi:10.1016/j.devcel.2010.06.012
Theveneau, E., Steventon, B., Scarpa, E., Garcia, S., Trepat, X., Streit, A. and Mayor, R. (2013). Chase-and-run between adjacent cell populations promotes directional collective migration. *Nat. Cell Biol.* **15**, 763-772. doi:10.1038/ncb2772
Turajlic, S. and Swanton, C. (2016). Metastasis as an evolutionary process. *Science* **352**, 169-175. doi:10.1126/science.aaf2784
Valentin, G., Haas, P. and Gilmour, D. (2007). The chemokine SDF1a coordinates tissue migration through the spatially restricted activation of Cxcr7 and Cxcr4b. *Curr. Biol.* **17**, 1026-1031. doi:10.1016/j.cub.2007.05.020
Vogelstein, B., Papadopoulos, N., Velculescu, V. E., Zhou, S., Diaz, L. A. and Kinzler, K. W. (2013). Cancer genome landscapes. *Science* **339**, 1546-1558. doi:10.1126/science.1235122
Welch, D. R. and Hurst, D. R. (2019). Defining the hallmarks of metastasis. *Cancer Res.* **79**, 3011-3027. doi:10.1158/0008-5472.CAN-19-0458
Westcott, J. M., Prechtl, A. M., Maine, E. A., Dang, T. T., Esparza, M. A., Sun, H., Zhou, Y., Xie, Y. and Pearson, G. W. (2015). An epigenetically distinct breast cancer cell subpopulation promotes collective invasion. *J. Clin. Invest.* **125**, 1927-1943. doi:10.1172/JCI77767
Zhang, S., Amourda, C., Garfield, D. and Saunders, T. E. (2018). Selective filopodia adhesion ensures robust cell matching in the drosophila heart. *Dev. Cell* **46**, 189-203.e4. doi:10.1016/j.devcel.2018.06.015