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.

KEY WORDS: Heterotypic cell adhesion, Homotypic cell adhesion, Cell migration, Chemotaxis, Contact inhibition, Contact activation of locomotion, Metastasis

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
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 (Khali 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 Mége, 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 (Khali 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 isof orm 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
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 chemotactant/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 homophilic 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 sprouting angiogenesis, which is crucial during development, wound healing, and tumor metastasis (Auspunk 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; Lamprugnani 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 (Ruhberg 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).
Semaphorin 3E and netrin-UNCSB signaling also guide developing vessels (Adams and Eichmann, 2010).

**Drosophila cardioblast matching**

A recent study describes collective cell migration during *Drosophila* cardioangiogenesis (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 toward 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’ pattern, in which four cells express the homeobox gene *timman* (*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 inflex tracts, whereas Tin-positive cells line the dorsal vessel and form cardiac vacuoles.

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 primordium ( 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 Nechpioruk, 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, chemokine SDF1a (or CXCL12). The chemokine receptor CXCR4B is expressed at higher levels in the leading zone, 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 *timman* (*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 inflex tracts, whereas Tin-positive cells line the dorsal vessel and form cardiac vacuoles.

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**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 Bromer, 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 Sdf1-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 adenyl 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 MVs 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 MVs 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
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 chemotactant-guided migration. However, when cells challenged with both a chemotactant 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; Stuelton 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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**Development at a Glance**

A high-resolution version of the poster is available for downloading in the online version of this article at http://dev.biologists.org/content/146/23/dev172056/F1. poster.jpg

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