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Review article

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Collective cell migration modes in development, tissue repair and cancer

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Abstract

Migrating cells have key functions in shaping tissues during development, repairing tissues after development and supporting cancer invasion and metastasis. In all these contexts, cells often maintain contact with their neighbours and move as a group, in a process termed collective migration. In this Review, we describe the elegant mechanisms used by collectively migrating cells in vivo to coordinate their movements and obtain directional information. We start by highlighting the diverse physiological roles that migrating collectives have within the body and then focus on dominant paradigms for the organization of migrating collectives including the roles of leader and follower cells, local cell–cell adhesion and signalling, and external guidance cues. By comparing collective migrations occurring during development and cancer, we bring into focus shared principles for collective cell movement and distinct strategies used by cancer cells for their own dispersal. Throughout, we pay particular attention to how migrating collectives display emergent properties not exhibited by individually migrating cells and how these properties provide the robustness needed for efficient cell movement.

Sections

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Introduction

Individually migrating cells rely on core mechanisms to turn discrete subcellular movements into coordinated action and productive translocation[1–4]. For example, mesenchymal migration of a single cell is defined by actin-based protrusions at its front, actomyosin contractility to retract its rear and transmembrane receptors such as integrins that work in conjunction with a dynamic cytoskeleton to generate traction forces against the substrate. This mode is used by many individual cells such as fibroblasts and other cell types that migrate on top of 2D substrates[5]. Studies of how individual cells move have led to a detailed physical and biochemical understanding of how their force-generating machinery operates and the feedback mechanisms that ensure individual cell polarization. However, during cell migrations that occur within developing and regenerating tissues, most cells maintain contacts with their neighbours and migrate as a group, a process termed collective migration. Likewise, in the cancer setting, many tumour cells also migrate collectively to invade surrounding tissues and reach the systemic circulation as tumour cell clusters to form distant metastases. In contrast to single-cell migration, this collective migration mode and the core mechanisms that guide it remain far less well understood.

The modes by which cells migrate collectively are remarkably diverse — the number of cells can range from a minimum of two, as seen with the cardiopharyngeal precursor cells of ascidians[6], up to thousands, as seen during the turnover of the intestinal lining in mammals[7]. The migrating cells can be organized into clusters, streams or sheets, the substrate over which they move can be extracellular matrix (ECM), other cells or both, and the distance they travel can range from a few cell lengths to nearly the length of the organism. Yet, all collective migrations share a fundamental challenge: when cells migrate collectively, each cell must coordinate its own individual movements with those of its neighbours. How do such diverse cell groups coordinate their actions to produce translocation? What are the rules that dictate when they start, the direction in which they move and how they stop? Gaining mechanistic understanding into these questions has been enabled by advanced microscopy, combined with genetic and biophysical manipulations and computational approaches. Moreover, new single-cell technologies have revealed a previously unrecognized heterogeneity in both developing and cancerous tissues. Since the comparison between normal and cancerous collective migrations was first made in this journal in an excellent review article published in 2009 (ref. 8), the field has advanced both conceptually and technically. New models of developmental collective migration have joined the well-established models to expand our understanding of how a migrating cohort can be organized. Moreover, the idea that collective cell behaviours underlie almost every aspect of the metastatic cascade has gained momentum. These studies have revealed that a major advantage of migrating collectively versus individually is that cell cohorts often display emergent properties not exhibited by the individual cells themselves, including self-organization, a decentralized decision-making process and tolerance of variable conditions (including dynamic signalling states and mechanical properties of the tissue microenvironment).

In this Review, we highlight the mechanisms used by collectively migrating cells in vivo to coordinate their movements and obtain directional information. We first provide examples of the diverse roles that collectively migrating cells have in tissue development and repair under physiological conditions and how migrating collectives give rise to metastases in cancer. We then describe how a migrating cohort is organized at multiple levels, for example, into leader and follower cells, by local mechanical and biochemical signalling, and by external guidance cues. For each section, we first discuss examples from 'normal' collective migrations and then explore the extent to which cancer cells deploy the same mechanisms or devise new ones for their invasive and metastatic spread. We pay particular attention to how collectivity provides the robustness needed to ensure efficient cell movement under adverse conditions, discuss areas of ongoing debate and identify key barriers in the field where technological development could be fruitful.

Because groups of cells move in many ways, a consensus definition of collective migration is a necessary starting point for this Review. Collectively migrating cells primarily move using force-generating machinery that is most similar to that used for mesenchymal migration of individual cells. However, this machinery is now polarized, not just at the level of the individual cells, but also at the level of the collective to ensure net movement in a common direction (Box 1). The cells also maintain physical contact with their neighbours and actively influence each other's movements. Given space limitations, some forms of tissue morphogenesis and metastatic dissemination that fall more broadly under the umbrella of collective rearrangement and transport are discussed only briefly (Box 2).

Roles of collective migration

Before delving into the mechanisms that allow cells to migrate collectively, it is important to know when and where collective migrations occur within the body and the diverse consequence of these migration events. Below, we highlight key examples of how collective migrations shape tissues during development, how they participate in the repair and renewal of tissues after development and how they promote the invasive spread of cancers. This section also serves as an introduction to the model systems from which many insights have been gained and that will be used throughout the Review to highlight key principles of how a migrating cohort is organized.

Collective migration in development

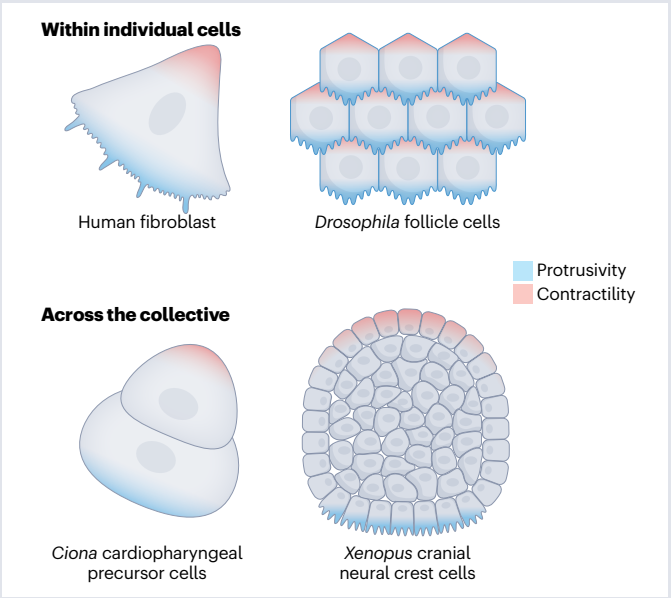
Collective migration events that occur during development provide an efficient means to transport cells to specific locations in the body where they are needed to perform their function. Collective motion also functions in shaping the tissues and organs to which the migrating cells belong. In some cases, migrating collectives provide the forces needed to deform the tissue. In other cases, this motion can be coupled with other processes such as ECM secretion or cell differentiation, as described below.

The border cell cluster of the *Drosophila melanogaster* egg chamber provides a prime example in which collective migration functions to transport cells to a specific location[9] (Fig. 1a). An egg chamber is an ovarian follicle that has a central cluster of germ cells, composed of 15 nurse cells and one oocyte, which is surrounded by a monolayer of epithelial cells called follicle cells[10,11]. The border and polar cells are specialized follicle cells that help to build the sperm entry channel in the eggshell[12,13]. However, they originate from a location far from where the channel needs to be built. To reach this site, six to eight border cells delaminate from the epithelium and migrate through the nurse cells, carrying two non-migratory polar cells along as passengers, in a linear movement from point A to point B. This translocation mode is also seen in the neural crest of vertebrates, which is a stem cell population that originates at the dorsal side of the neural tube and migrates ventrally through the body to form various cell types (Fig. 1b).

By contrast, in the zebrafish kidney, collective migration has a direct role in shaping the tissue in addition to translocating the cells

Box 1 | Supracellular polarization of migratory behaviours

Individually migrating cells are typically polarized, with protrusivity highest at their fronts and contractility highest at their backs. Collectively migrating cells need to have these same polarized behaviours, but the group dynamic expands the possibilities for how the polarization is deployed. Sometimes, each cell within the collective displays the same polarity as a single migrating cell, as seen in the follicle cells during their rotational migration[18,162]. However, there are also cases in which these behaviours are polarized across the group to form a 'supracell'[256]. In the simplest example of this phenomenon, two pairs of cardiopharyngeal precursor cells migrate through the ascidian embryo (*Ciona intestinalis*) in a tightly adhered leader–follower configuration[6,257–259]. Although both cells initially have the same shape, the cell that experiences higher cell–matrix adhesion adopts the flat, protrusive morphology of a leader cell, whereas the other cell takes on the tapered, contractile morphology of the follower. Together, they look remarkably like one migrating cell. A more complex example is seen in the cranial neural crest of *Xenopus laevis*[77]. Here, protrusions primarily form at the front of the cohort and a supracellular actomyosin cable forms along the back. Contraction of the cable creates tissue-level flows that propel the cluster forward in a 'rear-wheel drive' mode of collective motility[77]. In both the cardiopharyngeal precursors and the neural crest, experimental dissociation of the cells showed that the individual cells can migrate on their own, but they do so with less directional persistence[154,257]. Moreover, supracellular organization of the neural crest enhances its ability to follow directional cues[211,256]. Finally, mathematical modelling suggests that the additional force generated by two cardiopharyngeal cells migrating together allows them to better penetrate between tissue layers[257]. Thus, supracellular polarity appears to increase the speed and accuracy with which the cells reach their destinations.



(Fig. 1c). The functional unit of the vertebrate kidney is the nephron, which consists of a glomerulus that filters blood and a tubule that processes urine. The tubule develops a characteristic convolution near its attachment point with the glomerulus that places it in contact with the vasculature[14]. In zebrafish, this convolution forms when the epithelial cells of the tubule collectively migrate along their surrounding basement membrane ECM towards the glomerulus, and thereby create a pushing force that causes the tubule to bend outwards from this point[15]. The same migration also pulls against the tubule's other attachment point at the cloaca to induce the cells at the other end of the tubule to proliferate[16]. In this way, collective migration directly transforms a short straight tube into a longer curved one.

Notably, collective migration can also have an indirect role in shaping tissues, as shown by a separate migration event that also occurs in the *D. melanogaster* egg chamber (Fig. 1a). Before the migration of the border cells, the follicle cells migrate along the basement membrane that forms the outermost layer of the egg chamber[17,18]. This migration causes the entire egg chamber to rotate within this surrounding matrix[19]. By coupling this motion with the secretion of new basement membrane proteins[19,20], the follicle cell migration alters the mechanical properties of the matrix in a way that allows it to direct tissue growth along one axis and elongate the egg chamber[21]. Here, collective migration affects the structure of an ECM, which then acts as the primary driver of morphogenesis.

Finally, the posterior lateral line of zebrafish shows how collective migration can be coupled to a cell differentiation programme to build a set of structures with regular spacing[22] (Fig. 1d). The lateral line comprises a linear array of sensory organs called neuromasts that runs along each side of the body to detect water movement. To build the array, two clusters of about 100 cells each (primordia) crawl along the flanks of the embryo towards the tail. Neuromasts differentiate at the backs of the primordia at regular intervals and are deposited onto the substrate as the rest of the cells continue migrating forwards. In this case, the direction and speed at which the primordia migrate determine the location and spacing of the neuromasts as they differentiate.

Collective migration in tissue repair and homeostasis

Once development is complete, collective migration continues to fulfil central roles in tissue repair and homeostasis. For example, wounds to the skin cause otherwise stationary keratinocytes to activate a migratory programme and close the gap[23] (Fig. 2a). Hepatocytes can also migrate collectively in response to diverse types of liver injury to close the wound and initiate regeneration[24]. However, the true champions of post-development collective migration are the epithelial cells that line the mammalian intestine (Fig. 2b). These cells are constantly exposed to physical stress and pathogens, and therefore need to be replaced within days to maintain a healthy intestinal lining[25]. To accommodate this high turnover, new epithelial cells are continually generated at the bottom of invaginated crypts and then shed from the top of evaginated villi. The movement of cells between these points was once thought to be controlled solely by the pressure exerted by cell division. It was recently discovered, however, that the cells actively crawl up the villus in a continuous collective migration that is sustained throughout the life of the animal[7]. Thus, the same types of collective movement that shape tissues during development also maintain functionality after development.

Box 2 | Other types of collective transport and cellular rearrangements

There are other types of collective cell movement that share key features with collective migration but that are not powered by the crawling type of motility covered in this Review. For example, the sprouting of new blood vessels in vertebrates or of tracheal tubes in *Drosophila melanogaster* is led by cells that show a protrusive tip and that appear to actively migrate away from the parent tube; however, the migratory status of the cells behind the tip cells is not clearly defined, and the new tubes may instead extend through mechanisms such as cell division and cell intercalation[260,261]. Likewise, the morphogenesis of other branched tubular tissues such as the mammary gland can involve smooth budded fronts that penetrate into the surrounding mesenchyme[262]. Here, mitotically active cells at the multilayered bud front migrate intraepithelially to the back and intercalate into the trailing bilayered duct, to provide forward pushing' force[263,264]. There are also linearly directed movements of epithelial sheets that do not appear to rely on active crawling, such as the dorsal closure in *Drosophila* and certain wound-healing scenarios in which the gap closes with the aid of a contractile actomyosin purse string[76,265]. In cancer, tumour buds with inverted apical–basal polarity occur in some colon cancer subtypes[266–268]. These buds do not depend on adhesion-based protrusions, yet are nonetheless able to disseminate, possibly through collective amoeboid-type movements as have been observed in microfluidic channels ex vivo[268]. Furthermore, passive embolic transport of tumour cell clusters is common. These clusters dynamically reshape to traverse blood vessels and resist shear stress before making their way out of the vasculature into distant organs[57]. In these cases, actomyosin contractility appears to be essential for the disseminative potential of the clusters, independent of protrusive migration. Although deeper discussions of these movements fall outside the scope of this Review, many (if not all) use similar mechanisms of intercellular coordination and collective guidance to those described here.

Collective migration in cancer

Many cancers also display evidence of collective migration. In solid tumours, invasion is a key early step in the development of metastases, and these local movements are often collective, with strands and buds of tumour cells migrating from the main tumour mass accounting for nearly all invasion events into surrounding tissues in many tumour types[26–31]. Analogously to development, collective migration of tumour cells occurs concurrently with processes such as differentiation, proliferation and tissue remodelling. Often, cells at the front of migrating collectives display partial differentiation into morphologies that reflect their original cell type, and in epithelial tumours, lumenization and apicobasal polarization are observed[32–34]. Collective tumour cohorts are mixtures of actively migratory and proliferative cells, enabling tumours to perform both processes simultaneously — a property that similarly augments the efficiency of normal wound repair[35]. Further, collectively migrating cancer cells actively reshape the local ECM, not only by protease degradation, but also by secreting tumour ECM, to induce large-scale tissue pushing and buckling behaviours that are dependent on multicellular force transmission[36–39]. Thus, collective cancer invasion reflects partial recapitulation of a normal developmental process.

However, unlike development, in which collective migrations are highly reproducible and spatiotemporally precise, collective invasion in cancer is disordered (Fig. 3a). A single tumour can have coexisting regions that display different modes of collective migration, some resembling migrating cell sheets as observed on 2D substrates, others migrating as linear cell chains such as those seen in 3D fibrillar matrices or as multicellular buds as seen in 3D organoid cultures[26,29,31]. Furthermore, collectively invading tumour cells regularly cross tissue boundaries. Some developmental collective migrations, like that of the neural crest, can cross basement membranes during defined time windows. By contrast, cancer cells do so with higher frequency and can even invade smooth muscle, fat and bone[27,30]. They can then crawl along, penetrate and in some cases re-integrate into non-cancerous surrounding tissue structures including blood vessels, nerves and epithelial ducts[27,40–42]. The extreme spatial disorder of invading tumours is a barrier to decoding collective migrations in these systems, which is being overcome by advances in organotypic cancer models that recapitulate key features of cancer migration ex vivo, by techniques for reconstruction of invasion fronts and by advances in intravital imaging.

Beyond local tissue invasion, tumour cell collectives also disseminate systemically to form metastases (Fig. 3b). The dynamics of how tumour cell clusters enter circulation are only beginning to emerge. Most surprisingly, tumour cell clusters appear to disseminate from tumour areas associated with vascular compromise, hypoxia and tissue necrosis[43–48]. Because these processes are concentrated within specific regions, such as the tumour core, this lends support to the hypothesis that spatially distinct tumour ecosystems are involved in local invasion and systemic dissemination of clusters. Once in circulation, clusters of tumour cells, accompanied frequently by cells of the tumour microenvironment such as neutrophils, platelets and cancer-associated fibroblasts (CAFs), travel widely via systemic haematogenous (that is, through the bloodstream) and also lymphatic routes[49–59]. Subsequently, tumour cell clusters become trapped in distant capillary beds of vital organs such as brain, liver and lung and extravasate with assistance from endothelial cells and platelets[60–63]. Tumour cell clusters make considerable contributions to successful metastatic events and can contribute to genetic diversity through the formation of polyclonal metastases[64–72]. Thus, collective migration provides a compact mechanism for the delivery of tumour seeds with robust metastatic potential (Fig. 3c).

Leader cells in collective migration

In most collective migration events, the cells at the front of the cohort are inherently different from those that follow, in that their leading edges extend into free space instead of contacting other cells. Depending on the context, these cells can also show distinct behaviours and molecular signatures, including increased protrusive activity, ability to detect guidance cues, propensity to remodel the ECM and reduced apicobasal polarity[73–75]. The emergence of these 'leader cells' occurs through diverse mechanisms, some of which are shared by both physiological and cancerous migrations and some of which are not, as detailed below.

Leader cells in development and tissue repair

In collective migrations that have a leader cell population, it is common for every cell in the cohort to have the ability to assume the leading role. For example, there is no advanced warning when a wound forms in an

epithelial sheet, so logically each cell within the sheet must have the capacity to lead the healing process when necessary (Fig. 2a). In this case, the wound itself induces the leader-like behaviour in the cells at the edge[76]. Cells can also take turns occupying the leading role, as seen in the cranial neural crest of frogs and fish. Here, contraction of an actomyosin cable at the back of the cluster creates a constant flow of new cells into the lead position[77] (Fig. 1b). Finally, cells can compete to be leaders. In *D. melanogaster*, individual border cells regularly switch positions within the cluster and therefore take turns to occupy the leading role[78,79]. Each border cell expresses chemotactic receptors that activate cell-protrusive activity through the small guanosine triphosphatase (GTPase) Rac in response to diffusible, directional cues[9]. A border cell that has higher chemotactic ability and/or Rac activity than its neighbours is more likely to become stabilized in the lead position as this positional switching occurs (Fig. 1a). Indeed, photoactivation of Rac in one border cell is sufficient to make it the leader, steer the cluster and even reverse the direction of migration[80].

There are rarer examples in which cells are genetically defined to be leaders. This can be seen in the trunk neural crest of zebrafish, where the cells that lead each migratory stream appear to arise through a different genetic programme from that of the followers, and ablating them with a laser prevents the followers from continuing the migration[81]. However, even when genetically defined leader cells are present, there can still be cases of plasticity between leader and follower states. When the posterior lateral line primordium of zebrafish concludes its migration, the cell population at the front of the cluster, which has a more mesenchymal character, transitions to adopt the highly polarized epithelial character of the follower cells. This transformation both stops the migration and forms the final three neuromasts in the chain[22].

Importantly, the presence of a leader population does not mean that the followers are passive[82]. In many collective migration events, the follower cells also extend protrusions in the direction of tissue movement and actively contribute to collective motility[7,15,18,22,83]. This phenomenon was first described in epithelial sheets in vitro, where the protrusions of the follower cells are called cryptic lamellipodia[84]. Recent studies have revealed that migrating cell clusters use a similar strategy. Research on border cell migration has long focused on the large protrusion formed by the one or two cells at the front of the cluster. It has recently been suggested, however, that the lead protrusion largely steers the cluster[80,85,86], and it is smaller protrusions formed by the trailing cells that have the larger role in powering cluster movement[87] (Fig. 1a). This is also true in the posterior lateral line primordium, where cells well behind the leading edge also extend protrusions, and in vivo traction force experiments showed that these cells exert stronger forces against the substrate than the leader cells do[88,89].

Although leader-led forms of collective migration have long been assumed to be the norm, epithelial sheets can also undergo a leaderless form of collective migration in which all cells extend protrusions in the direction of migration and appear to contribute equally to tissue movement. This is best exemplified by the rotational motion of the follicle cells in *D. melanogaster* (Fig. 1a) and some organoid systems of development[19,90–93]. In these cases, the closed topology of the tissue precludes a leader population from forming. It is important to note, however, that leaderless migrations can also occur in epithelia with different geometries, such as in the kidney tubules (Fig. 1c) and optic cup in zebrafish[15,83,94], and during the turnover of the intestinal lining in mouse[7] (Fig. 2b), suggesting that this type of collective motion is more prevalent than previously thought.

Leader cells in cancer

Collectively invading cancer cells also display leader–follower dynamics, with the most common tissue architecture being strands of invasive cells extending from the main tumour mass (Fig. 3a). This front–back spatial organization enables the investigator to experimentally distinguish the molecular profiles of migratory leader cells from the less-migratory follower cells[95–100]. In various tumour types, this approach has revealed that leader cells differ from follower cells in their transcriptional programmes, chromatin state, genetic mutational profile, senescence state and complement of secreted proteins[95,98,100–106] (Fig. 3b). Following invasion, cooperative interactions between leader and non-leader cells in disseminating heterotypic clusters can further promote metastatic efficiency, for example, by enabling more-migratory tumour cells to aid in the dissemination of less-migratory tumour cells, the latter of which are in some cases more proliferative[66,107,108]. Given the cellular heterogeneity between tumour types, leader cell phenotypes and the mechanisms by which leaders arise appear to be tumour type dependent with no universal molecular programme, although common themes do emerge at the cellular level.

First, the emergence of cells that lead the invasive process frequently depends on bidirectional plasticity of cell states[75]. Leader cell plasticity can arise from intrinsic differentiation and/or regenerative programmes active in the normal tissue of origin, which can differ considerably between epithelia- and mesenchyme-derived tumours, or from aberrant activation of programmes not usually active in the cell type of origin[107,109–112]. In tumour types in which leader cells readily interconvert on short timescales into follower cells and vice versa, the notion of distinct cell types is blurred, and models for cooperative interactions become experimentally difficult to test rigorously. In addition, leader cells can exist in intermediate or hybrid states along the cell differentiation spectrum, such as partial epithelial–mesenchymal transition (EMT; Box 3) or lumino-basal epithelial states, instead of being locked in one state[95,113–115]. Intermediate states endow migratory potential at the leading edge but also retain cell–cell adhesion to follower cells at the trailing edge. Further, intermediate states allow for greater flexibility to switch between migratory and proliferative states advantageous for tumour regrowth after cancer therapy and metastatic colonization[66,107,116–118]. These cell state changes can depend on local matrix heterogeneities and long-range gradients in the tumour microenvironment that enable co-occurrence of multiple modes of migration[119–122].

Second, energetics is a key mechanism by which invasive cancer cells compete for pole position (Fig. 3b). Cell–cell adhesion, motility, invadopodial degradation of the matrix and other matrix remodelling events are all energetically costly, particularly in dense microenvironments[69,123–127]. By photo-ablation of leader cells or by tracking them with a photoconvertible marker, cells have been observed to rotate into the lead position, tire out, move to the rear and be replaced by new leader cells[128]. In some tumour types, leader and follower cells can even use different metabolic pathways, for example, oxidative metabolism and glycolytic pathways, respectively[129]. In nutrient-poor, hypoxic and acidic regions of a tumour, energy constraints may further limit the types of permissible cellular movement and possibly favour transitions towards less energetically costly migration modes[130,131]. These observations support the existence of spatially localized differences in metabolism in collective migrating tumours.

One difference from normal collective migrations is the major role of non-cancerous cells within the microenvironment to augment

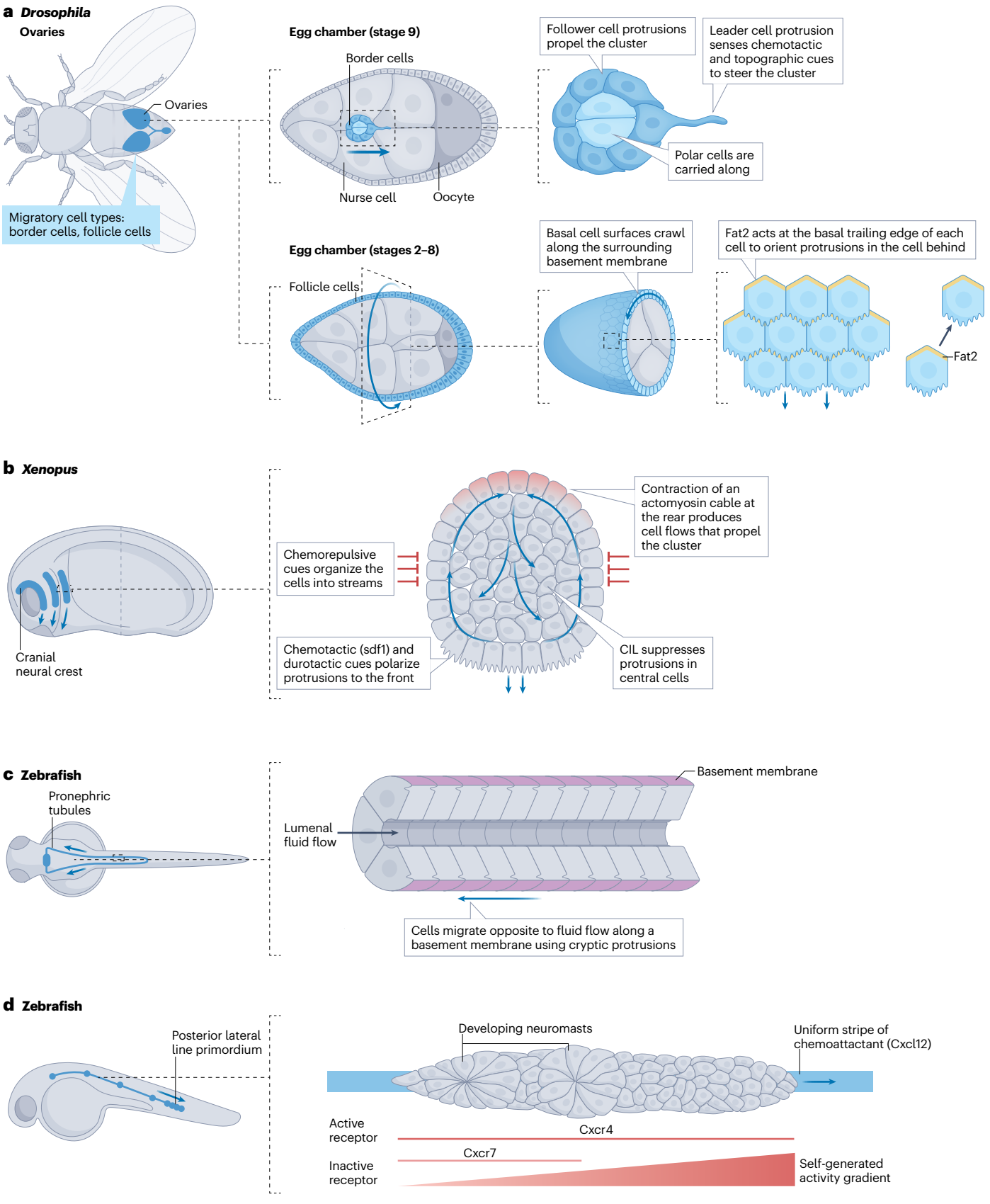

a Drosophila
Ovaries
Ovaries
Migratory cell types: border cells, follicle cells
Egg chamber (stage 9)
Border cells
Nurse cell
Oocyte
Follower cell protrusions propel the cluster
Leader cell protrusion senses chemotactic and topographic cues to steer the cluster
Polar cells are carried along
Egg chamber (stages 2–8)
Follicle cells
Basal cell surfaces crawl along the surrounding basement membrane
Fat2 acts at the basal trailing edge of each cell to orient protrusions in the cell behind
Fat2
b Xenopus
Cranial neural crest
Chemorepulsive cues organize the cells into streams
Contraction of an actomyosin cable at the rear produces cell flows that propel the cluster
Chemotactic (sdf1) and durotactic cues polarize protrusions to the front
CIL suppresses protrusions in central cells
c Zebrafish
Pronephric tubules
Lumenal fluid flow
Basement membrane
Cells migrate opposite to fluid flow along a basement membrane using cryptic protrusions
d Zebrafish
Posterior lateral line primordium
Developing neuromasts
Uniform stripe of chemoattactant (Cxcl12)
Active receptor
Cxcr4
Cxcr7
Inactive receptor
Self-generated activity gradient

Fig. 1 | Collective migration during development. Illustrations depicting five developmental models of collective migration that are highlighted in this Review. Each panel shows the organismal context for the migration on the left and the cellular arrangement of the migrating cohort and key cues that organize its movement on the right. Arrows indicate migration direction. **a**, Border cells and follicular epithelial cells (follicle cells) are two cell types within *Drosophila melanogaster* egg chambers (ovarian follicles) that migrate at different developmental stages. At oogenic stage 9, the border cells delaminate from the follicular epithelium and migrate though the nurse cells to the oocyte where they help to build the sperm entry channel in the eggshell. The border cell cluster is defined by a leader cell, which forms one large protrusion and senses guidance cues, several follower cells that appear to provide the motive force for forward movement and two non-migratory polar cells that are carried along passively by the others. By contrast, between oogenic stages 2 and 8, the follicle cells undergo a rotational collective migration along their surrounding basement membrane that helps to create the elongated shape of the egg. This migration requires the function of the atypical cadherin Fat2, which localizes to the trailing edge of each cell. From this location, Fat2 acts in trans to create a stable domain of protrusive activity in the cell behind and thereby orients all the cell protrusions in a common direction. **b**, The neural crest is a vertebrate stem cell population that arises on the dorsal side of the neural tube and migrates ventrally through the body to produce many cell types. The cranial neural crest of *Xenopus laevis* shows particularly high collectivity in its movement through N-cadherin-dependent contact inhibition of locomotion (CIL). CIL occurs when a migrating cell collides with another cell, retracts its protrusion and repolarizes to migrate away in a new direction. Although CIL typically leads to cell dispersal, neural crest cells overcome this behaviour through short-range, mutual chemoattraction. This causes the centrally located cells to experience CIL from all sides, which restricts protrusions to the periphery of the population, where an actomyosin cable also forms. The cohort is then polarized by the chemoattractant stromal cell-derived factor 1 (sdf1), which promotes protrusions and inhibits contraction at the front of the group. Contraction of the supracellular actomyosin cable at the rear then creates tissue-level flows that propel the cluster forwards in a 'rear-wheel drive' mode of collective chemotaxis. **c**, The pronephric tubule cells of the zebrafish kidney migrate towards a centrally located glomerulus (the filtering unit of the kidney), which causes the tubules to bend outwards from their glomerular attachment point and to lengthen. The direction of cell movement is specified by fluid flow through the lumen of the tubule, with the cells migrating against the flow. **d**, The posterior lateral line of zebrafish is an array of sensory organs (neuromasts) that detect water movement. This array is built by a cellular primordium that deposits the neuromasts at regular intervals as it migrates towards the tail. These cells migrate along a uniform stripe of the C-X-C motif chemokine 12 (Cxcl12). To ensure directional persistence, the migrating cells generate a local gradient of Cxcl12 activity across the primordium: This is based on expression of the signalling-competent C-X-C chemokine receptor type 4 (Cxcr4) in all cells of the primordium, whereas only cells in the back express the non-signalling Cxcr7 scavenger receptor.

and even lead tumour cell migration (Fig. 3c). For example, CAFs and tumour-associated macrophages (TAMs) have migratory, matrix-remodelling and endothelia-remodelling capacities that are often higher than those of the tumour cells themselves[98,132–135]. Interactions between these cells and cancer cells can involve direct physical contact such as when CAFs become tethered to cancer cells through heterotypic cadherin-based adhesion[132]. Alternatively, the cells can communicate via paracrine interactions: for example, TAMs instruct neighbouring cancer cells to invade by chemotactic signalling or inter-cytoplasmic exchange[134,136–138]. In cases in which non-cancerous cells and cancer cells use different signalling pathways to promote migration, dual targeting of both cell types may be required to suppress collective migration[98]. At the same time, non-cancerous cells such as CAFs can also antagonize cancer cell growth, for example, by compression of tumour cell nests[139,140], and a major question is at what phase of tumour progression therapeutic targeting of non-cancerous cells is most beneficial to restrict their invasion and metastasis-promoting effects.

Local coordination throughout the collective

Although leader cells have key roles in organizing many collective migrations, coordination between cells is not restricted to the front. For a group of cells to move in a directed way, all the cells in the cohort must ultimately coordinate their individual migratory behaviours with those of their neighbours. Some coordination occurs simply because the cells adhere to one another as they move. However, adhesion alone is typically insufficient to ensure robust collective migration. The cells must also actively polarize their migration machinery across the collective through a combination of local cell–cell signalling and external guidance cues (Fig. 4a). Here, we highlight a diverse set of adhesive mechanisms and local cell–cell signals that cells use to migrate collectively in both developmental and cancerous settings with the role of external guidance cues covered more fully in the next section.

Local coordination in development

Some migrating cohorts are organized with protrusivity higher at the front of the group and contractility higher at the back (Box 1). In two well-studied examples of this phenomenon, the same cadherins that hold the cells together also mediate the local signalling required to achieve this polarization[141]. E-cadherin has a major organizing role in the border cells. It links the border cells to the non-migratory polar cells at their centre and to each other[86,142,143]. E-cadherin also localizes to the periphery of the cluster where it forms traction-generating adhesions with E-cadherin found on the nurse cell substrate through which the border cells migrate[85,86,142,143] (Fig. 1a). From a signalling perspective, these peripheral adhesions are part of a positive feedback loop with the chemotactic receptors that guide cluster movement to amplify Rac activity in the lead cell and stabilize the large, forward-facing protrusion that steers the cluster[86]. The lead cell then pulls against the E-cadherin-based adhesions between the border cells, inducing a mechanical signal that works in conjunction with a supracellular actomyosin network at the periphery of the cluster to prevent the follower cells from forming large, outward-facing and leader-like protrusions[86,144–148]. Notably, the smaller protrusions that extend around the cluster and that power cluster movement form through a different mechanism in which Rac is activated by basolateral polarity proteins[87].

By contrast, cranial neural crest cells use N-cadherin-mediated biochemical signalling to restrict protrusions to the cluster periphery by contact inhibition of locomotion (CIL)[149–151] (Fig. 1b). In CIL, a migrating cell that collides with another cell retracts its protrusion from the point of contact, repolarizes and migrates away in a new direction — a mechanism that typically leads to cell dispersal[152]. Neural crest cells overcome this dispersal behaviour by also expressing the short-range chemoattractant C3a and its receptor C3aR[153], such that the cells are mutually attracted to each other in a manner that causes the centrally located cells to experience N-cadherin-mediated CIL from all sides. This restricts protrusion formation to the periphery of the population, where an actomyosin cable also forms[77]. As in the border cells, the same

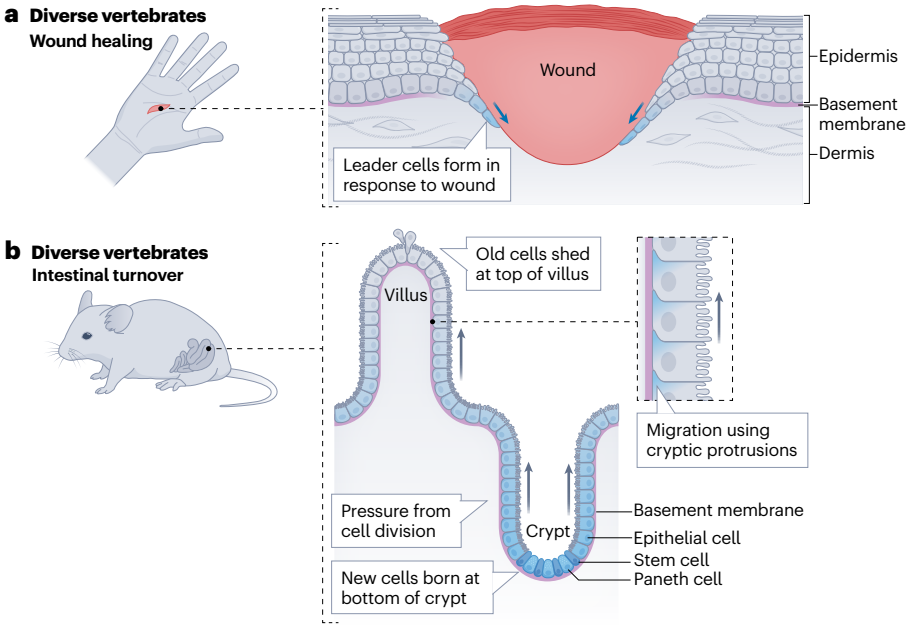


Fig. 2 | Collective migration during tissue repair and homeostasis. This figure depicts two collective migration events that occur during tissue repair and homeostasis; arrows indicate migration direction. **a**, Collective migration is a key mechanism contributing to wound closure in many tissues. The illustration shows this phenomenon in the context of mammalian skin, in which the epithelial cells of the epidermis are activated to migrate and close the wound gap. **b**, In the epithelial lining of the vertebrate intestine, cells are continually born at the bottom of invaginated crypts and shed from the top of evaginated villi. Recent work in mouse has shown that movement between these points is driven by both pressure from cell division in the crypt and active crawling along the epithelial basement membrane using cryptic protrusions (inset).

chemotactic cue that guides cell movement also polarizes the collective by promoting Rac-based protrusions and inhibiting contraction at the front of the group, thereby leading to collective chemotaxis[154].

Unlike the examples above in which the cells fulfill different functions, other collective migrations are more uniform, with each cell typically showing the same front–rear polarity as an individually migrating cell (Box 1). Here, the challenge is to align the front–rear axes of all cells in a common direction. The local signals that lead to this organization tend to occur at the interface between the rear of one cell and the front of the cell behind, with information flowing in one direction or the other, depending on the context, and cadherins once again performing both mechanical and biochemical roles in mediating this coordination[141].

During gastrulation in *Xenopus laevis* and zebrafish, certain populations of mesendodermal cells use mechanical signalling from the front of one cell to the rear of the cell ahead to orient their movement. Although these cells migrate as a largely mesenchymal population, a *X. laevis* cell that is isolated in vitro cannot form polarized protrusions or migrate persistently, even when given its native chemotactic cue and ECM substrate[155]. However, if a pulling force is applied to C-cadherin on the surface of that isolated cell, it forms a single protrusion that points away from that force[155]. Zebrafish use a similar strategy in which the protrusions of follower cells use E-cadherin to pull on the rear of the cell ahead and thereby orient its protrusions in the opposite direction[156,157]. Such observations show that mechanical information can propagate from follower cells to leader cells to orient all the cell protrusions in a common direction. Notably, studies of epithelial migration in vitro have identified several cases in which mechanical signalling occurs in the opposite direction — from the rear of one cell to the front of the cell behind[158,159], with one example leading to waves of Erk kinase activation that propagate the mechanical signal in a direction opposite to tissue movement[160,161].

Finally, the rotational migration of the follicle cells in the *D. melanogaster* ovary is an interesting case in which there are no external signals such as empty space or chemotactic cues to orient the cells for tissue-level movement (Fig. 1a). In fact, the direction of migration is not even fixed, as the cells migrate clockwise with respect to the anterioposterior axis of the egg chamber in roughly 50% of cases and anticlockwise in the remaining cases[19]. Here, the cells rely on local biochemical signalling coupled with mechanical feedback to align their migration machinery for sustained rotational motion[162–165]. Although E-cadherin and N-cadherin are the primary mediators of follicle cell adhesion[166], it is the atypical cadherin Fat2 that orchestrates the biochemical signalling needed to globally orient the cells[167]. Fat2 is localized to the rear of each cell[168,169], where it acts in trans to recruit two transmembrane signalling proteins to the front of the cell behind, the tyrosine-protein phosphatase Lar and semaphorin 5c[162,164]. Lar works with Fat2 to stabilize the front-facing protrusion in each cell and to align the protrusions of all cells in a common direction[162,165,170]. By contrast, semaphorin 5c signals back across the shared cell–cell interface through its receptor plexin-A in what appears to be a CIL-type mechanism to reinforce the overall front–rear polarity of the cells[163]. How the directional choice is made is unknown; however, once a direction is chosen, it quickly becomes self-sustaining, as it is the motion of the tissue itself that localizes Fat2 to the rear of each cell to orient the bidirectional cell–cell signalling[162]. How motion affects the localization of Fat2 is similarly unknown.

Local coordination in cancer

As in development, E-cadherin loss in epithelial cancers has profound effects on their migratory behaviour, increasing individual cell motility at the expense of directional, coordinated migration[171,172]. This effect is further heightened by local ECM density, with porous matrices promoting individualization of E-cadherin-deficient cells and dense matrices favouring multicellular migration, albeit in a less-coordinated manner than when E-cadherin is expressed[172,173]. Surprisingly, E-cadherin loss can even reduce EMT-induced dissemination of single tumour cells[174]. These observations highlight how local E-cadherin-based interactions

have effects beyond tissue cohesion, promoting coordinated cell movement through multiple mechanisms[175]. E-cadherin-based adherens junctions can transmit forces and mechanical stresses across migrating tumour collectives, propagating signals to induce multicellular polarity, and can be a reservoir for factors that promote the formation of cryptic lamellipodia in trailing cells[84,158,161,176,177]. Thus, in both development and cancer, adherens junctions coordinate directional movement between leading and following cells (Fig. 3d).

Importantly, complete loss of E-cadherin is generally not observed during cancer dissemination and metastasis, particularly for tumours of epithelial origin[171,172,178]. In fact, E-cadherin expression often persists in metastases and can even be higher than in the primary tumour from which the cells were derived[179]. The necessity of E-cadherin for these later metastatic steps may or may not depend simply on its earlier role in coordinating cell movements, as E-cadherin also promotes metastatic tumour cell survival through immune evasion and resistance to shear stress, oxidative stress and cell death owing to loss of cell–ECM adhesion (anoikis)[69,171,180]. There are also exceptions to E-cadherin dependence that should be noted, including lobular breast carcinoma, some gastric carcinomas and other tumour cells that lack E-cadherin completely or have fully transitioned into a mesenchymal state, and non-epithelial cancers such as some melanomas and sarcomas that typically use other adhesion proteins[181–184].

Although E-cadherin-based adhesion is among the best studied in multicellular coordination, other adhesion systems are also important for cancer invasion. In contexts in which E-cadherin is transcriptionally reduced, internalized from the cell surface at the protein level or genetically absent, P-cadherin or N-cadherin can become upregulated to support cell–cell cohesion[100,185]. This emergence of alternative cadherin states can also potentiate interactions between tumour cells and stromal cells to promote migration, such as in the case of squamous cell carcinomas interacting with fibroblasts and gliomas interacting with neurons[132,186]. Furthermore, loss of other adhesion systems besides adherens junction-based cadherins can drastically reduce metastatic dissemination and colonization potential[64,68,182,187]. Epithelial tight junction components are implicated in collective migration and metastasis, for example, as being necessary for cohesive migration downstream of the EMT factor Snail in squamous cell carcinoma[188]. Likewise, multiple components of desmosomes are required for tumour cell cohesion during dissemination and metastasis and these proteins have a major role in protection against mechanical stress[64,189].

Cell coordination in cancer is also potentiated by local biochemical signals that can manifest in various ways (Fig. 4a). For example, glioma cells form interconnected networks through long filamentous membrane microtubes that promote tumour cell viability and radiotherapy resistance through the formation of gap junctions and pulsatile rhythmic intercellular calcium transients[190]. Remarkably, these networks persist during collective brain infiltration and are necessary to promote directional migration through N-cadherin–p120–catenin-based adherens junctions[186]. Gap junction signalling can also contribute to collective invasion in breast and prostate cancer, potentially through intercellular communication but also through hemi-channel autocrine signalling[191].

Local signalling at the interface between tumour cells can contribute to switches between migratory and proliferative behaviour and between differentiation states (Fig. 4a). For example, juxtacrine Notch pathway interactions involving the Jagged1 ligand in leader cells stimulate collective motility of neighbouring cells in various cancer types[75,97,104,192]. Likewise, breast cancer cells can form intercellular compartments that act as an interface signalling system for local epithelial growth factor receptor (EGFR) signalling[193]. These compartments act as a reservoir to accumulate locally secreted and concentrated epithelial growth factor (EGF) family ligand, epigen, which in turn, regulates the switch from collective migration to increased proliferation necessary for metastatic colonization. Thus, tumour cell collectives can marshal their own intercellular communication to switch states in a way that is reminiscent of the migration–differentiation switch used by the posterior lateral line primordium during development, in which luminal fibroblast growth factor (FGF) signalling within closed epithelial rosettes promotes neuromast differentiation[194]. In developmental contexts, receptor–ligand systems at intercellular contacts are diverse, making it likely that many of these interfacial signals are hijacked during collective migrations in cancer but remain to be discovered.

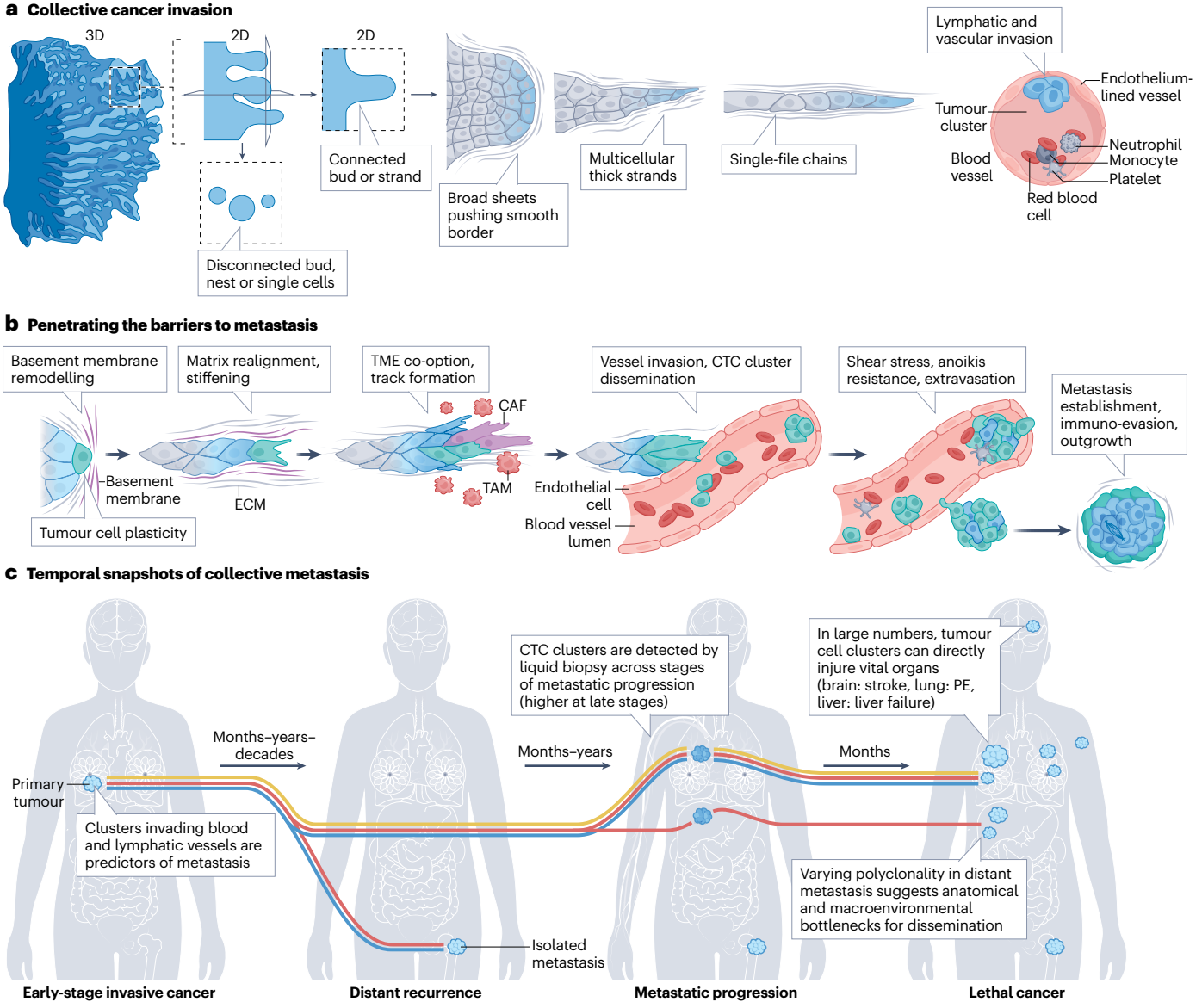
External cues that guide the collective

Cells migrating through the body encounter a complex set of chemical and physical cues that influence the direction of their movement[195]. In development and tissue repair, these cues are highly specific and guide the cells to defined destinations. Although cancer cells do not have a predefined destination per se, the cancer microenvironment does have a profound effect on the migratory ability of the cells and some of the same guidance cues are likely perceived by cancer cells to promote their dispersal. Below, we highlight the diverse sources of directional information that guide migrating collectives in both development and cancer.

External cues in development and tissue repair

Diffusible chemical signals provide a primary means by which cells navigate their environment — a process called chemotaxis[195]. In simple examples of this phenomenon, a chemical cue emanates from a point source and is cleared by cells at a distance from this source[196], thereby forming a gradient that migrating cells can follow. This is one mechanism by which the border cells find their way to the oocyte (Fig. 1a). The oocyte secretes soluble ligands that stimulate receptor tyrosine kinase signalling and thereby activate Rac in the lead border cell, which polarizes the cluster and guides it to its destination[197–201]. However, simple chemical gradients can be difficult to establish over long distances. Thus, longer range travel though the body requires that the cells actively shape the gradient they follow.

This gradient-shaping activity is best understood for the migration of the posterior lateral line primordium (Fig. 1d). These cells migrate along a stripe of the chemokine C-X-C motif chemokine 12 (Cxcl12, also known as Sdf1)[202], but the Cxcl12 stripe itself does not encode directional information. This was elegantly shown when researchers used a genetic perturbation to eliminate Cxcl12 expression selectively along posterior regions of the migration path and found that the primordium could turn around and migrate the opposite way with equal efficiency when it reached the end of the shortened stripe[203]. To ensure directional persistence, the migrating cells generate a local gradient of chemokine activity across the primordium itself. This is based on expression of a signalling-competent chemokine receptor in all cells of the primordium, whereas only cells in the back express a non-signalling scavenger receptor[204–207]. Two-colour fluorescent reporters that monitor signalling through ligand-dependent internalization of the active receptor showed that this dual-receptor system is key to generate the activity gradient[205,206]. This self-generated gradient can even adapt to non-physiological ‘floods’ of chemokine that might otherwise overwhelm the scavenger receptors and flatten the signalling gradient by



upregulating the scavenger receptors at the cell surface[208], establishing a highly robust navigation system.

Cranial neural crest cells similarly use Sdf1 to activate Rac at the front of the cohort and guide their collective migration[77,154,209] (Fig. 1b), but the way they shape the gradient is very different. Here, Sdf1 is expressed by placode cells that interact with the neural crest to form cranial nerves and that sit just ahead of them along their migration path[70]. The neural crest cells migrate towards this point source of chemoattractant. However, when they reach the placode cells, they induce a CIL response that causes the placode cells to migrate away from the point of contact[209]. This, in turn, creates a new chemotactic gradient for the neural crest cells to follow in what has been termed a 'chase and run' mechanism[209].

Although chemoattractants are widely used for cell guidance, they rarely provide the full information needed to navigate complex tissues and are therefore often combined with other chemical and/or physical cues. For example, cranial neural crest cells also sense the stiffening of the head mesoderm to trigger their exit from the neural tube[210] and then create a self-generated stiffness gradient through their interaction with the placode cells that provides a durotactic cue that they can follow in addition to the chemotactic cue[211] (Fig. 1b). Tissues that flank the migration path of neural crest cells additionally express chemorepellants such as semaphorins and ephrins, among others, that help to confine their migration into distinct streams[212–216] (Fig. 1b). Likewise, the *D. melanogaster* border cells use the forward-facing protrusion of their lead cell to probe the topography of the nurse cells through which they crawl and thereby identify a centrally located path that provides the most direct route to the oocyte[85] (Fig. 1a).

Finally, there is an increasing number of cases in which physical cues appear to have the dominant role in guiding migrating collectives. For example, it has long been known that electrical fields can be used to guide migrating cells in vitro, a process called galvanotaxis or electrotaxis[195]. It is now understood that the currents that are generated when there is a breach in the skin of a zebrafish or the cornea of a mouse

Fig. 3 | Collective migration during cancer metastasis. Illustrations depicting collective migrations in cancer at multiple spatial and temporal scales. **a**, In collective invasion, tumour cells share intercellular contacts but vary in their morphological arrangement. One reason for these diverse morphologies is technical: the invasion front may appear as disconnected or connected buds depending on how sections are cut. This is solved with the emergence of 3D optical clearing and automated reconstruction methods, which reveal that the invasion front is predominantly collective in organization, involving collectively organized tumour cells invading from the main tumour mass[26–31]. In addition, tumours can form various multicellular structures including sheets, strands and single-file chains driven by both intrinsic molecular characteristics such as cell adhesion and proteolysis and extrinsic tissue architecture and interactions with the tumour microenvironment (TME; for example, extracellular matrix (ECM) and cancer-associated fibroblasts (CAFs)). In the primary tumour, tumour cell clusters can invade the lymphatic and vascular circulation, and this pathological finding indicates heightened risk of metastasis. In many transplantable cancer models, invasion patterns are more often a mixture of collective and single-cell modes. **b**, This panel shows the penetration of local and systemic barriers by tumour cell clusters to establish distant metastases. Tumour cell plasticity gives rise to leader cells with migratory and proteolytic capacity that initiate invasion, matrix degradation and tissue remodelling[36,37,39,75,95,96]. This enables the formation of a polarized cellular organization including leader–follower transcriptional states, spatially restricted metabolism from front to back of the collective and heterotypic interactions between cancer and non-cancerous cells of the TME[95,98,100–106]. The cohort, in association with CAFs and tumour-associated macrophages (TAMs), is then able to invade tissues towards vessels based on chemotactic or other guidance cues[98,132–135]. Clusters then enter the circulation by direct invasion, intercalation into the vessel wall or vascular mimicry. Disseminating tumour cell clusters, which show characteristics of both stem cells and metastasis-initiating cells, have minutes to hours to survive within the haematogenous circulation, which is physically stressful[61]. Tumour cells are prone to detachment-induced cell death and immunosurveillance, factors ameliorated in part by multicellular clustering. The active dissociation of tumour cell clusters into individual tumour cells is being explored as a therapeutic modality[187,250–252]. Tumour cell clusters can persist within the vascular lumen and grow intravascularly or extravasate with assistance from active endothelial remodelling[60,253–255]. In the distant organ, multicellular clusters display heightened survival, outgrowth and resistance to immune cell attack[64–72]. **c**, Unlike developmental migrations, which occur over hours to days, metastasis occurs over years and sometimes decades. For any given patient, there is a limited number of snapshots of their disease. These snapshots reveal that collective invasion is prevalent in primary tumours and that circulating tumour cell (CTC) clusters are present in the blood of patients across the stages of metastatic progression. Paired with genomic studies that have demonstrated polyclonality of metastases at distant sites and experimental studies in animal models, these clinical observations suggest that tumour cell clusters make outsized contributions to successful metastatic dissemination. As patients develop fulminant metastatic disease, CTC clusters are detected in high abundance in peripheral blood, accompanied frequently by inflammatory and thrombotic complications including stroke, lymphangitic carcinomatosis, and pulmonary embolism (PE).

can also guide migrating cells to close the wound[217–219]. Another physical cue presents the major directional cue for the migrating kidney tubules of zebrafish, which are guided by fluid flow through the tube lumen[15] (Fig. 1c). However, how cells detect flow at their apical surfaces and then use this information to orient the migration machinery at their basal surfaces remains unknown.

External cues guiding collective cancer migration

By comparison with the developmental models described above, cancer cells experience a broader gamut of microenvironments during their collective migration. Tumour microenvironments display non-homeostatic matrix organization, biophysical properties and cell–cell interactions that diverge markedly from those of normal tissues. Further, the lack of a predetermined destination means that the external cues that influence cancer cell motility tend to be spatially and temporally heterogeneous. For example, migrating cancer cells experience distinct cues when they invade regions of dense fibroblast-rich stroma, lipid-rich adipocytes or hard tissues such as bone and muscle. Elegant studies have established that mechanical properties such as tissue confinement and stiffness strongly shape the potential of cancer cells to collectively migrate and in some cases even dictate their potential to undergo molecular EMT[122,172,210,213,220–223]. As in developmental collective migrations, however, evidence is emerging that multicellular cancer cohorts are not only shaped by their local microenvironments but can reshape their surroundings in ways distinct from those of individual cancer cells and through using properties of collective guidance, reinforce their directional persistence.

One such property is the ability of collectively migrating tumour cells to interpret chemotactic, topotactic, durotactic and galvanotactic cues differently from individually migrating counterparts[100,220,221,224,225]. Tumour collectives can detect shallower gradients of these cues by integrating directional information throughout the collective[221,224,226,227]. For example, in a model of collective durotaxis, contractile tensions generated in edge cells are transmitted across the multicellular cluster through cell–cell junctions, increasing the spatial range of durotactic sensitivity[221,224]. Likewise, in a model of collective chemotaxis, mammary epithelial organoids can sense weak EGF chemotactic gradients, which individual cells cannot detect, through cell–cell communication using gap junctions[227]. In addition, tumour collectives can sometimes even move in the opposite direction from that of an individual cell[226]. For example, whereas single lymphoma cells are more likely to migrate against the gradient, lymphoma cell aggregates migrate towards it, owing to the ability of clusters to move fresh cells to the leader cell position, thereby replenishing surface expression of chemotactic receptors. Remarkably, the choice to move up or down the gradient also appears to be predetermined in individual tumour subtypes[228,229]. For example, glioma cells preferentially migrate towards less stiff regions, instead of more stiff in the case of breast cancer cells[228]. This process appears to be dependent in part on the optimal matching of how the cytoskeleton interacts with focal adhesions inside the cell and stiffness of the local microenvironment outside the cell to achieve maximal traction force. In each of these cases, a core question is how these varied sensory cues are integrated. In some cases, such as durotaxis, mechanosensing through the actomyosin network is an obvious sensing mechanism, but in many other scenarios, the molecular mechanism for signal integration remains to be defined.

Tumour collectives can also pattern their local microenvironment to create polarity and enhance directional persistence. This phenomenon is classically associated with the alignment, proteolytic degradation, stiffening or cross-linking of collagen fibres and other ECM components to form tracks that facilitate follower cell migration[36,98,220,230–232]. But in addition, akin to developmental processes, self-generated gradients of chemoattractants can increase directional persistence of tumour cells by integrating information across the cohort to optimize path selection. Melanoma and pancreatic cancer cells locally degrade lysophosphatidic acid (LPA) to reshape

Box 3 | Epithelial versus mesenchymal characteristics in collective cell migration

Epithelial–mesenchymal transition (EMT) is a form of cellular plasticity first discovered in developing tissues and often implicated in cancer[269,270]. It is the process by which stationary epithelial cells with established cell–cell junctions and apicobasal polarity transition into individualized, motile, mesenchymal cells with front–rear polarity[271]. Collectively migrating cells frequently retain one or more characteristics of epithelia including cell–cell junctions and apicobasal polarity. For example, neural crest cells are largely mesenchymal, yet they retain the cell–cell junctions needed to coordinate their collective movement. Further, motile intestinal epithelial cells have such strong apicobasal polarity and cell–cell junctions that they can perform their barrier function and vectorial transport of nutrients as they migrate, and yet their basal surfaces exhibit the front–rear polarity associated with crawling mesenchymal cells[7]. Because of these hybrid characteristics, collectively migrating cells are often said to show 'partial EMT', 'intermediate EMT' or 'epithelial–mesenchymal plasticity'[271]. Instead of either/or, an alternative model is that collective migration and guidance are promoted cooperatively by cells in different states along the EMT continuum.

At the transcriptional level, EMT is associated with a canonical set of transcription factors that induce the cell state transition and promote migration[271]. These EMT transcription factors have well-characterized roles in single-cell migration but also roles in collective migration that are coming into view. For example, neural crest cells rely on EMT transcription factors for their exit from the neural tube and subsequent collective motility[272–274]. Likewise, forced expression of EMT transcription factors in some cancer cells can induce collective migration, circulating tumour cell clusters and polyclonal metastasis[114,188,275]. Single-cell transcriptomics and lineage tracing studies have also identified a continuum of EMT states in cancers, and early–intermediate or more epithelial-like EMT states but not late EMT states were found to be more metastatic[117,276–278]. It is important to note, however, that other transcriptional programmes, such as those that control aspects of cell fate, can also confer a migratory phenotype, with a prime example being the key part played by the CCAAT-enhancer-binding protein (C/EBP) family transcription factor, Slbo, in border cell migration[12,279,280]. Similarly, collective migration of cancer cells is supported by lineage plasticity between different differentiation states, as seen in breast, melanoma and colon cancer, suggesting that there are multiple ways to achieve the molecular transition required for collective migration[95,106,281–283]. Whether such factors overlap with EMT transcription factors or operate independently of EMT remains to be defined.

In addition, studies of collective migration have revealed emergent properties that challenge the notion that migration is governed principally by a few cells with more EMT-like states. For example, it has long been assumed that leader cells with more mesenchyme-like characteristics power the migration of follower cells with more epithelium-like characteristics. However, recent studies have revealed cases in various organisms and processes in which the bulk of the directed traction forces come from the rearward cells of the collective[77,87,88,257,284]. Likewise, studies of tumour tissue flows have found changes in mechanical plasticity mediated by changes in cell adhesion, crowding or cortical contractility[240,285]. These changes in physical properties induce tissue fluidization, in which a tissue goes from having a more solid-like state to a more liquid-like state, and in some cases driving persistent, 3D rotational motion[286–291]. These findings have suggested that a jamming–unjamming transition, a biophysical concept, alters migratory potential. In each of these examples, effective collective migration is best thought of holistically as involving interactions at the tissue level, instead of being mediated by the pulling action of a few tumour cells that fall along the EMT spectrum and are in association with a passive rear. The tissue, cellular and molecular states that govern these emergent programmes remain incompletely understood.

the gradient as a potential mechanism for information sharing across multiple cells[233–235]. In contrast to development, external cues not only shape multicellular behaviour but can also lead to transitions between individual and collective migration modes[172,236]. This switch is regulated by the local topographic landscape, particularly with respect to matrix rigidity and confinement, and by local gradients of transforming growth factor-β (TGFβ), EGF and SDF1 that alter cellular motility and cohesion[121,172,173]. Tumour cell collectives can also provide cues that influence the migratory behaviour of neighbouring individual cells[105]. In a mammary adenocarcinoma model, two tumour subpopulations coexist — a dominant, collectively migrating cell population and a minor, amoeboid-like single-cell population[105]. The tumour cells that invade collectively secrete the basement membrane protein and survival factor laminin-332, which increases the speed and directionality of the accompanying amoeboid cells. In many systems, a key challenge continues to be visualization of the gradient itself and how it influences and is influenced by the local tumour collective.

Finally, external cues from the local microenvironment have roles beyond collective invasion that are instrumental to form distant metastasis. Chemokines associated with self-generated gradients reoccur in distant organs where they are produced by bone stromal cells (SDF1) or by platelets (LPA) to promote metastatic colonization[237–239]. Likewise, shear stress from fluid flow normally limits tumour cell survival, and multicellular clusters are more resistant to this stress[61]. Although these external cues are broadly understood as metastasis promoting or metastasis limiting, the role of collective guidance in enabling tumour cells to robustly adapt to distant organ microenvironments is not yet understood.

Conclusion and perspective

In this Review, we detail the diverse mechanisms that collectively migrating cells use to coordinate their movements and navigate complex tissue environments. Importantly, however, the studies we highlight not only show 'how' cells migrate collectively but also suggest 'why' it is advantageous to do so, with four major themes emerging (Fig. 4b). First, cohorts can perform other processes in parallel with migration, including proliferation, differentiation, morphogenesis and, in the case of the intestinal lining, nutrient absorption. This ability to multitask ensures that developmental processes run on time, adult tissues remain vital and that cancer cells adapt to the fluctuating and often hostile environments through which they invade and disseminate. Second, cell collectives are generally resistant to the loss of individual cells or

mosaic loss of gene function — that is to say, individual cells are redundant. This allows for multicellular polarization and coordination in development to succeed when there are imprecise numbers of cells and for mutationally distinct clones of variable fitness within a cancer cluster to successfully metastasize to distant sites. Third, cell collectives actively shape the environment through which they move to augment their own migratory ability. From creating self-generated chemotactic and durotactic gradients, to sculpting tracks and tunnels in the ECM, collectives can induce enduring changes in their local microenvironment and long-range gradients that reinforce multicellular polarization. Fourth, intercellular adhesion and signalling within collectives also make the cells less sensitive to fluctuations in external cues and increase their ability to migrate persistently through their local surroundings. It is therefore not surprising that, in development, tissue repair and cancer, the collective mode of migration is the norm rather than the exception.

Although this Review focuses on studies of in vivo collective migration, it is important to note that the extent of our knowledge has benefited tremendously from in vitro and in silico experiments. In vitro engineered models have provided researchers with the flexibility to vary the biochemical and/or mechanical properties of the migratory environment, to impose different boundary conditions and to measure

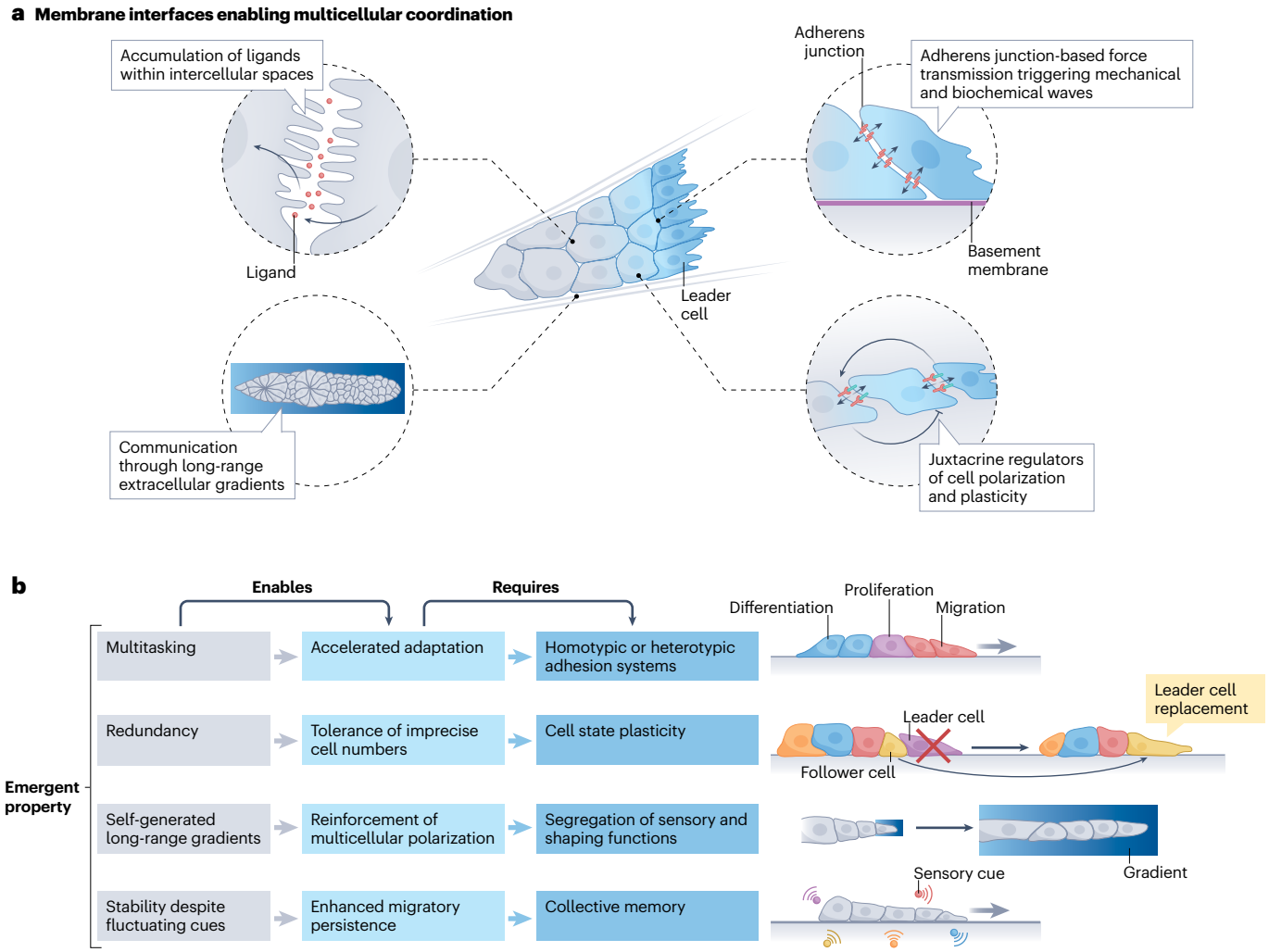


Fig. 4 | Intercellular coordination enables robust cell dynamics in collective migration. a, Migratory coordination between cells is enforced by multiple mechanisms operating at specific cell membrane interfaces including juxtacrine receptor–ligand interactions, adherens junction-based mechanotransduction, intercellular ligand accumulation and zones of localized matrix and gradient remodelling. In cancer, these collectively signalling interfaces also occur between tumour and cells of the tumour microenvironment. **b**, Intercellular coordination gives rise to emergent properties that promote tissue robustness in collective migrations in development and cancer. For example, multitasking of cells within collectives enables accelerated adaptation because different cells can migrate, proliferate and differentiate in synchrony. In turn, a key requirement is close cell contact supported by homotypic and heterotypic adhesion to support cohesion and intercellular communication. Likewise, collectives display high tolerance of imprecise cell numbers. This redundancy is mediated by migratory plasticity at transcriptional, protein and metabolic levels so that leader cells can be replenished. This role switching is important not only for leader cell functions, but also for segregation of sensory and shaping functions of the surrounding tissue microenvironment, such as generation of long-range spatial gradients. At the same time, collectively migrating cells display stable behaviours despite fluctuating cues and chemokine floods, suggesting the potential role of collective memory in enhancing migratory persistence. Together, these properties help to orchestrate execution of development, tissue repair and metastasis.

(or infer) the forces exerted by cells on their substrate and on each other[240–243]. This precise control has provided us with a quantitative understanding of how physical properties and geometrical constraints can shape collective migration. Indeed, the biophysical insights that result from in vitro studies invariably guide subsequent work in vivo where this information can be difficult, if not impossible, to obtain. Likewise, mathematical models have allowed us to efficiently evaluate a wide range of mechanisms by which a given type of collective migration might occur and rule 'in or out' mechanisms that cannot be readily tested with in vivo manipulations[244–247]. Models can also pinpoint the key experiments needed to distinguish between potential mechanisms. Of course, the in vivo studies provide the biological context for in vitro studies and allow the quantitative measurements that are needed to anchor the models. Thus, it is the synergistic interplay between all three approaches that ultimately drives the field forwards.

In the future, unravelling the mechanisms that allow cells to migrate collectively might enable us to even apply this knowledge to control the process and thereby provide a means to correct congenital defects, speed the healing of wounds and aid tissue engineers in creating functional neo-organs from naive stem cells. It could also enable the development of targeted therapeutics to thwart the ability of tumour cell collectives to metastasize successfully. A key conclusion of this Review is that multicellular migration supports key emergent properties that have large impacts on tissue-level behaviour. It is in tuning these properties that the tissue-level behaviours are likely to be controlled. However, there is still much to be learned before this will be possible, with some key outstanding questions highlighted below.

- What mechanisms confer robustness to the collective? Collectively migrating cells are remarkably robust to a wide range of perturbations[204,208]. Quantifying robust cell behaviour and understanding what makes cell collectives resilient will be key to being able to control their movement for therapeutic purposes in development, tissue repair and cancer.
- How do cell collectives integrate directional information from multiple sources? Cell collectives encounter a plethora of positive and negative cues that influence their direction of movement. A better understanding of how these cues are integrated and whether they act in a hierarchical or synergistic manner is needed if we want to guide cell collectives to the destinations we choose[248,249]. We further expect that these sensory mechanisms will differ between cell types and cell states, and a key objective now is to define the biophysical properties, biochemical transducers and genetic states that correspond to these integration modes.
- What are the individual molecular components that mediate intercellular coordination? Migrating collectives harbour intercellular contact zones with distinct signalling repertoires. Cadherin-based contacts are a major regulator of multicellular polarization and directed migration, but there are many other proteins that line these zones and engage in various signal–receptor relays. An understanding of these signalling components at the interface will be essential to target collective interactions therapeutically.
- How do collective migrations stop? In the posterior lateral line primordium, cells halt their movement by terminally differentiating just as they reach the end of the migration path. However, in other developmental contexts such as the rotational migration of the follicle cells, the path is never-ending and changes in differentiation state are less clear. Finding the 'kill switches' that induce cells to coordinately halt their migration could offer a way to stop cancer cells in their tracks.

Of course, paradigm-shifting discoveries often arise from the development of new technologies, and answering the questions above will almost certainly require new tools. Live imaging has long been the life blood of our discipline, and new microscopes that use super-resolution and light-sheet technologies can now reveal dynamic information about cell movement with unprecedented spatial and temporal resolution. However, these instruments need to become more accessible to the average lab, and new computational resources are needed to both store and analyse the enormous data files they produce. Likewise, recently developed methods to monitor the traction forces exerted on basement membrane by lateral line cells[88], or the metabolic state of leader cells in tumour cohorts[128], have revealed unexpected heterogeneities within cell collectives that are likely to be important for their migration. Building new live reporters that illuminate a wider range of dynamic cell states in living tissues should be a priority. Finally, in the cancer space, better tissue mimetic and organotypic models and technologies to look deeper into naturally occurring tumours and to systematically interrogate the heterogeneity in vivo are needed to monitor the diverse collective behaviours that emerge through the various phases of metastasis. In turn, these tools will enable the refinement of predictive models for collective migration across tissue types, developmental programmes and disease states. After all, when working at the tissue level, it is only by considering the system in its entirety that we begin to understand its workings.

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