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Collective cell migration in morphogenesis, regeneration and cancer

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Abstract | The collective migration of cells as a cohesive group is a hallmark of the tissue remodelling events that underlie embryonic morphogenesis, wound repair and cancer invasion. In such migration, cells move as sheets, strands, clusters or ducts rather than individually, and use similar actin- and myosin-mediated protrusions and guidance by extrinsic chemotactic and mechanical cues as used by single migratory cells. However, cadherin-based junctions between cells additionally maintain 'supracellular' properties, such as collective polarization, force generation, decision making and, eventually, complex tissue organization. Comparing different types of collective migration at the molecular and cellular level reveals a common mechanistic theme between developmental and cancer research.

Invasion
A hallmark of cancer, measured as cells breaking away from their origin through the basement membrane. We use this term to mean all forms of cell movement through three-dimensional tissue that involve a change in tissue structure and, eventually, tissue destruction.

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The migration of single cells is the best-studied mechanism of cell movement *in vitro* and is known to contribute to many physiological motility processes *in vivo*, such as development, immune surveillance and cancer metastasis[1,2]. Single cell migration allows cells to position themselves in tissues or secondary growths, as they do during morphogenesis and cancer, or to transiently pass through the tissue, as shown by immune cells. Collective migration is the second principal mode of cell movement[3,4]. This mode differs from single cell migration in that cells remain connected as they move, which results in migrating cohorts and varying degrees of tissue organization[3,5,6]. Collective migration of cohesive cell groups *in vivo* is particularly prevalent during embryogenesis and drives the formation of many complex tissues and organs. A similar collective behaviour, known as invasion, is displayed by many invasive tumour types. Whereas key aspects of single cell migration, such as the molecular control of protrusions, cell–extracellular matrix (ECM) interactions and shape generation[1,7–9], are well established and will not be discussed further here, the mechanisms that underlie different forms of collective migration are less well understood.

Here, we aim to define the cellular and molecular basis of collective migration using the best-studied examples, and discriminate it from other similar but mechanistically distinct types of cell movement in embryological development, tissue repair and cancer (BOX 1). We further discuss to what extent collective invasion in cancer can be considered to be dysregulated morphogenesis.

Defining collective cell migration

Three hallmarks characterize collective cell migration. First, the cells remain physically and functionally connected such that the integrity of cell–cell junctions is preserved during movement[4,6,10]. Second, multicellular polarity and 'supracellular' organization of the actin cytoskeleton generate traction and protrusion force for migration and maintain cell–cell junctions. Third, in most modes of collective migration, moving cell groups structurally modify the tissue along the migration path, either by clearing the track or by causing secondary ECM modification, including the deposition of a basement membrane.

Depending on the context, collective movement can occur by two-dimensional sheet migration across a tissue surface (FIG. 1a) or by multicellular strands or groups moving through a three-dimensional tissue scaffold (FIG. 1b–f). 2D sheets move as monolayers across tissues or along tissue clefts to form a single-layered epithelium (FIG. 1a) or, after subsequent proliferation and thickening, a multilayered epithelium. Multicellular 3D strands can 'differentiate' by basolateral polarization and the formation of an inner lumen (and therefore a tube structure), such as in morphogenic duct and gland formation (FIG. 1b) or vascular sprouting during angiogenesis (FIG. 1c), or they can move as a poorly organized strand-like mass, such as in invasive cancer (FIG. 1d). Alternatively, isolated groups or clusters can migrate through tissue if they detach from their origins; for example, border cells in the *Drosophila melanogaster* egg

REVIEWS

Collective migration needs to be distinguished from other types of multicellular translocation.

Invagination

Embryonic tissues can fold or invaginate by 'supracellular' constriction, an event that causes a directed shifting of cells together with surrounding tissues. Although this displacement resembles collective migration, it is actually a response to changes in the shape of other cells so that the cells move but do not change position relative to the underlying substrate. An example of invagination is dorsal closure in the *Drosophila melanogaster* embryo, whereby a large dorsal hole is sealed by an epithelium, the directed movement of which is almost entirely the result of apical constriction and apoptosis of the underlying amnioserosa cells[119].

Intercalation

Cell intercalation, also known as convergent extension, is similar to collective migration in that it leads to the directed coalescence of groups of cells at a common midpoint. However, rather than by directed migration, intercalation is driven by a coordinated series of cell–neighbour exchange events that can be autonomously controlled by myosin II constriction of certain cell–cell junctions (termed type I junctions)[120].

Expansive growth

Expansive growth of neoplastic lesions without active migration leads to a proliferation-driven position drift of daughter cells following cytokinesis. As a consequence, in a usually spherically growing tumour, cells passively translocate in a multicellular manner at bluntly shaped outward edges by a pushing mechanism.

Embolic transport

Embolic transport of cells and cell clusters in body fluids results from cluster detachment and passive displacement with the liquid stream. An example of embolic transport is the metastatic dissemination of cancer cell clumps following active engulfment by vascular endothelial growth factor-induced vascular sprouts[114,121]. As a consequence, the cell clumps gain access to the blood or lymph vessel system, passively detach from the primary site and undergo haematogenous or lymphatic dissemination[114,121].

Cell streaming

Cell streaming is the movement of individual cells behind each other to form single-cell chains, which lack tight cell–cell junctions and instead have repetitive, tip-like and loose cell–cell junctions. An example of cell streaming is the movement of neural crest cells from the somites to the epidermis in the chick embryo[122].

Basement membrane
A sheet-like layer of interwoven macromolecules, including laminin, collagen IV and link proteins, that structurally anchor an epithelium or endothelium to the adjacent interstitial tissue. Epithelial or endothelial cells and stromal cells cooperate and deposit the macromolecules from either side.

Border cell
One of a small cluster of cells that delaminate from the follicular epithelium of the *Drosophila melanogaster* egg chamber and migrate in a stereotypical pattern towards the developing oocyte. Ablation studies suggest that the function of border cells is to generate the micropyle, a structure at the dorso-anterior side of the oocyte that allows sperm entry.

chamber (FIG. 1e) and metastatic cancer cell clusters that penetrate the tissue stroma (FIG. 1f). Finally, the structures that the cells migrate through or along can vary. These structures can be interstitial tissue, such as connective tissue composed of fibrillar collagen, or a tissue predominantly formed by other cells, such as the *D. melanogaster* egg chamber comprising so-called nurse cells.

These distinct forms of collective migration serve different purposes. Simple 2D monolayers of cells move either constitutively across an intact basement membrane, such as the gut intestinal epithelium, or on demand, such as epidermal keratinocytes during wound closure. Alternatively, sprouting ducts and glands often comprise distinct cell types that move together and form a ductal tree or network. Collective migration in lower eukaryotes, such as in *Dictyostelium discoideum*, comprises similar actin dynamics and cell–cell binding to collective migration in multicellular vertebrates, as defined here, but it lacks defined interactions with the surrounding tissue environment and perhaps differs in how front–rear polarity is induced (BOX 2). Thus, the term collective migration applies to many forms and purposes of cohesive cell movement, which are all variations of the same fundamental process.

Models for collective cell migration

Different *in vitro* and *in vivo* experimental models are suitable for the study of the mechanisms of collective migration in vertebrate systems (TABLE 1).

In vitro models. 2D *in vitro* models include the popular scratch wound assay that allows polarization, force generation and mechanisms of cell–cell cohesion to be studied during the movement of confluent monolayers[7,11,12]. The collective invasion of finger-like cell strands into 3D ECM can be modelled *in vitro* by overlaying 3D scaffolds with cells, which then generate vertical invasions into the tissue matrix[13], or by implanting multicellular spheroids that generate horizontal invasions into a 3D ECM culture[14,15]. To take stromal cells and stroma-derived growth factors into account, live tissue can be explanted into 3D ECM cultures to cause cellular emigration as a single invasion pattern or, in the cases of cancer invasion and vascular sprouting (the aortic ring assay), as collective invasion patterns[16,17].

In vivo models. Many different forms of collective migration are observed in developing embryos of diffent species, but most mechanistic insights have been obtained from *D. melanogaster* and zebrafish models as they offer the ability to combine genetics with *in vivo* imaging approaches. In *D. melanogaster*, genetic studies of tracheal network branching or border cell migration have greatly advanced our understanding of collective migration[18,19]. In zebrafish, the migrating primordium of the mechanosensory lateral line organ is an example of a collectively migrating epithelium that becomes organized during migration[20]. Vascular sprouting *in vivo* is monitored by the matrigel plug assay, leading to *de novo* blood vessel invasion into an otherwise cell-free implant[21]. Alternatively, vascular sprouting can be observed by intravital imaging of spontaneous or injury-induced corneal, retinal or subcutaneous vessel formation in mice[22,23], or of the developing intersegmental vessels in zebrafish[24]. Direct evidence for collective invasion of cancer cells was recently obtained by injecting 3D spheroids into the deep dermis of mice that were monitored through a window chamber[25]. Indirect evidence for collective invasion of cancer cells is apparent from histopathological analysis of human cancer lesions, in which neoplastic multicellular strands and masses have crossed the tissue boundaries and have extended into the tumour stroma while retaining intact cell–cell junctions[26].

Given the complexity and versatility of the process and the impact of tissue-derived signals, *in vivo* models coupled to live-cell imaging generally provide the highest fidelity, whereas simpler *in vitro* models are better suited to molecular screens and high-resolution subcellular and molecular imaging.

Mechanisms of collective migration

The common molecular principles of collective migration will first be summarized in general, using examples from different models (TABLE 1), and then discussed in detail for each context. Irrespective of the diversity

Glossary

Neural crest
A population of migrating, pluripotent cells that appears transiently in the dorsal neuroectoderm. In the chick embryo, neural crest cells move as loosely associated strands or streams throughout the entire embryo and give rise to different tissues, including craniofacial bones and cartilage, the enteric and peripheral nervous systems and pigment cells.

Stroma
Interstitial tissue consisting of extracellular matrix and mesenchymal cells. The interface between stroma and adjacent epithelia and vessels is formed by a basement membrane layer.

Lateral line
A series of mechanosensory hair cell organs along the skin in fish and amphibia that detect changes in the surrounding water. Its precursor consists of neurogenic placodes, which migrate along defined paths and deposit clusters of cells behind them. These clusters differentiate into sensory hair cells that are analogous to those of the mammalian inner ear.

Matrigel plug assay
An experiment in which tumour cells are suspended in matrigel solution and injected into a mammal, usually a mouse or rat. Because of the avascular matrigel barrier, vessels from the host sprout into the transplant and generate a *de novo* vessel network.

Adherens junction
A punctated or linear cell–cell adhesion that contains cadherins and nectin, which are coupled to the actomyosin cytoskeleton by the adaptors α-, β- and γ-catenin and afadin (also known as AF6), respectively. Adherens junctions are dynamic structures that undergo continuous remodelling and provide cell–cell adhesion and signalling.

Integrin
A heterodimeric protein that consists of an α- and a β-chain that both mediate extracellular ligand binding and intracellular engagement of cytoskeletal and signalling proteins. Integrins provide adhesion and mechanotransduction as well as intracellular signal transduction.
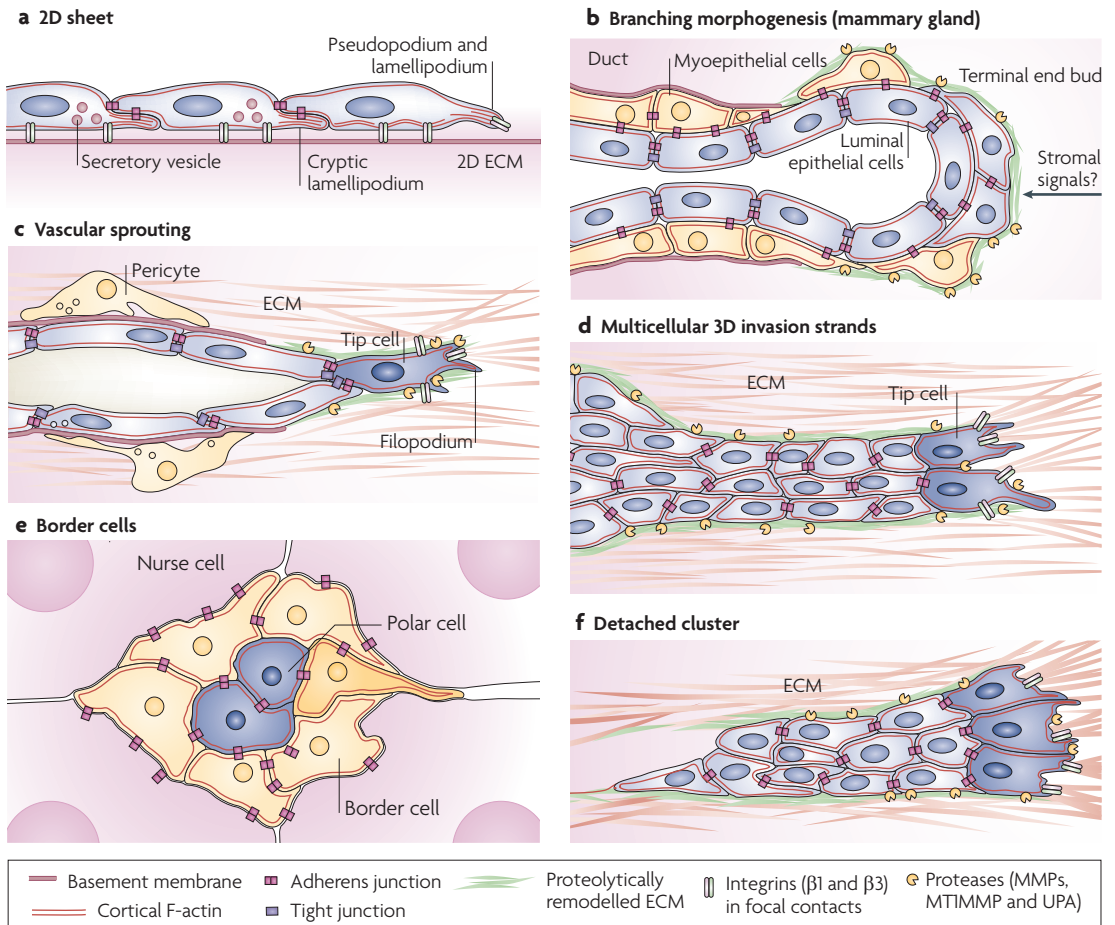

Figure 1 | **Types and variants of collective cell migration.** Cell morphology and cell–cell and cell–extracellular matrix (ECM) adhesion in different forms of collective migration. **a** | A coherent epidermal monolayer moving across a two-dimensional ECM substrate. Actin-rich pseudopodia and lamellipodia lead the migration and follower cells connect through adherens junctions. Cells interact with the basement membrane, deposited previously by secretory vesicles, through integrins in focal contacts. **b** | Terminal end bud sprouting in the developing mammary gland during branching morphogenesis. Induced by stromal signals, the end bud extends from a duct through the protrusive movement of tight junction-connected luminal epithelial cells and loosely connected myoepithelial cells. After proteases released from the bud have locally degraded the pre-existing ECM, secondary remodelling leads to the deposition of a basement membrane around the duct. **c** | Vascular sprouting in newly forming or regenerating vessels. A tip cell with filopodial protrusions leads the migration and a basement membrane deposited by both endothelial cells and pericytes serves as a guidance track. **d** | Invasion of poorly differentiated multicellular masses and elongated strands in cancer. **e** | Border cell cluster consisting of mobile outer cells and two less mobile polar cells migrating along cell–cell junctions of nurse cells in the *Drosophila melanogaster* egg chamber. **f** | Collective invasion of detached cancer cells that are moving as a small cluster. F-actin, filamentous actin; MT1MMP, membrane type 1 matrix metalloproteinase (also known as MMP14); UPA, urokinase-type plasminogen activator.

of collective migration modes, the underlying cellular and molecular mechanisms of collective migration all require cell–cell cohesion, collective cell polarization and coordination of cytoskeletal activity, guidance by chemical and physical signals, and a collective position change relative to the substrate. This group behaviour further requires supracellular cytoskeletal organization; that is, the cytoskeletal dynamics is shared between multiple cells to function as a single unit to jointly generate force, migration tracks and secondary ECM remodelling. Last, collective movement often involves intimate interaction with accessory stromal cells that release polarity-inducing and pro-migratory factors.

Cell–cell cohesion and coupling. Cell–cell adhesion is mediated by adherens junction proteins, including cadherins, other immunoglobulin superfamily members and integrins, all of which directly or indirectly connect to the actin and/or intermediate filament cytoskeleton and thereby provide mechanically robust but dynamic coupling. Many migrating cell collectives are derived from, or related to, epithelia and thus display cadherin-based interactions, particularly adherens junctions[27]. Cadherin–cadherin binding between cells can be rapidly remodelled and thus allow cell sorting and a change in cell position in the group[28,29]. Homophilic cell–cell adhesion (that is, symmetrical adhesions composed of the same components in both cell types) and

Box 2 | **Collective migration in *Dictyostelium discoideum***

One of the best-studied examples of collective migration in lower organisms is that displayed by the social amoeba *Dictyostelium discoideum*[123]. *D. discoideum* cells normally migrate as individuals; however, under starvation, cells undergo a transition from individual to collective migration and stream together to form a multicellular slug comprising several thousand cells. Early aggregation is achieved by individual cell streaming in a head to tail manner, coordinated by intercellular signalling by the chemoattractant cyclic AMP, which is released from the rear of each chemotaxing cell[124]. This polarized secretion results in the alignment of moving cells with loose front–rear interactions that are successively stabilized by the Ca^{2+}-independent cell adhesion molecule GP80 (REF. 125). With further stability of cell–cell junctions, the moving slug forms an inner cell core encased by slime sheath. Here, the migration of leader and follower cells is again coordinated by cAMP, which spreads as waves from the tip of the slug rearwards[126]. Despite their mechanical stringency, cell–cell contacts in the slug remain highly dynamic, which allows for considerable internal rearrangement and cell sorting despite ongoing slug movement[127]. Thus, *D. discoideum* provides a simple but powerful model of collective migration, whereby multicellular polarity is coordinated by internally produced chemoattractants, a mechanism that remains to be shown in higher organisms.

coupling to the cortical actin cytoskeleton are mediated by epithelial, neural or vascular endothelial cadherins (E-cadherin, N-cadherin or VE-cadherin) in epithelium formation, stromal cell–cell contacts and angiogenesis, respectively[30–33]. Cadherin-based junctions are important in branching morphogenesis of the mammary ducts and the trachea, in epidermal regeneration, in the sprouting of blood vessels and in different invasive cancers[30–33]. In both morphogenesis and cancer models, the loss of E-cadherin results in weakened cell junctions followed by cell detachment and the onset of a single-cell mode of migration, termed the epithelial–mesenchymal transition (EMT). This effect implicates E-cadherin as the dominant mediator of collective cell interactions, the loss of which may or may not be compensated for by other cell–cell adhesion pathways[31,34–36].

Other immunoglobulin family members that mediate cell–cell binding are the neural cell adhesion molecule (NCAM) proteins, activated leukocyte cell adhesion molecule (ALCAM; also known as CD166) and L1CAM[30,31,37,38]. These alternative, homophilic N-cadherin and non-cadherin adhesion systems are often upregulated after the downmodulation of E-cadherin, which results in higher migration capability, and therefore are upregulated with the transition from a quiescent, less mobile state to an activated, mobile state that retains a certain number of cell–cell junctions[34,35,37–40]. In addition to their well-defined role in mediating cell–substrate interactions, integrins contribute to cell–cell cohesion indirectly through intercellular ECM components, such as by the binding of $\alpha5\beta1$ integrin to intercellular deposits of fibronectin[41] or by the binding of $\alpha6\beta1$ integrin to intercellular laminin[42].

In branching epithelia, sprouting vessels and epithelial cancer, cell–cell junctions also contain desmosomal proteins, which include desmocollins and members of the junctional adhesion molecule family, the loss of which favours cell detachment and EMT-like cell scattering[43,44]. Likewise, tight junction-related proteins (claudin 1, claudin 4, occludin and ZO1) are localized apically to cadherin-based adherens junctions in migrating epithelia[45,46]. Consistent with functional cell–cell coupling, the gap junction proteins CX43 and CX26 (also known as GJA1 and GJB2, respectively) are present in cell–cell junctions of sprouting epithelia and invading cancer types[47–49], yet their specific contribution to collective migration is unclear.

Polarity mechanisms. Several mechanisms polarize the cell cohort into 'leader' or 'pioneer' cells that guide 'followers' at their rear[50]. This front–rear asymmetry is a feature of all migrating collectives described to date. Leader cells in the front row or 'tip' display distinct, polarized morphologies, detect extracellular guidance cues and generate greater cytoskeletal dynamics than follower cells in the cohort[50]. Important polarity mechanisms include a genetically determined differentiation into a protrusive leading tip cell fate and a less dynamic stalk cell fate[13,23,24]; the asymmetric stiffening of cortical actomyosin networks mediated by Rho GTPases and myosin II[50,51]; and polarized remodelling of the ECM by proteolytic degradation and/or release of pro-migratory degradation products[14,52,53]. In multicellular strands, such as vessels and branching ducts, collective polarity further results from lateral confinement of the cell strand by secondary ECM modification, including the degradation of chemokines and ECM components[54] and the deposition of basement membrane components[55,56].

The differences between leaders and followers are associated with clear differences in cell morphology and gene expression. Whereas cells at the leading edge are often less ordered and mesenchyme-like, cells at the rear tend to form more tightly packaged assemblies, such as rosettes or tubular networks. Rear portions often have tight junctions that tend to be absent from leading cells[57]. Such polarity differences might result from the differential expression of surface receptors, such as the chemokine receptors CXCR4 and CXCR7, in front cells compared with rear cells[58].

Extracellular induction of cell polarization in the direction of migration is determined by different mechanisms, including chemokines and growth factors that might be either freely diffusing (chemotaxis) or tethered to the ECM macromolecules (haptotaxis), leading to local receptor-mediated signalling and cell polarization[59]. Soluble factors are either produced by stromal cells in a paracrine manner[60] or are released from cells in the group in an autocrine or juxtacrine manner[58]. Collective migration-inducing signals include chemokines, such as stromal cell-derived factor 1 (SDF1; also known as CXCL12), and members of the fibroblast growth factor (FGF) and transforming

Epithelial–mesenchymal transition
(EMT). The detachment of individual cells from an epithelium after downmodulation of cell–cell junctions, followed by single cell migration. The concept of EMT was established for morphogenic delamination of single cells into the mesenchyme and is discussed here in the context of early steps of cancer invasion.

Desmosomal protein
Desmoglein 1–4 and desmocollin 1–3 connect through desmosomal adaptor proteins (plakoglobin, plakophilin, desmoplakin and desmocollin) to the intermediate filament cytoskeleton. These cadherins form homophilic adhesions and provide mechanically strong intercellular junctions between epithelial cells.

Tight junction
A linear cell–cell adhesion complex in polarized epithelial and endothelial cells. Mediated by homophilic adhesion proteins, junction adhesion molecules, occludin and claudins, tight junctions form a tight barrier for the regulation of liquid, ion and nutrient flow across the epithelial barrier and contribute to cell polarity and signalling.

Pseudopodium
A morphologically dynamic cylindrical cell protrusion of <3 μm thickness. Pseudopodia are controlled by the small GTPase Rac and CDC42, result from rapid filamentous actin polymerization, and allow cells to elongate, probe and adhere to other cells and to the extracellular matrix.

Lamellipodium
A flat, cellular protrusion that is rich in branched actin filaments. Filament formation and branching are controlled by the small GTPase Rac and downstream effectors, including the actin-related protein (Arp)2/3 complex and formins, including mammalian diaphanous 1 (mDIA1; also known as DIAPH1) and mDIA2 (also known as DIAPH3).

growth factor-β (TGFβ) families[20,50,61]. Preferential expression of substrate-binding integrins in leader cells can generate polarized attachment to the substrate and traction-mediated translocation[11,50,62,63]. After binding to native collagen of the interstitial tissue, β1 integrins cooperate with epithelial discoidin domain-containing receptor 1 (DDR1) to activate focal adhesion kinase (FAK; also known as PTK2) and protein Tyr kinase 2 (PYK2; also known as PTK2B), which signal through the mechanosensory docking and signalling protein p130 CRK-associated substrate (p130CAS) and the small Ras-like GTPase RAP1, respectively, to induce the upregulation of N-cadherin and individual as well as collective cell movement[59].

An alternative to pulling by the front row is pushing from the rear. This mechanism might be employed during branching morphogenesis in the mammary gland, in which a mechanically stiff stalk drives the blunt-shaped leading front, which is devoid of pseudopodia and lamellipodia[32]. A further, and arguably the least efficient, alternative to pulling by the front row is the poorly or non-coordinated slow translocation of non-polarized, randomly moving cells that fill the open space from the edge (collective random walk)[12,50]. In conclusion, front–rear asymmetry can either be genetically hard-wired, such that leader and follower cells are specified from the onset, or can result from a temporary, functional state that renders the cell collective more responsive and adaptive to the environment than the individual cell.

Cytoskeletal organization and force generation. The molecular principles of actin turnover and polarized force generated by moving cell groups are similar to those in the migration of individual cells, but they are shared and coordinated between cells at different positions. The cortical actin network in the cell group shows supracellular organization, such that anterior protrusion activities and posterior retraction dynamics involve many cells[16,50,62,64]. The mechanisms of supracellular cytoskeletal organization are not clear, but they probably reside in the combined actions of cadherin- and gap-junctional cell–cell coupling, as well as in the paracrine release of cytokines and growth factors.

Table 1 | **Models to study collective cell migration**

Model	Cell type, tissue or species	Substrate or organ	Parameters assessed	Comments	Refs
In vitro *assay*					
2D scratch wound assay	Epithelial cells (keratinocytes and colonic epithelium)	Plastic or glass	Width of the defect, cohesiveness of the cell–cell junctions and individual or collective cell polarization and migration	Defined starting point is suited for monitoring focal contact dynamics and the assay is suited for automated high-content segmentation and image analysis; the planar 2D surface and the lack of ECM components are disadvantages	7,11,12, 50,128
3D sprouting and invasion assay from mesenchymal cells overlaid on to a 3D ECM or implanted as a multicellular spheroid	Endothelial, epithelial or mesenchymal cells	3D ECM (containing fibrin and collagen) or functionalized hydrogels	Strand length, cell number and extracellular proteolysis	Can include stromal components and supports high-resolution microscopy pre- and post-fixation; requires 3D imaging for analysis	13,14, 129
3D organ explant culture	Mammary ducts or primary cancer tissue	3D matrigel or 3D collagen	Strand length, branching and location of epithelial and stromal cells	Recapitulates *in vivo* behaviour with fidelity and monitors functional subsets	15–17, 32
In vivo *process*					
Branching morphogenesis	Zebrafish or fly	Trachea or mammary ducts	Position change and morphology	A striking homology between mammals and insects	18,19
Border cell migration	Fly	Egg chamber	Position change, cell polarity and gene expression	Specialized model for cluster migration through ECM-free, cell-rich tissue	130
Lateral line migration	Zebrafish	Cranial placode	Position change and receptor expression	Suited for high-resolution *in vivo* microscopy and genetic interference; small cell number limits potential for biochemical analysis	58,63
Skin wound healing	Mouse or pig	Epidermis or dermis	Speed of wound closure	The *in vivo* equivalent of the *in vitro* scratch wound assay	131
Vascular sprouting into a matrigel plug	Mouse or rat	Dermis	Vessel density post-fixation and calibre	Usually combined with co-injection of cancer cells; poorly visible by intravital microscopy	21
Cancer invasion	Mouse or human cancer cells	Deep vascularized dermis	Invasion depth and track route	Requires 3D injection to recapitulate human invasion characteristics	25

2D, two-dimensional; 3D, three-dimensional; ECM, extracellular matrix.

Likewise, little is known about how mechanotransduction is propagated during collective cell migration. In 2D sheets, the front row of cells forms a continuous rim of lamellipodia that bridge multiple cell bodies and drive the leading edge forwards[3,7,11]. In scratch wound assays, the leading edge undergoes integrin-mediated binding to extracellular ligands, followed by the recruitment of cytoskeletal adaptor proteins, which include cortactin, paxilin, talin and vinculin, and thereby couples integrins to the actin cytoskeleton[7,65]. Pseudopodia and filopodia are controlled by the Rho GTPases Rac and CDC42, respectively. Their direct and indirect downstream effectors include the formin actin nucleator mammalian diaphanous 2 (DIA2; also known as DIAPH3) and the insulin receptor Tyr kinase substrate p53 (IRSp53; also known as BAIAP2), which link Rac to the actin nucleators WAVE2 and Ena/VASP-like protein. Rac and CDC42 thereby enhance actin filament growth and control cell protrusion and outward deformation of the plasma membrane[7,8]. The force generated by leader cells is sufficient to pull and coordinate migration persistence of five to ten cells behind the front edge[50]. In some but not all 2D sheet models, not only leader but also follower cells develop polarized lamellipodia in basolateral regions of moving cell sheets, which help maintain the coordinated translocation[11,66].

In the case of collective 3D tissue invasion, tip cells lack lamellipodia but protrude by filopodia or pseudopodia, as observed in sprouting blood vessels or invading cancer strands, respectively[14,67–69]. Actin-rich cell protrusions not only establish directionality and sense and attach to tissue structures at the cell front, they also cross-signal rearwards to and foster attachment of follower cells through E-cadherin[67,70]. p120 catenin has a dual function as it interacts with cortactin, an activator of actin-related protein (Arp)2/3 complex-dependent actin polymerization, to generate leading edge protrusions and simultaneously strengthens the actin cortex along the cell–cell junctions[66]. If collective migration occurs along or through a multicellular tissue rather than an interstitial ECM, direct E-cadherin–E-cadherin adhesions, rather than integrin-based adhesions, mediate the interaction between the motile group and the adjacent tissue cells[71]. Thus, distinct receptor–ligand pairs mediate collective force coupling to the actin cytoskeleton in different contexts.

Track generation and secondary ECM remodelling. Collective invasion through 3D interstitial tissue occurs either along or through immature, provisional ECM, such as hyaluronan-, fibronectin- or fibrin-rich tissue, or along or through mature tissue consisting of interstitial fibrillar collagen. In both cases, two types of modification of the ECM are associated with collective cell migration: the formation of hollow, tube-like ECM defects and secondary lateral ECM modification, such as the deposition of basement membrane components. In 3D tissues, collective cell migration is spatially more constrained than single cell migration. To generate tracks wide enough to accommodate multicellular strands, collective cell migration through a 3D ECM is dependent on local ECM degradation and the generation of a path of least mechanical resistance[13,14]. In interstitial fibrillar collagen, an initially small degradation track is generated by the tip cell using the surface-localized protease MT1MMP (membrane type 1 matrix metalloproteinase; also known as MMP14) and is enlarged by additional ECM degradation by follower cells[54,72]. Alternatively, collective invasion strands can use preformed anatomic tracks of least resistance, such as pre-existing basement membrane, vascular tracks or, even, the lumen of lymph vessels[73].

In addition to ECM degradation, epithelial sheets, strands and tubes deposit basement membrane components, including laminins, nidogen 1, perlecan and type IV collagen, to generate a smooth scaffold and guidance track between the cell group and the interstitial ECM[74,75] (FIG. 2a). The basement membrane supports almost resistance-free lateral cell gliding and the polar engagement of focal contacts with adhesion receptors into basolateral compartments as the cells move[11,56].

Function of accessory cells. As the cell group moves, there is often extensive communication with cells of the surrounding stroma, which leads to the recruitment of stromal cells, including fibroblasts, pericytes and myoepithelial cells. During skin regeneration, epidermal keratinocytes cooperate with dermal fibroblasts to build the basement membrane by jointly depositing laminin 1, laminin 5, collagen IV and nidogens[55,76]. In sprouting blood vessels, the perivascular basement membrane is jointly deposited by endothelial cells and pericytes and serves as a guidance track for the dynamic vessel structure[75]. In collective cancer cell groups, fibroblasts cooperate with the leading edge, remodel the ECM and guide the cancer cells along the newly formed track[13]. Whereas fibroblasts use RhoA and Rho-associated protein kinase 1 (ROCK1) to move and remodel the ECM in a MT1MMP-dependent manner, cancer cells depend on CDC42 to follow the tracks, which suggests that distinct collective migration programmes exist[13].

In conclusion, despite their morphological and functional diversity, all forms of collective migration depend on dynamic and adaptive cell–cell cohesion, polarized actomyosin motor function and signalling crosstalk in the cell cluster and towards the surrounding tissue. Most of the information on the role of tissue-specific regulators of guidance and polarity that are needed for collective cell migration stems from *in vivo* forward-genetics studies in morphogenesis models, whereas mechanisms of cell–cell cohesion and cell–ECM interaction and remodelling were mostly established using *in vitro* models of mammary gland development, vascular and epidermal regeneration, and cancer invasion.

Morphogenic collective cell migration
Collective migration is one of the hallmarks of embryonic morphogenesis. Genetic studies in embryonic model systems have not only helped to identify ligand–receptor pairs that are involved in persistent directional migration and guidance *in vivo*, but have also shown how they mediate the initial breaking of symmetry that determines the leader–follower organization of the group.

Filopodium
A finger-like and highly dynamic cell protrusion, 1 µm in diameter and up to 5 µm in length. Filopodia are formed by anterograde polymerization of actin bundles in parallel and lack microtubules. Their formation is controlled by the small GTPase CDC42.
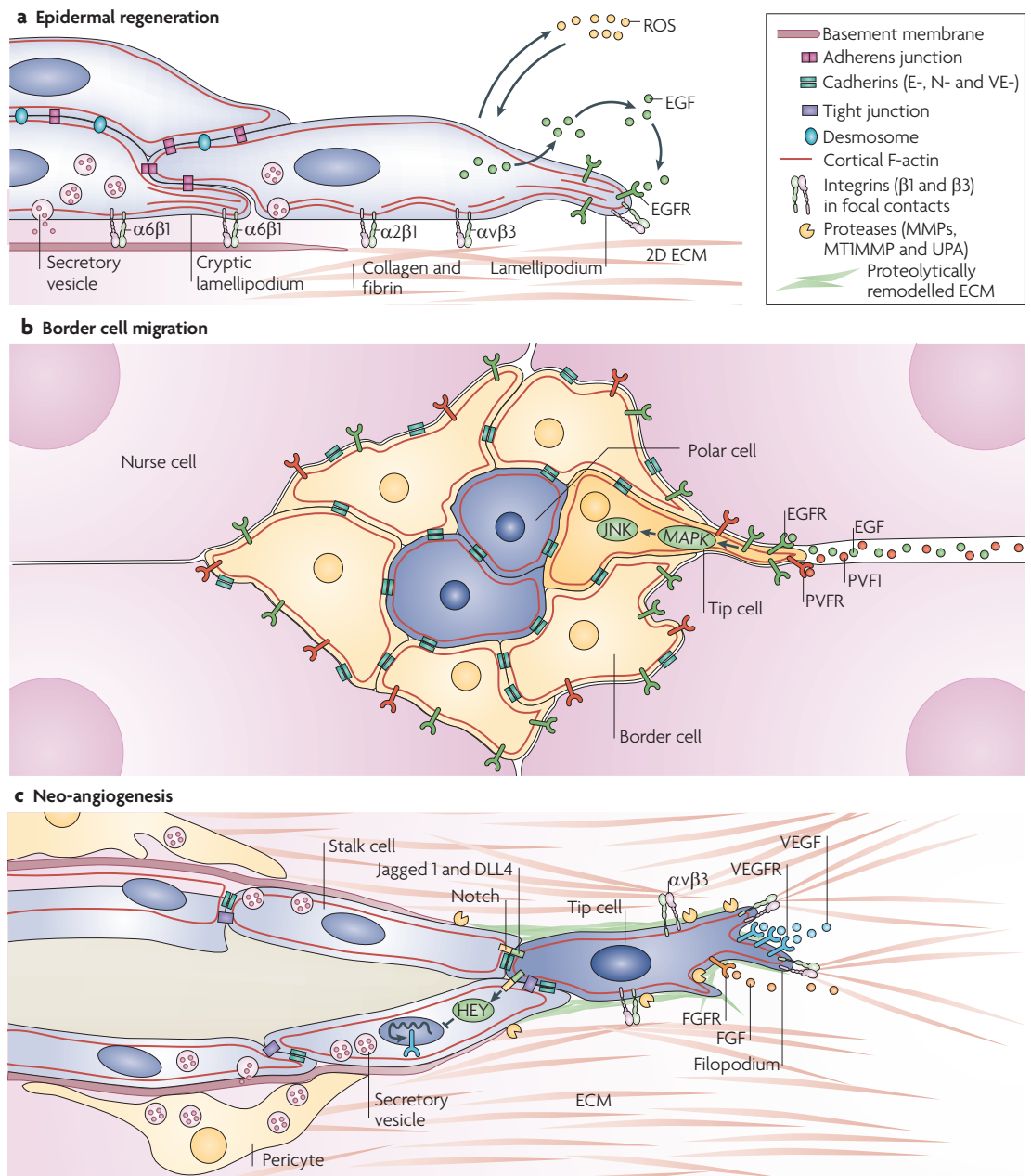
Figure 2 | Molecular mechanisms of different forms of collective migration. a | Actin organization, cell–cell cohesion and extracellular matrix (ECM) remodelling during epidermal regeneration. Whereas the first cell row, with its actin-rich lamellipodia, interacts at focal contacts with the two-dimensional substrate through α2β1 integrin or αvβ3 integrin with collagen- or fibrin-rich wound surfaces, respectively, α6β1 integrin in follower cells interacts with the basement membrane that has been secreted by the front row of migrating cells. Front row polarity is enhanced by autocrine and paracrine secretion of epidermal growth factor (EGF) binding to its receptor (EGFR), and by reactive oxygen species (ROS). **b** | Polarity induction and guidance in border cell migration. EGF and PVF1 (platelet-derived growth factor- and vascular endothelial growth factor (VEGF)-related factor 1) bind to their respective receptors EGFR and PVFR and induce preferential mitogen-activated protein kinase (MAPK) signalling and JUN N-terminal kinase (JNK)-mediated gene transcription in the leading tip cell. The cluster of border cells, organized by two central, poorly mobile polar cells, moves along the cell–cell interface with nurse cells by epithelial (E)-cadherin-mediated interactions. **c** | Polarity induction, guidance and branching during neo-angiogenesis (angiogenic sprouting) in morphogenesis and regeneration. Tip cell differentiation is maintained by FGFR (fibroblast growth factor receptor) and VEGFR (VEGF receptor) signalling and leads to the expression of the Notch ligands Delta-like 4 (DLL4) and Jagged 1, which signal to rear cells through Notch. Notch, in turn, signals through the cellular transcriptional repressor protein HEY, silences VEGFR transcription and maintains stalk cell differentiation. Whereas the tip cell, with filopodial protrusions, engages αvβ3 integrin with membrane type 1 matrix metalloproteinase (MT1MMP; also known as MMP14) to proteolytically remodel the ECM, the stalk cells, together with stromal pericytes, deposit a basement membrane. Cell–cell contacts are mediated by vascular endothelial (VE)-cadherins and tight junctions. F-actin, filamentous actin; N-cadherin, neural cadherin; UPA; urokinase-type plasminogen activator.

Border cells. During oogenesis in *D. melanogaster*, border cells form a tightly packed cluster of six to ten follicle cells surrounding two less motile polar cells; together, these migrate along the nurse cells in the egg chamber[6,71,77]. Border cells generate anterior Rac-dependent actin-rich protrusions in one or two leading cells[78,79], traction for migration by direct E-cadherin-mediated cell–cell contact with nurse cells[80,81] and coordinated multicellular rear retraction mediated by myosin II[82].

The directional migration of the border cell cluster occurs in two sequential phases that provide distinct types of directional guidance information[83] (FIG. 2b). During the first 'posterior' migration phase, border cells migrate directly towards the oocyte under the combined guidance of two classes of ligand, EGF (epidermal growth factor) and PVF1 (platelet-derived growth factor- and vascular endothelial growth factor (VEGF)-related factor 1) and PVF2, which are secreted by the oocyte and presumably form diffusion gradients[83]. The subsequent 'dorsal' migration phase depends on the detection of EGF alone. Genetic mosaic experiments, in which cells that lack different intracellular regulators were juxtaposed with normal cells, revealed that during the first phase a single cell of the cluster becomes selected as the leader by signalling through EGF receptors, similar to canonical chemoattractant receptor signalling[84]. In the second phase, cluster polarity is determined collectively by differences in absolute signalling levels between cells, so that cells with constitutively active EGF receptor signalling reach a competitive advantage over wild-type neighbours to become leaders. The importance of cell–cell cohesion in collective decision making was also shown by reducing JUN N-terminal kinase (JNK) signalling, which causes a partial EMT-like dissociation of the border cell cluster and results in a loss of coordinated migration, with border cells moving in random directions[85,86]. Border cell clusters thus provide an *in vivo* example of a distinct collective mechanism of polarity and guidance.

Tracheal branching morphogenesis. The *D. melanogaster* tracheal network is a powerful *in vivo* model for genetic and *in vivo* imaging studies of the morphogenesis of branched tubular organs[18,19]. As tracheogenesis occurs without mitosis, collective migration can be studied without interference from cell proliferation. Tracheogenesis begins when an ellipse-shaped ectodermal placode invaginates and becomes exposed to the FGF ligand Breathless, which is expressed by defined patches of surrounding cells[87]. Single cells that are closest to the FGF patches subsequently adopt a tip cell fate, produce dynamic cytoskeletal protrusions, including pseudopodia and filopodia, and migrate towards the FGF source[68,69]. High levels of FGF signalling in tip cells additionally increase the expression of the Notch ligand Delta, which, in turn, silences actin dynamics in neighbouring stalk cells by rendering them less responsive to the FGF signal[88,89]. Tip cell-led protrusions form the primary branches of the tracheal network and the process is reiterated in subsequent branching steps. Therefore, the pattern of tracheal branching emerges from the interplay between a spatially restricted extracellular chemoattractant and collective decision making that uses a Notch–Delta negative-feedback loop to restrict the number of tip cells that respond to this chemoattractant.

Mammary gland development. During puberty, the mammary gland develops by the branching morphogenesis of the terminal end buds (TEBs)[90]. Each TEB extends from primary ducts through the synchronous collective migration of two distinct cell types: the luminal epithelial cells that form the bud tip and myoepithelial cells that ensheath and stabilize the bud shaft[32] (FIG. 1b). Whereas the myoepithelial cells are more loosely connected, the junctions between luminal cells contain ZO1 towards the luminal surface, which is consistent with baso-apical polarity during sprouting[32]. Live-cell imaging of organoid cultures reveals that TEB formation is distinct from other types of branching morphogenesis owing to the absence of clear leader cells at the extending bud tip, which instead forms a blunt-shaped multilayered bulb with cells continually exchanging positions[32]. Mammary gland sprouting and branching are dependent on FGF receptor 2 expression[91], implicating FGF as a key regulator of different types of collective morphogenic sprouting. Because the tip lacks actin-based cell protrusions, TEB movement could be the consequence of a pushing, rather than a pulling, mechanism.

Zebrafish lateral line. The primordium of the zebrafish lateral line organ is a cohesive cohort of more than 100 cells that migrate along the flank of the embryo and become assembled into a series of connected epithelial rosette-like mechanosensory organs[92]. The directional persistence of the group is determined by a Sdf1–Cxcr4 chemokine signalling axis[93] (FIG. 3). Whereas all cells express Cxcr4, only cells at the leading tip need to activate this receptor to direct cell strand polarity of the entire tissue[63]. While the cell group still moves, Fgf10, which is expressed in discrete spots in the adjacent tissue, induces the radial epithelialization and the apical constriction of follower cells to generate the rosette-like organ progenitors[57,94]. The deceleration and subsequent arrest of migration correlates with the expression of a second Sdf1 receptor, Cxcr7, at the trailing edge[61,95]. Although the precise function of Cxcr7 is unclear, studies from other systems suggest that it might be an 'Sdf1 sink' that sequesters Sdf1 and thereby suppresses Cxcr4 activity in trailing regions[96]. The spatially restricted expression pattern of Cxcr7 in trailing regions is affected in embryos deficient in FGF signalling, implicating FGF in the modulation of chemokine receptor expression and signalling[58,94]. The lateral line thus allows the interplay between multicellular movement and differentiation.

Collective movement in regeneration
Similar to morphogenesis, tissue repair after wounding requires the creation or recreation of functional multicellular organ and tissue patterns, such as regenerative collective migration during vessel sprouting and the closure of an epithelium.
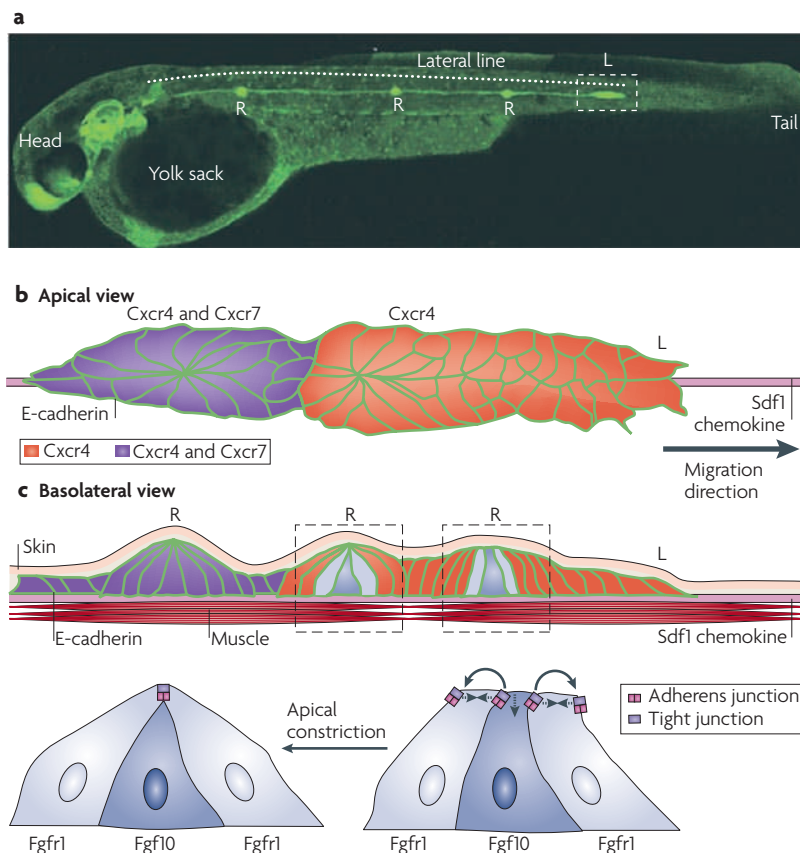
Figure 3 | The lateral line primordium couples collective migration to differentiation.
a | Confocal micrograph of the zebrafish lateral line primordium labelled with a glycosyl phosphatidylinositol–green fluorescent protein as a membrane marker, allowing the leading edge (L) and rosettes (R) to be distinguished. **b** | Apical depiction of the primordium migrating along a pre-patterned stripe of the chemokine stromal cell-derived factor 1 (Sdf1; also known as Cxcl12, shown in pink), which it detects using the Cxcr4 receptor (shown in red). Trailing regions express an additional Sdf1 receptor, Cxcr7 (overlap of Cxcr4 and Cxcr7 shown in purple). Cell–cell contacts are mediated by epithelial (E)-cadherin. **c** | From a basolateral view, cells in the primordium can be seen to assemble into rosettes by an internal fibroblast growth factor (FGF) signalling circuit. Fgf10 is released in a spot-like manner from a few cells in the cluster (shown in blue) and acts in a paracrine manner on FGF receptor 1 (Fgfr1)-positive surrounding cells (shown in grey), which form rosettes by concerted apical constriction of adherens and tight junctions.

Vascular sprouting. In both morphogenesis and regeneration, collective strands of endothelial cells penetrate a provisional fibronectin- and fibrin-rich wound matrix to form a network of new vessels[56,97]. Endothelial cells in sprouts are guided by a single tip cell that protrudes multiple actin-rich filopodia and is followed by a multicellular stalk of endothelial cells, which are connected by VE-cadherin at cell–cell junctions and successively form an inner lumen[23,24,98] (FIG. 2c). By these means, the same extracellular ligand, VEGF, controls both the directed migration of tip cells and the proliferation of following stalk cells. Elegant experiments carried out on the mouse retina have revealed that a differential response to VEGF is generated by extracellular gradients of VEGF isoforms with distinct heparan sulphate-binding and, thus, different retention properties to ECM and cell surfaces[99]. Similar to tracheal morphogenesis, the Notch–Delta axis also determines tip and stalk cell fate in angiogenic sprouts in zebrafish

and mice[23,24]. For preferential VEGFR3 expression in tip cells, Delta-like 4 (DLL4)–Notch signalling needs to remain silenced, whereas in stalk cells Notch signalling is active and limits VEGFR3 expression, thereby preventing migratory protrusion and outbranching[23,24].

Epidermal wound closure. During repair of the skin or the corneal epithelium after injury, collective cell migration of keratinocytes occurs across the provisional wound bed leading to epidermal wound closure[100,101]. Keratinocytes move initially as a monolayer sheet that, after hours to days, undergoes multilayered stratification and forms *de novo* epidermis. The initial cell rows use $\alpha2\beta1$, $\alpha5\beta1$ and $\alpha v\beta3$ integrins to generate force on a collagen and fibrin substrate[102] and cells in the rearward position use $\alpha6$ integrin to move along the new basement membrane as it is synthesized[103]. The cell–cell contacts during migration are mediated by E-cadherin, desmoglein 1, desmoglein 3 and desmosomes and are stabilized by the cortical actin cytoskeleton, which is dependent on the small GTPase Rho[104,105]. Keratinocytes further receive signals from stromal fibroblasts, including FGF, keratinocyte growth factor and TGFβ, which generate intracellular mitogen-activated protein kinase (MAPK) signalling, which propagates in a wave-like manner from cell to cell in a rearward direction[106]. By moving as a continuous multicellular sheet that retains mechanically robust cell–cell connections and early basement membrane deposition[107], the closing wound provides immediate coverage and preliminary protection of the underlying regenerating tissue.

Collective cell migration in cancer

Collective invasion is prevalent in many cancer types. However, because cancer is a slow, long-term process that is not readily amenable to direct microscopic observation, the mechanisms of collective cell dynamics in cancer are less well studied to date compared with morphogenesis and regeneration.

Morphological pattern. In histopathological sections, most epithelial cancers display the hallmarks of collective invasion into surrounding tissues, including intact cell–cell junctions, expression of E-cadherin and other cadherins and expression of other homophilic cell–cell adhesion receptors in tumour regions deep inside the normal stroma[4,25,26]. Many cancers, including not completely de-differentiated forms of rhabdomyosarcoma, oral squamous cell carcinoma, colorectal carcinoma, melanoma and breast cancer, exhibit predominantly collective cell invasion when explanted *in vitro*[16,62,108]. Likewise, cell lines from colorectal carcinoma, breast cancer, fibrosarcoma and endometrial carcinoma move as 2D sheets or as 3D strands in scratch wound or spheroid-invasion cultures (O. Iliyna, K. Wolf, M. Ott and P.F., unpublished observations).

Molecular mechanisms. Whereas multicellular invasion in cancer is highly reminiscent of morphogenic movements (BOX 3), the mechanisms and kinetics of *in vivo* lesions are poorly understood. In cancer invasion,

## Box 3 | Cancer-mimicking morphogenic movements?

Common to cellular and molecular principles of collective cell migration, invading cancers seem to reactivate embryonic pathways and patterns of cell movement (see the figure). However, this is dependent on the degree of de-differentiation and the concomitant loss of cell–cell and cell–extracellular matrix adhesion receptors; an arguably greater variability of cell cohesivity and organization; and the lack of checkpoints that otherwise limit uncontrolled expansion. These conditions thereby limit further expansion.

Typically, those tissues that use collective migration during morphogenesis will regain similar invasion patterns during neoplastic progression. For example, most highly differentiated epithelial cancers show collective invasion patterns in histopathological sections, thus representing a defunct form of branching morphogenesis or regenerative epithelial sheet migration[4,8,26]. In contrast to viewing cancer invasion as a predominantly single cell phenomenon, collective invasion suggests a coordinated process in which cancer cells form a 'socially' invading mass that, similar to morphogenic movement, slowly remodels but then ultimately destroys adjacent tissue structures.

However, if monitored in a time-resolved manner, invasion programmes are a continuous range of states from stringently collective, through partial to complete but temporary individualization, rather than discrete states. The related concepts of epithelial–mesenchymal transition (EMT) and mesenchymal–epithelial transition (MET), as well as 'partial EMT/MET' in cancer[34,35], aim to discriminate such different types of invasion. Furthermore, the role of leader (or pioneer) and follower cell interactions in neoplasia might be homologous to genetically or epigenetically determined stable or temporary division of tasks (job sharing) among cells in the same group. Likewise, many morphogenic signalling pathways are relevant in cancer, such as Wnt, fibroblast growth factor and bone morphogenetic protein signalling, yet their roles in collective cell dynamics in cancer remain to be shown. In conclusion, homologies between morphogenic and neoplastic collective migration stresses the need to better link and distil experimental data from both fields and, most notably, to reassess developmental models in human cancer contexts.

The top panel of the figure shows the morphological pattern and epithelial (E)-cadherin-mediated cell–cell junctions during collective invasion of the lateral line in zebrafish *in vivo* (labelled with glycosyl phosphatidylinositol–green fluorescent protein as a membrane marker). The middle panel shows human MCF-7 mammary carcinoma cells invading a three-dimensional collagen matrix (labelled with E-cadherin; shown in green) and the bottom panel shows collective melanoma cell strands approaching a vessel in the deep dermis of a primary human lesion *in situ*. 4′,6′-Diamidino-2-phenylindole (DAPI)-stained nuclei are shown in blue.
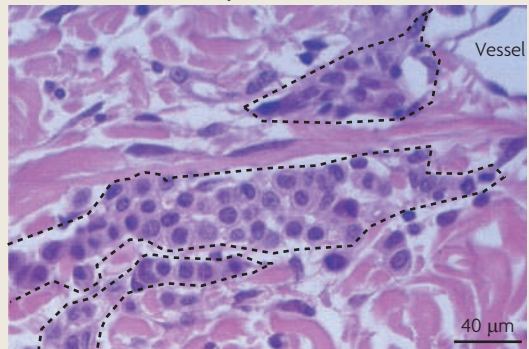

Lateral line primordium — Tip cells

Mammary carcinoma — Tip cell — 20 μm
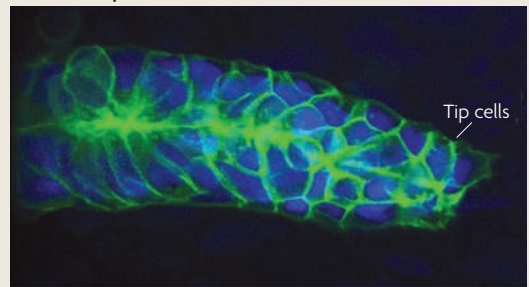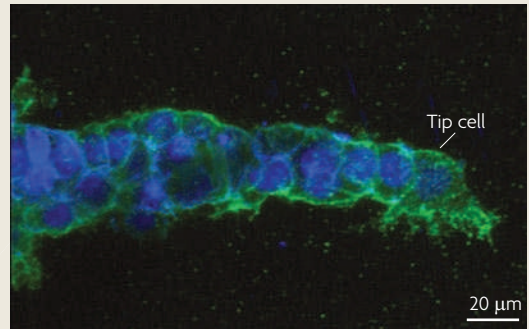
Human melanoma in deep dermis — Vessel — 40 μm

Mesenchymal–epithelial transition
An experimentally induced aggregation of moving individual cells to form a multicellular complex that maintains cell–cell junctions. Its role in physiological contexts is unclear.

Gap junction
An intercellular hexameric channel between directly adjacent cells that transfers ions, small compounds and messengers between the cytosol of both cells and provides adhesive coupling independent of channel function. Gap junctions synchronize mechanical and metabolic cell functions in multicellular tissues.

cell surface proteases, including MT1MMP and MMP2, become engaged and degrade the ECM substrate along both the leading lamellipodium in 2D sheet migration of colon adenocarcinoma cells in liquid culture, and in tip cells during fibrosarcoma invasion into 3D fibrillar collagen[14,52]. This implicates structural ECM remodelling as an early event in collective cancer cell movement. Invasive tumour masses *in vitro* and *in vivo* express cell–cell adhesion molecules, including E- and N-cadherin, L1CAM, desmosomal and tight junction proteins and, in correlation with a high cell density, gap junction proteins. Consequently, cancer cells exhibit gap junctional communication, which suggests cell–cell coupling and multicellular organization[31,49,109–111].

Collective invasion of cells in oral squamous cell carcinoma *in vitro* is stimulated by paracrine SDF1 and hepatocyte growth factor, which are produced by fibroblasts of the tumour stroma in response to cancer-derived cytokines, such as interleukin 1α (IL-1α)[112]. Likewise, FGF, TGFβ and other morphogenic proteins that are involved in collective processes in morphogenesis contribute to cancer progression, but their specific contribution to collective cancer invasion remains unclear[34,35]. Although direct proof is presently lacking, local tissue remodelling caused by collective invasion, termed macropatterning of the ECM[14], might contribute to invasive tumour growth and consecutive tissue destruction[54]. In experimental metastasis models, clustered

Collective amoeboid transition
The detachment of amoeboid cells from a multicellular complex as a consequence of loosened cell–cell junctions. Detached cells then use a leukocyte-like amoeboid migration mode because of the low adhesion and traction force generated.

cancer cells survive in the blood stream and generate lung metastases[113,114], and in certain cancers, such as inflammatory breast cancer, multicellular strands travel inside lymphatic vessels[110] and are associated with a high risk for lymphatic metastasis[115]. However, the contribution of collective invasion to systemic haematogenous metastasis and overall prognosis remains unclear.

Plasticity of collective cancer cell invasion. Because intact and coordinated cell–cell junctions are critical for mass invasion, the gain or loss of cell–cell coupling determines whether cancer cells move collectively or individually, or use transition patterns. Pathways that lead to the down-regulation of E-cadherin, including growth factor and MAPK signalling[33,35,40], or the upregulation of extracellular MMP3, which cleaves E-cadherin[116], also initiate the upregulation of N-cadherin and the mesenchymal marker vimentin. These changes are followed by either collective strand-like migration, whereby cell–cell junctions remain intact (incomplete EMT)[33,40], or cause the loss of cell junctions followed by single cell detachment from the group and integrin-mediated mesenchymal invasion (complete EMT)[35].

Similar plasticity results from blockade of β1 integrin in collective invasion from primary melanoma explant cultures, which, similar to loss of E-cadherin in other models, causes single cell detachment and amoeboid migration (a process known as collective amoeboid transition)[62]. In an *in vitro* fibrosarcoma model, conversion from multicellular strands to amoeboid dissemination of single cells is obtained after interference with pericellular proteolysis, forcing cells to individualize and squeeze through small gaps and spaces in interstitial tissue[14,117]. Thus, rather than stopping the movement, interference with cell–cell and cell–ECM adhesion leads to transitions in cancer cell invasion modes[118]. Although the polarity and guidance mechanisms of collective cancer invasion are not clear, both pattern and tissue remodelling

capabilities strongly suggest that collective invasion in cancer recapitulates key steps of morphogenic movement in a dysregulated manner (BOX 3).

Conclusions and outlook

Collective cell migration provides an example of how many diverse cellular functions and behaviours, such as cell motility, cell–cell adhesion, signalling and ECM remodelling, combine to produce one concerted outcome — multicellular migration. With the advent of live-cell microscopy, many multicellular tissues have been shown to be much more dynamic than previously thought. We predict that many of these multicellular rearrangements will display some, if not all, of the defining characteristics of collective migration. Thus, rather than only distributing cells, collective cell dynamics contribute to building and maintaining patterned and functional tissues.

Whereas the framework of collective cell migration has gained impetus in recent years, we still lack a mechanistic understanding of many of the underlying concepts. In particular, it remains unclear as to how the various mechanical and chemical inputs from neighbouring cells or surrounding stroma become integrated to allow coordinated multicellular movement. Understanding the common rules and differences between different collective invasion programmes, in contrast to single cell movement, will lead to the development of strategies that either suppress or enhance collective movement in a defined manner. It is therefore significant that when compared at the molecular and cellular level, different types of collective cell migration reveal a common mechanistic theme. Consequently, regenerative and neoplastic collective movements are likely to recapitulate morphogenic movements and vice versa, albeit with different spatiotemporal regulation. Identifying collective migration as a shared theme might encourage greater links and cross-fertilization between morphogenesis, regeneration and cancer biology.

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FURTHER INFORMATION

Peter Friedl's homepages: http://www.ncmls.nl/NCMLS/MenuStructures/PI/theme2/PeterFriedl.asp

http://www.virchow.uni-wuerzburg.de/forschung_en/index.php?rubric=friedl_en

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