Collective Cell Migration

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guidance, cell polarity, adhesion, morphogenesis, cancer

Abstract

For all animals, cell migration is an essential and highly regulated process. Cells migrate to shape tissues, to vascularize tissues, in wound healing, and as part of the immune response. Unfortunately, tumor cells can also become migratory and invade surrounding tissues. Some cells migrate as individuals, but many cell types will, under physiological conditions, migrate collectively in tightly or loosely associated groups. This includes invasive tumor cells. This review discusses different types of collective cell migration, including sheet movement, sprouting and branching, streams, and free groups, and highlights recent findings that provide insight into cells' organization and behavior. Cells performing collective migration share many cell biological characteristics with independently migrating cells but, by affecting one another mechanically and via signaling, these cell groups are subject to additional regulation and constraints. New properties that emerge from this connectivity can contribute to shaping, guiding, and ultimately ensuring tissue function.

Contents

INTRODUCTION TO SINGLE-CELL AND COLLECTIVE CELL MIGRATION

Cell migration is an important process for animal development and physiology. A few cell types, principally of the immune system, are on the move for much of their life span and may be considered professional migrators. The behavior of these cells is well studied in tissue culture and to some extent in the physiological context in the animal (Halin et al. 2005). They are adept at responding quickly to unexpected stimuli and usually migrate alone. Many other cell types can move but only do so at a specific developmental time or in distinct situations. Their migration places, shapes, or repairs the tissue of which they are part. Importantly, such cells often move in groups rather than as singular cells. Cell migration in loosely or closely associated groups can be referred to as collective cell migration. This occurs in developmental contexts for cells such as neural crest, the vasculature, and many epithelial tissues, including in wound healing. Also, it has recently become appreciated that collective movement is highly relevant for tissue invasion by many types of tumor cells. This review describes examples of different types of collective cell migration and discusses recent results from these systems with particular emphasis on findings that illuminate general issues and questions pertaining to collective cell migration.

Cell migration at the single-cell level has been studied extensively over many decades (Ridley et al. 2003, Van Haastert & Devreotes 2004). In brief, migration of a typical cell can be described as follows (see also **Figure 1*a***): The cell expands by making protrusions, generally driven by actin polymerization; these can be large lamellipodia, small filopodia, and combinations thereof. Local cortical blebbing can also drive cell expansion. The cell needs adhesion to, and traction on, the substratum. Integrin-based focal adhesions, or related contacts with the extracellular matrix (ECM), can support traction. If the substrate is other cells, cell-cell adhesion molecules can mediate these contacts. Finally, the cell exerts a pulling force to translocate the cell body forward and also retracts its rear. Both of these generally require actin- and myosin-based contractions. These processes must be polarized within the cell such that there is at least transiently a front (more protrusion and adhesion) and a back (more pulling and less adhesion), or no movement occurs. Many migrating cells are induced to move in a particular direction by positive and negative guidance signals. In the absence of external guidance, cells may move randomly. It should be noted that details of how specific cell types move can differ quite a bit, including cell morphology, degree of polarization, migration speed, and dynamics, but the general features outlined above are always relevant.

To discuss collective cell migration, a definition is useful. A cell migration phenomenon can

ECM: extracellular matrix

be considered collective if cells move together, making contact at least some of the time, and if they affect one another while migrating. For illustration, see **Figure 1*b***: If cell 1 is physically coupled to cells 2 and 3, then its movement will depend on its own activity and on the behaviors of cells 2 and 3 (which may cooperate to promote movement or may impede it). The criterion of moving together is easy to evaluate by simple observation. The criterion of influencing one another is often inferred but not always established. However, the second criterion is important, because it distinguishes a group effect from many cells independently doing the same thing at the same time.

Some cell movements are definitively collective with the moving cells very tightly connected. For others, the degree of interdependence can be debated. Pure single-cell movement clearly also occurs in the animal, well-studied examples being immune cells and germ cells (Doitsidou et al. 2002, Halin et al. 2005, Kunwar et al. 2006, Redd et al. 2006, Reichman-Fried et al. 2004). As collectivity of movement is linked with cell-cell contact, the distinction between collective and single-cell migration also reflects behavior of epithelial versus mesenchymal cells. Completion of epithelial to mesenchymal transition (EMT) generally results in single-cell movement, whereas collective movement is seen without EMT or with incomplete EMT. For recent reviews on EMT, see Shook & Keller (2003), Thiery & Sleeman (2006), and Baum et al. (2008).

Why do cells move collectively if they can move individually? Collective migration can (*a*) keep a tissue or structure intact and continuous while remodeling it; (*b*) allow mobile cells to carry other, immobile cell types along; (*c*) allow migrating cells to influence each other, thereby ensuring appropriate cell distribution and shaping of a tissue; and (*d*) allow collective decisions that may be more robust for the system. Collective migration is one example of how multicellular organisms are not just a collection of independent cells but interdependent cells that act together to make a whole.

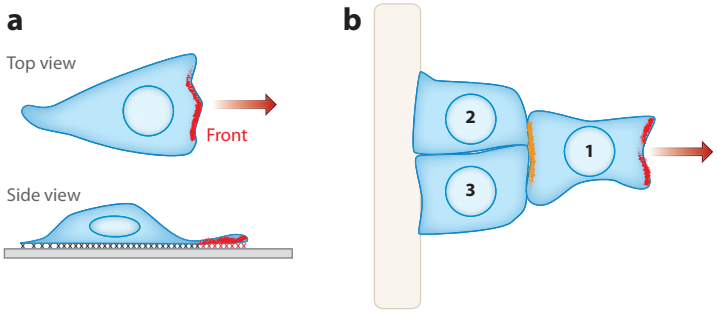

Figure 1

Basics in individual and collective cell migration. (*a*) A single cell migrating on a flat (2D) surface, seen from above (*top*) and from the side. Red shading indicates front membrane with more actin-protrusive activity. Also indicated in the lower panel are contacts with the substrate that allow traction. The quantity or quality of front adhesion may differ from the back. On specialized substrates the forces exerted by the cell can be measured. (*b*) Some basic elements of collective cell migration. Cell autonomous motility is important, but net cell movement is also interdependent: If cells 1, 2, and 3 are mechanically connected (cell-cell adhesion) and/or transmit contact-dependent signals, then the movement of cell 1 can be either constrained or enhanced by behaviors of cells 2 and 3. If cells 2 and 3 stretch or move forward, intercalate, or multiply, forward movement of cell 1 may be enhanced. Conversely, strong attachment to rigid and immotile cells will impede movement. In addition, cells may provide nonautonomous polarization effects: The front of cell 1 (*red*) may, in part, be defined as that opposite from where it is contacted by other cells (*orange*).

Traditional models for studying cell migration have relied on tissue culture: plating cells on a flat surface, a coverslip, and observing their motility. This is technically a superb model, because it allows high-quality imaging and easy manipulation, but it is also quite far from the normal situation that most cells encounter in the animal. The substrate is two-dimensional (2D), hard, and simple. The opposing cell surface encounters only liquid medium (**Figure 1*a***). These biophysical characteristics are far from physiological. The flat tissue culture system provides such technical advantages, however, that it remains a very powerful approach. Modifications of the traditional setup have been introduced to try to approximate natural, three-dimensional (3D) substrates such as the use of matrigel (Cukierman et al. 2001, Even-Ram & Yamada 2005, Griffith & Swartz 2006, Zaman et al. 2006). The 2D tissue culture system can also be used for studying some types of collective movement, for example, that of epithelial sheets. Many cell

EMT: epithelial-to-mesenchymal transition

types can perform 2D sheet migration, such as endothelial cells [e.g., human umbilical vein endothelial cells (HUVEC)] or kidney cells [Madin-Darby canine kidney cells (MDCK) cells]. These cells perform more complex collective movements in vivo or in 3D culture such as sprouting and branching. Thus, the behavior of particular cell types in 2D culture systems reflects some, but not all, features of normal physiological migration behaviors.

Human umbilical vein endothelial cells (HUVEC): primary endothelial cells

Madin-Darby canine kidney (MDCK) cells: commonly used epithelial cell line

Eph/Ephrin: ephrins are membrane-tethered ligands for Eph receptors; bidirectional signaling can occur

Generally, studying migrating animal cells in their natural environment poses significant challenges with respect to both imaging and manipulation. For the systems discussed in this review, these limitations have at least in part been overcome, and real-time imaging and analysis in situ is possible. In this context, it is also worth mentioning studies of the slime mold, *Dictyostelium discoidium*. This has been a very useful model for migration and chemotaxis of individual eukaryotic cells (Van Haastert & Devreotes 2004). As it is a free-living amoeba that can detect both food and the presence of other cells, detailed analysis and imaging can be done under close to physiological conditions. The amoebas can also organize themselves into a moving multicellular slug and perform collective movement (Weijer 2004). Readers are referred to recent reviews to learn more about this interesting model system (Van Haastert & Devreotes 2004, Weijer 2004). This review focuses on collective cell migrations directly relevant to animal physiology. Some of the movements to be discussed are generic and have clear examples in all or most animals studied, such as sheet movement and sprouting or branching behavior. Others are more specific, such as migration of the lateral line in zebrafish and border cells in *Drosophila*. All are reasonably well studied and have features that illustrate different aspects of collective cell migration and the regulatory mechanisms involved.

MOVEMENT OF CELLS WITHIN AN EPITHELIUM

Several examples of collective migration discussed below involve epithelial tissues and cell groups. Although epithelia are generally considered as a constrained environment where cells are fixed in position, it has been appreciated for some time that morphogenesis in early embryos, for example, convergence-extension, can involve cell movements within a tissue sheet (Solnica-Krezel 2005). Dramatic net tissue morphogenesis can occur when many cells in a tissue rearrange slightly but in a highly coordinated way (Keller 2006). Such cell rearrangements can exert force at the tissue level and can also respond to mechanical strain (Beloussov et al. 2000). The ability to image morphogenesis at single-cell resolution has also revealed cases of dramatic cell movements that occur without major changes in the tissue geometry (Chuai et al. 2006, Larsen et al. 2006). These findings highlight the inherent ability of cells within an epithelium to move relative to one another while retaining tissue integrity. The possibility of dynamic remodeling and/or lateral mobility of cadherin-mediated cell-cell adhesion complexes (Cavey et al. 2008, Kametani & Takeichi 2007, Nelson 2008) may provide the flexibility required for such cell rearrangements.

Embryonic tissues appear to have a relatively higher degree of mobility compared to adult differentiated epithelia. However, some differentiated epithelia, such as the intestinal epithelium, turn over constitutively; others, such as mammary glands, remodel occasionally. In such cases, cell rearrangements must occur, and recent analyses suggest that there is more cell movement than might be expected. In the intestinal epithelium, differentiated cells are constantly replaced, and cells must move from stem cell niches and proliferative zones to their ultimate destination. The net movement of cells is slow but directional. Mutants that disrupt Eph/Ephrin signaling cause increased cell intermingling, suggesting that cells are intrinsically quite motile but normally avoid straying into wrong territories by monitoring their neighbors (Batlle et al. 2002). Imaging of the mammary gland has shown that extracellular signal-regulated kinase (ERK) activation can induce movement of cells within intact acini

(Pearson & Hunter 2007). This may reflect the normal process of cell rearrangement that occurs during mammary gland morphogenesis (Ewald et al. 2008). Unraveling how such cell rearrangements are controlled will be interesting and possibly important for understanding cancer progression in these tissues.

CATEGORIES OF COLLECTIVE MIGRATION

Sheet Migration

One common type of collective cell movement that is well studied both in the natural contexts and in simplified culture systems is that of epithelial sheet migration (**Figure 2**). A characteristic of sheet migration is that the cells maintain close contact and continuity while the sheet moves forward. There is a clear front of the moving structure and a seemingly simple directionality of movement provided by where the free space is (**Figure 2*b*,*c***). As sheet movement essentially occurs in two dimensions, it is convenient for imaging. Specialized 2D substrates have been developed to measure strength and direction of forces exerted by migrating cells. One such study found that a migrating cell group exerted much larger forces than a single cell (du Roure et al. 2005), providing evidence for the collective nature of group movement. Primary cells and cell lines of epithelial or

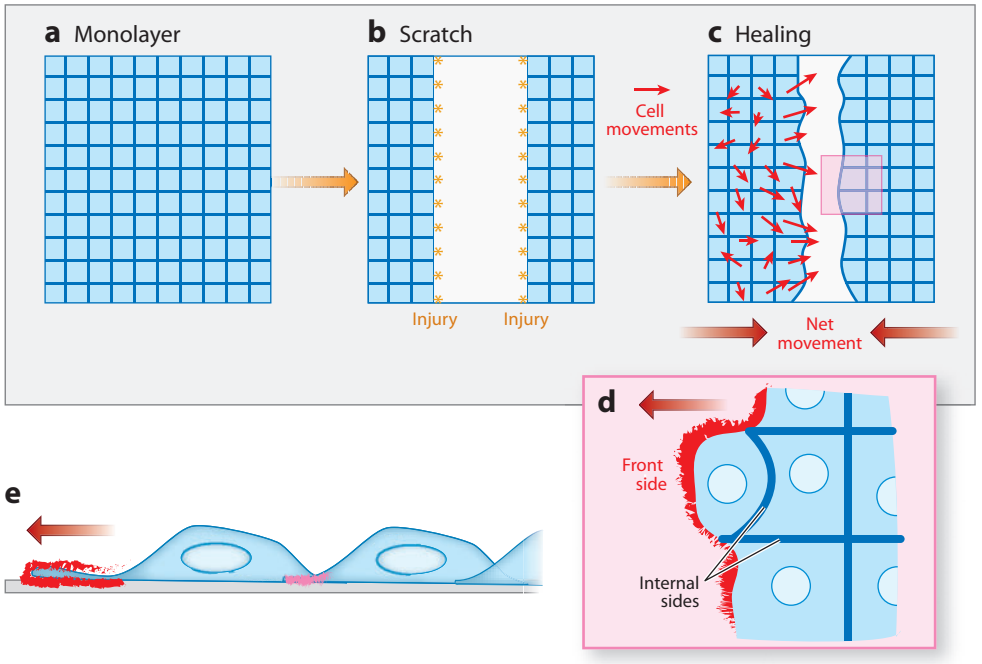

Figure 2

Sheet migration in 2D. (*a*) An unperturbed, confluent monolayer of (epithelial) cells, seen from above. (*b*) Upon mechanical scratching away of one sector of cells, edge cells may be injured (orange asterisks) and are now adjacent to free space—a gap (*white*). (*c*) The cell sheets move in to close the gap. Small red arrows indicate displacement vectors for individual cells at one time point. (*d*) Higher magnification of area from (*c*). Note how a front cell automatically has polarity, a front (*red*) surface abutting the free space and back surfaces. Internal cells do not automatically have a front. (*e*) Side view of cells moving in to fill the gap, with the front cell's free surface extension in red. Cells behind the front cell may also make direct extensions (*pink*), even if not quite as prominent.

FGF: fibroblast growth factor

Microtubule organizing center (MTOC): a region surrounding the centrioles with high microtubule nucleating activity (prominent in many tissue culture cells)

endothelial origin perform sheet migration if a gap is generated in a cellular monolayer, for example, by mechanically scratching away a broad sector of a confluent cell layer (**Figure 2*a*,*b***). The reaction to a scratch involves a specific response to cell injury at the scratch site as well as response to deconstraining cells perceiving the appearance of unoccupied substrate space (Nikolic et al. 2006, Poujade et al. 2007). Deconstraining is sufficient to elicit sheet movement (Block et al. 2004, Poujade et al. 2007). Cell proliferation may also occur under these conditions, but it is not required for most of the gap-filling response and can be experimentally separated from it (Poujade et al. 2007, Vitorino & Meyer 2008). It should be added that confluent fibroblastic cells can also respond to a scratch wound but appear to do so primarily as independent cells, not as cohorts (Matsubayashi et al. 2004). Finally, epithelial cells can perform variants of sheet migration that are also collective in nature (Biname et al. 2008, Haga et al. 2005).

A recent systematic analysis of gene requirements and cell behaviors in sheet migration of fibroblast growth factor (FGF)-stimulated HUVEC endothelial cell sheets provides a useful overview of the processes involved (Vitorino & Meyer 2008). The first set of conclusions from this and related studies concerns the contributions of individual cells within the sheet to net movement: The tracking of individual cells within the sheet (**Figure 2*c***) and detailed observations of cellular protrusions (**Figure 2*e***) indicate that both cells at the front and those behind it are actively motile (Farooqui & Fenteany 2005, Fenteany et al. 2000, Poujade et al. 2007, Vitorino & Meyer 2008). Cells at the front edge generally exhibit more protrusive and motile activity; those with extreme front behavior are defined as leaders or pioneers (Omelchenko et al. 2003, Poujade et al. 2007, Vitorino & Meyer 2008). Leader cells appear to emerge stochastically, but their abundance can be influenced by growth factors. Note that front cells have an induced polarity provided by the sheet, that is free edge versus cell-cell contact edge (red versus dark blue edges in **Figure 2*d***). Microtubules and the microtubule organizing center (MTOC) of these cells may be polarized as well, possibly induced by the same free edge. For physically connected sheets of cells, any specific increase in motile activity of such free edges increases the overall forward-directed migration. For example, directional movement of a HUVEC sheet is stimulated by uniform application of FGF and requires genes important for FGF perception (Vitorino & Meyer 2008). Such directional output for a cell group as a consequence of cell-cell interactions can be regarded as an emerging feature of collective cell migration.

Another characteristic of collective behavior found in a sheet is coordination between the movement vector of one cell and its neighbors (Poujade et al. 2007, Vitorino & Meyer 2008) (**Figure 2*c***). The fact that coordination is not perfect supports the observation that each cell makes an individual migratory contribution. The fact that coordination exists may primarily reflect significant cell-cell adhesion and mechanical coupling of the moving cells. However, there is also evidence for signaling interactions; for example, multicellular Ca^{2+} waves. Ca^{2+} waves may be transmitted from cell to cell by extracellular ATP rather than gap junctions and can be modulated by growth factors (Klepeis et al. 2001, 2004). A slower wave of coordinated ERK (MAP kinase) activation has been observed that may be initiated or augmented by the initial injury at sheet wounding (Nikolic et al. 2006). The ERK wave may be important for migration, and its propagation is, in turn, affected by the process of cell migration, suggesting it could be mechanically induced (Matsubayashi et al. 2004).

Sheet movement occurs in physiological contexts. Examples are wound healing, related developmental processes such as dorsal closure in *Drosophila*, and early morphogenetic movements in some animals (Martin & Parkhurst 2004, Solnica-Krezel 2005). If an epithelial hole is small, then wound closure may occur with the sheet surrounding, rather than abutting, the gap to be covered. Leading cells can form an actin-rich superstructure as a ring around the gap.

This has led to the hypothesis that gap closure occurs by a purse string mechanism, with contraction of the ring driving tissue movement (Young et al. 1993). This could represent extreme nonautonomy in morphogenesis with many cells passively following the pull of one edge-generated structure. However, physical cutting experiments, as well as genetic manipulations of subsets of cells, have shown that forward movement can occur without an intact purse string (Hutson et al. 2003, Jankovics & Brunner 2006, Kiehart et al. 2000). Measuring and modeling of forces in dorsal closure indicate that a combination of the purse string contraction, pulling from an adjacent tissue, and active cell autonomous forward movement of the sheet cells generates tissue translocation. Thus, sheet movement in vivo is likely to be more democratic and involve the processes outlined above for sheet movement in tissue culture. Notably, the full process of wound healing in skin is more complex than sheet migration in culture. It involves cells other than the epithelial layer as well as interactions with a fibrous clot. The latter adds mechanical strain to the process, which may explain why intermediate filaments are required for keratinocyte sheet migration in wounds (Long et al. 2006, Wong & Coulombe 2003).

Sprouting and Branching

Sprouting and branching are types of collective movement that can be used to generate elaborate cellular networks. Some sprouting and branching behaviors can be recapitulated in culture systems by placing cell clumps or tissue explants in 3D matrigels (Bruyere et al. 2008, O'Brien et al. 2002, Pollack et al. 1998). Sprouting behavior is characterized by the formation of a moving multicellular outgrowth from a preexisting structure. The outgrowth has a leading sprout, or tip cell, that maintains connection to other cells (**Figure 3*a–c***). As for front cells in sheets, the tip cell has automatic polarity with a free front end and an attached back end. However, the tip cell may have significant freedom in terms of direction of movement (in 3D), and

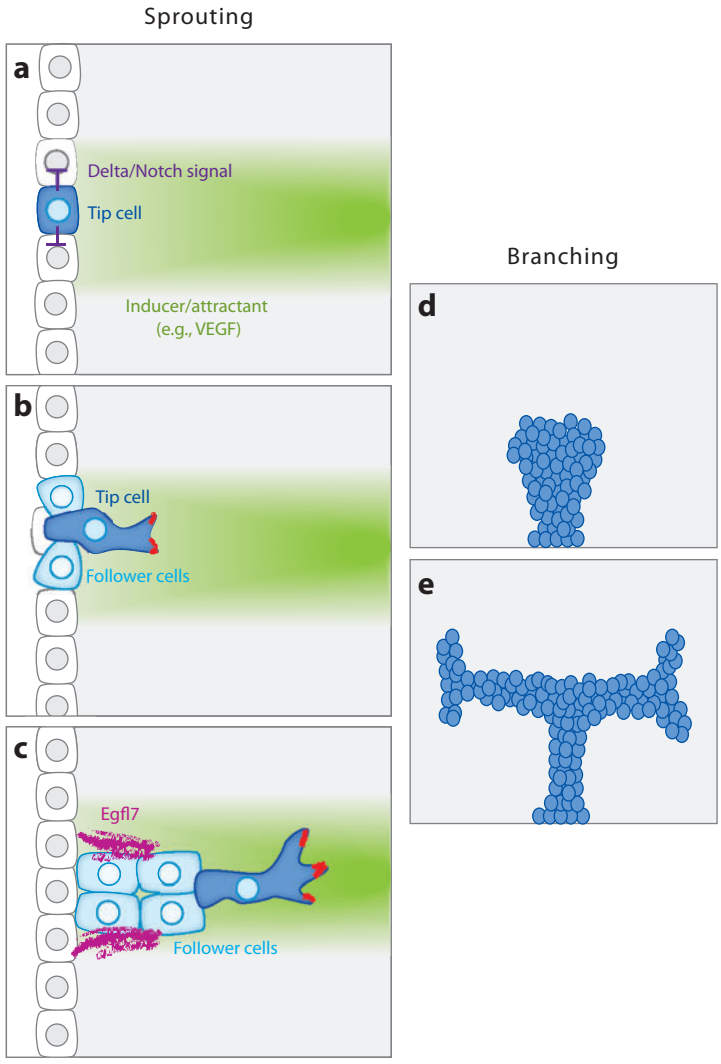

Figure 3

Sprouting and branching migration. (*a–c*) Model for initiation, growth, and guidance of a new sprout in the vasculature. (*a*) Tip cell fate is induced in one cell, triggered for example by vascular-endothelial growth factor (VEGF) and possibly other factors. By using Delta to activate Notch signaling in adjacent cells, the adjacent cells are prevented from being tip cells. (*b*) The tip cell becomes motile and initiates departure from the epithelium but remains attached to adjacent follower cells that are also able to reorganize. (*c*) The tip cell is actively guided toward the source of VEGF by chemoattraction. Meanwhile, follower cells make and extend the trunk, their proliferation possibly stimulated by VEGF. Specialized molecules deposited into the extracellular matrix (ECM) (e.g., Egfl7) can help define and maintain the overall shape of the outgrowth. (*d–e*) Branching morphogenesis involves the growth, shaping, and reshaping of large groups of cells into branched structures. By reiteration, the structure can become very elaborate in 3D. Cells may change position within a branching structure in an erratic manner.

RTK: receptor tyrosine kinase

Vascular-endothelial growth factor (VEGF): a family of growth factor RTK receptors (VEGFR)

external guidance influence can be crucial. Typical examples of such behavior during development include sprouting of endothelial cells to form vasculature in vertebrates and formation of air tubes, called trachea, in *Drosophila* (Adams & Alitalo 2007, Affolter & Caussinus 2008). In both cases, the final tissue function requires strict continuity, while at the same time the detailed geometry should be sensitive to signals from the tissue environment such as those indicating a need for oxygen. These two requirements make sprouting morphogenesis a good approach.

Another mechanism for the formation of complex 3D structures is branching morphogenesis as seen by lung, mammary gland, and other forming epithelial tissue (**Figure 3*d*,*e***). Branching morphogenesis does not utilize a unique tip cell, or sprout, but it can produce very elaborate structures such as the alveolae of the lung or the glomeruli of the kidney. It can involve very significant internal cell rearrangements and mobility as demonstrated by live imaging of the forming mouse salivary gland (Larsen et al. 2006), ureteric bud (Shakya et al. 2005), and mammary gland (Ewald et al. 2008). In addition to roles during development, branching and sprouting movements are relevant in physiology and disease such as mammary gland reorganization and tissue neovascularization, respectively. From a clinical perspective, understanding neovascularization is of particular importance, as it may be a limiting step for tumor growth and dissemination (Gimbrone et al. 1972).

Recent studies have provided significant insights into the control of sprouting morphogenesis and, with it, evidence that key regulatory mechanisms are evolutionarily well conserved. When these findings are considered together, they provide a generalized model for this collective movement. There are multiple steps, starting from a preexisting vessel or group of cells: (*a*) selection of a new sprout or tip cell (**Figure 3*a***); (*b*) looser association of the tip cell with the group and its guided movement forward (**Figure 3*b***); and (*c*) organization, proliferation, and movement of the cells behind the tip cell (followers) to elongate the outgrowth (**Figure 3*b*,*c***). Notch-Delta signaling is critical for appropriate overall organization of structures formed by sprouting morphogenesis. Notch activation prevents the formation of tip cells that are too close to one another (**Figure 3*a***), thus allowing other cells to become followers (Ghabrial & Krasnow 2006, Hellstrom et al. 2007, Siekmann & Lawson 2007). This results in overall well-organized morphogenesis. This organizational principle appears to be important for productive neovascularization of tumors as well, specifically the Delta-like ligand 4, making it a potential target for clinical intervention (Noguera-Troise et al. 2006, Ridgway et al. 2006).

The original positive trigger for differentiation of a tip cell can be the presence of extracellular VEGF [generally induces vasculature in mammals (Ferrara et al. 2003)] or FGF [for trachea in *Drosophila* (Ghabrial & Krasnow 2006)], both of which are receptor tyrosine kinase (RTK) ligands. Interestingly, the same ligands can subsequently guide the movement of the sprouting cell and its thin front extensions, analogous to growth cone chemotaxis (Affolter & Caussinus 2008, Gerhardt et al. 2003). VEGF signaling can be intricately spatially modulated at the level of ligand isoform expression with different isoforms having different solubility and matrix attachment properties (Ruhrberg et al. 2002). Expression of different receptor isoforms also contributes to fine-tuning of the response (Kearney et al. 2004). VEGF can also promote basal motility as well as proliferation and survival of vascular cells (Ferrara et al. 2003). These effects are relevant for sprouting morphogenesis, as a local increase in proliferation can contribute directly to extension of a multicellular outgrowth by promoting expansion of the trunk (**Figure 3*c***), the length of which is dependent on cell number. This example illustrates how one signal can affect multiple aspects of collective migration by simultaneously affecting cell differentiation, guidance, motility, and proliferation.

Although the outline above provides a useful framework and illustrates conserved features,

it is also a simplification. Sprouting morphogenesis comes in many variants, and there are limitations in the knowledge of each system. In vertebrates, vascular morphogenesis has been directly monitored in a few accessible systems such as zebrafish (Blum et al. 2008, Parker et al. 2004), the primary vasculature of mouse allantoides (Perryn et al. 2008), and the chick (Rupp et al. 2004) as well as in tissue explants (Bruyere et al. 2008). The primary vascular plexus has different elements of morphogenesis and multiple migratory components, not simply sprouting (Rupp et al. 2004). Tracheal development of *Drosophila* is limited as a model by not having a contribution of cell proliferation in the embryo and having limited accessibility at later stages. Each system has provided some information about the requirements for proper sprouting morphogenesis. One important issue is that vascular sprouts grow in a tissue, and thus, as for other migratory cells, the sprout cells need to express specific adhesion molecules for appropriate cell-cell and cell-matrix interaction (Carlson et al. 2008, Perryn et al. 2008, Rupp et al. 2004). Also, the morphogenesis of vascular sprouts can be organized by regulated deposition of ECM and specific embedded ligands such as Egfl7 (**Figure 3*c***; Parker et al. 2004, Schmidt et al. 2007). Finally, it has been shown that the orientation of cell outgrowths can be shaped by mechanical forces in the tissue, either transmitted directly or via effects on ECM organization (Korff & Augustin 1999).

Streams

Neural crest (NC) cells are a fascinating group of cells that play a key role in vertebrate embryogenesis. The fascination comes in part from the diversity of cell types that they contribute to in the body but also from their massive streaming migration out of the neural tube where they are born (LaBonne & Bronner-Fraser 1999). The changes that make NC cells migratory have been the focus of much interest and may reflect typical EMT. In addition, direct imaging of moving NC cells has allowed analysis of how these cells interact with their environment and with each other (Kasemeier-Kulesa et al., 2006 Kulesa & Fraser 1998, Kulesa et al. 2000). Another migrating stream that has attracted attention is the rostral migratory stream (RMS) of neuronal precursors that migrate in the brain, specifically from the subventricular zone to the olfactory bulb (Murase & Horwitz 2004, Nam et al. 2007). The activity of the RMS can continue into adulthood—at least in rodents—and provides a conduit of new neurons in the adult. After streaming, RMS cells disperse actively, apparently in a reelin-dependent manner (Hack et al. 2002). Reelin is known for its regulatory influence on other migratory neurons—individual neurons migrating on glia cells during development of the cortex (Rice & Curran 2001). Interestingly, transplanted embryonic stem (ES) cells can follow the endogenous RMS (Hoehn et al. 2002), and transplanted melanoma cells will follow the NC migration (Kulesa et al. 2006).

For both NC cells and the RMS, the term stream is used to indicate that the cells migrate together but in a loose arrangement (**Figure 4*a***). Such migration is also called chain migration. The cell shapes are elongated and polarized; cell movement is relatively fast, often over 1 μm per minute. To what extent such movement is collective and to what extent it is a mass movement of individuals are matters of discussion. For the RMS, the relative tightness of the stream, the importance of a cell adhesion molecule NCAM for the stream (Chazal et al. 2000), the existence of robust adhesion plaques between the migrating cells (Chazal et al. 2000), and the ability to form migratory chains in 3D culture (Wichterle et al. 1997) all favor the view that this is a collective migration. However, the requirement for integrin expression in the RMS cells and the behavior of single migratory cells within the stream give the impression that the cells are migrating as individuals on a limited path of defined ECM (Belvindrah et al. 2007, Murase & Horwitz 2002). As a complication, the migrating cells secrete matrix components themselves (Belvindrah et al. 2007). Likely, both individualistic and collective elements of cell migration are relevant for the RMS. To sort

Neural crest (NC): migratory derivate of neural crest in vertebrates

Rostral migratory stream (RMS): specific population of immature neurons that migrate to olfactory blub

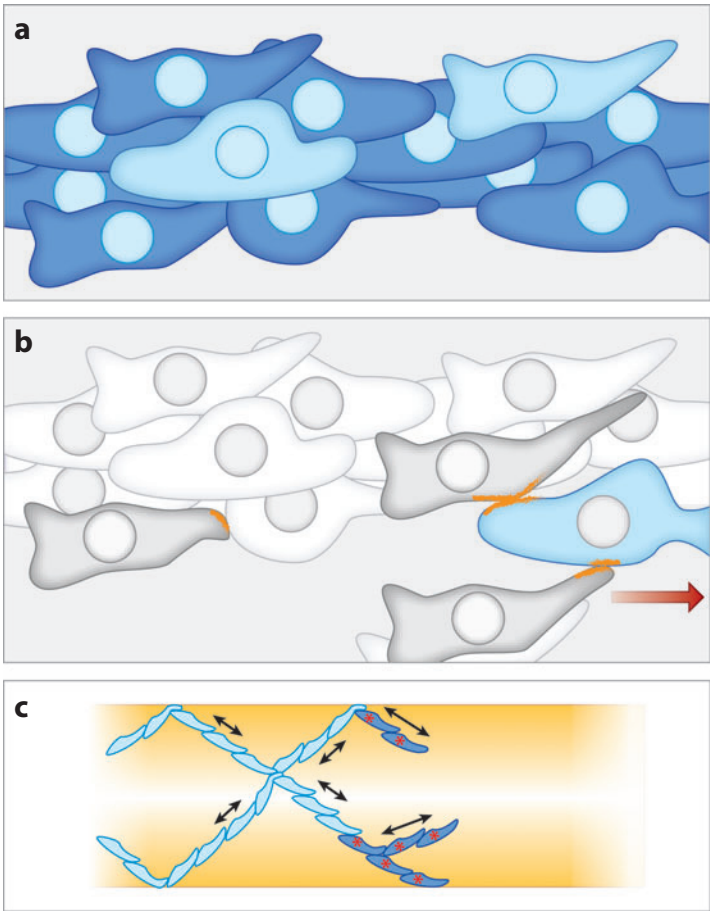

Figure 4

Cells migrating in streams. (*a*) If cells are migrating in dense streams, a fixed image or even live analysis revealing all cells at once will highlight the stream as an entity, whereas labeling only a few cells will highlight their individual behaviors. Neither approach alone reveals whether the migration is collective or whether a dense path is confining them. (*b*) Cell-cell contact (*orange*) between moving cells may mediate changes in the cytoskeleton and thereby help polarize the cells. If contact locally prevents front activities, the blue cell will move to the right. (*c*) Cell contact-dependent effects on cell movements (contacts retained, bidirectional movement allowed) and on cell proliferation (only cells that have recently contacted free space will divide; *red asterisks*) can give an organized expanding network of cells. The schematic represents the neural crest (NC) of the gut. (Redrawn from Simpson et al. 2007).

out the relative contributions, it may be helpful to simultaneously analyze the behavior of individual cells and their immediate neighbors (**Figure 4*a***).

Apart from advances in imaging of migratory streams, two recent developments regarding NC cells merit discussion. The first is the analysis of a molecular mechanism by which NC cells affect one another while migrating. Noncanonical Wnt signaling has previously been shown to be important for NC migration (De Calisto et al. 2005), and in recent studies this signaling has been dissected at the cellular and molecular level (Carmona-Fontaine et al. 2008, Matthews et al. 2008). Noncanonical Wnt signaling elicited by NC cell to NC cell contact inhibits protrusive activity and prevents the two cells from moving across one another, a version of contact inhibition of locomotion. This may prevent intermingling of adjacent NC streams. Within the migratory stream, such a signal would prevent cellular protrusions toward other cells of the stream and promote cell dispersal unless there are counteracting influences. Considering that cells at the front of a stream have free, noncontacted front surfaces, this signal could also contribute to coordination of cell behaviors within the stream as illustrated in **Figure 4*b***. The noncanonical Wnt signal involves local activation of the small GTPase Rho and might contribute to polarization of NC cells by locally reinforcing back behavior at sites of cell-cell contact.

Once NC cells reach their target tissue, their collective motile behavior can also contribute to dissemination and organization of the cells in situ. NC cells can proliferate while migrating, and the resulting increase in cell number may be crucial for tissue function, for example, to ensure that the cells forming the enteric neuronal network distribute over the full length of the gut (Burns & Douarin 1998, Young et al. 2004). Contact-dependent motility and contact-regulated proliferation at the moving front of the enteric NC system, followed by differentiation into stationary or less motile neurons, may explain the continuous network formation (Simpson et al. 2007) (**Figure 4*c***). How such control is exerted at the molecular level is not clear; nor is it clear whether the same signals control motility and proliferation directly. However, a similar spatial control of NC proliferation may help shape NC contributions in other contexts (Kulesa et al. 2008).

Another stream-type migration involving smaller groups of cells is glia migration. In some contexts, glia clearly follow pioneer axons (Aigouy et al. 2004, Gilmour et al. 2002). And importantly, live imaging and experimental manipulations indicate that the migrating glia affect one another (Aigouy et al. 2004). In other contexts, neurons can also migrate on glia or be directed by glia. Overall, multiple cell types of the nervous systems appear to use stream-like migration with loose cell-cell interactions.

Slug-Like: Lateral Line as Model

The primordium of the posterior lateral line in zebrafish has become a popular model for collective cell migration, in part because of the ease with which it can be imaged in vivo (Ghysen & Dambly-Chaudiere 2007). It is a slug-type movement, where the moving entity is a large group of tightly associated cells (**Figure 5**). Another movement with these characteristics is the migration of the pronephric duct, as imaged in amphibians (Drawbridge & Steinberg 1996). The lateral line is a complex entity of several hundred moving and proliferating cells that deposits differentiated multicellular sensory structures at regular intervals as it traverses the length of the body. The moving structure has intrinsic polarity with a front consisting of many motile cells and groups of cells differentiating and ceasing movement toward the back. The axons and glia that are essential for the functionality of the lateral line sensory system are apparently towed along—or at least directed—by the lateral line primordium as it moves (Gilmour et al. 2004). Recent data have indicated that the overall polarity of the structure requires a combination of FGF signals promoting a differentiated state and organizing regular deposition of multicellular structures at the rear (Aman & Piotrowski 2008, Lecaudey et al. 2008, Nechiporuk & Raible 2008) and a counteracting Wnt front signal (via canonical Wnt signaling). The two signals affect one another with long-range secreted activators and inhibitors. This reaction-diffusion signaling system appears to maintain tissue polarity during movement (Aman & Piotrowski 2008).

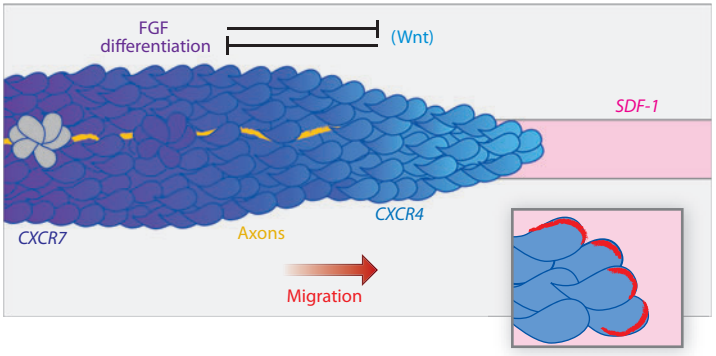

Figure 5

The posterior lateral line of zebrafish. The lateral line primordium (slug) contains hundreds of cells moving to the right, towing, or directing along a bundle of axons (*yellow*). At the back, cells are differentiating in clusters into lateral line organs (*gray*) and ceasing migration in a fibroblast growth factor (FGF)-dependent way; cross-regulation of FGF and Wnt may help keep the slug polarized with nondifferentiated cells in the front. Guided movement of the slug requires the ligand stromal-derived factor (SDF)-1 to define a path and the receptor CXCR4 in front cells. Without CXCR4, cells are motile, but the slug does not move forward (CXCR7 may perform a similar function in rear cells). The enlarged region shows how the intrinsic polarity of the slug makes each front cell polarized; in combination with a permissive strip of SDF-1 expression, this can give precisely directed migration.

Directionality or guidance of lateral line migration has been analyzed in some detail. The chemokine stromal-derived factor 1 (SDF-1) and its expression pattern in the target tissue as well as the receptor CXCR4 expressed by lateral line cells were found to be essential for directed migration (David et al. 2002). CXCR4 is a G-protein–coupled receptor, and SDF-1 acting via CXCR4 has been shown to mediate chemotaxis in vivo for other cells (Doitsidou et al. 2002, Knaut et al. 2003, Lapidot & Kollet 2002, Muller et al. 2001). However, in the case of lateral line migration, SDF-1/CXCR4 signaling appears to act as an essential permissive signal (David et al. 2002, Gilmour et al. 2004) rather than as a classical chemoattractant. SDF-1 expression defines the path of migration but not the direction as the moving primordium is itself inherently polarized with a clear front, providing a path is normally sufficient for correct directional migration (**Figure 5**). CXCR4 expression is only needed in a few front cells to direct

Noncanonical Wnt signaling: signaling downstream of Frizzled receptors that does not go via β-catenin stabilization; can involve Rho or Ca^{2+} effects

CXCR4: a G-protein–coupled chemokine receptor; responds to SDF-1

SDF-1: stromal-derived factor-1, ligand for CXCR4

movement of the slug (Haas & Gilmour 2006). Another SDF-1 receptor, CXCR7, is expressed and required in the rear cells of the primordium (Dambly-Chaudiere et al. 2007, Valentin et al. 2007). Whether the cellular activities of these two receptors are similar or different remains to be worked out. Overall, these studies indicate that most cells of the slug-like primordium not only are motile themselves, physically contributing to the overall movement, but that they also react directly to both tissue-intrinsic and -extrinsic signals.

Free Group: Border Cells as Model

The border cell cluster of the *Drosophila* ovary is another well-studied collective migration (**Figure 6**; reviewed in Montell 2003). This small cluster consists of about eight cells. They initially delaminate from an epithelium but, once migratory, they form a free migrating group in the sense that there is no inherent back or front to the group. Recent analysis has confirmed that cells often exchange position within the cluster and that the front is not preestablished or fixed (Bianco et al. 2007, Prasad & Montell 2007). The migrating group is a tightly associated cluster and includes two central cells (called polar cells) that are themselves apparently not motile but that are carried along by the actively migratory outer cells (**Figure 6**). All the outer cells normally contribute to migration but, owing to their tight association, even nonmotile, mutant cells can be carried along by their wild-type neighbors. Another intriguing feature of border cells is that they invade another tissue, the germ line. The giant germ line cells (nurse cells) are the substrate on which border cells migrate. To get proper adhesion to the cellular substratum, border cells use the classical adhesion molecule, E-cadherin (Niewiadomska et al. 1999). There is no ECM and no empty space in this context. Therefore, border cells have no free unattached surfaces. They must use the traction they get from adhering to the nurse cells to squeeze between these large cells on their way to the oocyte.

Part of the attractiveness of the border cell model comes from the ease of genetic

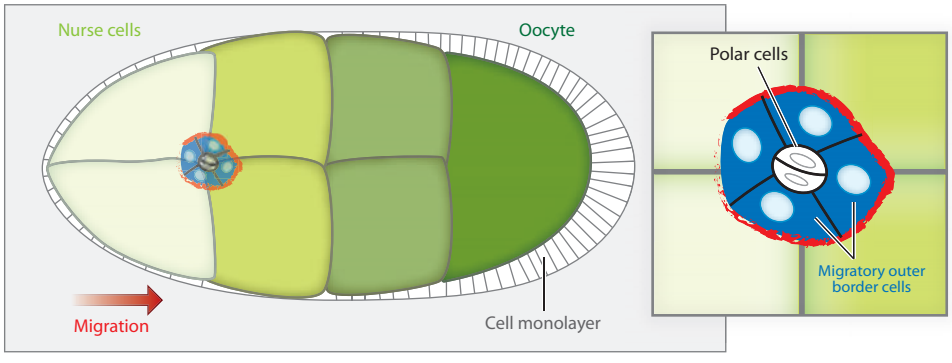

Figure 6

Border cell migration: a free group. Germ line cells are shown in shades of green. The border cells delaminate from an epithelium surrounding the germ line cluster and migrate to the oocyte by squeezing between the giant nurse cells. The nurse cells also serve as a migration substrate. The migrating cluster contains two nonmigratory polar cells at its center surrounded by migratory outer border cells (*blue*). Once migratory, the cluster has no inherent orientation relative to the tissue (free group), and its migration is guided by attractant produced by the oocyte, perceived by a PDGF/VEGF-related receptor (PVR) and epidermal growth factor receptor (EGFR) in the border cells. Within the cluster (*side panel*), each outer border cell has some intrinsic polarity provided by intracluster contacts (inner surface; *black*) versus substrate contacts (outer surface; *red*). The collective guidance hypothesis (described in Rørth 2007) suggests that clusters of cells use a combination of the intrinsic polarity and whole-cell read-out of the level of the guidance cue to direct the group migration.

manipulations in *Drosophila*. This has been enhanced by the recently established techniques for live imaging (Bianco et al. 2007, Prasad & Montell 2007). Specifically, in the context of collective migration, this model offers the opportunity to analyze group behavior where the cells of the group are polarized with respect to each other, but where the group does not have an inherent polarity in the tissue. As might be expected for such a free group, directional migration is controlled by localized external guidance cues. They act as chemoattractants and are perceived in the migrating cells by two RTKs, EGFR and PVR (Duchek & Rørth 2001, Duchek et al. 2001). In contrast to the lateral line situation, these two receptors act in the same cells. Indeed, for much of the migration they are largely functionally redundant in the sense that either receptor can direct cluster movement. However, recent results indicate that two different modes of guidance signaling operate in border cells (Bianco et al. 2007). One mode is dependent on localized signaling within each cell, comparable to the situation in single cell chemotaxis. The other mode is described as collective guidance. Collective guidance relies on the fact that the moving cells are a group: Each cell senses the amount of chemoattractant, and the cell with the highest level of signal migrates most effectively at each point in time (Rorth 2007). As discussed for other modes of collective migration, cells at the edge of a group have a discreet outer surface and internal contact surfaces (**Figure 6**, *side panel*). This provides an intrinsic cell polarity and thus potentially a vector along which each cell will attempt to pull the cluster. Whether such a collective guidance mechanism is sufficient to guide a migrating group has yet to be rigorously tested.

COLLECTIVE CELL MIGRATION DURING TUMOR INVASION

It is becoming clear that collective migration is involved in the dissemination of tumor cells, in particular for tumors such as squamous carcinomas, which are of epithelial origin (Christiansen & Rajasekaran 2006, Friedl et al. 2004, Sahai 2005). In the classical view of metastasis, tumor cells are thought to need to undergo EMT to migrate as single cells (**Figure 7*a***). However, imaging of the behavior of tumor cells placed in a 3D culture has revealed that epithelial-type tumor cells can spread as groups or sprouts (**Figure 7*b***). That this is likely to be relevant to cancer progression is indicated by the frequent observations of such outgrowths in clinical samples of advanced-stage carcinomas. Thus, full EMT appears not to be essential for tumors to spread into surrounding tissue (Christiansen & Rajasekaran 2006). On the other hand, the activity of matrix metalloproteases (MMPs) appears to be critical for collective migration of tumor cells (Nabeshima et al. 2000, Soulie et al. 2005, Wolf et al. 2007). In one study, the forced expression of an MMP was sufficient to promote tissue invasion by grafted MDCK cells in vivo (Soulie et al. 2005). Remarkably, small groups of tumor cells could be recovered in draining lymph vessels, suggesting that a cell cluster may be able to access the lymphatic system.

Together, these findings are quite significant, because they indicate that EMT is not the only gateway for tumor spreading. They also suggest that targeting processes required for collective migration may be effective in combating certain types of tumors. Full EMT may be obligatory for the formation of distant metastases by spreading of tumor cells through the vasculature. However, given the time frame of actual tumor progression and given the potential survival advantage of cells in a group, it is reasonable to question whether this behavior is the only route to metastasis.

Several recent studies have added molecular and cellular insight to the studies of collective tumor cell migration. For carcinoma cells placed in a 3D matrix, matrix degradation by MMPs is absolutely required for tumor cells to spread collectively (Wolf et al. 2007). Interestingly, this function can be provided by normal stromal fibroblasts, which can be recruited by tumor cells (Gaggioli et al. 2007). In this situation, both cell types contribute directly to the movement. Such heterologous

PDGF/VEGF-related receptor (PVR): RTK in *Drosophila* related to mammalian VEGFRs and PGFRs

Matrix metalloprotease (MMP): a family of secreted proteases that can cleave ECM

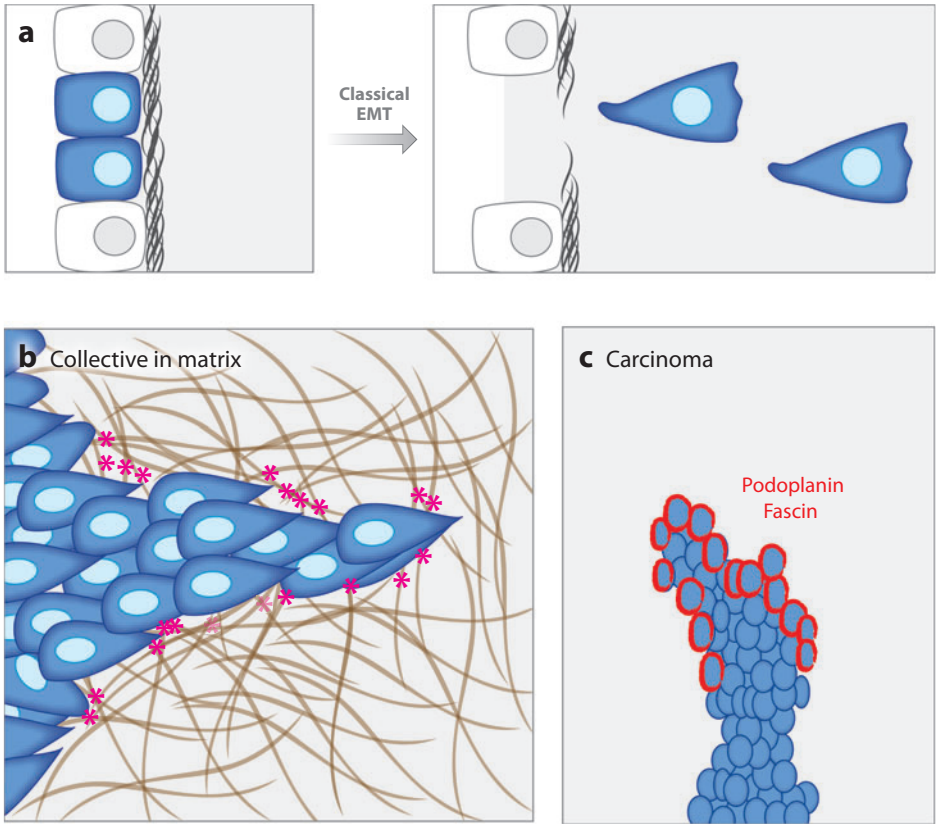

Figure 7

Migration and tissue invasion by tumor cells. (*a*) In classical epithelial-to-mesenchymal transition (EMT), epithelial-like tumor cells change their behavior completely to become mesenchymal and migrate as single cells, as indicated in the right panel. The fibrous basement membrane extracellular matrix (ECM) is shown underlying the epithelial cells. Degradation of this special ECM structure allows access to underlying tissues and the ECM. (*b*) Many carcinoma cells, when cultured as solid cell clumps in a 3D matrix, invade this ECM environment in clusters or strands collectively. The ECM serves as a migration substrate, but cell-associated matrix metalloprotease (MMP) activity (*pink asterisks*) is required for the strands of cells to move out. (*c*) Noncontained carcinomas seen in sections of biopsies from cancer patients also show tumor strands or outgrowths. Podoplanin is found specifically in boundary cells and can promote non-EMT invasion in mouse models (Wicki et al. 2006), similar to Fascin (Vignjevic et al. 2007).

collaborations are also observed for tumor cells that migrate individually (Condeelis & Pollard 2006). Cell coherence within a migrating group of tumor cells may also promote collective migration. For example, studies on the E-cadherin-adhesion stabilizing protein p120ctn in tumor cells indicate a positive role in 3D migration despite having a negative role in 2D migration (Macpherson et al. 2007). Finally, in a genetically controlled in vivo model for pancreatic tumor progression, expression of a protein called podoplanin caused invasion without EMT (Wicki et al. 2006). Podoplanin has a similar effect on human breast cancer cells and is found in vivo at the invasive leading edge of human carcinomas (**Figure 7*c***). The actin regulator Fascin is also enriched in front cells of colorectal carcinomas and promotes non-EMT invasiveness (Vignjevic et al. 2007). These studies highlight the importance of investigating how tumor cells migrate in a physiological environment and not simply as isolated cells

in culture. A full appreciation of how tumors invade may suggest ways to stop them.

CELL BIOLOGY OF COLLECTIVE CELL MIGRATION

Cell Migration and Tissue Dynamics

Cell migration is a dynamic process that requires proper polarization and active use of the cytoskeleton, but it also involves dynamic interaction between the migrating cell and its environment. These interactions are physical (mechanics) as well as chemical (signaling). The interactions are essential for cell movement but may also restrict and guide movement. When migration is performed by a group of cells that also interact with one another, new constraints and regulatory opportunities emerge. Thus, for collective migration, the relevant cell biology is that of a single migratory cell plus the features added by the community effects. These additional features are discussed below in reference to examples of collective cell migration described in the preceding sections.

For each of the systems analyzed in detail, whether sheet migration in tissue culture or in vivo collective migration models, it appears that all cells of the collective actively contribute to movement. The rare exceptions are cells of a different type that may be moved along by a group of motile cells. However, the speed of cell and collective movement and the degree of coordination vary widely between systems. In addition, it is now well appreciated in a number of contexts that cells may rearrange actively within an epithelium. Together these findings highlight that motility is not only an ancient characteristic of animal cells; it is also a characteristic that is exploited in many different ways in animal development and physiology. Cells are not just motile or stationary; many cells display some elements of motility and coordinate within a tissue such that it is utilized productively. A nuanced view also seems reasonable when considering the underlying molecular characteristics. For example, classical cadherin-mediated adhesion can provide stable interactions between stationary cells. However, it can also be modulated to allow cells to rearrange actively in an epithelium, and it can be used for migration-associated dynamic adhesion to a (cellular) substrate, for example, DE-cadherin in border cells and N-cadherin in neuronal cells. Finally, appreciating the spectrum of states between motile and stationary is also necessary for understanding tumor dissemination: It is a matter not just of undergoing EMT or not, but of different types of movement that depend on the cell type. Thus, the quest to understand cell motility has shifted focus to emphasize cellular dynamics and regulation for many potentially motile cells.

Cell-Cell Interactions Within the Group

Cell-cell interactions and coordination of cell movement within a collective are considered here from two perspectives. One is how the cells affect one another: To what extent does cell attachment simply transmit force, and to what extent do the cells specifically communicate to transmit information? The other perspective is how cell interactions can affect their individual and collective behavior.

How do cells of a collective affect one another? If two cells adhere strongly to one another, the expectation is that they will be mechanically coupled and that their behavior will be highly coordinated. Thus, if both cells are motile, they should tend to move in the same direction with the same speed and so on. Conversely, adhesion to cells that are immotile can be a mechanical impediment to migration. The strength of a cell-cell adhesion bond depends on both the adhesion molecules themselves and on the associated cytoskeleton. To fully evaluate cell-cell coupling, this adhesion needs to be considered relative to the other forces exerted on or by the cell. With a high degree of mechanical coupling, tissue movement could, in principle, be generated by forces from a few cells pushing or pulling all other cells, as in the purse string model for wound closure. Although not fully excluded, experimental manipulations and

imaging of cell behaviors within groups have not supported such models (at least in the simplest formulation). Cells may also be coordinated and coupled, and all contribute to movement. Such successful mechanical coupling can lead to physical outputs from a collective that far exceed the capacity of a single cell as, for example, measured by forces exerted on the substratum (du Roure et al. 2005). For most collective systems, the degree of cell-cell coordination has not been established. It seems likely that it will vary with cell type.

Cell-cell coordination based purely on strong adhesion may be considered passive, but adhesion-based coordination can also be active, influenced at the signaling level by mechanical forces. In single-cell contexts, force-dependent signals have been shown to allow cells to monitor stiffness of a substratum and modulate their contacts accordingly (Bershadsky et al. 2003). Mechanical coupling between migratory cells may result in the production of force-dependent signals by which the cells influence each other. One of the big challenges going forward will be to find a way to measure forces within a moving collective and dissect the contributions and effects.

Even without strong adhesion and mechanical coupling, the cells of a collective may influence each other by signaling. Signals that do not depend on direct cell contact, such as secreted molecules, can have profound effects on the overall organization of cell collectives. A prime example is the organization of *Dictyostelium* amoebae to aggregate and form multicellular migratory slugs by extracellular cyclic adenosine monophosphate (Weijer 2004). In animals, FGF and Wnt also act in this mode in polarization of the fish lateral line (Aman & Piotrowski 2008). However, contact-mediated signals are particularly relevant in the context of collective movement.

Contact-dependent signaling that leads to the inhibition of movement can be elicited by repulsive Eph/Ephrin combinations (Poliakov et al. 2004). Ephrin signaling controls interaction between cells or axons and their substrate during pathfinding, but it can also contribute, via cell sorting, to cell organization within tissues (Poliakov et al. 2004). As discussed previously, noncanonical Wnt signaling leading to local Rho activation is proposed to mediate contact inhibition of locomotion in NC cells (Carmona-Fontaine et al. 2008). These signals could also provide a mechanism by which tissue organization helps polarize cell behavior. Motile cells must display some degree of polarity, a difference between the front and the rear, in order to move rather than spread or shrink (see **Figure 1*a***). For illustration of cell contact effects, see **Figure 1*b***: The rear surface of cell 1 (*orange*) may be defined by a signal from cells 2 and 3, contributing to making it different from the front surface of cell 1 (*red*). In molecular terms, high activity of the small GTPase Rho is often associated with rear behavior of a moving cell including actin- and myosin-mediated contraction (Ridley et al. 2003). Signals that locally increase Rho activity would contribute to more rear-like activity in that region of the cell. As motile cells often have an intrinsic ability to amplify differences between front and rear features, a small bias generated by contact with other cells could help orient cell movements. **Figure 4*b*** illustrates such contributions in the context of a more complex migrating group. This proposed coordinating role is somewhat analogous to planar cell polarity, a process known to be controlled by noncanonical Wnt signaling. The Eph/ephrin signaling system has the added feature of providing distinct bidirectional signals, potentially allowing separate information flow in each of the interacting cells. These ideas illustrate some of the possibilities for regulation of collective cell migration by cell-cell signaling.

Cell-Substrate Interactions

From a cell biological point of view, cells that are part of a moving collective usually have at least two different cell surfaces that provide distinct interactions. One surface provides interaction with the substratum, which is often ECM, but can be other cells. Cells within a sheet

all touch the substratum (**Figure 2*e***). Cells of other collectives all interact with the substratum as well unless cells are completely internal to the moving group. The second surface provides interaction between the moving cell and its neighboring cells of the collective—the cell-cell interactions discussed above. This interaction surface may be perpendicular to that of the substratum interaction (as in a sheet), but other geometries are possible. Understanding the behavior of collectively migrating cells will necessarily involve considering simultaneously the cell-cell and the cell-substrate interactions. Cell-substrate interactions are altered and more complex when going from 2D to 3D culture systems, even for cells migrating individually (Even-Ram & Yamada 2005). For cell migration in vivo, the understanding of substrate interactions is quite limited. Even for the most studied systems, we only know which molecules are required with little or no quantitative or dynamic information.

For cells that are at the edge of a collective (the front cells in the schematics), there is an additional anisotropic feature, namely the free, or front, edge of the cell. This gives an orientation to this cell—a polarity. With this structurally imposed polarity, a uniform stimulus can promote forward movement of a cell sheet (**Figure 2**), as appears to be the case for FGF-stimulating movement of HUVEC cells (Vitorino & Meyer 2008). Thus, with an intrinsically polarized cell group, directional movement or guidance can be achieved at least in part by the interplay of nondirectional external cues with internal organization. Guidance of the lateral line may be another example of this (**Figure 5**). An external cue may also give concentration-dependent activity to migratory cells of a collective. Together with intrinsic organization of the collective and cell polarities, such graded output can, in the form of collective guidance, give directional movement even to a free cell group (Rorth 2007). Generally, when individual cells of a collective have multiple interaction surfaces, they may be provided with intrinsic polarity. This gives additional information to the system beyond what an individual cell can have on its own. It does not mean that cells of a collective cannot individually react to the external information as well, but it adds another layer of potential regulation.

Collective Migration as a Coordination Mechanism

Collective migration can shape a tissue. This is particularly obvious in cases of sheet migration and branching or sprouting morphogenesis. When a tissue is shaped in this manner, motility and directed migration are not the only cell features that contribute. There are related morphogenetic events such as cell shape changes and local cell rearrangements. Such changes may be individually small but, if coordinated, they exert a large effect on the tissue level. Other relevant factors are cell proliferation and cell survival. Directional expansion of a multicellular structure may depend on addition of cells at the appropriate positions. Finally, if a mode of collective movement involves specialized roles for different cells of the moving group, as in sprouting, then appropriate cell fate specification also becomes important for shaping the final tissue. With this in mind, it is interesting to observe that the same signal can be used in a biological context to modulate all of these processes. For vascular development, the example was given of VEGF regulating cell fate specification, chemoattractive guidance of tip cells, cell motility, and cell proliferation (of follower cells). Such multitasking complicates genetic and molecular analyses of how a system is regulated. However, from the point of view of the tissue, it may be logical by allowing all the processes that contribute to shaping it to be coordinately modulated by one factor. Changing the location, concentration, or the precise molecular features of the factor can then effectively remodel the tissue overall.

From the examples discussed in this review, it should be clear that collective migration is not an unusual process or rare variant of single-cell migration. It is an integral and important aspect of animal development and physiology. Collective migration allows coordination of

behavior of many cells, usually in a complex 3D environment. This, in turn, can help build complicated but robust and continuous tissue structures. I have presented a diverse spectrum of processes that vary in their degree of collectiveness. In most cases, it is probably not accurate to simply interpret movement of a cell group as many independent cells going the same way. The other extreme, viewing the collective as one superstructure with all individual cell behaviors subservient to it, also does not provide the full picture. Models of collective migration, even relatively simple in vitro models, are technically and conceptually more challenging to work with than single cells. They have more interdependent moving parts. However, given the considerable advances made in studying single cells, it should now be possible to more fully dissect and appreciate the emergent properties of the collective.

SUMMARY POINTS

1. Motility is a graded phenotype: Even within epithelia, cells often move under normal physiological conditions, as cell-cell adhesion can be dynamic.
2. A migration is collective if cells migrate together and affect each other's movement either owing to physical coupling or to signaling. Many cell types migrate collectively.
3. Where analyzed, most or all cells of a collective appear to contribute directly to the overall movement of the tissue or group.
4. A cell at the edge of a group has distinct intragroup cell-cell contact surfaces and free or outer contact surfaces, which may polarize the cell; this can provide basic directionality of movement for an anisotropic, attached collective.
5. Contact-dependent polarization plus cell-based perception of an extrinsic gradient can give directionality of movement to an isotropic free group (collective guidance).
6. Cell-cell contacts between collectively migrating cells may elicit signaling such as noncanonical Wnt or Eph/ephrin signaling that repel or polarize the contacted cell.
7. A single extrinsic signal, such as VEGF, can shape and direct a moving collective by simultaneously influencing multiple cell behaviors: guidance, motility, proliferation, and survival.
8. Many cancer cells, in particular from squamous carcinomas, perform collective migration in 3D cultures and in tissues; thus, EMT is not essential for invasiveness.

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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MDCK cells overexpressing MT1-MMP perform invasive, collective migration when grafted in vivo; cell clumps are found inside collective lymph vessels.

Systematic analysis of cell behaviors in sheet migration; RNAi of 100 different regulators give phenotypes classified as motility, directed migration, coordination, or cell density.

Forced expression of podoplanin promotes tumor progression & invasion in vivo without EMT; protein is found in edge cells of carcinomas.

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