

Collective guidance of collective cell migration

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Some cells migrate and find their way as solitary entities. However, during development of multicellular animals and possibly during tumor dissemination, cells often move as groups, associated tightly or loosely. Recent advances in live imaging have aided examination of such 'multicellular cell biology'. Here, I propose a model for how a group of cells can process and react to guidance information as a unit rather than as a gathering of solitary cells. Signaling pathways and regulatory mechanisms can differ substantially between solitary- and collective-guidance modes; a major difference being that, in collective guidance, similar to in bacterial chemotaxis, the signal need not be localized subcellularly within the responding cell. I suggest that collective-guidance signaling occurs alongside individual cell reactions. Both produce directional migration.

Directional cell migration – how and why?

Directional cell migration has been studied extensively in chemotactic eukaryotic cells, such as *Dictyostelium* and mammalian leukocytes. These crawling cells can perform effective chemotaxis in a simple tissue culture environment making them amenable to manipulations as well as high-resolution imaging. Significant advances have therefore been made in the understanding of how such solitary cells can respond to chemotactic cues [1,2]. However, many of the cells that migrate directionally in the context of complex multicellular animals, during development or in disease, face a different situation. Their environment is complex and 3-dimensional, which changes many features of migrating cells, such as shape, adhesion and force generation [3–5]. In addition, they might migrate as groups or collectives rather than as single cells. In the following article, I will discuss the hypothesis that migrating groups of cells can process guidance information as a collective. In such a scenario, the processing unit that computes the direction in which to migrate would not be in the individual cell but the multicellular group.

Why do cells migrate? Some free-living cells, such as *Dictyostelium* amoeba, move to find food or to find each other in times of crisis. Many immune cells move to locate and incapacitate intruders within a multicellular organism. In these cases, both speed and directionality are important, as is rapid response to change. For hardwired developmental migrations, cells are born in one place and migrate to act in another place or whole tissues are

remodeled. In such cases, precision, coordination and robustness are likely to be key and migrations are generally slower. Tumor cells can co-opt different migratory mechanisms [6]. The resulting diversity and plasticity in invasive movement might contribute to the difficulty of fighting metastasis. Collective movement of tumor cells might present additional problems with cell groups potentially having survival advantages over solitary cells in new environments owing to permissive homophilic cell–cell contacts or the secretion of autocrine survival factors.

Collective migration – migration of cell groups

In multicellular animals, many cells migrate in groups but they do so in different constellations (Figure 1). Advances in live imaging in different model organisms have made it possible to visualize many group movements directly in their natural context (including all of those discussed later). Groups can be associated loosely with occasional contact and much of the apparent cohesion might come from essentially solitary cells following the same tracks and cues (Figure 1a,b). Examples of these are germ cells in many organisms [7] as well as, in mammals, the rostral migratory stream supplying neurons to the olfactory bulb (RMS) [8,9] and neural crest (NC) cells migrating from the developing neural tube to many distant locations in the embryo [10]. The interactions between, for example, NC cells are dynamic [11,12]. How much these cells need to be aware of, and react to, one another is an open question [12].

Other migrating groups are more tightly associated and the cells normally never dissociate. Examples are the fish lateral line [13] (Figure 1c), structures performing branching and sprouting morphogenesis such as trachea [14,15] or the vasculature (Figure 1d) and finally moving sheets of cells in morphogenesis or wound healing [16] (Figure 1e). These groups have an additional feature, in that the moving structure has an inherent polarity, a free 'front' and an attached 'back'. Such directionally migrating groups can also be created artificially by enabling epithelial-type tissue-culture cells to organize on a collagen-gel substrate [17]. Finally, *Drosophila* border cells [18,19] are a group or cluster of cells performing a directional movement during oogenesis. These migrating cells are associated tightly but the cluster is free, without an inherent 'back' (Figure 1f).

Tight cell–cell association is expected to impose physical constraints on movement. This will depend on the cell–cell adhesive forces within the group relative to the cell–substrate forces exerted during movement. Maintaining cell–cell cohesion during migration and remodeling is probably an advantage when making a continuous tissue. Cell–cell

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Available online 8 November 2007.

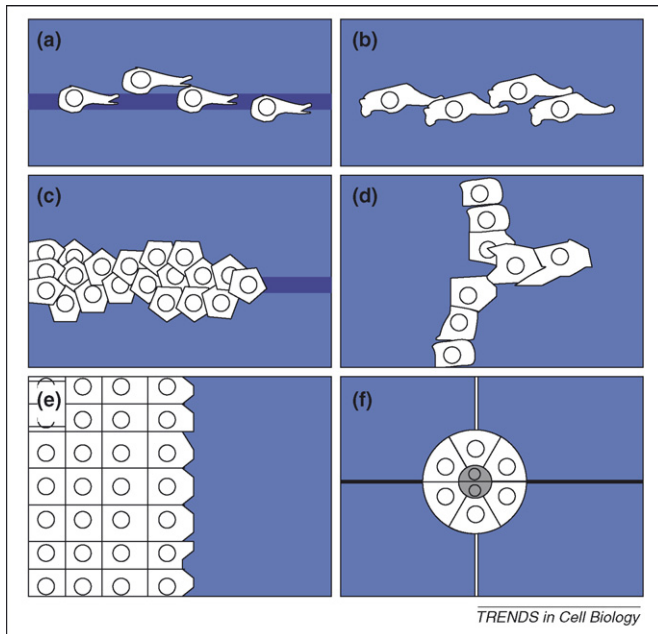


Figure 1. Different types of collective cell migration. Throughout the figure, the moving cells are in white, with gray circles indicating nuclei. Only a rough outline of the cell shape is given. The substrate is blue and purple, with the purple lines being examples of migration-permissive 'tracks': a favorable substrate for the cells to adhere to and migrate on or a line of cells expressing a stimulatory, secreted molecule. Movement is from left to right. (a) and (b) show loosely associated groups of cells that make contact either rarely (a) or frequently (b) with each other. They mostly contact the substrate with a high degree of freedom, sometimes restricted by tracks. Examples are germ-line cells (in various animals) and neural-crest cells. (c) The moving neuromast cells of the fish lateral line. The overall structure, consisting of many associated cells, has a front and a fixed back. (d) An example of tracheal or vascular-type branch outgrowth. The new growth (central) buds from an existing epithelium and the cells remain in contact, in this case with a single front cell. (e) An epithelial sheet moving to close a gap; the moving cells are likely to have a low degree of freedom (can possibly only move forward). (f) A border-cell cluster moving among giant nurse cells (squares). The nurse cells are also the substrate.

contacts also enable specific and efficient signaling interactions. The question to be considered here is whether the 'groupness' gives different guidance properties to the migrating cells. If so, we would expect it to be most obvious in obligate, tightly associated groups but it might also contribute to the behavior of the more loosely associated groups.

Guidance for a migrating group versus guidance for solitary movement

I will illustrate the potential differences in guidance of groups and solitary cells by first focusing on the border-cell cluster [18,19]. Recent advances in culturing and live imaging of the tissue enable the dynamics of the process to be appreciated [20,21]. Two receptor tyrosine kinases (RTKs) are used as guidance receptors in this system [22,23] and we have found evidence recently that this cluster displays collective processing of guidance signals [21]. To discuss the concept of collective guidance, consider first the well known solitary eukaryotic cell performing chemotaxis in response to a gradient of attractant (Figure 2a). The cell responds locally and the local response might be reinforced by a local-excitation and global-inhibition mechanism [24], by mutual inhibition of frontness and backness [25] and/or by additional feedback mechanisms. Proper directionality might also result from direct

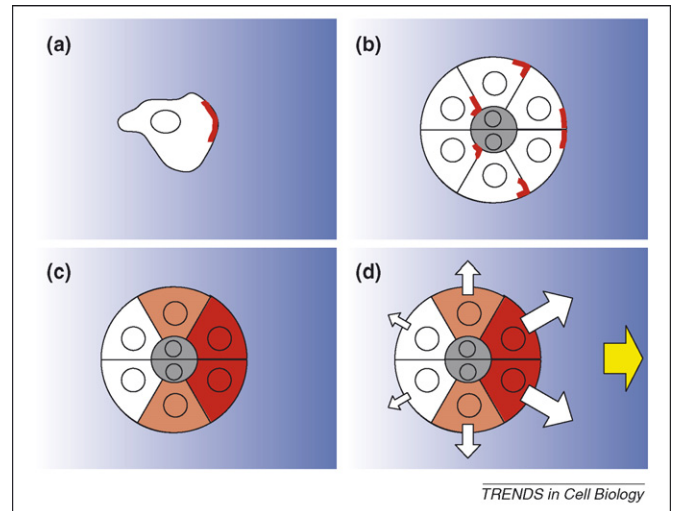


Figure 2. Guidance signaling: solitary mode and collective mode. Throughout the figure, the extracellular concentration of guidance cue (attractant) is indicated by shades of blue. The intracellular response relevant for the directional response is in red (intensity indicating strength). (a) and (b) show localized, classical guidance signaling; (c) and (d) show the proposed collective guidance signaling mode. (b–d) show a border cell cluster with six migratory cells. The central two cells (gray) are non-migratory. (a) Localized signaling and response in a solitary cell. The cell perceives a higher level of attractant at the front, which induces a local response in the front that, in turn, promotes direction movement. (b) Localized response in cells of the border-cell cluster, each perceiving the gradient (which might also exist among the cells). Each migratory cell is reacting like the cell in (a) without influence from neighbors. (c) The gradient of attractant is read out by each cell measuring the local concentration (amount of ligand) around the cell and giving a proportional and delocalized signal. The gradient of attractant and therefore desired direction of movement is in this way encoded in the cluster but not in the individual cells. (d) How a signal that is delocalized within each cell can nevertheless give directional output or migration for the group is illustrated. White arrows indicate the direction that each cell would pull the cluster by extending its free membrane surface onto the substrate and crawling forward. The size of each arrow indicates the strength of this action for each cell, as determined by the level of guidance signal in each cell. Counteracting forces, such as adhesion between the cells, are not indicated but would cancel each other out if they are equal for all cells. The yellow arrow indicates the net direction for the cluster.

coupling without global feedback mechanisms in a polarized cell [26]. The key issue is the preservation of, or enhancement of, spatial information about where the higher concentration of attractant is perceived on the cell surface, leading to a localized reaction within the cell (Figure 2a).

Now consider a group of cells, such as the border-cell cluster, in which each cell has contacts to the other cells as well as an 'outside' surface touching the substrate (Figure 2b–d). In terms of guidance, each cell could behave as a solitary cell and mount a local response (Figure 2b). There is evidence that border cells do this and that the localized response is crucial at one phase of their migration [21,27]. However, the guidance information could also be encoded in the cluster by virtue of different levels of signaling in different cells, the front one or two cells having the highest level (Figure 2c). We found evidence that the levels of signaling from the guidance receptors are indeed different among cells, that apparently delocalized signaling contributes to guidance and, more importantly, that the level of guidance signal can determine which is the front cell [21]. Individual border cells with higher levels of RTK signaling or even with higher level of (delocalized) Raf–mitogen-activated protein kinase (MAPK) signaling appear to win the constant competition

Box 1. Linking motility and guidance in collective migration

Some isolated cells perform chemotaxis in a gradient (e.g. in Dunn or Zigmond chambers) and random motility is stimulated by non-graded application of the same ligand [43,44]. In such cases, the ligand would be said to be motogenic as well as providing directional information. The combined feature of stimulating motility when uniform and giving direction when graded, although not universal, is seen for several chemoattractants, including those that stimulate RTKs. These effects seem to be relevant *in vivo*; for example, stimulation of the c-Met receptor appears to affect both motility and directionality of muscle precursors as well as cancer cells [45]. Other RTKs are used to guide several cell movements in complex multicellular animals [15,46].

That ligands should have the combined effects of orientation and stimulating motility is not obvious intuitively, however, this can be modeled successfully for solitary cells [26,44]. The proposed collective guidance mechanism provides an additional, direct link between directionality and motility. If cells are tethered to one another and one cell becomes more motile than the rest owing to higher level of motility signaling, but is spatially constrained by the other cells as to how it can perform the motile behavior, then this can lead to the type of collective guidance discussed in the main article text. In multicellular organisms, ligands might have evolved both activities to enable guidance of cell groups by a combination of solitary and collective modes.

for front position. This might reflect that they are more motile (Box 1). As discussed later, such differences among cells can give directionality to the group as a whole. If the information about guidance cue concentrations and thus the intended direction of migration is encoded such that an individual cell of the cluster does not have the information but the cluster does (as illustrated in Figure 2c), then this would be 'collective signaling' or 'collective guidance'.

It is relatively straightforward to understand how guidance information could be encoded in a group of associated cells, as a collective (Figure 2c). The front is where the cell with the highest level of signaling is. But it is less obvious how directional movement would occur in response to this. We think normally that a polarized, local response is required to produce directional movement. But even in the extreme form where the signal within each cell of the group is completely delocalized, group behavior can still give directional movement if the cells differ from one another. The reason is that each cell of a cluster has a directional vector (Figure 2d). Each cell contacts other cells of the cluster on all sides except where it contacts the substrate. Because the intragroup contacts are probably different in nature from the cell-substrate contacts, this gives each cell a 'movement vector', which can be thought of as the direction in which this cell would pull the cluster if it was the only cell to have productive interactions with the substrate. The guidance information (the level of signaling) then gives a value to each cell or each vector, essentially saying how dominant this direction is. The combined force, the net vector, determines the overall directional movement of the cluster (yellow arrow in Figure 2d). Counter-acting forces of adhesion will keep the cluster from flying apart. This general, simple logic can be applied to any associated cell group, with differences in details based on whether the cells are stuck to each other physically or communicate through their lateral connections or a combination thereof.

The description here is a static, general view. However, both migration and reading of guidance information are dynamic processes and should reflect continuous evaluation of the environment. Solitary migratory cells are probing the environment constantly, some generating new pseudopods (fronts) regularly to do so. Similarly, the border-cell cluster, when viewed in real time, is dynamic, having many cells probing the environment and, interestingly, the cells changing position over time [20,21]. Thus, taking the lead and becoming the front cell is not a single decision and does not represent cell-fate determination. It is a dynamic situation in which cells are competing with one another constantly, consistent with a guidance function. Such dynamics might ensure reassessment of the environment during the course of migration rather than adhering to a fixed direction. The opposing forces generated by competing cells might make net forward movement slower, although high speed is probably not of primary importance for migrating groups.

Other migrating tissues: morphogenesis

What about other migrating groups? In some cases, the moving cohort of cells has an inherent polarity: a 'front' with more extensive contacts to the substrate and a 'back' with more connection to rest of the tissue (Figure 1c–e). In such cases, there is additional information in the system that can be used to direct the group if the cells behave as a collective and not just as many solitary cells. In the case of the fish lateral line, which is a 'slug' of cells with an attached rear (Figure 1c), the guidance receptor CXCR4 [28] is indeed only essential in the front cells [29]. Behavior of the lateral-line cells in embryos with altered distribution of the ligand stromal cell-derived factor 1 (SDF1) suggests that ligand expression might serve to define a permissive track for movement rather than giving absolute directionality [28,30]. The combination of a defined track and 'tissue polarity' given by cell-cell interactions could be sufficient for directionality in this and similar cases. Finding the tract would probably require direct cell-substrate contact. But, in fact, many cells migrating in tissues make long extensions and sample the environment continuously by touch [12,31].

Navigating vascular (vertebrate) or tracheal (fly) progenitors also have inherent polarity (Figure 1d). Such structures can be directed by RTK ligands; for example, fibroblast growth factor (FGF) in the case of tracheal outgrowths [15,32,33]. For embryonic trachea, a difference in the level of FGF signaling among cells is used to define a fixed leading-cell fate [34], rather than guidance. In addition, the leading cell can be influenced by FGF to produce filopodia in a directional manner [33,35], indicating guidance by localized signaling. Recent analysis of late tracheal development indicates that the MAPK pathway and a nuclear response, in other words, non-localized signals (as discussed later), are important for directional migration driven by FGF [36]. This raises the possibility that a combination of localized and collective signaling modes could be at work downstream of FGF.

Finally, true epithelial sheets of cells moving forward, for example, to close a surface hole or wound, have the fewest degrees of freedom (Figure 1e). In this case, it is

clear that the stimulation of front-cell motility, coupled with a difference among the free front membranes and the intraepithelial contacts, could be sufficient to give directionality. Of course, the non-front cells also have to move forward for sheet movement to occur and appear to do so actively [37,38]. These cells might be directed by the front cells by signaling and/or mechanical coupling [38,39]. Usually, 'guidance' is not invoked for sheet movement; perhaps because self-organization would be sufficient to direct the process. However, the localized electric fields generated at wounding might serve as an environmental cue to direct the migration process actively [40], making it a guided process. In general, to understand complex morphogenesis, it is not sufficient to see cells as isolated entities. The additional information at higher levels of organization should also be considered.

Guidance-receptor signaling in collective versus solitary migration

There are many questions raised when considering a collective guidance mode (Figure 2c,d). First, what is the output of collective-guidance signaling? In other words, what cellular property is changed in direct response to the amount of signal perceived by each individual cell? There are multiple options. Relative to the low-signal cell, the high-signal cell could make more or more robust extensions or protrusions; alternatively, the cell or the cellular protrusions could be more strongly adhesive or be able to exert more pulling force on the substrate. For each case of collective guidance, the detailed answer might be different. What sets it clearly apart from the guidance of solitary cells is that the regulation need not be localized to a specific subcellular region. In the case of classical solitary eukaryotic cell guidance, the signal and the cellular response to it are coupled and localized: setting and making the front (Figure 2a). By contrast, in the collective mode, a signaling output that is distributed throughout the cell can be used for guidance, even a nuclear signal. The placement of each contributing cell relative to the others is what gives the directional information. Owing to the difference in requirements for localization, guidance signaling can be different biochemically in collective versus solitary mode, as appears to be the case in different phases of border-cell migration [21]. Also, motility effects can become guidance effects in a collective mode (Box 1).

The general concept of delocalized signaling giving directionality to movement has an important precedent in bacterial chemotaxis, a fascinating process that has been studied in great detail [41,42]. Here, the cellular response to guidance cues (attractants or repellants) is also not localized to a subcellular position that reflects the direction of the incoming signal. Instead, it is diffusible intracellularly and communicates with fixed flagellar motors. The cells are in constant motion and use changes in signal level over time as the source of directional information. Overall, there are likely multiple fundamentally different solutions to the problem of moving directionally, rather than simply a eukaryotic (localized signaling) and a prokaryotic (timing) one. Animal systems appear to have found an additional means of processing directional information in a form that, like the prokaryotic mode, is not

local but instead of time uses multicellularity as the underlying principle for evaluation of information.

Why collective signaling?

Because solitary eukaryotic cells carry out chemotaxis well, one might ask why would collective guidance exist? One way of looking at it is that the possibility of encoding information in this multi-cellular way exists – as long as cells respond in a dosage-sensitive manner with motility or related behavior (Box 1). It is therefore used as part of the complex developmental repertoire. Collective guidance might also have some advantages for robust directional migration of groups: each cell measures an average guidance signal over a large area, enabling the group to disregard local fluctuations; collective guidance could also help to ensure a coordinated response.

Another interesting question is whether, in addition to the physical interaction, the cells in a group communicate with one another directly and compare signaling levels directly. Cells might even interact to enhance differences, analogous to the front and back end of one cell influencing each other in the solitary-guidance mode. But, if they do so, they must maintain receptiveness and flexibility to respond dynamically to cues in the environment.

Future directions

How can the model for collective-guidance signaling be further tested? Not detecting a localized signal does not necessarily mean it is not there (the wrong molecule, modification or time frame might have been analyzed), just as seeing a localized signal does not necessarily mean it needs to be localized for the biological effect. More manipulations and observations in the native environment are needed, as has been initiated in the border-cell system [21]. Further live analysis in the border-cell model might elucidate the details of signaling output, cellular responses to different levels of signal and whether and how cells of a cluster compare signaling levels. Border cells migrate in an environment that is constrained physically. Live analysis of other group migration with different constellations of cells and a higher degree of freedom in movement might also be informative. The collective-guidance model predicts that inducing modestly elevated (delocalized) signal in one cell of a group in a situation in which external cues are uniform or weak should make it the front cell and thereby set a new direction for movement of the cluster. This can be tested.

There are certainly many more questions than answers at this point. We are complex multicellular animals and have to be understood as such, however, multicellular cell biology has a long way to go. What has been learned about the behavior of parts – in this case of individual cells – is absolutely crucial, just not the whole story.

Acknowledgements

I would like to thank Adam Cliffe for help with Figure 2, Stephen Cohen for comments on the manuscript, my laboratory and colleagues for discussions and EMBL for prior support.

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