ELSEVIER

Organizing moving groups during morphogenesis

Virginie Lecaudey and Darren Gilmour

The directed migration of cells drives the formation of many complex organ systems. Although in this morphogenetic context cells display a strong preference for migrating in organized, cohesive groups, little is known about the mechanisms that coordinate their movements. Recent studies on several model systems have begun to dissect the organization of these migrating tissues *in vivo* and have shown that cell guidance is mediated by a combination of chemical and mechanical cues.

Addresses
European Molecular Biology Laboratory, Meyerhofstrasse 1, 69117 Heidelberg, Germany

Corresponding author: Gilmour, Darren (gilmour@embl.de)

Current Opinion in Cell Biology 2006, **18**:102–107

This review comes from a themed issue on
Cell structure and dynamics
Edited by J Victor Small and Michael Glotzer

Available online 13th December 2005

0955-0674/$ – see front matter

DOI 10.1016/j.ceb.2005.12.001

Introduction

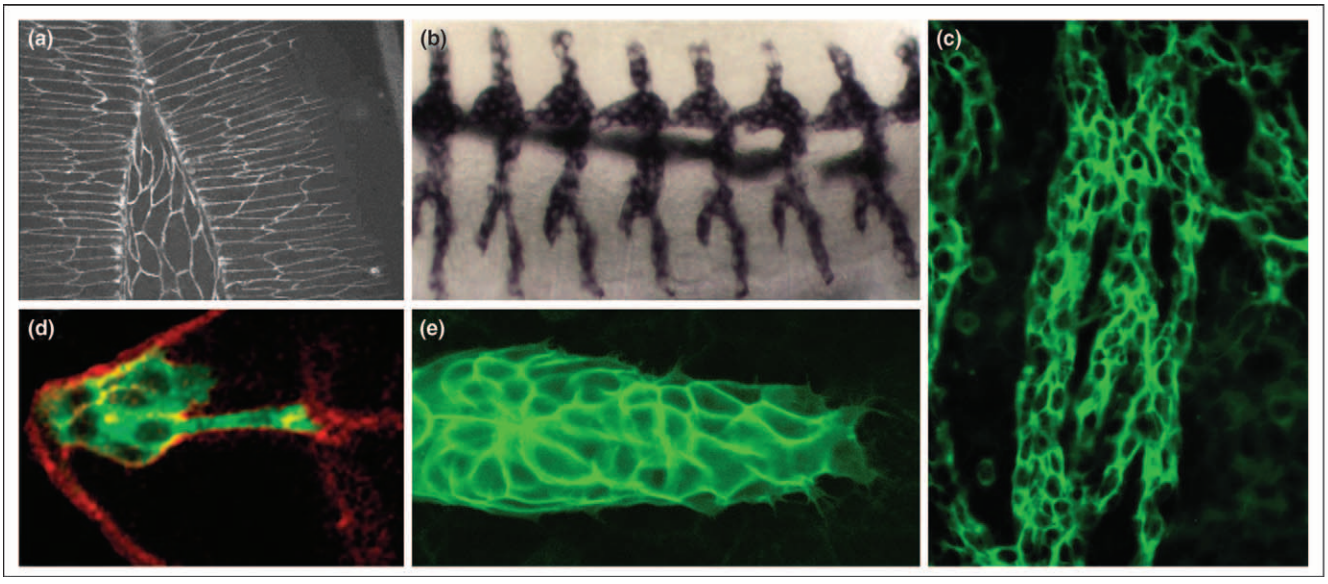
Cell migration is essential to many physiological and disease processes such as embryonic morphogenesis, wound healing and cancer metastasis. Studies on single motile cells in culture have lead to a well-established model whereby cells move via the extension and adhesion of a leading edge pointed in the direction of migration and the retraction and loss of adhesion of the trailing edge at the rear. Here, the forces required for the translocation of the cell body are generated at the points of contact with the flat substrate provided by the Petri dish. While these studies have been crucial in understanding the mechanics of cell motility, it is clear that this controlled experimental environment is very different from what cells experience in the three-dimensional context of living tissues. However, thanks to improvements in microscopy technology it is now possible to observe cells migrating in their natural habitats, such as the intact developing embryo. What has become clear from imaging studies is that during morphogenesis cells do not usually travel alone but rather prefer to undertake journeys together, often moving in very large numbers. In some cases cells move as dense streams of freely migrating chemotactic individuals that coalesce at particular locations, with each cell apparently being guided directly by extrinsic cues [1••]. However, during the morphogenesis of many organ systems it is more common to find cells migrating in some form of adherent group or as tissues. These 'tissue migrations' are the focus of this review.

Migrating tissues come in many shapes and sizes and show varying degrees of cohesion and organization (for more details see [2]) (Figure 1). These range from rather loose networks, such as chains of neuronal progenitors in the CNS [3,4] and migrating neural crest cells [5•], to tightly adherent sheets of epithelial cells, where a large number of cells move as a single coherent unit and maintain constant positions throughout [6]. Elsewhere, they can be found as clusters of motile cells, as exemplified by *Drosophila* border cells (BCs) [7,8] or the migrating primordium of the lateral line (LLP) in amphibia and fish [9,10]. Migrating tissues are often employed in sculpting complex three-dimensional forms, including the intricate tubular networks present in the vasculature and the respiratory system. While their forms and functions are diverse, it is clear in all cases that the migratory behaviour of cells within these various tissues must be coordinated to ensure proper movement of the entire group. The aim of this review is to integrate some recent results from several experimental models that shed light on the mechanisms ensuring the concerted movement of tissues during morphogenesis. Because of space limitations, we will not discuss convergent-extension movements during gastrulation, a very important example of collective cell behaviour that has been covered by several excellent recent reviews [11,12].

Getting organized for the journey

What guides cell groups on their journey? Genetic studies in a wide range of model systems have shown that tissue migration is regulated by the very same extrinsic chemical cues that guide single cells. Examples include members of the epidermal growth factor and fibroblast growth factor families, which are detected through receptor tyrosine kinases present in the plasma membrane. As these are known to guide single cells via a chemotactic mechanism, it is likely that graded distributions of these factors also determine the directionality of tissue migration in many cases [1••,13]. An important issue regarding cells moving as a cohesive tissue is the extent to which external gradients penetrate multicellular cohorts to control migration behaviour within. It is becoming clear that extrinsic cues drive the movement of tissues not by acting directly on all members of the group but rather by instructing smaller numbers of peripheral leader cells that in turn are responsible for the guidance of naïve followers. This is

Figure 1



Cells move in groups of varying shape and size *in vivo*. **(a)** The concerted movement of epithelial sheets is a very prevalent feature of morphogenesis, as demonstrated here during dorsal closure in the *Drosophila* embryo. **(b)** The coordinated migration of groups of epithelial cells also drives the formation of branched tubular networks, such as the *Drosophila* tracheal system. **(c)** Chain migration of neuronal precursors in the subventricular zone of the adult rodent brain. **(d,e)** *Drosophila* border cells and the zebrafish lateral line primordium as two examples of cells that migrate in clusters or cohorts. (Reproduced with permission of (a) Ferenc Jankovics and Damian Brunner; (b) Stefan Luschnig; (c) Arturo Alvarez-Buylla, in [4]; (d) Pernille Rorth, in [18]).

suggested by the fact that in many contexts only a subset of cells within a tissue display morphological features, such as filopodia and pseudopodia, characteristic of migratory cells [14]. Further support comes from several studies where guidance receptor activation is assayed directly using antibodies that bind specifically to active forms of receptors or downstream signalling components, allowing the identification of responsive cells. This approach was first used with anti-phospho-MAPK (Erk) antibodies to show that FGF signalling becomes restricted to the tips of *Drosophila* tracheal branches soon after they begin to extend [15]. More recently, anti-phosphotyrosine antibodies have been used as a read-out of guidance receptor activation to show that during normal migration only a subset of BCs responds to the cue secreted by the oocyte [16]. Similarly, during eyelid closure in mouse embryos, the EGF-like growth factor HB-EGF binds to and activates the EGF receptor and the downstream ERK signalling cascade only at the leading edge of the migrating epithelial sheet [17]. The most direct experimental demonstration that not all cells within migrating tissues need to respond to cues *in vivo* comes from genetic mosaic studies that juxtapose wild-type and migration-defective mutant neighbours. This approach has been particularly informative in the case of *Drosophila* BC clusters, where wild type cells have been mixed with several different immotile mutants including *slbo*, *shg* (E-cad) and *sqh* (myosin II). Here the wild-type cells can rescue the migration of immobile mutant clusters with an efficiency depending on their proportion [18–20]. These combined findings demonstrate clearly that guidance within tissues can be non-cell-autonomous, and that groups are composed of cells that respond directly to extrinsic cues and cells that do not.

Coordinating individual movements within moving groups

Chemotaxis: tips from a slimy collaborator

How do these leading cells transmit this extrinsic directional information to the remainder of the group? One paradigm for how cells within motile groups can organize each other's behaviour comes from *Dictyostelium* slugs, which are comprised of many thousands of migrating cells that move collectively [21]. Here, a specialized set of cells at the tip of the slug, known as the prestalk cells, form an internal source of the diffusible chemoattractant cAMP that drives periodic waves of migration throughout the entire mass. Responding posterior cells are dependent on this internally generated gradient for their motility; if the tip region is cut off, it continues to migrate while the remainder of the slug is rendered immobile [22]. While tissues moving through embryos are guided by extrinsic cues, it is possible that leading cells adopt a similar strategy to organize the migratory behaviour of neighbours through a relay of guidance molecules. It will be interesting to determine whether the expression of chemoattractants within moving cohorts provides a mechanism for coordinating their behaviour *in vivo*.