or enhance dynamic instability by severing actin filaments which then undergo barbed end disassembly. The use of TIR fluorescence microscopy to image individual actin filaments in living cells will also undoubtedly provide insights into the mechanisms for actin polymerization and turnover in lamellipodia and other structures. □

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Unconventional ways to travel

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Recent studies of border cells in the *Drosophila melanogaster* ovary have identified a novel mechanism that is involved in cell migration. Binding of the minus-end-directed motor, Myosin VI, to the cell adhesion molecule, *D*E-Cadherin, stabilizes the cadherin–catenin complex. This interaction might promote the formation of long cellular extensions (LCEs) at the leading edge of migrating border cells.

Border cells are organized in a group of eight cells that are specified at the anterior pole of the somatic follicle cell epithelium (Fig. 1a). These specialized cells exit the epithelium, invade the germline cluster and migrate in between the nurse cells towards the oocyte, where they eventually contribute to the formation of the egg micropyle. Analysis of mutations that perturb border cell migration has provided numerous insights in our general understanding of cell migration[1]. For example, loss of the cell adhesion protein *D*E-Cadherin in either border cells or germline cells induces severe border cell migration defects[2]. This suggests that *D*E-Cadherin-dependent interactions between border cells and nurse cells are responsible for generating the traction required for cell migration. In addition, the *slow border cells (slbo)* transcription factor is pivotal in the control of cell migration[3], presumably through its ability to regulate the expression of proteins such as *D*E-Cadherin[2]. Two recent studies published in *Nature Cell Biology* provide additional insights into the cell biology of border cell migration. Fulga and Rorth[4] discovered that one cell of the border cell cluster forms a LCE at the start of migration. Furthermore, they present evidence that this LCE is involved in migration through a 'grapple and pull' mechanism. Geisbrecht and Montell[5] report that Myosin VI is strongly expressed in border cells, where it seems to have a dual role. Myosin VI can bind to *D*E-Cadherin and β-Catenin, resulting in the formation of a

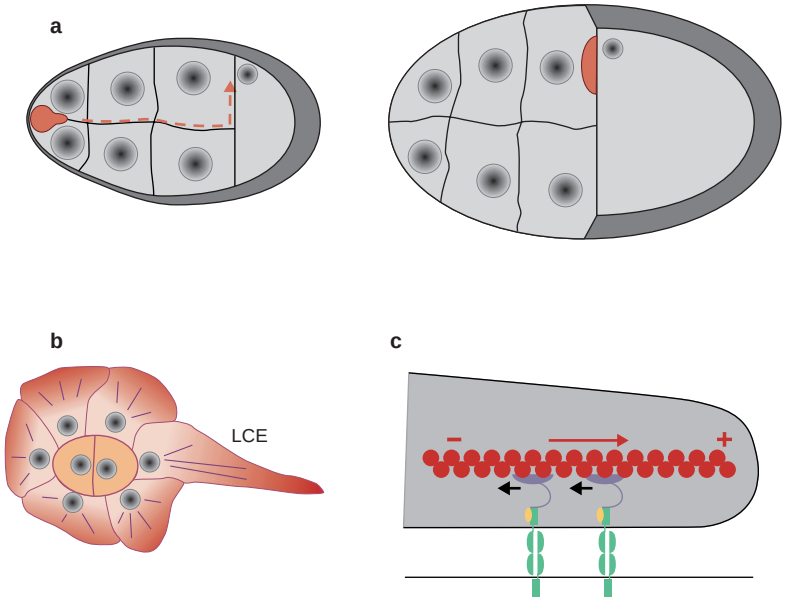

Figure 1 **Long cellular extensions in migrating border cells.** a, **Border cells (red) delaminate from the anterior pole of the somatic follicle cell epithelium (dark grey) to invade the germline cluster (light grey). They follow a route (red line) between the nurse cells to migrate to the border between the nurse cells and the oocyte.** b, **Border cells migrate as a cluster of two inner non-migratory cells (orange) surrounded by six outer migratory cells (red). One of the outer border cells forms a long cellular extension (LCE) in response to guidance cues and facilitates migration by a 'grapple and pull' mechanism.** c, **Myosin VI (blue) binds the cadherin–catenin complex (green/yellow) and connects it to cortical filamentous actin (red). The minus-end-directed motor Myosin VI pushes the actin filaments towards the leading edge. Simultaneously, Myosin VI is captured by the cadherin–catenin complex that connects the border cell and nurse cell membranes.**

stable complex[5]. In addition, this cortical adhesive complex is simultaneously linked to the cytoskeleton[5]. Apparently, these features are critical for border cell migration, as *Myosin VI* mutant border cells fail to migrate.

When cells become motile, they often change their shape, polarity and adhesive properties. Although genetic studies have identified a variety of genes that control border cell migration, little is known about the morphological changes that occur in border cells when they become motile[6]. To address this issue, Fulga and Rorth[4] expressed a green fluorescent protein (GFP) marker specifically in border cells and found that a LCE forms at the beginning of migration in one of the border cells within the cluster (Fig. 1b). Although live imaging of border cell migration has not yet been achieved, it became apparent from the variability in LCE length that they represent highly dynamic structures. Therefore, it is possible that, in common with neuronal growth cones, LCEs probe their environment for guidance cues before the cell body moves in a specified direction. Fulga and Rorth further investigated the cues that regulate the activity of the epidermal growth factor receptor (EGFR) and PDGF/VEGF-like receptor (PVR) receptor tyrosine kinases in border cells[7,8]. They found that LCEs are sensitive to the levels of guidance cues, supporting the hypothesis that EGFR and PVR promote the polarized growth of actin filaments, resulting in the formation of extensions[8].

Although the reception of spatial and temporal signals is critical, the formation of LCEs also requires traction, which in this instance is provided by *D*E-Cadherin. Interestingly, Geisbrecht and Montell[5] report that Myosin VI is expressed in extensions and is required for the formation of protrusions at the start of migration. Myosins represent a large superfamily of actin-dependent molecular motor molecules with a wide variety of specificities. The unconventional myosin, Myosin VI, is a two-headed structure that is unique among myosins, as it is the only known minus-end-directed motor. Previously, Myosin VI has been implicated in endocytosis and the transport of cargo from the periphery of the cell towards the centre[9]. As a result of its minus-end-directed motor activity, cortically bound Myosin VI has also been proposed to promote cell migration by facilitating the formation of cellular extensions (Fig. 1c). However, its role in cell migration has remained obscure. The study in border cells[5] provides a clear example where Myosin VI binds to the E-Cadherin–β-Catenin complex and couples it to the cytoskeleton.

Further insights into the role of myosins in border cell migration was obtained when Fulga and Rorth[4] analysed the border cell phenotype associated with mutations in the regulatory light chain of non-muscle myosin II, a plus-end-directed motor. In earlier studies, non-muscle myosin II was found to be required for border cell migration, although its function remained elusive[10]. After analysing LCEs in non-muscle myosin II regulatory light chain mutants, it became evident that LCEs are more abundant, longer and crooked, presumably because of a lack of tension. This finding highlights the importance of LCEs in border cell migration and supports a grapple and pull hypothesis, in which Myosin VI promotes LCE formations that contract as a result of myosin II activity, inducing movement of the border cell body.

These two new reports on border cell migration are of general importance as they clearly show that cell migration relies on the concerted action of a variety of mechanisms, in particular the interaction between the actin cytoskeleton and myosins. Although the highly dynamic and polarized structure of the actin cytoskeleton is known to be critical for cell migration, it was unclear whether myosins provide additional force. Classical actin labelling studies suggested the existence of actin nucleation sites along the leading edge of migratory cells that promote the rapid growth of actin filaments, and hence the formation of protrusions, such as lamellipodia or filopodia. Components of the Arp2/3 complex, WASP family members, and the small Rho GTPases Rac and Cdc42, promote the cortical nucleation of new actin[11]. Although the function of most of these components is unclear in border cell migration, it became evident that Cofilin and Rac are crucial for migration[8,12]. Interestingly, Cofilin seems to have a direct role in lamellipod extension in EGF-stimulated adenocarcinoma cells, suggesting there may be mechanistic similarities[13].

Although the highly dynamic architecture of actin might itself be capable of generating the required force to form protrusions, this seems unlikely *in vivo*. In the native environment of multicellular organisms, migrating cells may require an additional burst of energy as they squeeze in between other cells and pass barriers, such as the extracellular matrix or cell–cell contacts. Motor molecules, such as Myosin VI, might provide this additional force to facilitate the formation of protrusions. One possible model is that cortically captured Myosin VI moves towards the minus end of actin filaments and thereby promotes the formation of protrusions. However, there are a number of alternatives. For example, biochemical studies have demonstrated that Myosin VI binds to the cytoplasmic linker molecule, CLIP-170, a microtubule binding protein that localizes specifically to the growing ends of microtubules directed towards the cell periphery. The localization of CLIP-170 and its interaction with Myosin VI suggests the existence of an interaction between the actin and microtubule networks. It will be important to determine if this interaction is involved in cell migration. The current consensus is that cell migration is driven mostly by actin polymerization, without the involvement of microtubules. However, dynamically growing microtubules are required for directional cell movement. Additionally, special cortical sites of localized Rac1/Cdc42 were found to recruit CLIP-170 and the Rac activator IQGAP1 to form a complex that connects microtubules with the cortical actin meshwork, triggering cell polarization[14]. The proteins Par3, Par6 and aPKC also localize to these special cortical sites, and Par6 binds directly to Cdc42 (ref. 15). As these molecules are critical for the polarization of a variety of cell types, it is interesting to speculate that these proteins might also be involved in polarizing the leading edge of migratory cells.

In conclusion, these findings underscore the importance of studying complex cellular processes, such as cell migration, *in situ*. Improved imaging techniques and the possibility of tissue-specific gene interference methods[16] should help us to address the mysteries of cell migration in a native environment. These studies will find interesting similarities between different model systems, but will also uncover differences that may be crucial for our understanding of basic cellular processes in a developmental context.

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