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Fat-like cadherins in cell migration—leading from both the front and the back

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When cells migrate through the body, their motility is continually influenced by interactions with other cells. The Fat-like cadherins are cell–cell signaling proteins that promote migration in multiple cell types. Recent studies suggest, however, that Fat-like cadherins influence motility differently in mammals versus *Drosophila*, with the cadherin acting at the leading edge of mammalian cells and the trailing edge of *Drosophila* cells. As opposed to this being a difference between organisms, it is more likely that the Fat-like cadherins are highly versatile proteins that can interact with the migration machinery in multiple ways. Here, I review what is known about how Fat-like cadherins promote migration, and then explore where conserved features may be found between the mammalian and *Drosophila* models.

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Introduction

Much of what we know about how cells migrate has come from studies of isolated cells *in vitro*. When cells migrate *in vivo*, however, their movements are continually influenced by interactions with other cells. This phenomenon is best seen during the collective cell migrations that shape tissues during embryonic development, and that underlie wound healing and the spread of many cancers, but it is also true for migrating immune cells, and for neurites as they seek their synaptic targets. In addition to mediating cell–cell adhesion, members of the cadherin superfamily function as signaling proteins that provide directional information to migrating cells [1–4]. This review highlights the emerging role that Fat-like cadherins play in this process.

The Fat-like cadherins are one of the two subfamilies of Fat cadherins. The first subfamily is typified by the *Drosophila* protein Fat, which plays critical roles in planar cell polarity and growth control [5,6]. Fat's mammalian homolog is Fat4. The Fat-like subfamily includes the *Drosophila* protein Fat2 (also known as Kugelei) and the mammalian proteins Fat1, Fat2 and Fat3. Here, I will call the *Drosophila* protein dFat2 to distinguish it from the mammalian protein of the same name. These proteins are among the largest in the cadherin superfamily, with sizes exceeding 500 kDa [7,8] (Figure 1). Unlike classic cadherins who's ECDs form rigid rods, the massive ECDs of at least one Fat family member adopts a folded tertiary structure [9], which is likely necessary for it to fit into confined intercellular spaces.

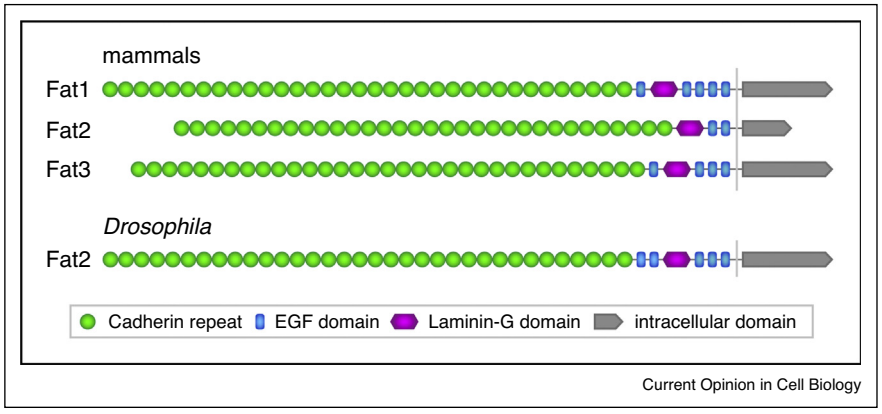
Recent work has indicated that Fat-like cadherins function as a pro-migratory signaling proteins for multiple cell types. This finding has been accompanied by the discoveries that mutations in human *fat1* cause a lethal kidney disease and an increased susceptibility to bipolar disorder [10,11,12••], and that FAT1 levels are altered in a wide range of cancers [8,13]. Given that defects in cell motility may underlie many of these conditions, there is growing interest in understanding how these massive proteins affect a cell's migratory ability.

Here, I review what is known about how the Fat-like cadherins guide cell motility from studies primarily performed in mammals and *Drosophila*. The current literature suggests that the Fat-like cadherins promote migration differently in the two models. This discrepancy could be due to an evolutionary change between organisms. Alternatively, it may indicate that the Fat-like cadherins have a remarkable ability to interface with the migration machinery differently depending on the cell type. With this second possibility in mind, I then highlight three scenarios where conserved functions are likely to be found between the mammalian and *Drosophila* proteins.

Role of Fat-like cadherins in guiding cell migration in mammals—leading from the front

The first indication that Fat-like cadherins act as pro-migratory signaling proteins came in 2004 from two papers examining Fat1's function in cultured mammalian epithelial cells [14,15••]. For cells to migrate efficiently in a scratch wound-healing assay, they must become polarized across the tissue plane with their Golgi oriented toward the wound edge. Fat1 depletion disrupts this

Figure 1



The Fat-like cadherins of mammals and *Drosophila*. The domain organization for each protein is as described in Ref. [8].

polarization process [14,15••]. Fat1-deficient NRK-52E kidney cells also have reduced protrusive activity and a clear migratory defect [14]. Fat1 localizes to both cell-contacts and to the edges of cellular protrusions [14,15••]. Later work in NRK-52E cells showed that these two populations represent different isoforms of the protein, and that the population of Fat1 that localizes to leading edge protrusions mediates its pro-migratory function [16] (Figure 2a). Finally, both papers showed that Fat1 promotes F-actin assembly by recruiting enabled/vasodilator-stimulated phospho-protein (Ena/VASP) to its intracellular domain (ICD) [14,15••]. Altogether, these data suggested that Fat1 plays two roles in epithelial cell migration: polarizing the tissue in the direction of movement, and stimulating the formation of the leading edge protrusions though Ena/VASP-mediated F-actin assembly. Building from this work, Fat1 and Fat2 have since been shown to promote the migration of numerous cell types *in vitro* [12••,14,16–20].

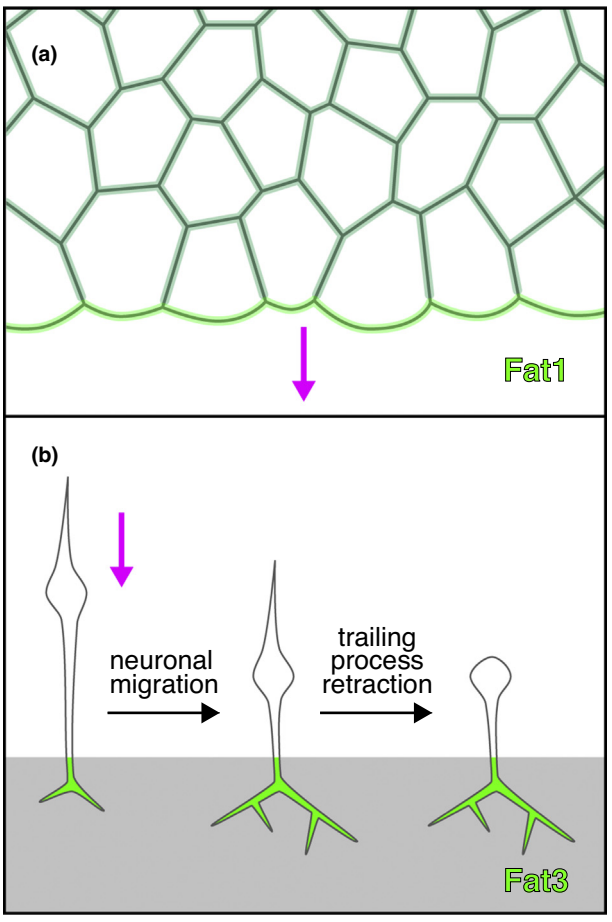
Fat-like cadherins also guide cell migration *in vivo* during muscle development and retinal development in mice. During muscle development, formation of certain muscles in the shoulder and face depends on the migration of chains of myoblasts to the muscle formation site. When Fat1 is mutated, the myoblasts show a range of migratory defects, including: failure to organize into chains, migration to ectopic locations, and reduced leading edge protrusions [21]. During retinal development, amacrine cells initially have a bi-polar morphology, with a leading process projecting into a synaptic layer called the inner plexiform layer (IPL), and their trailing process projecting toward the outer retina. Over time, the cell body migrates toward the IPL and the trailing process is retracted (Figure 2b). Fat3 localizes to the portion of the leading process that is within the IPL [22]. When Fat3 is mutated, the cell body eventually reaches its destination, but it undergoes frequent directional changes as it migrates, and the trailing process never retracts [23••]. Similar to Fat1, Fat3 recruits Ena/VASP to its ICD, and Ena/VASP is mislocalized in *fat3* mutant retinas [23••]. Remarkably, mis-localizing Ena/VASP within the amacrine cells by other means can recapitulate aspects of the *fat3* mutant phenotype [23••]. The authors thus proposed that Fat3's primary function may be to polarize F-actin assembly toward the cell's leading edge, similar to how Fat1 is thought to promote the migration of epithelial cells.

Role of Fat-like cadherins in guiding cell migration in *Drosophila*—leading from the back

In *Drosophila*, dFat2's role in cell migration has been exclusively studied in the egg chamber. An egg chamber is an organ-like structure in the ovary that gives rise to one egg. It is comprised of a germ cell cluster, surrounded by a somatic epithelium of follicle cells. During early oogenesis, the follicle cells embark on a circumferential migration wherein their basal surfaces crawl along the basement membrane ECM that ensheaths the organ (Figure 3a,b) [24,25]. This migration helps to transform the egg chamber from a spherical to an ellipsoidal shape [26,27].

A recent paper proposed that dFat2 promotes follicle cell migration similarly to the way that the mammalian proteins function [28]. Although dFat2 lacks Ena/VASP binding sites in its ICD [15••], it does have predicted binding sites for the Wave regulatory complex (WRC) [28,29•], which helps to build the branched actin network found in lamellipodial protrusions. Consistent with this observation, this paper showed that dFat2 is required for the formation of protrusions at the leading edge of each follicle cell, and that the WRC binds to dFat2's ICD *in vitro* [28]. From these data and others, the authors concluded that dFat2 stimulates the formation of leading

Figure 2



Role of Fat-like cadheins in guiding cell migration in mammals. **(a)** Fat1 is required for epithelial cell migration in a scratch would healing assay. One isoform of Fat1 (light green) localizes to lamellipodial protrusions of cells at the front of the migrating collective, whereas a different isoform (dark green) localizes to cell–cell contacts. Whether the 'lamellipodial' isoform also localizes to cryptic lamellipodia in cells behind the tissue's leading edge has not been reported. **(b)** Fat3 is required for proper neuronal migration and morphology in retinal amacrine cells. Fat3 localizes to the portion of the neuron's leading process that is within a synaptic layer called the inner plexiform layer (grey bar). Illustration adapted from Ref. [23••]. (a,b) Magenta arrows indicate direction of migration.

edge protrusions on a cell-autonomous basis by recruiting an actin assembly factor to its ICD.

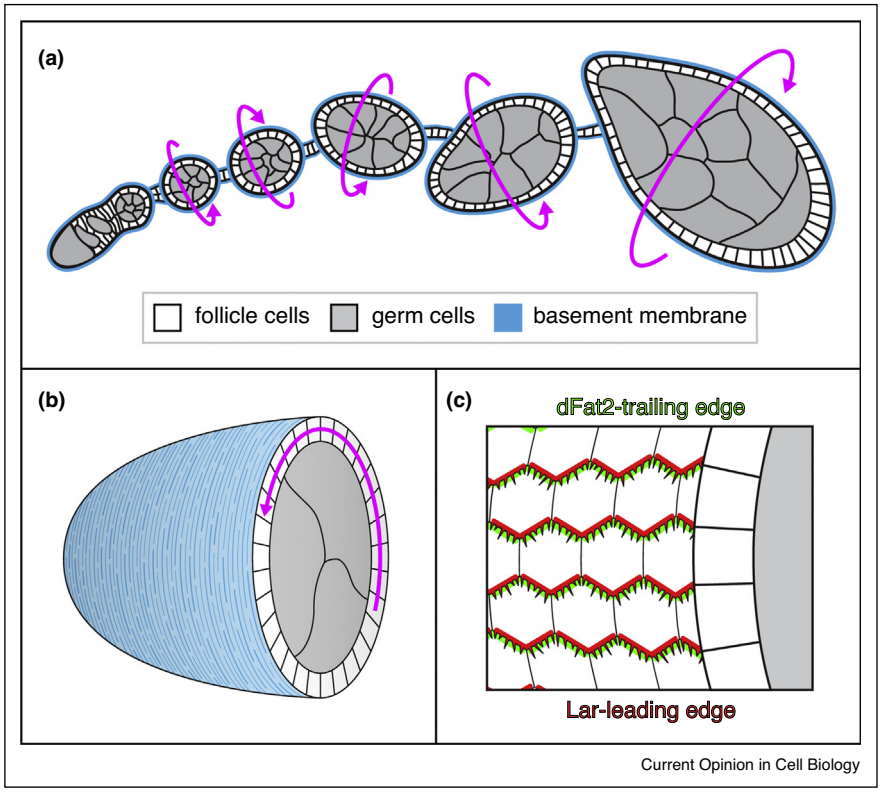
This model conflicts, however, with data showing that dFat2 localizes to the trailing edge of each cell [30•,31], and that it does so throughout the migratory period [32••]. Subsequent work from my lab analyzed dFat2's role in motility using epithelia that contained a mixture of wild-type and *dfat2* mutant cells, and showed that dFat2's role in protrusion formation is, in fact, non-cell-autonomous. dFat2 signals from each cell's trailing edge to induce the formation of leading edge protrusions in the cell behind [32••]. Moreover, the receptor tyrosine phosphatase Lar localizes to each cell's leading edge, and dFat2 induces protrusions, in part, by stabilizing Lar in this location [32••]. In migrating epithelia, most cells' leading edge protrusions extend beneath the trailing edge of the cell ahead. This geometry necessitates that trailing edge retraction in the leading cell be coordinated with protrusion formation in the trailing cell. Consistent with this notion, this work also introduced a role for dFat2 and Lar in trailing edge retraction, showing that Lar signals from each cell's leading edge to stimulate retraction in the cell ahead, and that dFat2 plays a cell-autonomous role in this process [32••].

The model that has emerged is that dFat2 and Lar participate in a planar signaling system that coordinates leading and trailing edge dynamics between neighboring cells (Figure 3c). In this way, dFat2 functions similarly to Fat, which is well-known for its role in planar polarity [5,6]. There are key differences between the two signaling systems, however. Whereas Fat and its binding partner Dachsous operate near the apical surface to transmit long-range information across an epithelium, Fat2 and Lar operate near the basal surface to transmit short-range information between adjacent cells. It is also important to emphasize that it is not yet known whether dFat2 and Lar bind to one another directly, or whether they act within a larger complex with other transmembrane proteins.

Notably, work in *Caenorhabditis elegans* has shown that the Fat-like cadherin CDH-4 also appears to function in a signaling relationship with Lar to guide the migration of Q neuroblasts, with Lar (also known as PTP-3) acting cell-autonomously within the neuroblast and CDH-4 acting non-cell-autonomously in another tissue [33,34,35•]. Thus, signaling between a Fat-like cadherin and Lar may be a widely used mechanism to direct cell migratory behavior.

Studies of the follicle cells have further suggested that dFat2 also influences cell migration through effects on microtubules (MTs). MTs near the basal epithelial surface are aligned in the direction of movement both before and during migration, with MT plus-end growth biased toward the trailing edge of each cell [30,36•]. dFat2 is required both for the biased plus-end growth and for tissue-level MT alignment at different developmental stages [30,36•], and dFat2's ICD mediates its role in MT alignment [37]. Although the follicular epithelium always migrates perpendicular to the egg chamber's anterior–posterior axis, this migration can occur in either a clockwise or counterclockwise direction [25]. The observation that dFat2 biases the direction of MT plus-end growth before migration begins has led to the proposal that dFat2 helps to determine which way the epithelium will go

Figure 3



Role of Fat-like cadherins in guiding follicle cell migration in *Drosophila*. **(a)** A developmental array of egg chambers highlighting the stages when rotation occurs (magenta arrows). Illustration depicts central saggital sections through each egg chamber. **(b)** Rotation occurs because the basal surfaces of the follicle cells collectively migrate (magenta arrow) along the basement membrane ECM that surrounds the egg chamber. Illustration shows a central transverse section through an egg chamber. **(c)** Illustration of the basal surface of the follicular epithelium with the baement membrane removed. dFat2 localizes to the trailing edge of each follicle cell and Lar localizes to the leading edge. dFat2 and Lar promote epithelial motility by coordinating leading and trailing edge dynamics between neighboring cells.

[30,36•]. Given that dFat2's trailing edge localization also depends on MTs, it has also been proposed that dFat2 may promote both epithelial motility and its own localization through a MT-dependent feedback amplification loop [30•,37].

Can we find common ground between the mammalian and *Drosophila* models?

The studies described above suggest that the way that Fat-like cadherins promote cell motility is different in mammals versus *Drosophila*, with the mammalian proteins acting at the cell's leading edge and the *Drosophila* protein acting at the trailing edge. Can we find common ground between these two models? Given the high functional conservation that is typically seen between mammalian and *Drosophila* proteins, it seems likely that both mechanisms are used by both mammals and flies, but that we have simply not yet identified the instances where the conserved behaviors occur. If true, this would indicate that the Fat-like cadherins are highly versatile signaling proteins that can interface with the migration machinery in different ways depending on the cellular context. Below, I highlight three scenarios where these points of conservation may eventually be found between the mammalian and *Drosophila* models.

A first point of conservation may come from the way that Fat-like cadherins interact with MTs. Both Fat and dFat2 help to establish planar polarized MT arrays in *Drosophila* epithelia, making this a function that is shared by both subfamilies of Fat cadherins [30•,36•,37–40]. Moreover, similar to dFat2, the mammalian Fat cadherins appear to require MTs for their subcellular localizations. Fat1 and Fat3 share a conserved motif in their ICDs that targets them to the leading edge of migrating cells and to the tips of neurites, respectively [16,41]. Fat3 uses this motif to bind the plus-end directed MT motor Kinesin [41]. Fat1's ICD also binds to Kinesin, but whether it is through the same motif is unknown [42]. Although there is generally low sequence conservation between dFat2's ICD and the ICDs of Fat1 and Fat3, the putative Kinesin-binding motif appears to be present in the *Drosophila* protein

[16]. Thus, all three proteins may interact with Kinesin to attain their polarized localizations and/or to influence MT dynamics.

A second point of conservation may occur in the role that Fat-like cadherins play in neuronal migration and/or neurite outgrowth. Thus far, Fat-like cadherins are known to help wire the nervous system in both mice and *C. elegans* [23,33]. Although dFat2's role in the nervous system has not yet been explored, it is widely expressed in *Drosophila* neurons [43]. Given that dFat2's ICD binds to the WRC [28], and that Fat1's and Fat3's ICDs also have predicted WRC binding sites [29•], all three proteins might influence neuronal development via cell-autonomous polarization of the F-actin assembly, as proposed for Fat3 in amacrine cells [23••]. Moreover, since Lar plays critical roles in axon guidance and synapse formation [44–46], it is interesting to speculate that Fat-like cadherins could interact with Lar to guide neuronal connectivity as well.

Finally, a third point of conservation may come from the discovery of cell migrations in mammals in which Fat-like cadherins promote motility from the cell's trailing edge. To date, no clear function has yet been ascribed to the massive ECDs of the mammalian Fat-like cadherins. It therefore seems likely that there are inter-cellular signaling functions for these proteins that remain to be found, and that may prove to be conserved with that of the *Drosophila* protein. For example, it is not yet known whether Fat1 functions at the leading edge or trailing edge during myoblast migration in mice [21]. Moreover, because the Fat cadherins have overlapping functions in some mammalian tissues [47,48], careful analysis of double and triple knockouts may be required to identify all of the cell migratory events that are guided by these proteins.

Conclusions

In the thirteen years since Fat1 was first shown to be a pro-migratory signaling protein, the interest in understanding how Fat-like cadherins direct cell motility has steadily grown. There has been good progress in identifying intracellular binding partners, and determining how the Fat-like cadherins promote motility on a cell-autonomous basis. To date, however, the functions of the massive ECDs that define this protein class have gone largely ignored. Given that the first migratory phenotype described for loss of Fat1 is a failure of tissue-level polarization in an epithelial migration assay [14,15••], it is likely that Fat1 plays a central role in cell–cell communication. Going forward, it will be essential to identify the Fat-like cadherins' extracellular binding partner(s) and to dissect how these proteins signal to neighboring cells. With the first clear extracellular signaling function for a Fat-like cadherin having recently been identified in *Drosophila* [32••], information gleaned from both mammalian and *Drosophila* models will likely be the key to achieving this goal.

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