Expect the unexpected: conventional and unconventional roles for cadherins in collective cell migration

C. Luke Messer and Jocelyn A. McDonald*
Division of Biology, Kansas State University, Manhattan, KS 66502

*Correspondence: jmcdona@ksu.edu

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Abstract

Migrating cell collectives navigate complex tissue environments both during normal development and in pathological contexts such as tumor invasion and metastasis. To do this, cells in collectives must stay together but also communicate information across the group. The cadherin superfamily of proteins mediates junctional adhesions between cells, but also serve many essential functions in collective cell migration. Besides keeping migrating cell collectives cohesive, cadherins help follower cells maintain their attachment to leader cells, transfer information about front-rear polarity among the cohort, sense and respond to changes in the tissue environment, and promote intracellular signaling, in addition to other cellular behaviors. In this review, we highlight recent studies that reveal diverse but critical roles for both classical and atypical cadherins in collective cell migration, specifically focusing on four *in vivo* model systems in development: the *Drosophila* border cells, Zebrafish mesendodermal cells, *Drosophila* follicle rotation, and *Xenopus* neural crest cells.

Introduction

Cell migration is fundamental to many key events during embryonic development such as gastrulation and organ formation, whereas dysregulation drives progression of diseases such as cancer. Often, individual cells unite to move together in a process called collective cell migration. Like single cells, collectives undergo a motility cycle: polarized protrusions form at the leading edge, cells attach to the migratory substrate, adhesions are released at the rear, then the cells can move forward (1,2). In collectives, however, cells within the group also must stay together to move as a single unit (3). Cell-cell adhesions help maintain such group integrity, especially given the space constraints imposed by the tissue environment and help convey information across the cohort. More detail on collective cell migration and the general roles of diverse adhesion proteins in cell collectives can be found in several recent reviews (4–8). Here, we focus on the cadherin family of proteins, whose numerous functions together are integral to the success of collective cell migration.

The cadherin superfamily of calcium-dependent transmembrane proteins connect cells together and aid in cell-cell recognition (9). The highly conserved cadherins share a common feature, an extracellular domain of cadherin repeats that facilitates homophilic and heterophilic interactions. A great diversity of cadherins exist, with 114 different cadherin coding genes in humans, such as the ‘type 1’ classical cadherins E-cadherin and N-cadherin, protocadherins (PCDHs), and the so-called ‘atypical’ cadherin-related proteins (CDHRs) Dachsous and FAT (9,10). Classical cadherins are the main components of the adherens junction that serve as primary mechanosensitive contacts between adherent cells (11). The intracellular domain of type 1 classical cadherins bind to p120-catenin, β-catenin, and α-catenin, which in turn provides direct connection to the F-actin cytoskeleton (12). Atypical cadherins such as Fat (Ft) and Fat2 have very large extracellular domains consisting of 34 cadherin repeats and signal through their intracellular domains (10,13).

While cadherins are well known for their roles in mediating junctional adhesions between cells, they serve many additional functions in collective cell migration. Besides keeping collectives cohesive, cadherins help follower cells maintain their attachment to leader cells, facilitate information transfer across groups of cells, sense the environment, and facilitate intracellular signaling and remodeling events that are required for efficient migration. In this review, we highlight roles for both classical and atypical cadherins in collective cell migration during development. Specifically, we focus on recent studies that find both expected and unexpected functions of cadherins in four models of *in vivo* collective cell migration, border cells, polster cells, rotating follicle cells, and neural crest cells.

An efficient multitasker: E-cadherin controls many facets of *Drosophila* border cell migration

E-Cadherin has a surprising number of roles in the migration of border cells during *Drosophila* oogenesis. Border cells are a small group of six to ten epithelial follicle cells that are recruited by a pair of specialized ‘polar cells’ to form a migratory ‘cluster’ (**Figure 1A**). Within this cluster,

outer migratory border cells completely surround the inner, non-motile polar cells (**Figure 1A**). The border cell cluster then detaches from the surrounding follicular epithelium, moves between 15 large nurse cells, and finally stops at the oocyte. Eventually, border cells and polar cells together form the micropyle (14,15). During migration, border cells stay tightly attached to each other and to the polar cells, form directional protrusions toward the oocyte, and crawl between the nurse cells. E-cadherin is required for all these functions – and more.

Before border cells even begin their migration, there is a marked increase in E-cadherin mRNA levels compared to non-migratory epithelial follicle cells (16). This is reflected at the protein level, where high levels of E-cadherin and associated complex members such as β-catenin are found at cell-cell contacts between polar cells, between polar and border cells, and between border cells (**Figure 1A**). Precise levels of E-cadherin are critical for migration; complete loss of E-cadherin, β-catenin, or α-catenin, causes border cells to stay stuck in the epithelium and prevents their ability to move (16–18). Increased levels are also detrimental, as overexpression of E-cadherin blocks border cell migration (19).

E-cadherin mechanically couples border cells to provide directional information to the cluster (**Figure 1A**). Border cells typically extend one or more dynamic actin-rich protrusions toward the direction of migration (20,21). High Rac GTPase activity in a lead cell polarizes the cluster and cell-cell communication suppresses protrusions from the other border cells (22,23). Cai and colleagues (2014) found a key role for E-cadherin in this process (24). Specific knockdown of E-cadherin in just the migratory border cells disrupts overall directional migration and leads to more protrusions from the other, non-leading border cells. Further, loss of E-cadherin delocalizes Rac activity from the leading border cell. These phenotypes closely resemble those caused by inhibition of the guidance receptors EGFR and PVR, which together respond to secreted ligands from the oocyte (20,23,25,26). Co-expression of dominant-negative forms of EGFR and PVR increases Rac activity in all border cells and causes all border cells to produce non-directed protrusions (20,23). Thus, E-cadherin, downstream of guidance activation through EGFR and PVR, connects border cells to communicate localized Rac activity information to all cells within the cluster for directed migration (24). Similarly, E-cadherin (Cadherin-1; Cdh1) helps direct the collective migration of the zebrafish lateral line primordium (27). Lateral line cells in the lead pull follower cells through Cdh1-dependent cell-cell adhesion, which, together with chemokine signaling, results in directional migration. Likewise, during zebrafish gastrulation, mesendodermal cells migrate and require E-cadherin (28). While individual mesendodermal progenitor cells are motile, they require E-cadherin-based cell adhesion between cells to provide greater coordinated migration, speed and directionality at the collective level.

One way E-cadherin could communicate among border cells is via mechanical connection through the actomyosin cytoskeleton. At the outer periphery of the border cell collective, non-muscle myosin II (myosin II) is locally restricted yet dynamic (29,30). Localized myosin II promotes the overall shape of the border cell cluster and the ability to migrate as a group (18,29). F-actin is highly enriched on the outside of the border cell cluster resembling what has been termed ‘supracellular,’ or ‘above the cellular level,’ organization in other cell collectives

(31). This supracellular F-actin helps suppress protrusions from non-leading border cells (18,32). Interestingly, E-cadherin regulates the localization and dynamics of myosin II within the border cell cluster (30). Loss of myosin II causes non-leading border cells to protrude, similar to loss of E-cadherin (24,30). Physical linkage of the cadherin-catenin complex to the localized actomyosin cortex at the cluster periphery through α-catenin thus could keep individual border cells mechanically coupled.

In a perhaps more expected role, E-cadherin keeps cells within the border cell cluster adhered to each other. The cluster contains two cell types, the central polar cells, and the outer surrounding border cells, with high levels of E-cadherin between all cells (**Figure 1A**). Specific knockdown of E-cadherin in either polar cells or in border cells using RNA interference (RNAi) causes border cells to fall off the cluster (18,24,33). Interestingly, wild type border cells that fall off E-cadherin-deficient polar cells are still motile and form protrusions, though their speed is slower than normal (24,34). RNAi knockdown of E-cadherin, β-catenin, or α-catenin only in border cells, or simultaneously in polar cells and border cells, causes the cluster to fall apart with poor border cell movement (18,33). Thus, heterotypic cadherin-catenin adhesion keeps border cells attached to polar cells and homotypic adhesion keeps border cells attached to each other.

Border cells do not migrate on an extracellular matrix. Instead, E-cadherin provides traction for border cells to migrate upon their nurse cell substrate (**Figure 1A**). Complete loss of E-cadherin in just the nurse cells blocks border cell migration, similar to loss of E-cadherin only in border cells (16,24,35). When nurse cells are mutant for E-cadherin, border cells cannot invade between nurse cells and instead they migrate up the side of the egg chamber, along the epithelial follicle cells that still express E-cadherin (24,35). E-cadherin is thus required in both border cells and nurse cells for proper collective movement and likely needs to be carefully regulated in both cell types. More work, however, is needed to determine the mechanism by which E-cadherin mediates dynamic adhesion of border cells to nurse cells. Intriguingly, although E-cadherin is required for traction, the physical packing of nurse cells acts as a topographic cue for border cells to journey down the correct central pathway between nurse cells (35). Other migrating cells also use E-cadherin for movement on other cells. For example, during zebrafish gastrulation, the internalizing mesendodermal cells migrate along the overlying epiblast epithelial cell layer and during gonad formation, primordial germ cells migrate upon adjacent somatic cells, both of which require E-cadherin (36,37).

Guiding from behind: E-Cadherin mediates backseat driving behavior of Zebrafish polster cells

Within cell collectives, follower cells also contribute to migration of the group. In some cases, the followers drive movement from behind, which requires cadherins. Such is the case with zebrafish polster cells and cells of the closely associated prechordal plate in the gastrulating embryo (**Figure 1B**). During gastrulation of the zebrafish embryo, the polster cells are the first, anterior-most mesendodermal cells to internalize (38). The polster cells migrate from the

blastoderm margin towards the yolk layer, then turn at the yolk surface to migrate along the epiblast towards the animal pole (36,39,40). The polster cells are followed by the anterior axial mesendodermal cells that give rise to the prechordal plate; behind both cell types are the posterior axial mesodermal cells (36,39,41).

E-Cadherin is expressed in prechordal plate cells and is required for their efficient cell movement (36). At the tissue level, downregulation of E-Cadherin in the axial mesendoderm allows their efficient migration through application of a “push” from the posterior cells (42). Intriguingly, cells at the front, middle, or rear positions of the prechordal plate all have similar migration speeds and extend actin-rich protrusions toward the animal pole (41). While this might suggest that prechordal plate cells move as single cells, elegant transplant experiments show that these cells migrate collectively (41). When transplanted ahead of the endogenous prechordal plate, prechordal plate cells lose protrusion directionality. However, protrusion orientation is regained once the endogenous plate catches up to the transplanted cell population. E-Cadherin, along with Rac1 and planar cell polarity signaling, orients individual cell protrusions. Dumortier and colleagues propose a model in which the directional cue emerges as an intrinsic property of the collective migration of the cell cohort (41).

The polster cells and prechordal plate undergo directional migration, but who does the steering? In a follow up study, Boutillon and colleagues find that the rearmost posterior mesodermal cells actively orient the direction of the polster and prechordal plate cells (**Figure 1B**) (39). Using laser ablation, cuts at the leading edge do not alter speed or protrusions, but cuts in the middle of the polster cells or between the polster cells and the posterior mesoderm significantly reduces both speed and protrusion orientation of the cells ahead of the ablation site. Thus, polster cells not only receive directional information from contact with the rear posterior axial mesodermal cells but also require active migration of the axial mesoderm (39,41). α-catenin, which links the cadherin complex to the actin cytoskeleton, orients polster cell protrusions and accumulates at protrusion contacts with the cell in front (39). Laser ablation experiments at these contact sites indicate that the protrusions are under tissue tension. Together the authors conclude that follower cells, by actively migrating and forming protrusions, generate a mechanical cue that guides the cells ahead of them. Successful communication of this cue requires E-Cadherin through linkage to α-catenin and vinculin (39).

Seamless motility: The atypical cadherin Fat2 drives *Drosophila* follicle cell rotation

The atypical cadherin Fat2, rather than classical cadherins, regulates the collective rotation of *Drosophila* follicle cells, an emerging model of edgeless collective cell migration (9,43). The follicular epithelium is a continuous sheet of cells that surrounds the inner germline cells (**Figure 2A**). There are no gaps in this tissue; thus, follicle cells lack the typical cues that *a priori* dictate who is a leader and who is a follower in collective migration, yet they still move directionally. Migration of the entire follicle cell layer occurs along an overlying basement membrane (44). This rotational movement begins as soon as egg chambers form and continues until stage 8 of oogenesis (44,45). Failure to rotate causes the resultant eggs to become round (44,46,47). A combination of follicle cell migration, expansion of the germline, and stiffening of the basement

membrane layer cooperate to elongate the egg into its final ellipsoid shape (44,45,48–51). Importantly, mammalian epithelial cell collectives can undergo similar ‘seamless’ rotational collective migration (52–55).

In the absence of free edges, the atypical cadherin Fat2 breaks symmetry in the epithelium and establishes the direction of follicle cell migration. Loss of Fat2 (also called Kugelei) prevents egg elongation and disrupts the orientation of F-actin filaments and microtubules (47,56,57). Further live imaging revealed that Fat2 promotes egg chamber rotation (47). Fat2 localizes to the trailing edge of follicle cells, suggesting a role in migration direction (47,57). Egg chambers are able to rotate either clockwise or counterclockwise, which requires Fat2-dependent polarized microtubule growth (47). Interestingly, follicle cell migration begins shortly after the egg chamber forms in the germarium (45). Even this early, Fat2 promotes the orientation of microtubule plus-ends, which predicts the direction of follicle migration inside the germarium (58).

After helping establish the direction of rotation, Fat2 fine-tunes the machinery for motility to help establish leading and trailing (lagging) edges of migrating follicle cells. Although a seamless epithelium, follicle cells are planar polarized in the direction of migration. F-actin-based protrusions orient to the leading edge of each cell (45,56,59). These lamellipodial protrusions are required for rotation (45). Fat2 promotes proper protrusion extension and retraction at the leading edge (59–61). Loss of *fat2* prevents protrusion formation (60,61). This requirement is counterintuitive, as Fat2 localizes to the trailing edge of migrating follicle cells (47). However, subsequent work identified a non-cell autonomous role for Fat2 in promoting the extension of protrusions from the cell immediately behind (**Figure 2A**; (59,61).

How does Fat2 control protrusions? Closer analysis of *fat2* mutant follicle cells reveals that while the cells are less protrusive overall, some protrusions still form though they are no longer oriented in the direction of migration (59). It was already known that the WASP family verprolin homolog regulatory (WAVE) complex, which stimulates F-actin growth, promotes follicle cell protrusion formation during migration (45). Interestingly, Fat2 functions non-cell autonomously at the lagging edge to polarize and stabilize WAVE complex members at the leading edge of the immediately-following cell (59). Live analysis of cells with fluorescently tagged proteins reveal tight punctate colocalization of both Fat2 and WAVE complex proteins at the leading-trailing interface. Fat2 also promotes the localization of the receptor tyrosine phosphatase Lar to the leading edge of follicle cells (**Figure 2A**) (61). Lar is required for leading edge protrusions and WAVE complex localization (60,61). Fat2 thus recruits and stabilizes WAVE complex to cell-cell contacts, along with Lar, thus inducing leading edge protrusions to direct the rotational collective migration of follicle cells.

Cadherins in contact: CIL and CIL-like behaviors in collective migration

Another type of collective cell migration that requires cadherins is the coordination of streams of closely associated cells through contact inhibition of locomotion (CIL). First described 70 years ago, CIL is the process by which cells that collide into other cells pause, reorient, and then

move away from each other (62). CIL functions as both a barrier to cancer metastasis and a promoter of normal embryonic development and wound healing (63). Cadherins are an increasingly appreciated component required for CIL. This includes the cellular avoidance responses commonly associated with CIL, which together lead to directional collective movement, migrating cell interactions with their substrate, and a variation termed contact-stimulated locomotion (64–68).

Cadherins and CIL are key to the directed migration of the cranial neural crest, which undergo a collective migration to populate craniofacial structures during development (**Figure 2B**) (64,69). Specifically, an E-cadherin to N-cadherin switch is required for CIL in *Xenopus* neural crest cell migration (64). Pre-migratory neural crest cells express E-cadherin and cannot perform CIL, whereas migratory neural crest cells express N-cadherin and can now undergo CIL. Cell-cell contacts form between colliding migratory neural crest cells, but these adhesions are transient. N-cadherin-expressing migratory neural crest cells polarize Rac1 activity and protrusions opposite to the sites of cell-cell contact, thus allowing separation and migration of the cells away from each other after cell collision. Ectopic expression of E-cadherin in migratory neural crest cells disrupts protrusions and cells can no longer orient traction forces away from the point of cell-cell contacts. Thus, E-cadherin blocks CIL and N-cadherin promotes CIL. This cadherin switch during neural crest development regulates Rac1 activity, providing forces to disassemble cell-cell junctions, leading to classic CIL avoidance behaviors (64). Altogether, migration of the neural crest requires CIL through adhesion and oriented protrusion regulation, along with mutual ‘co-attraction’ through chemoattractant signaling (64,70). Simultaneously, a physical supracellular actomyosin cable that surrounds the rear edge of the neural crest cells actively contracts to help drive persistent forward movement of the group (71).

In addition to initiating Rac1 activity required for CIL through polarized protrusions, cadherins have other important roles in neural crest migration. Cells undergoing CIL need traction with the migratory substrate to provide the forces to move apart. In migratory neural crest cells, N-cadherin mediates the local disassembly of focal adhesions at neural crest-matrix contacts (66). Specifically, transient N-cadherin adhesion between the colliding cells upregulates Src kinase activity, disassembly of cell-matrix adhesions at cell-cell contacts, and a redistribution of forces (**Figure 2B**). This leads to separation of neural crest cells and their movement away from each other. Similarly, N-cadherin mediates the heterotypic ‘chase-and-run’ behavior of neural crest and their neighboring epithelial placode cells (**Figure 2B**) (65). In this case, the placode tissue secretes a chemoattractant, the chemokine Sdf1 (CXCL12), that draws the neural crest forward. Then, N-cadherin-mediated neural crest-placode heterotypic cell contacts result in a CIL, where the placode cells migrate away from the neural crest (**Figure 2B**). Recent biophysical studies further revealed a stiffness gradient in the retreating placodal tissue upon neural crest migration (67). N-cadherin helps generate the stiffness gradient for neural crest migration. The neural crest then chases this retreating gradient of stiffer tissue. Together, these results underscore the importance of cadherin-based cell-cell contacts in both homotypic and heterotypic CIL mechanisms.

Finally, a new model of collective cell migration was recently described in the *Drosophila* testis that uses an interesting twist on CIL called ‘contact-stimulated locomotion’ (CSL; (68). During pupal development, nascent myotubes migrate collectively to eventually cover the entire testis in a muscular sheath (72,73). Much like in neural crest cells, N-cadherin regulates cell-cell and cell-matrix adhesions (68). Testis myotubes migrate using filopodia, rather than broad lamellipodia, to drive their collective locomotion. Laser ablation experiments reveal that testis myotubes migrate towards and fill in tissue gaps. N-cadherin knockdown blocks the ability of nascent myotubes to cover the testis (73). Rather than preventing cell motility, cells with reduced N-cadherin still migrate but are prevented from moving together in a directional manner (68). Notably, knocking down N-cadherin increases the number of myotubes with free edges that have stable cell-matrix adhesions, which in turn promote forward movement. Bischoff and colleagues propose that nascent testis myotubes move through CSL, a variant on CIL that was described more than 30 years ago in quail neural crest and human primary melanocytes (68,74). In the case of CSL of testis myotubes, N-cadherin biases cell-matrix adhesions towards the free space, but the cells need to touch and reinforce their cell-cell contacts for directional migration (68).

Conclusions

While cadherins contribute to diverse roles beyond the classical view of epithelial cell-cell adhesion, the complexity of these mechanisms is just beginning to be uncovered in collective cell migration. In this review, we highlighted both expected and unexpected functions of classical and atypical cadherins in collective cell migration. Several themes emerge from recent studies of four *in vivo* models of collective cell migration, border cells, polster cells, follicle rotation, and neural crest cells. Cadherins often mediate cell-cell adhesion to keep cells cohesive and adhered to each other during migration. Counterintuitively, in CIL, cadherins provide contact cues for cells to move away from each other. In the case of neural crest cells, directional protrusions, along with other mechanisms, help the cells move together. Cadherins can promote traction of cell collectives onto migratory substrates, either other cells or extracellular matrix. A major emerging theme is that cadherins help to determine the direction of migration. Directional information via cadherins often occurs through connections to the cytoskeleton, such as direct linkage of E-cadherin to F-actin via α-catenin in border cells and polster cells, but also by asymmetric Fat2-dependent WAVE localization and directed protrusions in follicle rotation. A major open question is whether the roles for classical and atypical cadherins are conserved, for example during various types of collective cell migrations in human development and diseases such as cancer. Moreover, are unique roles for cadherins truly unique? For example, do atypical cadherins like Fat2 have broader roles in the directed migration of cell collectives? Finally, collective cell migration is a common mode of tumor metastasis (3,8), thus understanding these diverse cadherin functions may ultimately offer new therapeutic targets.

Perspectives

- Many cells migrate as collectives during development, in wound healing, and in tumor invasion and metastasis. Cell adhesion proteins, such as classical and atypical cadherins, are required for collective cell migration.
- Classical and atypical cadherins have many functions in collective cell migration, ranging from keeping cells together, communicating where and when protrusions form, which direction the group will move, and the efficiency of group movement.
- It is still unclear how these highly similar cadherin proteins have such diverse functions in collective cell migration. New optogenetic and optochemical tools to manipulate cadherins and/or cell-cell junctions, though challenging to create and implement especially inside tissues, may be needed to help disentangle these functions (75,76).

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Abbreviations

CIL, contact inhibition of locomotion; CSL, contact-stimulated locomotion; CDHR, cadherin-related; PCDH, protocadherin

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Figure Legends

Figure 1. E-cadherin-dependent collective migration of border cells and zebrafish polster cells.

(**A**) E-cadherin has multiple functions in *Drosophila* border cell migration. E-cadherin (E-Cad, orange lines on schematic) helps form the cluster at stage 8 (top) and promotes directed migration at stage 9. Zoomed-in images show the organization of cells within the cluster (border cells, bc; polar cells, pc) and localization of E-cadherin (green on micrograph). E-cadherin helps cells stay together, form directional protrusions at the leading edge, and crawl upon the nurse cells (nc). (**B**) Zebrafish mesendodermal polster cells require E-cadherin for directional migration, with steering from behind during gastrulation. E-cadherin-dependent directional cues (E-cad arrow) are relayed from the posterior axial mesoderm to the prechordal plate and polster cells, which helps the cells move towards the animal pole. All cells express E-cadherin but a mechanical cue, via α-catenin and the actin cytoskeleton, orients protrusions and movement of the collective (36, 39).

Figure 2. Roles for atypical cadherin Fat2 in follicle rotation and N-cadherin in neural crest migration.

(**A**) Follicle cell rotation in *Drosophila* oogenesis requires the atypical cadherin Fat2. Fat2 breaks the symmetry and permits follicle cell (fc) rotation (top, arrows) around the axis of the egg chamber. Nurse cells (nc); A, anterior; P, posterior. Zoomed-in schematics (bottom) illustrate that Fat2 promotes WAVE/Lar activity (cyan; bottom left) and WAVE/protrusions at the leading edge of the cells (cyan; bottom right), behind Fat2-enriched lagging cell surfaces (orange). (**B**) *Xenopus* neural crest cells require N-cadherin (N-Cad, orange) for polarized disassembly of cell-cell junctions and for cell matrix focal adhesion remodeling during CIL (zoomed-in view, top). Shown are two neural crest cells undergoing CIL to move away from each other (arrows). The neural crest cells (gray) interact with, but stay separate from, the adjacent epithelial placode cells (blue; zoomed-out view, bottom). As neural crest cells make N-cadherin-mediated contacts with placode cells (gradient arrow), a 'chase and run' behavior is initiated that further contributes to successful tissue development.