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Previews

Fat2 and Lar Dance a Pas de Deux during Collective Cell Migration

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What coordinates the internal leading and trailing edges in collectively migrating cells is largely unknown. In this issue of *Developmental Cell*, Barlan et al. (2017) delineate a Fat2/Lar planar signaling pathway at the basal, motile cell-cell contacts of *Drosophila* egg chamber follicle cells.

A single migrating cell often has a protrusive leading edge and a contractile trailing edge. However, when many cells migrate collectively, such as during development and cancer, they must coordinate individual motility to avoid an internal traffic jam. One way to achieve this is for follower cells to repress their own leading and trailing edges via contact inhibition of locomotion and to rely on motility of strongly polarized leader cells to power the entire group (Mayor and Etienne-Manneville, 2016). However, a free leading edge is not always an option, such as in the case of the *Drosophila* egg chamber. Its follicular epithelium is composed of many polarized cells, each with a leading and a trailing edge at the basal surface. The collective motility of follicle cells drives the egg chamber to rotate and elongate, with equal contribution from each individual follicle cell (Cetera and Horne-Badovinac, 2015). Therefore, it is crucial to coordinate the activity of juxtaposed protrusive leading and retractile trailing edges for effective collective migration. Because each leading edge is in close contact with the trailing edge of the neighboring cell, this coordination must involve a cell-contact-based mechanism. In this issue of *Developmental Cell*, Barlan et al. (2017) delineate a planar polarized signaling pathway at work at the basal, motile cell-cell contacts of *Drosophila* egg chamber follicle cells, involving a signaling couple between receptor tyrosine phosphatase Lar and the atypical cadherin Fat2.

Looking for a basally operating planar signaling pathway, Barlan et al. (2017) decided to focus on transmembrane proteins that localize basally at the leading and trailing edges of follicular cells. There were two potential candidates: the atypical cadherin Fat2 and the receptor tyrosine phosphatase Leukocyte antigen related (Lar). Both proteins were recently shown to be required for planar polarized basal actin protrusive activities and follicle cell motility (Squarr et al., 2016). To understand how information is exchanged between the leading and trailing edges during their coordinated activity, it is crucial to pinpoint the subcellular localization of candidate proteins. To this end, it is known that when Fat2 becomes planar polarized, it localizes at the trailing edge (Viktorinová and Dahmann, 2013), but less was known about the localization of Lar. Barlan et al. (2017) used mosaic analysis to reveal that Lar localizes at the leading edge and is thus juxtaposed with Fat2 from the trailing edge in the neighboring cell (Figure 1A). The authors further demonstrated that this complementary pattern exists at the onset of the migratory period and that Fat2 and Lar colocalize in discrete puncta along cell membranes, suggesting that they may form a signaling complex integral for follicle cell motility.

Based on their subcellular localization, and because both Lar and Fat2 are required for leading-edge protrusion, one would expect that Lar is required cell-autonomously, while Fat2 plays a non-cell-autonomous role. Elegant mosaic analyses confirmed this by showing that loss of Fat2 in a cell inhibits protrusion in the cell directly "behind" it, while loss of Lar in a cell inhibits protrusion in the same cell. Next, the authors explored the functional relationship between these two complementarily localized transmembrane proteins. They found that Fat2 is essential in a non-cell-autonomous manner for Lar accumulation at the leading edge of cells directly behind, while Lar has no obvious effect on Fat2 localization (Figure 1C). This suggests that Fat2 and Lar may form a complex in *trans*, across cell membranes. By generating a Fat2 mutant lacking its intracellular domain, the authors demonstrated that Fat2's extracellular domain is sufficient both for its planar polarized localization and for recruitment of Lar to the leading edge of the cell behind. They further demonstrated this *trans* interaction with dissociated follicle cells, demonstrating that Fat2 and Lar colocalize when they are expressed in adjacent cells, but not when they are only present in the same cell.

What about trailing-edge retraction? Mosaic analysis revealed the converse functional requirements as leading-edge protrusions: a non-cell-autonomous role for Lar and a cell-autonomous one for Fat2 in promoting retraction. The authors hypothesized that the trailing-edge retraction might be caused by leading-edge protrusion, perhaps via mechanical means (Figure 1B). However, trailing-edge retraction is severely affected in cells ahead of Lar mutant cells, but not as much when they are placed ahead of cells with protrusion defects (such as mutant clones perturbing the Wave regulatory complex [WRC]) that still retain Lar function. This suggests the existence of a chemical signal from Lar that promotes trailing-edge retraction in *trans* (Figure 1B). Because Lar is a tyrosine phosphatase, its non-autonomous function will likely require a molecular intermediate that remains to be identified.

Together, the work described in Barlan et al. (2017) provides strong evidence for

a basally localized, intercellular signaling complex containing Fat2 and Lar for planar cell motility. It is the most recent entry to a list of exciting papers exploring the central role of Fat2 in the framework of basal PCP signaling and follicle cell motility (Viktorinová and Dahmann, 2013; Aurich and Dahmann, 2016; Chen et al., 2016; Squarr et al., 2016). Fat2 is considered to both generate and translate the initial symmetry breaking, involving an early microtubule plus-end bias into planar polarized actin protrusive activity. This, in turn, would cause the alignment of basal actin stress fiber and ECM fibrils, and eventually power egg chamber rotation and elongation (Cetera and Horne-Badovinac, 2015). However, in the current work from Barlan et al. (2017), they show that when whole egg chamber rotation is blocked via perturbing the WRC, both Fat2 and Lar continue to localize in puncta but lose their planar polarity. This is not due to a local, cell-autonomous requirement for actin protrusions, as Lar and Fat2 are still properly polarized in small clones deficient in WRC activity. This suggests that larger-scale tissue motility may also be required to feed back upon Fat2 for proper planar polarization.

The so-called core planar cell polarity (PCP) pathway polarizes cell contacts in several contexts of planar cell motility, such as contact inhibition of locomotion during collective migration, mesenchymal convergence extension, and epithelial cell intercalation (Mayor and Etienne-Manneville, 2016; Devenport, 2016). This apically localized signaling pathway is composed of another intercellular, transmembrane protein complex involving Fz and Vang (Figure 1D). In a striking parallel to the Fat2/Lar system, Fz and Vang interact in *trans*, form discrete puncta along polarized cell-cell contacts, and occupy opposite ends of a cell. Though Fat2 can recruit Lar via *trans*-stabilisation, Lar is not required for Fat2 polarity. By contrast, Fz and Vang are mutually required for each other's polarity via *trans*-stabilization and *cis*-destabilization/exclusion (Figure 1E). However, whereas the Fz/Vang asymmetry propagates at a distance, the Fat2/Lar system only propagates polarity one cell diameter away. The global alignment of Fat2/Lar planar polarity therefore likely involves another mechanism, such as using a mechanical signal on the whole-tissue level. Interestingly, core PCP components can also be aligned over a long distance by global mechanical signals (Aigouy et al., 2010; Aw et al., 2016). This suggests that the interplay between short-range chemical and long-range mechanical signals may be a general principle in diverse planar signaling systems. Future work will continue to reveal convergent strategies underlying planar cell polarization in animals.

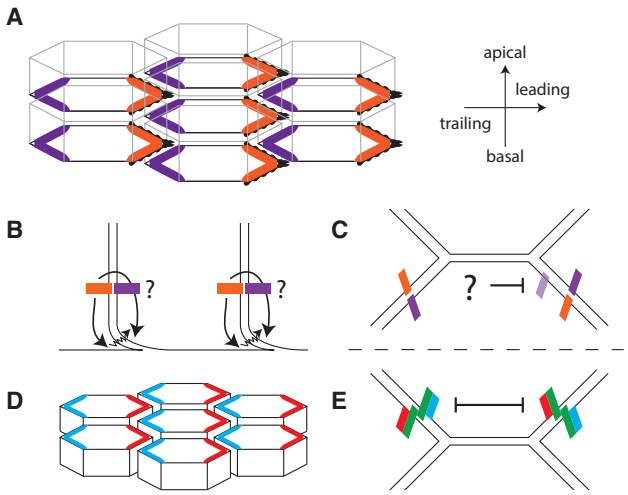

Figure 1. Fat2/Lar Defines a Basal Planar Polarity Signaling Pathway That Coordinates Leading- and Trailing-Edge Dynamics during Collective Cell Migration

(A) 3D view of cells with basally localized Fat2 (purple) and Lar (orange). Black waves show actin-rich protrusions. (B) 2D side view of migrating epithelial cells, focusing on the basal side. Smooth arrows represent unknown chemical signals from Lar to the leading edge in the same cell and to the trailing edge in the adjacent cell, while zigzag arrows represent putative mechanical signals from the leading edge to the trailing edge. (C) A planar view of the subcellular distribution Fat2/Lar components. Flat arrows indicate an unknown signal repressing Fat2 localization at the leading edge. (D) 3D view of cells with apically localized core PCP components. (E) A planar view of the subcellular distribution of core PCP components. Flat arrows show repression between Fz/Dsh/Dgo and Vang/Pk. Color scheme in all panels: orange, Lar; purple, Fat2; red, Fz/Dsh/Dgo; blue, Vang/Pk; green, Fmi.

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