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Lamellipodin branches out

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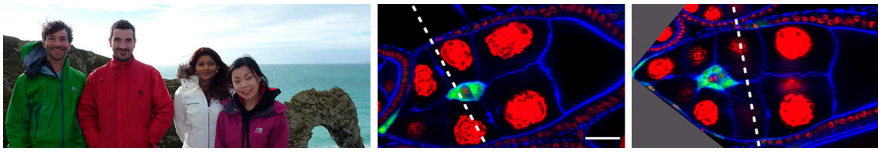
Focal Point



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(Left to right) Matthias Krause, Cristian Bodo, Upamali Perera, Ah-Lai Law, and colleagues (not pictured) investigate how a protein called Lamellipodin (Lpd) induces membrane protrusions. The researchers find that Lpd binds to the Scar/WAVE complex, a key activator of the Arp2/3 complex that nucleates branched actin networks. Formation of membrane protrusions by Lpd and the Scar/WAVE complex is critical for the migration of a variety of different cell types in different organisms, from the neural crest cells of mice and *Xenopus* embryos to the border cells of *Drosophila* egg chambers. Wild-type border cells (green, center) collectively migrate between surrounding nurse cells toward the oocyte at the chamber posterior. The border cells' progress past the most anterior position of the overlying follicle cells (white dashed line) is reduced in the absence of Pico, the fly homologue of Lpd (right). This suggests that Lpd functions as an essential, general regulator of cell migration via the Scar/WAVE complex.

Migrating cells move forward by harnessing the force of actin polymerization to form a protrusive lamellipodium at the leading edge. A protein called Lamellipodin (Lpd) promotes lamellipodium formation, but how it does so is unclear. Law et al. reveal that Lpd generates membrane protrusions in association with a key regulator of actin branching called the Scar/WAVE complex and that this interaction is essential for the migration of a variety of cell types in multiple organisms (1).

Lpd localizes to lamellipodia and promotes actin polymerization by recruiting members of the Ena/VASP family of actin regulators (2). Together, Lpd and Ena/VASP proteins promote the endocytosis of clathrin-coated vesicles (3), but whether the proteins combine to stimulate lamellipodium formation is much less clear. Matthias Krause, from King's College London, who identified Lpd as a postdoc, explains that depleting Lpd has a much stronger effect on lamellipodia than the loss of Ena/VASP proteins does. "Lamellipodia show different dynamics in cells that don't express Ena/VASP proteins," Krause says. "But cells lacking Lpd have a hard time making any lamellipodia at all."

Lpd might, therefore, stimulate membrane protrusion by interacting with additional actin regulators. "The most likely suspect was the Scar/WAVE complex, a major regulator [of lamellipodia and cell migration]," Krause says. By recruiting the actin-nucleating Arp2/3 complex to the leading edge of migrating cells, the Scar/WAVE complex helps generate the branched actin network that drives lamellipodial membrane protrusion.

> "Lamellipodin may help decide where cells form lamellipodia."

Krause and colleagues, led by postdoc Ah-Lai Law, found that Lpd bound to the Abi subunit of the Scar/WAVE complex (1). Lpd also bound to active Rac GTPase, a well-known regulator of the Scar/WAVE complex, and this interaction boosted Lpd's association with Abi. "The binding of Rac to Lpd may lead to a structural change that allows it to bind Abi," Krause suggests.

The researchers then examined the functional significance of Lpd's interaction with the Scar/WAVE complex. Although loss of Lpd inhibits lamellipodia formation, the protein's effects on cell migration have never been tested. Law et al. found that fibroblasts lacking Lpd migrated slowly and aimlessly in comparison to wild-type cells. On the other hand, breast cancer cells overexpressing Lpd migrated faster than normal. Crucially, however, Lpd promoted migration independently of Ena/VASP proteins but couldn't enhance the movement of cells lacking the Scar/WAVE complex.

Law et al. then generated Lpd knockout mice. Many of these mice died shortly after birth, but the few surviving animals showed white patches on their bellies. "So Lpd likely plays a role in neural crest migration," says Krause, referring to the population of cells that moves out of the neural tube and, after differentiating into melanoblasts, spreads throughout the epidermis to pigment the hair and skin. To test this idea, Krause enlisted the help of Roberto Mayor's laboratory at University College London, which studies neural crest migration in *Xenopus* embryos. Mayor's group found that Lpd promoted the migration of *Xenopus* neural crest cells through its interaction with Abi and the Scar/WAVE complex.

Krause and colleagues then collaborated with Daimark Bennett's lab at the University of Liverpool to investigate the extent of Lpd's function in cell migration. Neural crest cells, melanoblasts, and fibroblasts are all mesenchymal cells, but Bennett's group found that knocking down Pico, the *Drosophila* homologue of Lpd, inhibited the collective migration of border cells, a cluster of epithelial cells that move across fly ovaries during oogenesis. "Overexpressing Pico also reduces border cell migration because the cells form protrusions at the back as well as at the front," says Krause. "So Lpd may help decide where cells form lamellipodia."

Lpd may guide lamellipodium formation, and thus the direction of cell migration, by regulating both Scar/WAVE and Ena/VASP proteins. Branched actin networks assembled by the Scar/WAVE complex induce relatively stable protrusions, whereas Ena/VASP proteins promote the formation of dynamic lamellipodia (4). "A cell could steer lamellipodia by allowing one function or the other," says Krause. "We're now trying to find out how this might be regulated."

1. Law, A.-L., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201304051.
2. Krause, M., et al. 2004. *Dev. Cell*. 7:571–583.
3. Vehlow, A., et al. 2013. *EMBO J.* 32:2722–2734.
4. Bear, J.E., et al. 2002. *Cell*. 109:509–521.