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Playing with Arp2/3 uncovers cellular rudder

Study shows that lamellipodia allow cells to move in a specific direction.

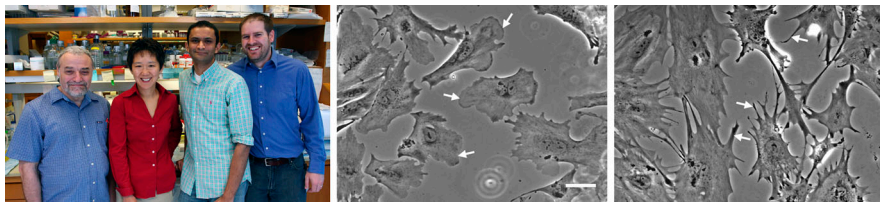
Membrane protrusions called lamellipodia enable crawling cells to steer, Suraneni et al. show (1). Their work also confirms that cells require the actin-polymerizing Arp2/3 complex to produce these structures.

A crawling cell extends two kinds of protrusions from its leading edge. Filopodia are thin and spiky, whereas lamellipodia are broader and resemble ruffles. The internal structure of these extensions also differs. Instead of the bundles of actin filaments found in filopodia, lamellipodia carry a branched network of actin, with the fibers arranged at roughly 78-degree angles to one another (2). Researchers think that elongation of actin fibers in these protrusions helps push the leading edge of the cell forward.

The current model for lamellipodium extension is that the Arp2/3 complex, with help from a few other proteins, spurs actin branching, nudging the lamellipodium ahead (3). Several studies support this hypothesis, including some that used RNAi to deplete certain Arp2/3 subunits (4, 5). These findings aren't conclusive, however. RNAi targeting a particular Arp2/3 component might not eliminate the molecule, and even minute amounts of the complex can trigger actin polymerization. In addition, the studies did not track what specific features of cell movement were impaired.

Suraneni et al. took a different approach to disable the complex. After crossing mice that carried one faulty gene for ARPC3, an Arp2/3 subunit, the researchers obtained early embryos that had two defective copies of the gene and thus couldn't make ARPC3. Although these embryos died during development, Suraneni et al. were able to isolate embryonic stem cells and differentiate them into fibroblasts, the paradigm for studying cell migration. Unlike control cells, fibroblasts lacking ARPC3 only showed filopodium-like structures. To confirm that the cells didn't produce lamellipodia, the researchers transferred them to fresh coverslips and observed as they settled down. Fibroblasts missing ARPC3 sprouted only filopodium-like extensions as they spread over the surface. Disabling the Arp2/3 complex also modified actin organization, and the cells' protruding edges sported the actin-associated proteins characteristic of filopodia but not lamellipodia.

Focal Point



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(Left to right) Boris Rubinstein, Rong Li, Praveen Suraneni, Jay Unruh, and colleagues (not pictured) explored how loss of the Arp2/3 complex affects cell movement. Cells that are able to make ARPC3, an Arp2/3 component, extend ruffle-like lamellipodia (center, arrows) and can crawl in a specific direction. But cells lacking ARPC3 only sprout filopodia-like extensions (right, arrows) and meander.

To determine whether disrupting the Arp2/3 complex alters cell movement, the researchers tested the cells' ability to heal a wound, one of fibroblasts' main jobs. The team created gaps in layers of control or ARPC3-deficient cells. Control fibroblasts sealed the opening within 30 hours. By contrast, the cells lacking ARPC3 still hadn't closed the wound after 54 hours.

Suraneni et al. then tracked individual cells to quantify their speed and direction of movement. Although wild-type and ARPC3-null cells slithered at about the same speed, net movement was higher in control cells because they followed a straighter path than did fibroblasts devoid of ARPC3. In fact, analyzing the trajectories of ARPC3-lacking cells with a technique called mean square displacement showed that "basically, they are doing a random walk," says senior author Rong Li.

By measuring the cellular response to epidermal growth factor (EGF), Suraneni et al. confirmed the effects of Arp2/3 disruption on directional cell movement. EGF attracts fibroblasts, and the researchers determined that 85% of control cells headed for the EGF source. But less than half of cells missing ARPC3 ventured in that direction.

The study demonstrates the importance of the Arp2/3 complex for lamellipodia formation, says Li. It also shows that the two types of cell extensions have different functions when cells crawl. "Cells can still move if they don't have lamellipodia," she says. However, they cannot maintain a straight course and end up wandering. A question for future research, she says, is whether the Arp2/3 complex is important for growth in other cell types such as neurons, which elongate at protrusive tips called growth cones.

> "Cells can still move if they don't have lamellipodia."

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