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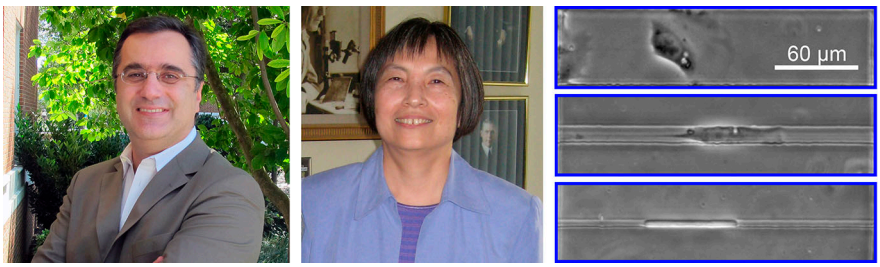
Crawling cells feel the squeeze

Study finds that cells alter movement style in tight spaces.

Focal Point



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Konstantinos Konstantopoulos (left), Joy Yang (center), and colleagues (not pictured) investigated how cells control their movement when crawling through a channel of varying width. When the channel is 50 µm wide, a cell can slide through unhindered (right, top) using a movement style regulated by Rac1. Narrowing the channel to 10 µm (right, center) constrains the cell. When the width is 3 µm (right, bottom), the cell has to compress itself to fit through, and its movement is driven by myosin II.

You drive differently on narrow streets than you do on an open stretch of highway. Similarly, migrating cells rely on different movement mechanisms depending on whether they have ample space or are in cramped conditions, Hung et al. reveal (1).

In the body, migrating cells usually must slither through spaces in the extracellular matrix or slip through narrow channels that run between connective tissue and the basement membrane in muscles, nerves, and epithelial layers (2). These passages can be so narrow that cells are barely able to squeeze through. Only rarely do cells have the luxury of crossing wide-open spaces.

But to study the mechanics of movement, researchers typically unleash cells on glass slides without confining them. Using such techniques, scientists have uncovered an important role in migration for integrins, particularly the α4β1 variety that spurs cells to extend lamellipodia and crawl forward. The extracellular head of the α4β1 integrin grips molecules in the substrate, such as fibronectin. The intracellular tail of the molecule, by contrast, serves as a control point. When the protein paxillin latches onto the tail, the combination inhibits the movement-stimulating protein Rac1 and reins in forward progress (3). Phosphorylation of serine 988 in the tail prevents paxillin binding, permitting Rac1 activation and cell movement (4). However, researchers haven't determined whether the same mechanism operates when cells travel through cramped spaces.

> **"The physical microenvironment can alter the mechanisms of cell migration."**

To investigate this, Hung et al. tested the crawling prowess of fibroblast-like ovary cells that carried particular mutations in the tail of the α4β1 integrin. They allowed the cells to slither through channels whose length and height were constant but whose width could vary from 50 µm to 3 µm, a tight squeeze for the cells. Regardless of the width of the channel, control cells moved at about the same speed. In contrast, cells that sported a tail mutation that prevents phosphorylation of serine 988 sped up as the channel narrowed, whereas cells with a mutation that blocks paxillin attachment to the tail crawled more slowly in smaller channels.

The researchers discovered they could duplicate the impact of these mutations by blocking two migration-regulating molecules. A Rac1 inhibitor hindered control cells that were crawling through the widest channel, but its effect dwindled as the channel shrank. One of Rac1's jobs is to block myosin II, which helps control cell migration and extension of protrusions. Consistent with this function, the researchers determined that a myosin II inhibitor, blebbistatin, didn't slow control cells in wide channels but did restrain control cells sliding through narrow channels.

These results indicate that cells can adopt two movement styles that are useful in different environments. When a cell has plenty of space, it opts for the bold, mesenchymal-like style, sending out long protrusions and undergoing dramatic shape changes. When a cell is hemmed in, however, it moves in an ameboid-like fashion and only extends protrusions a short distance. These two styles are under the control of different molecular circuits that interfere with each other. In spacious surroundings, Rac1 predominates and serine 988 is phosphorylated, excluding paxillin from α4β1 integrin's tail and keeping myosin II in check. But in cramped conditions, cells permit paxillin to bind to the integrin's tail and lift Rac1's inhibition of myosin II.

This system has another nuance, the team discovered. Myosin comes in two varieties—myosin IIA and myosin IIB—and each has a different role in cell movement. Hung et al. showed that cells crawling in narrow channels need myosin IIA, whereas cells traveling in wide channels require myosin IIB.

"Cells are more plastic than what we anticipated, and the physical microenvironment can alter the mechanisms of cell migration," says co–senior author Konstantinos Konstantopoulos. Some cell types might be able to switch between the mechanisms, depending on their surroundings, whereas others might favor one or the other. The work suggests that studies that probe migration mechanisms by allowing cells to crawl in the open might not capture reality, Konstantopoulos says. "Confined spaces are more physiologically relevant."

1. Hung, W.-C., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201302132.
2. Friedl, P., and S. Alexander. 2011. *Cell*. 147:992–1009.
3. Nishiya, N., et al. 2005. *Nat. Cell Biol.* 7:343–352.
4. Han, J., et al. 2001. *J. Biol. Chem.* 276:40903–40909.