Protein complex affects cells' ability to move, respond to external cues

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In a paper published today in the journal, *Cell*, a team from the University of North Carolina at Chapel Hill has explained for the first time how a long-studied protein complex affects cell migration and how external cues affect cell's ability to migrate.

Cell migration is one of life's basic processes, from development in the womb to immune system response, to learning and brain development, wound healing and – when it goes wrong – in cancer.

Jim Bear, PhD, principal investigator on the study, says, "The ARP 2/3 protein complex is – evolutionarily speaking – very old, but very little is known about what happens to cells when it is eliminated. It was thought previously that cells could simply not survive without it. Thanks to Norman Sharpless' lab here at UNC, we were able to find a cell line where the protein can be eliminated without loss of viability in order to see what happens to cells."

The result, says Bear, was fascinating. With the ARP 2/3 protein complex intact, cells migrate by forming a fan-shaped structure, called a lamellipodia, at the leading edge. The team found that eliminating this protein complex caused cells to switch to making finger-shaped protrusions instead – called filopodia. The cells with "fingers" on the leading edge move much more slowly than those with "fans".

Bear, who is an associate professor of cell and developmental biology and a Howard Hughes Medical Institute Early Career Scientist, has

focused his laboratory's work around how cell movement responds to environmental cues. Once his team figured out that loss of ARP 2/3 could change cells actual structure and movement, they went on to look at how those changes affected the ability of cells to respond to external cues.

"Cells sense a wide variety of soluble chemical cues through 'chemotaxis' – a process that is the basis behind many drugs that target cell behavior. They also respond to attached cues from the surface that they are crawling upon – a much less well understood process called haptotaxis," says Bear, who is also a member of UNC Lineberger Comprehensive Cancer Center.

So Bear's team set out to test the widely held idea that the cells require lamellipodia "fans" to respond to chemotactic cues. They found that cells with lamellipodia "fans" and filopodia "fingers" (with and without the ARP 2/3 protein complex) respond to chemotaxic cues indistinguishably, although they move faster with lamellipodia.

"The really interesting finding came when we looked at how each type of cell responds to hapotactic cues," says Bear. The team developed a new laboratory technique that uses a microfluidic device to lay down a gradient of a surface molecules (or substrate) for the cells to 'crawl' across in a way that could be measured in the lab. They could then look at whether the cells could 'sense' a gradient in the matrix. With the ARP 2/3 protein complex, the cells with "fans" on the leading edge followed the gradient of the surface proteins in an orderly, predictable faction. Without it, the cells with "fingers" moved randomly.

"This experiment – which was possible only with the help of many diverse UNC colleagues ranging from genetics to biomedical engineering – finally tells us what lamellipodia and the ARP 2/3 protein complex do: help the cell respond to clues from the extracellular

environment. It has long been assumed that the protein was important for chemotaxis, but that is not the case."

The study opens the way for a new frontier of investigation in the area of hapotaxis, or behavioral clues that cells get from the extracellular matrix. Also, says Bear, "We don't understand chemotaxis as well as we thought. What are the forces in the cell that respond to soluble cues?"

Both areas of investigation could be important for future breakthroughs in areas requiring precisely controlled cell migratory behavior including wound healing and tissue repair, cancer and cardiovascular disease.

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