New type of cell movement discovered

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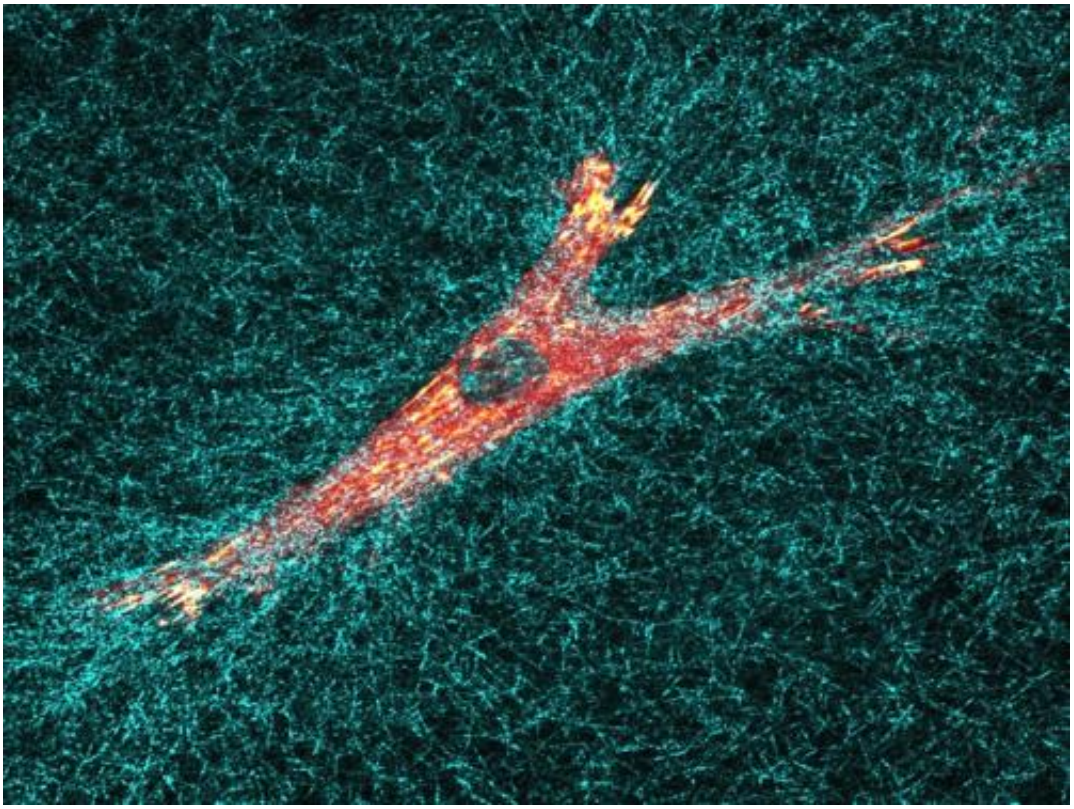

Penn and NIH researchers measured the internal pressure of individual fibroblast cells (in orange) moving through a three-dimensional matrix (in blue). They found that, in this environment, the cells' nuclei operate like an engine's piston to push the cell forward. Credit: University of Pennsylvania/NIDCR

For decades, researchers have used petri dishes to study cell movement. These classic tissue culture tools, however, only permit two-dimensional movement, very different from the three-dimensional movements that

cells make in a human body.

In a new study from the University of Pennsylvania and National Institute of Dental and Craniofacial Research, scientists used an innovative technique to study how cells move in a three-dimensional matrix, similar to the structure of certain tissues, such as the skin. They discovered an entirely new type of cell movement whereby the nucleus helps propel cells through the matrix like a piston in an engine, generating pressure that thrusts the cell's plasma membrane forward.

"Our work elucidated a highly intriguing question: how cells move when they are in the complex and physiologically relevant environment of a 3-D extracellular matrix," said Hyun (Michel) Koo, a professor in the Department of Orthodontics at Penn's School of Dental Medicine. "We discovered that the nucleus can act as a piston that physically compartmentalizes the cell cytoplasm and increases the hydrostatic pressure driving the cell motility within a 3-D matrix."

Koo worked with lead author Ryan Petrie and senior author Kenneth Yamada, both of the National Institutes of Health's NIDCR, on the study, which is published this week in *Science*.

"We think it's a very important normal physiological mechanism of cell movement that has not been characterized previously," Petrie said.

The team studied fibroblasts, the most common type of cell found in connective tissue. Fibroblasts themselves produce proteins including collagen and fibronectin that connect in a complex matrix that is found in the skin, the intestines and other tissues in the body.

The researchers used this fibroblast-created matrix to test how cells migrate through a three-dimensional structure. The matrix is crosslinked, meaning its fibers are resistant to bending and flexing as the cells move

through.

Studies of fibroblasts on two-dimensional surfaces indicated that the most typical form of movement involved protrusions called lamellipodia, created by the polymerization of the protein actin into fibers that push the cell membrane forward. In 2012, however, Petrie and Yamada showed that when fibroblasts migrate they can switch to a different movement strategy when placed in a three-dimensional matrix, using blunt protrusions called lobopodia.

What the researchers did not know was how these lobopodia were formed. Suspecting they might be generated from increased intracellular pressure, the team used sophisticated microelectrodes to measure the hydrostatic pressure of the fluid inside the cell. They found that the pressure was significantly higher in cells moving in a three-dimensional extracellular matrix compared to cells moving along a two-dimensional surface or in a three-dimensional matrix that wasn't cross linked like the fibroblast-derived matrix.

To drill down further and see how the pressure was distributed within the cell moving in a three-dimensional matrix, they measured pressure from in front of and behind the nucleus. Cells moving using lobopodia have elevated pressure in front of the nucleus but not behind it, generating energy to propel the cell forward. Using live-cell confocal microscopy, they observed that the nucleus could be pulled forward, away from the rear of the cell, with the nucleus dividing the cell into low-pressure and high-pressure compartments.

"When a cell is in the matrix, the nucleus tends to be at the back of the cell, and the cell body is very tubular in shape," Petrie said. "It really looked like a piston."

They found that the nucleus is actually pulled forward by the actin

filaments that connect the nucleus to the front of the cell. This movement "pressurizes" the cell. The scientists were also able to identify the protein components responsible for moving the nuclear piston, including actomyosin, vimentin and nesprin.

"The pressure itself is what pushes the plasma membrane," Petrie said.

Because this only happened to cells moving in the three-dimensional cell-created matrix and not cells moving in other substrates, the researchers note that the cells must be sensing their physical environment to determine what type of movement to use.

This type of cell migration might be common in other tissues of the body, the researchers noted. When they took chondrocytes from knee cartilage and myofibroblasts from intestinal tissue and placed them in the matrix, those cells used the same type of lobopodia-driven motion.

The discovery could have implications for understanding diseases such as cancer as well, because cancerous cells tend to move in distinct ways from normal cells.

"It might give us leverage to find out what is unique about cancer cells so we can target them therapeutically and not affect normal cells," Petrie said.

Importantly, these findings could have broader relevance to other biological systems where living cells are enmeshed within and surrounded by an extracellular matrix, such as in biofilms, which are associated with many human infectious diseases.

"This work illustrates how the physical structure of the matrix can influence cellular properties to govern biological function," Koo said. "We are now applying these fascinating principles to further understand

how biofilm matrix modulates bacterial virulence to cause oral diseases, such as dental caries."

More information: "Generation of compartmentalized pressure by a nuclear piston governs cell motility in a 3D matrix" *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.1256965

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