Missing molecule hobbles cell movement

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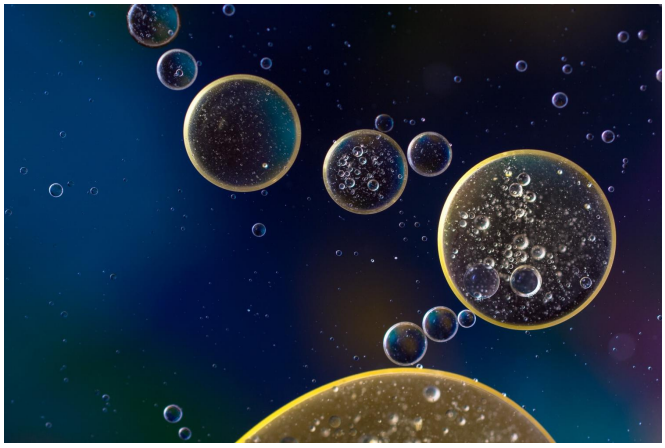

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Cells missing a certain protein on their surface can't move normally, UConn researchers report in *Science Signaling*. The research could give insight into how cells move and repair wounds in normal tissue, as well as how cancer spreads through the body.

Cells are the body's workers, and they often need to move around to do their jobs. Frequently, a cell will move through a tissue—say, the wall of a blood vessel—the way a rock climber scales a cliff, using a protein called integrin to grab onto a spot and pull itself in that direction. When the cell moves forward, it releases the integrin grip at its rear and brings it inside itself for recycling to the front, where it is then reused to make a new grip and move forward.

This type of movement is important when cancers metastasize, breaking away from the primary tumor and spreading through the rest of the body. Cancer cells need to crawl through a tissue using integrin until they reach a blood vessel they can use to travel long distances. Disabling the integrin mode of transport might be one method of preventing cancer from spreading.

UConn Health vascular biologists Mallika Ghosh and Linda Shapiro wondered how a common protein found in a cell's skin, called the cell membrane, affected this type of movement. The protein, called CD13, spikes through the cell's membrane, with one end interacting with the inside of the cell and the other with the outside world. CD13 has many different functions, including binding a cell in place and helping cells communicate with each other.

To test CD13's role in cellular movement, Ghosh, Shapiro, and their colleagues first looked at mouse fibroblasts, a type of cell that makes the scaffolding that holds tissues and organs together. They added the fibroblasts to petri dishes filled with fibronectin, a material found outside of the cell that integrin grasps. Integrin, remember, is the protein that cells use to grab on and drag themselves through a tissue. Some of the fibroblasts were normal; others had had the gene for CD13 knocked out.

The researchers found that normal fibroblasts could move through the petri dish using their integrin method with no trouble, but CD13 knock-out fibroblasts couldn't move at all.

Then they stained the cell nucleus blue and the integrin on the cell surface green, and watched to see what happened. The normal fibroblasts pulled all their integrin inside, and after about two hours for recycling, it reappeared on the surface. The CD13 knock-out fibroblasts also pulled all their integrin inside after two hours, but the integrin never reappeared.

They tried the same experiment with human cervical cancer cells and got the same result. What appeared to be happening is that CD13 acts as an organizer, gathering the freshly recycled integrin and other necessary proteins at the cell membrane so it's ready to be pushed out when the cell needs to move.

"Without CD13, the integrins go inside and don't come back out," Shapiro says. The details of how

CD13 gathers the integrin in the right place involves assembly of the cell's recycling machinery by the part of CD13 that extends inside of the cell in response to signals detected by the segment of CD13 that protrudes outside.

"And all these steps are critical for the cells to process information from the outside environment and move forward," Ghosh says.

The researchers are now looking at different versions of integrin proteins and various binding materials such as collagen and laminin, to see if CD13 plays the same role in cell movement in tissues that use those proteins for structure.

More information: Mallika Ghosh et al, CD13 tethers the IQGAP1-ARF6-EFA6 complex to the plasma membrane to promote ARF6 activation, ?1 integrin recycling, and cell migration, *Science Signaling* (2019). DOI: 10.1126/scisignal.aav5938