Biochemists zero in on key molecules that enable cells to crawl

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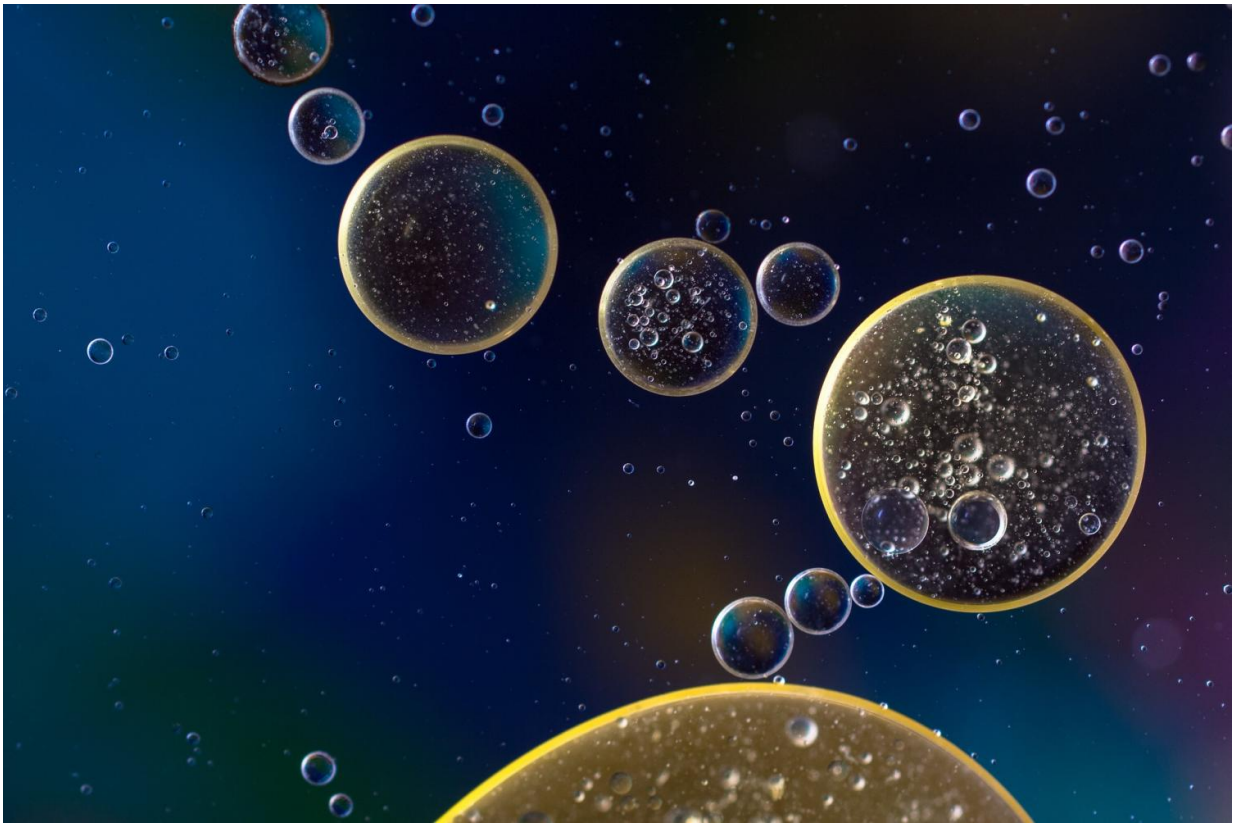

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Biochemists have made a discovery that sheds light on the molecular machinery that allows some cells, such as immune cells or even malignant cancer cells in humans, to wiggle their way through tissues

like organs, skin or bones.

The work, conducted in the University of Oregon laboratory of Brad Nolen, a professor in the Department of Chemistry and Biochemistry, was described in a paper in the Feb. 13 issue of the *Proceedings of the National Academy of Sciences.*

The researchers examined a fibrous rope-like protein in cells called actin, which grows and branches the way limbs on trees do. When actin branches grow, they push on the cell membrane and create arm-like protrusions. These arms can pull an immune cell forward, allowing it to chase foreign invaders and wrap around and swallow them.

Nolen and colleagues looked at the actin-related complex, Arp2/3, a large assembly of proteins that is required for actin to branch. When Arp2/3 sits down on actin it promotes a new branch to form at that site.

This Arp2/3 complex is critical to cell motility—the ability to move and perform myriad duties—and for initializing the construction of a network of filaments known as the actin cytoskeleton that provides structural support for cells.

The researchers identified two locations on Arp2/3 where an activator protein touches it. This activator protein resides in the membrane and can sense when the cell needs to crawl or engulf a foreign agent. It then triggers the branching response inside of the cell by touching Arp2/3.

To find the precise locations where the activator protein meets Arp2/3, the research team extracted Arp2/3 and the activator protein from cells, mixed them together, and used a special method that chemically marks the two proteins at the sites where they touched. In collaboration with researchers at the University of Washington, the team zeroed in on the location of those marks using a technique called mass spectrometry.

"What we discovered was exciting because knowing precisely how the activator protein binds to Arp2/3 complex is the first step in understanding how it turns on its branching activity," Nolen said.

Understanding how this branching activity is turned on in malignant cells could be applicable in the development of new drugs to target cancer, the researchers said. In some disease states, including viral infections such as HIV and cancer, cells can lose control of their actin cytoskeleton.

For example, Nolen said, a drug that blocks the site on Arp2/3 where the activator protein touches would prevent actin branching. That could stop tumor cells from crawling, or metastasizing.

Pharmaceutical companies used similar approaches to develop paclitaxel, a cancer drug that targets another filament-forming protein called tubulin. Nolen and his colleagues said that their findings could eventually lead to new opportunities to improve human health by expanding the arsenal of disease-fighting drugs.

More information: Qing Luan et al, Identification of Wiskott-Aldrich syndrome protein (WASP) binding sites on the branched actin filament nucleator Arp2/3 complex, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1716622115

Provided by University of Oregon

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