Study reveals a unique mode of cell migration on soft 'viscoelastic' surfaces

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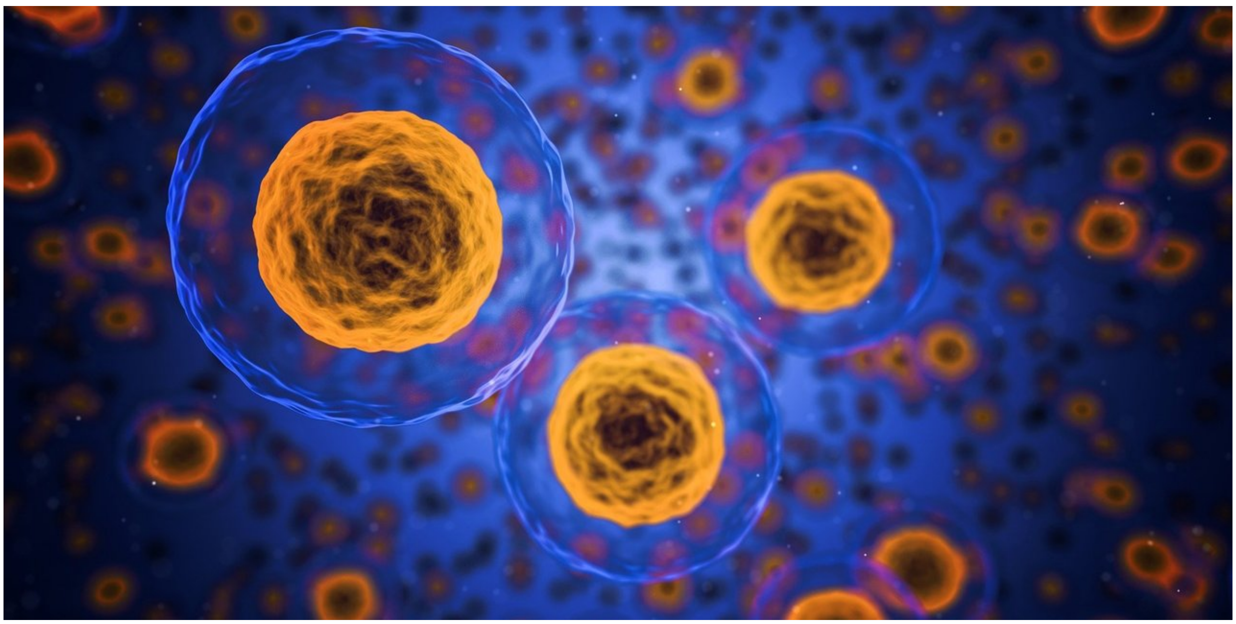

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Inside your body, cell movement plays a crucial role in many significant biological processes, including wound healing, immune responses and the potential spread of cancer.

"Most people don't die from having a primary tumor," said Kolade Adebowale, a graduate student in chemical engineering, and a member of the Chemical Biology Interface (CBI) graduate program in Chemistry, Engineering & Medicine for Human Health (ChEM-H) at Stanford University. "The problem is when cancer cells from the tumor acquire the ability to metastasize or move to different parts of the body."

As an attempt to advance studies of cell migration, Adebowale and colleagues in the lab of Ovijit Chaudhuri, associate professor of mechanical engineering at Stanford, have worked to develop and test new types of material that closely imitate the real tissue that surrounds cells. New findings built on this work, published April 19 in *Nature Materials*, upend the "textbook" view of cell migration and bring better insight into the impact of a material's elastic and viscous properties on cells.

"We found that it makes a big difference if the cancer cells are on a very rigid plastic or if they're on a soft and viscoelastic material, like a Jell-O," said Adebowale, who is lead author of the paper. "This adds to a lot of recent evidence that the behavior of cancer is not just about the cancer cells—it is also about the environment that the cancer cells interact with."

Like silly putty

Cell migration is traditionally studied on a hard, transparent piece of polymer called "tissue culture plastic" or elastic hydrogels, like soft contact lenses. Based on these studies, the current belief is that cells cannot migrate on hydrogels that are too soft. However, the researchers aim to mimic the real-life biological tissues on which cells migrate—which are soft and not purely elastic, like a rubber band, but viscoelastic.

"They are solid materials, but they also have viscous and liquid characteristics that allow them to flow over longer timescales," Adebowale said.

Examples of viscoelastic materials like the ones created for the research include bread dough, mozzarella and silly putty, according to Chaudhuri. These materials initially resist deformation, like an elastic material, but viscously relax that resistance over time.

When the researchers studied the movement of cancer cells on their more tissue-like substrate, the results contradicted existing expectations.

"We found that when the substrate is viscoelastic, the cells can migrate quite robustly, even though it is soft," said Chaudhuri, who is senior author of the paper.

Not only did the study find that cells can migrate on soft, viscoelastic substrates, the researchers also discovered the migration movement is unique. On a stiff, 2D surface like tissue culture plastic, cells adhere to the surface and form a fan-like protrusion. This protrusion, called a lamellipodium, drives forward motion by extending the leading edge forward and pushing off the surface. On the viscoelastic materials the team created, the cells didn't spread out so extensively. Instead, they used thin, spike-like protrusions called filopodia to drive their movement. Further, their experiments showed the cells use what's called a "molecular clutch" to migrate on the substrates.

"Imagine you're moving on ice. If you don't have enough adhesion to the ice, and try to run, you're not going to go anywhere," said Chaudhuri. "You really need a strong grip to push off and move forward. That's what the molecular clutch does for cells."

Robustly migrating cells on rigid tissue culture plastic form strong adhesions to the substrate. The authors observed that cells on soft, viscoelastic substrates are also able to migrate robustly but, importantly, these cells are able to do so with fewer, weak adhesions—like the cells are moving on their tippy-toes, not their entire foot.

"I think what was most surprising was that the material property—viscoelasticity—can have such a dramatic impact on the ability of cells to migrate," said Adebowale.

Viscoelasticity and cell culture

The fact that the mode of cell migration that the researchers observed is not seen on hard substrates or substrates that are only elastic shows how viscoelasticity is essential to the behavior of cells—and therefore important to replicate in future studies.

"This challenges the textbook view of how we understand cell migration," said Chaudhuri. "Cells migrate differently on viscoelastic tissue than they do on glass, plastic petri dishes or elastic gels. So, if we want to study cell migration, we need to use viscoelastic substrates."

While the study looked at single-cell migration, cancer cells migrate as a group in the body and various stages in development involve the collective movement of cells. Next, the researchers hope to answer the question of how viscoelasticity impacts collective cell migration.

More information: Kolade Adebowale et al, Enhanced substrate stress relaxation promotes filopodia-mediated cell migration, *Nature Materials* (2021). DOI: 10.1038/s41563-021-00981-w

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