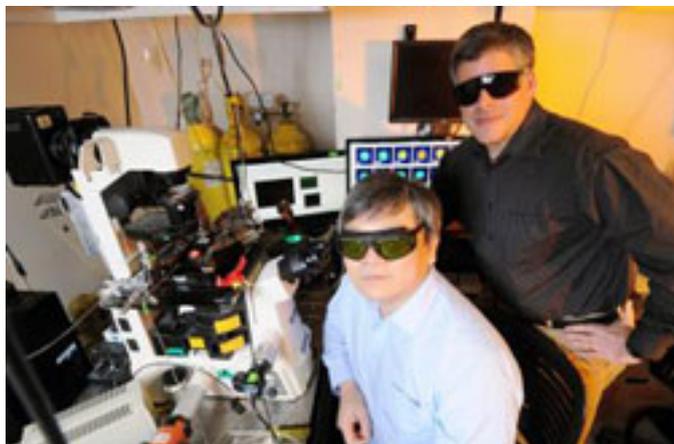


Why cells stick: Phenomenon extends longevity of bonds between cells



Research carried out by scientists at the Georgia Institute of Technology and The University of Manchester has revealed new insights into how cells stick to each other and to other bodily structures, an essential function in the formation of tissue structures and organs. It's thought that abnormalities in their ability to do so play an important role in a broad range of disorders, including cardiovascular disease and cancer.

The study's findings are outlined in the journal *Molecular Cell* and describe a surprising new aspect of cell adhesion involving the family of cell adhesion molecules known as integrins, which are found on the surfaces of most cells. The research uncovered a phenomenon termed "cyclic mechanical reinforcement," in which the length of time during which bonds exist is extended with repeated pulling and release between the integrins and ligands that are part of the extracellular matrix to which the cells attach.

Professor Martin Humphries, dean of the faculty of life sciences at the University of Manchester and one of the paper's co-authors, says the study suggests some new capabilities for cells: "This paper identifies a new kind of bond that is strengthened by cyclical applications of force, and which appears to be mediated by complex shape changes in integrin receptors. The findings also shed light on a possible mechanism used by cells to sense extracellular topography and to aggregate information through 'remembering' multiple interaction events."

The cyclic mechanical reinforcement allows force to prolong the lifetimes of bonds, demonstrating a mechanical regulation of receptor-ligand interactions and identifying a molecular mechanism for strengthening cell adhesion through cyclical forces.

"Many cell functions such as differentiation, growth and the expression of particular genes depend on cell interaction with the ligands of the intracellular matrix," said Cheng Zhu, a professor in the Coulter Department of Biomedical Engineering at Georgia Tech and Emory University and the study's corresponding author. "The cells

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respond to their environment, which includes many mechanical aspects. This study has extended our understanding of how connections are made and how mechanical forces regulate interactions."

The research was published online by the journal on February 14th. The work was supported by the National Institutes of Health (NIH) and the Wellcome Trust.

Cells of the body regulate adhesion in response to both internally- and externally-applied forces. This is particularly important to adhesion mediated by proteins such as integrins that connect the extracellular matrix to the cytoskeleton—and provide cells with both mechanical anchorages and the means to initiate signaling.

Using delicate force measuring equipment, researchers in Zhu's lab and the laboratory of Andres Garcia—a professor in the Woodruff School of Mechanical Engineering at Georgia Tech—collaborated to study adhesion between integrin and fibronectin, a protein component of the extracellular matrix. What they found was that cyclic forces applied to the bond switch it from a short lived state—with lifetimes of about one second—to a long-lived state that can exist for more than a hundred seconds.

"Force can be very important in biology," said Zhu. "Force has direction, magnitude and duration, so in describing its effects on biological systems, you have to use a more complete language."

Zhu, Garcia and Georgia Tech graduate students Fang Kong, William Parks and David Dumbauld—along with postdoctoral fellow Zenhai Li—used two different mechanical techniques to study the strength of bonds between integrin and fibronectin. One technique measured the bond strengths in purified molecules, while the other studied the effects of them in their native cellular environment.

"We have very precise force transducers that allow us to measure force on the scale of pico-newtons," said Zhu. "We prepare the samples in such a way that we engage only one bond, then we control the application of force and observe what happens."

The researchers first used an atomic force microscope to bring the integrin molecule together with the fibronectin, then separate the two. Instruments measured the pico-newton forces required to separate the molecules, and found that the duration of the bonds increased with the repetition of the contacts.

The second technique, known as BFP, involved the use of a fibronectin-bearing glass bead attached to a red blood cell aspirated by a micropipette. Integrin expressed on the micropipette-aspirated cell was pressed into the bead, then pulled away over repeated cycles. Lifetime measurement confirmed that repeated pulling increased the longevity of the bonds.

The researchers studied two integrins, part of a family of 24 related molecules that operate in humans. In future work, they hope to determine whether or not the cyclic mechanical reinforcement they observed is a universal property of many cellular adhesion molecules.

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The researchers also hope to explore how cells use this cyclic mechanical reinforcement. Because many disease processes result from abnormal cellular adhesion mechanisms, a better understanding could provide insights into how cardiovascular disease, cancer and immune system disorders operate.

"The findings of the paper have deep implications for our understanding of force-regulated signaling," added Humphries. "There is abundant biological evidence for profound effects of extracellular tensility and elasticity in controlling processes such as cancer cell proliferation and stem cell differentiation, but the mechanisms whereby this information is transduced across the outer cell membrane are unclear."

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CITATION: Kong, F., et al., Cyclic Mechanical Reinforcement of Integrin-Ligand Interactions, *Molecular Cell* (2013).

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