Science News

Bioengineers Say Cellular Workouts Strengthen Endothelial Cells' Grasp

ScienceDaily (May 14, 2010) — University of Pennsylvania bioengineers have demonstrated that the cells that line blood vessels respond to mechanical forces -- the microscopic tugging and pulling on cellular structures -- by reinforcing and growing their connections, thus creating stronger adhesive interactions between neighboring cells.

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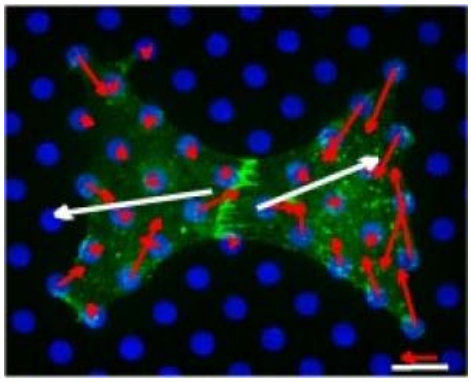
Adherens junctions, the structures that allow cohesion between cells in a tissue, appear to be modulated by endothelial cell-to-cell tugging forces. Both the size of junctions and the magnitude of tugging force between cells grow or decay in concert with activation or inhibition of the molecular motor protein myosin.

The findings extend the understanding of multi-cellular mechanics. The dynamic adaptation of cell-cell adhesions to forces may explain how cells can maintain multi-cellular integrity in the face of different mechanical environments. Understanding how forces affect cell-cell adhesion could provide new opportunities for therapies targeting acute and chronic dysfunction of blood vessels.

Because these adhesions between endothelial cells are what allow these cells to form a tight seal between the blood inside vessels and the surrounding tissues, the research also suggests that changes in mechanical forces might induce endothelial cells to modulate the "tightness" of adhesions with each other, which may then modify the permeability of blood vessels. In many disease states, such as septic shock, diabetes and in tumor vasculature, endothelial cells fail to form the type of tight adhesions with each other that are necessary to prevent the vessels from leaking into the surrounding tissue.

It is known that myosin activity is required for cell-generated contractile forces and that myosin affects cellular organization within tissues through the generation of mechanical forces against the actin cytoskeleton; however, whether forces drive changes in the size of cell-cell adhesions remained an open question. The team demonstrated that, when "exercised," the actomyosin cytoskeleton in a pair of cells can generate substantial tugging force on adherens junctions, and, in response, the junctions grow stronger. To prove a causal relationship, the group showed that exogenous forces, applied through a micromanipulator, also cause junction growth. This study marks the first time cell-generated forces at the adherens junction have been measured.

To investigate the responsiveness of adherens junctions to tugging force, bioengineer Chris Chen and his laboratory adapted a system of microfabricated force sensors to determine quantitative measurements of force and junction size. Researchers fabricated microneedles (3 microns wide, 9 microns tall, or one-fiftieth the size of a human hair) from a rubber polymer, polydimethylsiloxane, and coated them with an adhesive protein to allow cell attachment. This adhesive protein was transferred to the microneedle substrates in



Blue dye show microneedles, red dye represent cell nuclei. Tugging forces shown in white. (Credit: Image courtesy of University of Pennsylvania)

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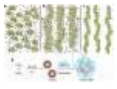

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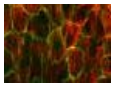

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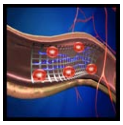

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"bowtie patterns" which coaxed the cells to form pairs of cells with a single, cell-cell contact between them. Each cell in the pair attached to about 30 microneedles, and the researchers were able to measure the deflection of the needles as cells exerted traction (inward pulling) forces. The deflection of the needles was proportional to the amount of force generated by the structure.

"The role that physical forces play in cellular behavior has become better understood over the last ten years," said Chen, the Skirkanich Professor of Innovation in bioengineering in the School of Engineering and Applied Science at Penn. "Now we know that cell structures under mechanical stress don't necessarily break; they reinforce. Unlike passive adhesion such as with glue or tape, the cell-matrix and cell-cell adhesions that cells use as footholds to attach to surfaces and each-other are adaptive; when they experience force, they hold on tighter."

In prior research, Chen's team has demonstrated that the push and pull of cellular forces drives the buckling, extension and contraction of cells during tissue development. These processes ultimately shape the architecture of tissues and play an important role in coordinating cell signaling, gene expression and behavior, and they are essential for wound healing and tissue homeostasis in adult organisms.

This study was conducted by Chen, Zhijun Liu, Daniel M. Cohen, Michael T. Yang, Nathan J. Sniadecki and Sami Alom Ruiz of the Department of Bioengineering at Penn and John L. Tan and Celeste M. Nelson of the Johns Hopkins School of Medicine.

The research, published in the current issue of the journal *Proceedings of the National Academy of Sciences*, was funded by grants from the National Institutes of Health, Material Research Science and Engineering Center, Center for Engineering Cells and Regeneration of the University of Pennsylvania and Whitaker Foundation.

Story Source:

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Journal Reference:

1. Z. Liu, J. L. Tan, D. M. Cohen, M. T. Yang, N. J. Sniadecki, S. A. Ruiz, C. M. Nelson, C. S. Chen. **Mechanical tugging force regulates the size of cell-cell junctions**. *Proceedings of the National Academy of Sciences*, 2010; DOI: 10.1073/pnas.0914547107

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