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A Bed of Microneedles: Johns Hopkins Scientists' Gadget Measures Muscle Cell Force

Using the same technology that creates tiny, precisely organized computer chips, a Johns Hopkins research team has developed beds of thousands of independently moveable silicone "microneedles" to reveal the force exerted by smooth muscle cells.

Each needle tip in the gadget, whose development and testing is reported this week in the advance online edition of the *Proceedings of the National Academy of Sciences*, can be painted with proteins cells tend to grab onto. By measuring how far a contracting muscle cell moves each needle, the scientists can calculate the force generated by the cell.

"What we have is a tool to measure and manipulate mechanical interactions between a single cell and its physical and biochemical surroundings," says Christopher Chen, Ph.D., associate professor of biomedical engineering at Johns Hopkins. "Cellular mechanics is really important to many normal and pathologic processes in people, and there's a lot we don't understand, even with available technology."

Because smooth muscle cells control the expansion and contraction of airways and blood vessels, the microneedle bed's ability to measure how a cell's environment affects the strength, duration and timing of cellular contractions should one day help shed light on medical conditions like asthma and high blood pressure, the researchers say.

The new device complements an ever-growing array of techniques to measure forces exerted by a contracting cell and overcomes some of their limitations, the researchers say. For example, one common method examines a cell lying on a thin sheet of material, which wrinkles when the cell contracts.

"This is like a person lying on a bed sheet and scrunching up part of the sheet," says first author John Tan, a graduate student in biomedical engineering. "Wrinkles appear all over the place, and it can be hard to figure out where the initial force was applied."

To overcome that complexity, scientists have to make mathematical assumptions -- which are difficult to verify. The one-piece microneedle bed, however, lends itself to much simpler calculations because each needle moves independently of the others and requires exactly the same force to move.

"We know how difficult each needle is to move, and we know where it was originally," says Tan. "By measuring the direction and magnitude of the deflection of each needle, we can calculate the force the cell exerts."

Tan and his colleagues painted the needle tips with fibronectin, a protein that forms part of the

natural scaffolding between cells. Each smooth muscle cell spread out on the bed of microneedles and then contracted, displacing the needles.

From their experiments, the researchers have already discovered that a cell's shape affects how it contracts. For example, a cell confined to a small area of fibronectin-painted needles, unable to spread out, exerted little force (i.e., didn't contract).

They also uncovered the answer to what seemed to be conflicting scientific reports about cellular forces. Some reports indicated that the greater an area grasped by a cell, the greater force the cell exerted, while other reports showed no such correlation. Because the microneedle bed is the first device that can directly measure the forces generated at the cell's "adhesions," or gripping regions, the researchers were able to prove that both observations are actually correct.

"Force increases with adhesion size only above a certain level; for smaller areas, force and size aren't correlated," says Tan. "The same cell can actually exhibit both scenarios."

The Johns Hopkins team, composed of three biomedical engineers, a physicist, a molecular biologist and a chemical engineer, next plans to use the device to measure the effects of various proteins thought to stimulate or reduce cells' contraction, see how the amount of protein affects force, and determine how different types of cells react on the bed. The scientists also plan to make grids with needles of different lengths (shorter posts are harder to bend) to challenge cells' contractile forces.

The studies were funded by the National Institute of Biomedical Imaging and Bioengineering, the Defense Advanced Research Planning Agency, the Whitaker Foundation, and the Office of Naval Research. Authors on the paper are Tan, Chen, Joe Tien, Dana Pirone, Darren Gray and Kiran Bhadriraju, all of Johns Hopkins. Tien is now at Boston University.

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