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Home
Research
Funding
Training
Health & Education
e-Advances
Stories of Discovery
Science Snippets
Health Information
Science Education
Resource Library
News & Events
About NIBIB
Información en Español

Picture Gallery

Video Gallery

e-Advances
Linking NIBIB-supported research to improvements in health

Nanoplatform Offers Key to Rare Lung Disease: March 31, 2008

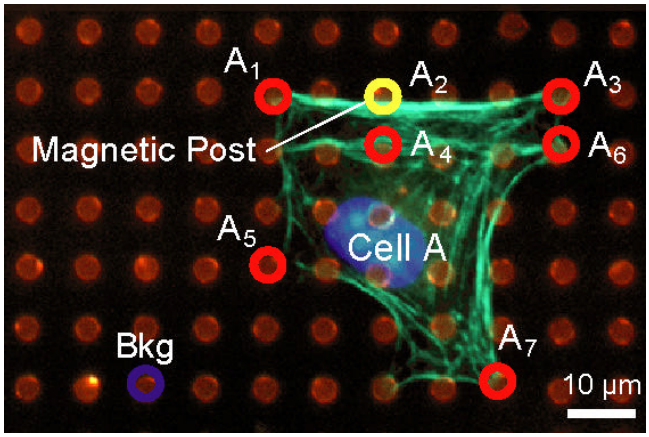
What do a world-class swimmer, a former marketing executive, a teacher, and a kindergartner have in common? They each have a rare, incurable lung disease – idiopathic pulmonary arterial hypertension (IPAH). Because some of IPAH's symptoms, such as shortness of breath, fatigue, and chest pain, are similar to many heart and lung conditions, misdiagnosis is typical. By the time symptoms become intolerable, the disease has usually progressed to advanced stages.

In IPAH, the blood pressure in the pulmonary artery (the blood vessel that leads from the heart to the lungs) rises far above normal levels. In response to this pressure increase, the wall of the artery thickens, causing the heart to work harder and, without treatment, eventually fail. Quality of life and life expectancy have improved with new medications and lifestyle modifications. Before 1990, individuals survived an average of 2.8 years after diagnosis. That outlook has nearly doubled to 5 years, with some patients now living 10 to 20 years after diagnosis. To further extend survival, researchers are looking at what causes the pulmonary artery wall to thicken.

Scientists theorize that for those with IPAH, the pulmonary artery walls thicken because the muscle cells in the artery are overly responsive to mechanical stress. When these cells feel the stress caused by blood pressure, they contract or shorten – like our skeletal muscles – but instead of moving bones, these muscles constrict blood vessels to control blood flow. To better understand the connection between stressed-out cells and IPAH, researchers may be able to use a new tool developed by a team from the University of Pennsylvania and Johns Hopkins University.

Quantifying Cell Response

Christopher Chen, Skirkanich Associate Professor of Innovation in Bioengineering at the University of Pennsylvania; Daniel Reich, Professor of Physics at Johns Hopkins University; and their colleagues developed a platform based on magnetic nanotechnology to study how cells generate forces. Peter Lloyd Jones, Director of the Penn Idiopathic Pulmonary Arterial Hypertension Center for Cell Studies, thought this nanoplatform could provide much-needed quantitative data on cell reaction to stress.



Using a nanoscale array of microposts, researchers can measure and apply forces to cells, as with this 3T3 fibroblast cell. The cell responds to an external force applied to its local

The nanoplatform allows researchers to study how cells contract and to compare their mechanical properties. “With this work, we can now quantify the responses of cells to applied forces,” says Jones. “The mechanical properties of cells are altered in individuals with IPAH and differ from patient to patient. This altered contractility [shrinking] could be a result of an inherent error in the genomes of these patients or it could be because of an extraneous insult such as environmental damage.”

tether (A2) by making abrupt changes in cytoskeletal tension at the perimeter of the cell (A1, A3-A7).

The nanoplatform, which looks like a mini bed of nails, incorporates magnetic nanowires into a subset of the “nails” called microposts. Cells under study are placed on top of the microposts. Chen describes what happens next as “tickling the cells.” A magnetic field applied to the nanoplatform activates the nanowires, which in turn apply a force to different parts of the cell. The team has found that a cell’s reaction to an external force occurs at the perimeter of the cell rather than where the force was initially applied. They also found that even small applied forces can lead to large changes in the cell’s internally generated traction forces – forces used to power cell contraction.

These cellular contractions quite literally “power” the cell’s ability to move parts of its surrounding matrix, and thus affect local mobility. The amount of force exerted by a cell can be measured by the displacement of flexible microposts included in the “bed of nails” array on which the cell grows [see figure]. The amount of bending of the post is directly proportional to the force applied by the cell, and can be measured by various techniques that can obtain a view of the surface of the microplatform.

In the future, the nanoplatform may also offer a way to screen drug compounds to determine if they alter cell shrinking. Cells from patients treated with a specific drug aimed at IPAH would be tested on the nanoplatform after drug therapy to monitor their response. “Drug screening currently uses cells growing flat on a plastic surface as a test bed. But cells in the body don’t live on plastic,” says Jones. “We can reevaluate pathways that were hidden because traditional approaches don’t provide a quantitative readout.”

Building a Stronger Scaffold

Understanding the interplay of internal and external forces in cells could provide important information about the spread of certain cancers, the development of high blood pressure, as well as how to engineer stronger tissue outside the body. “We’re trying to understand the basics of how forces affect decisions that cells make like vascularizing [building blood vessel networks] or not vascularizing tissues,” explains Chen.

To engineer tissue, cells are grown on a scaffold or framework that influences the shape and function of the cells. Knowing how cells react to forces could give clues on how to build more robust tissue scaffolds. Some researchers have determined that varying the scaffold’s firmness can impact its ability to support different cell functions. The information collected with the nanoplatform also could suggest new pathways for tissue engineering and create a series of new questions to consider, says Chen, such as “Do we need to take those forces into account in order to control how cells differentiate?”

Versatility in the Future

Many diseases result from changes in the way cells handle mechanical forces. Chen and Reich’s nanoplatform gives researchers a new tool to discover the impact physical effects have on the disease process. “It opens up a lot of possibilities,” says Jones. One difficulty that has plagued cell biology is a lack of tools to quantify cell activity and response. “The novel aspect of Chris’ work is the ability to quantify cell response to forces,” explains Donald Ingber, Judah Folkman Professor in Vascular Biology, Children’s Hospital and Harvard Medical School.

To make the nanoplatform even more powerful, the team wants to explore alternative approaches to device fabrication. Their aim is to create a platform that can help researchers measure cell/force response when the cells are inside a three-dimensional structure. “So far we’ve just looked at single cells, but we would like to look at layers of cells. That certainly would help our colleagues,” he says. “If it turns out that applied force causes critical changes in cells, and if we can find a mechanism for those changes, then we could amplify, circumvent, or interrupt the effect” to alter a disease process, says Chen.

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References

Sniadecki NJ, Anguelouch A, Yang MT, Lamb CM, Liu Z, Kirschner SB, Liu Y, Reich DH, Chen CS. Magnetic microposts as an approach to apply forces to living cells. Proc Natl Acad Sci. 2007 Sep 11;104(37):14553-8.

Doyle RL. Early diagnosis and treatment of pulmonary arterial hypertension. Medscape Pulm Med. 2005; 9(1).

Ingber D. Mechanobiology and diseases of mechanotransduction. Ann Med. 2003; 35:564-577.

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