Nuclear deformation research could advance artificial tissue engineering

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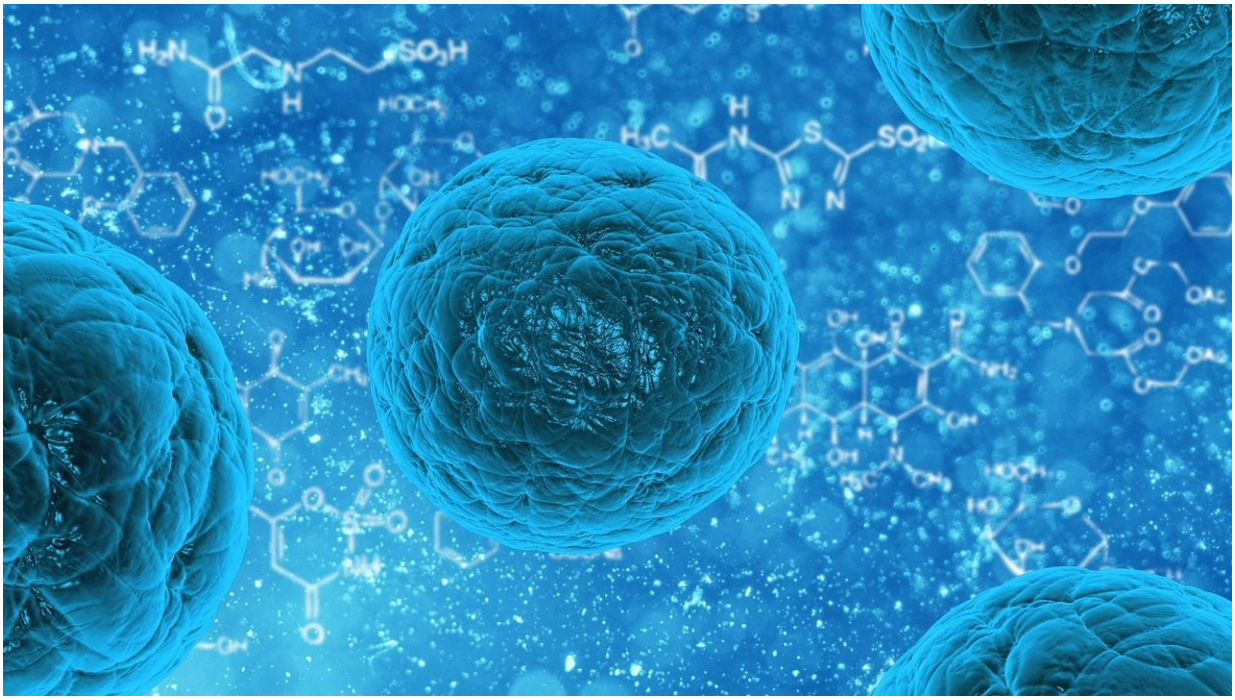

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Biomedical Engineering Professor Corey Neu and Ph. D. student Benjamin Seelbinder of the University of Colorado at Boulder wanted to answer two fundamental questions. How do cells adapt to their environment and how does a mechanical environment influence a cell?

What they discovered during their more than six years of research has

the potential to tackle major health obstacles and advance artificial tissue engineering.

Their research, published on Dec. 2 in *Nature Biomedical Engineering* and titled "Nuclear Deformation Guides Chromatin Reorganization in Cardiac Development and Disease," found that mechanical forces guide the development of a cell through the reorganization of its nucleus and could influence future pathologies.

"We were interested in the development of healthy cells, and the health of a cell requires that the nucleus senses mechanical forces in a particular way," Neu said.

One of those forces is tension, Neu and Seelbinder explained. Tension stretches the cell in a defined way, resulting in the reorganization of the nucleus. That modification changes the expression of genes, which could indicate certain diseases in patients.

This understanding of the cell developmental process also helped Neu and Seelbinder conclude that scientists could influence a cell themselves. Researchers can change the environment by manipulating the tension moving through a cell, which could be used to create more authentic artificial tissues.

The discovery

Seelbinder, who is now a postdoctoral associate at the Max Planck Institute of Molecular Cell Biology and Genetics, first discovered that mechanical forces shape nuclei while studying the cardiovascular cells of embryotic mice.

"The nucleus was a very interesting thing to investigate when looking at force integration in cells because it is big, contains all of the gene

information and has mechanical connections to all parts of the cell," Seelbinder said. "We just started exploring and found there is a clear pattern that should be investigated more closely."

Seelbinder used heart cells because they contract on their own, making them the perfect model to study nuclear deformation. The cells are known to be very sensitive to their mechanical environment.

Seelbinder noticed the contractions caused the nucleus to be stiff, rigid and dense in certain areas, he and Neu explained. In other areas, the nucleus appeared to be loosely organized.

"There is a certain well-defined structure that the nucleus takes on; it is not just a soft gel," Neu said. "There are also defined forces that are happening because suddenly the heart cells are contracting during development. The mechanics are fascinating—the forces are not just happening, they are being transferred to the cell substructures."

Neu and Seelbinder concluded the contractions result from mechanical forces and tension moving through cells. Those contractions reorganize each cell's chromatin, which are some structural elements of the nucleus.

Neu said the discovery launched a major collaborative effort centered at the College of Engineering and Applied Science. With help from researchers at the University of Colorado's Paul M. Rady Department of Mechanical Engineering, the Department of Molecular, Cellular and Developmental Biology, the University of Pennsylvania and Purdue University, they confirmed that the same patterns occur in humans.

Impacts on human health

Understanding how the chromatin in a nucleus is organized is a fundamental subject area. The location of genes within the nucleus is

important for their expression and has paramount implications.

Neu and Seelbinder also found animals that experienced nuclear reorganization later in life developed pathology with symptoms that an older human with cardiovascular disease or hypertension might experience.

When looking at adult mice with induced hypertrophy, they observed the gene expression established during development reorganized again in the adult stage. That lead to the loss of cell identity and cell activity. In the case of heart cells, contractions stopped, leading to cardiac arrest.

"It is not just about the development, but the role of the mechanics and the organization of the nucleus is also really important at later stages of life," Neu said. "When someone develops heart disease, for example."

The researchers studied patients with heart conditions like cardiomyopathy, a disease that makes it harder for the heart to pump blood. Seelbinder explained that the condition was well-suited for their work because cardiomyopathy changes the heart's mechanical environment.

Cardiomyopathy thickens the heart muscle, causing fewer contractions and less nuclear deformation. The chromatin reorganizes and cellular identity declines.

"If you use markers like how much blood does the heart pump and correlate it over the reorganization of the nucleus, it was highly predictive," Seelbinder said. "That means you can take a little bit of the tissue, look at the organization of the nucleus and can tell whether that organ functions well or not."

Seelbinder and Neu said those findings became one of the most

impressive things they discovered. It opened the door not just for diagnostic potentials, but for therapeutic possibilities as well.

Artificial tissue engineering

Neu and Seelbinder's research could help change the landscape for artificial tissue engineering. Their work fills in gaps in understanding of the relationship between mechanical forces and cell development in regenerative medicine.

Neu said if researchers know how the heart develops—what triggers the transition from a collection of cells to a fully functional organ or organism—there is the potential to mimic developmental processes.

Their research is a blueprint of the developmental path, which could also set the stage for new regenerative technologies and the possibility of organ-on-chip models used in drug discovery.

"Pharmaceutical companies may want to screen new kinds of drugs, for example," Neu said. "If you have a replicated heart tissue with the correct nuclei and function, if you can create a miniaturized model of a person, then it may be possible to screen candidate drugs that might be most effective in humans."

More information: Benjamin Seelbinder et al, Nuclear deformation guides chromatin reorganization in cardiac development and disease, *Nature Biomedical Engineering* (2021). DOI: 10.1038/s41551-021-00823-9

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