Bioengineers provide adult stem cells with simultaneous chemical, electrical and mechanical cues

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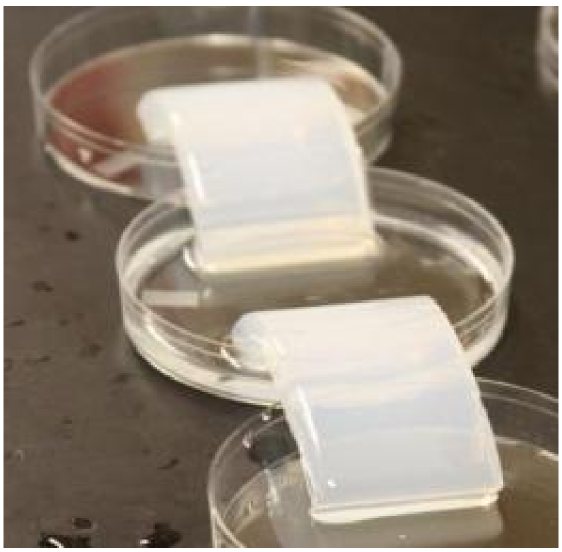

The translucent materials bridging the dishes are “agarose salt bridges” -- part of the electrochemical cell that UC San Diego undergraduate bioengineering researchers used to subject hydrogels to an electric field. The bioengineers achieved the “Triple Crown” of stem cell culture - they created an artificial environment for stem cells that simultaneously provides the chemical, mechanical and electrical cues necessary for stem cell growth and differentiation. Building better microenvironments for nurturing stem cells is critical for realizing the promises of stem-cell-based regenerative medicine, including cartilage for joint repair, cardiac cells for damaged hearts, and healthy skeletal myoblasts for muscular dystrophy patients. The advance could also lead to better model systems for fundamental stem cell research. Credit: UC San Diego / Daniel Kane

Bioengineers from the University of California, San Diego have achieved the "Triple Crown" of stem cell culture – they created an artificial environment for stem cells that simultaneously provides the chemical, mechanical and electrical cues necessary for stem cell growth and differentiation. Building better microenvironments for nurturing stem cells is critical for realizing the promises of stem-cell-based regenerative medicine, including cartilage for joint repair, cardiac cells for damaged hearts, and healthy skeletal myoblasts for muscular dystrophy patients. The advance could also lead to better model systems for fundamental stem cell research.

This work appears in a paper published online in *Advanced Functional Materials* on November 13.

While researchers have already created artificial environments for stem cells that provide chemical cues combined with either mechanical or electrical cues, the UC San Diego bioengineers say this is the first material reported in the scientific literature, to the best of their knowledge, that simultaneously provides all three cues to stem cells in a three dimensional supportive environment. Remarkably, the development of the new material was led entirely by bioengineering undergraduate students at UC San Diego.

In nature, stem cells communicate with other cells and with the extracellular matrix through chemical, electrical, and mechanical cues. "We mimicked all these cues that the native environment provides to the cells. This work is therefore fundamental to creating more life-like environments for stem cells in order to steer stem cells toward specific cell types such as chondrocytes, osteoblasts, myoblasts or cardiomyocytes," said Shyni Varghese, the bioengineering professor who advised the student researchers working in her Biomimetic Polymers and Stem Cell Engineering laboratory at the UC San Diego Jacobs School of Engineering.

Realistic in vitro microenvironments for stem cells would also serve as excellent model systems for systematically studying cell function, signaling pathways, disease progression, and tissue growth and development.

Multifunctional Gel Matrix

The stem cells are embedded in a gelatin-like hydrogel bathed in an electrolyte solution compatible for cell growth. When an electric potential passes through the hydrogel, the gel bends and exerts mechanical strain on the cells that is designed to mimic the mechanical cues stem cells experience in natural microenvironments.

"Our hydrogel provides the chemical cues, and when you expose them to an electric field, the hydrogel surrounding the stem cells bends, which provides mechanical strain to the cells," said Varghese.

In the new paper, the bioengineers report results of human bone marrow derived mesenchymal stem cells growing in the new microenvironment. The chemical, electrical, and mechanical cues steered the embedded cells to differentiate into cartilage cells.

The researchers continue to improve their system, with the goal of coaxing healthy tissue from stem cells. "The ultimate goal of regenerative medicine is to make healthy tissues and differentiated cells with regenerating ability that can save lives. We are not there yet, but this work takes us one step closer," said Varghese, who is a faculty member of the UC San Diego Institute of Engineering in Medicine.

In addition, the work will be useful to researchers involved in basic stem cell research as well as stem-cell-based clinical trials. For example, in current clinical trials involving human stem cells, the cells are often conditioned in an artificial environment so that when they are implanted into humans, they are more apt to differentiate into the right kinds of cells. Additional control over the cues the cells receive during this conditioning phase could be critical to future regenerative therapy successes.

Crucial Undergraduate Input

"A significant portion of the credit goes to Han Lim, who did this work as an undergraduate bioengineering student. A lot of ideas bounced back and forth between he and I," said Varghese. "Han also sought out collaboration with NanoEngineering professor Gaurav Arya in order to incorporate mathematical modeling into the project. Han and the other undergraduates on this project were very active. They were coming to me and saying, 'Why don't we do this, why don't we do that? Let us do this, let us do that!'," said Varghese.

"I feel really excited and privileged to be given this opportunity to work independently with my colleagues, all of them being undergraduates except Professors Arya and Varghese. I must say initially it was very daunting, but I received a lot of help along the way," said Han Lim, the first author on the paper who performed this work as a bioengineering undergraduate, including a 2008 stint at a Calit2 Summer Undergraduate Research Scholar.

"I'd like to thank all my collaborators for their contributions, and especially Dr. Varghese for believing in our potential. With this research, I hope that somewhere in the future we will be able to manipulate chemical, mechanical, and electrical cues such that one can create better biomimicking materials for applications in tissue engineering. As for myself, it would be great if I can further my studies in this field by looking at other ways of studying and manipulating cell behavior. After my studies, I aim to pursue a career in academia and continue to work for the advancement of the field as well as improve the quality of medicine and life," said Lim.

Varghese's bioengineering research projects span the continuum from basic research to translational work aimed at bridging the bench-to-bed divide. The lab, however, is united by one overarching goal: to treat dysfunctional tissues or organs using stem cells and healthy tissues derived from stem cells.

"I strongly believe that if we don't fundamentally understand the science, then the translational work cannot happen. We need to know what is happening in nature before we can successfully mimic it," said Varghese.

More information: "Dynamic Electromechanical Hydrogel Matrices for Stem Cell Culture," by Han L. Lim, et al., is published in the journal *Advanced Functional Materials.*

Provided by University of California - San Diego

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