Mechanical cues reprogram normal cell lines into stem-like cells

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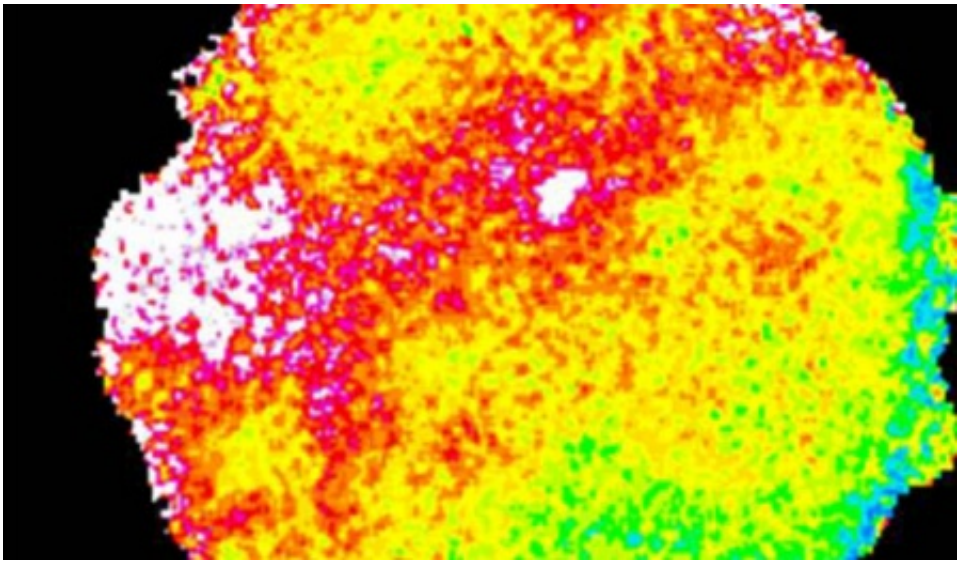

Probe developed at UB reveals high force levels, as shown, in actin in cells that have been reprogrammed as stem-like cells, with force increasing from green to red.

Scientists at the University at Buffalo and other institutions have turned cells normally used as model cells, known as immortalized cells, into stem or, as they call it, "stem-like" cells, using nothing more than mechanical stress. They have done it without employing the potentially hazardous techniques previously used to obtain similar results.

The researchers use the term "stem-like" cells to describe cells in tissue

culture that have many of the biochemical markers of stem cells. Determining whether or not they can differentiate will be the focus of future research.

The finding is described in a paper published recently online before print in the *Proceedings of the National Academy of Sciences*. The researchers discovered that by changing the mechanical stresses on neuronal and other cell types in tissue culture allowed them to be reprogrammed into "stem-like" cells.

"Normal cell types in tissue culture are spread out and have differentiated internal structures, but changing cell mechanics caused the cells to turn into clusters of spherical cells that had many of the biochemical markers of cells," says Frederick Sachs, PhD, SUNY Distinguished Professor in the UB Department of Physiology and Biophysics and senior author.

The stem cell advance was made possible by the development of a genetically encoded optical probe by Fanje Meng, PhD, research assistant professor in the Department of Physiology and Biophysics and lead UB author. The probe measures the mechanical stress in actin, a major structural protein present in all cells. Actin is involved in muscle contraction and numerous cellular processes, including cell signaling, how cells are shaped and how they move.

The actin probes will provide researchers with a method of studying how mechanical forces influence living cells, tissues, organs and animals in real-time.

"This probe allows us, for the first time, to measure the stress in actin within living cells," explains Sachs. "We saw gradients of stress in actin filaments even in single living cells.

"Much of existing biomechanics will have to be rethought, since many studies have assumed that the stresses are uniform," Sachs continues. "The actin stress probe showed that the tension in actin fibers in stem cells is higher than in normal cells. That was very surprising to us."

He adds that while mechanics are well-known to have a role in cellular processes, the details are poorly understood because there have been few ways to measure the stress in specific proteins. A clinically relevant example is that metastatic cancer cells, the fatal variety, have different mechanics than cells of the parent tumor.

"This probe will allow cancer researchers to better understand what allows cells to become metastatic," says Sachs.

The UB researchers have created transgenic animals (worms and flies) that express these probes, demonstrating that the probes are not toxic to cells, and thus, can be studied in whole animals.

A key advantage of the UB team's use of mechanics to reprogram normal cells into stem cells is that it requires no chemical transcription factors that bind to specific DNA sequences and can prove clinically hazardous.

"The use of stem cells in the clinic has been held up, in part, by the need to use transcription factors that can be toxic," he explains. "The possibility that we may be able to obtain stem cells simply by altering cell mechanics could bring stem cell therapy closer to the clinic."

Stem cells are of interest in medicine because they have the potential to differentiate into any type of cell in the body, regenerating and repairing damaged tissue.

More information: "Actin stress in cell reprogramming." *PNAS* 2014

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