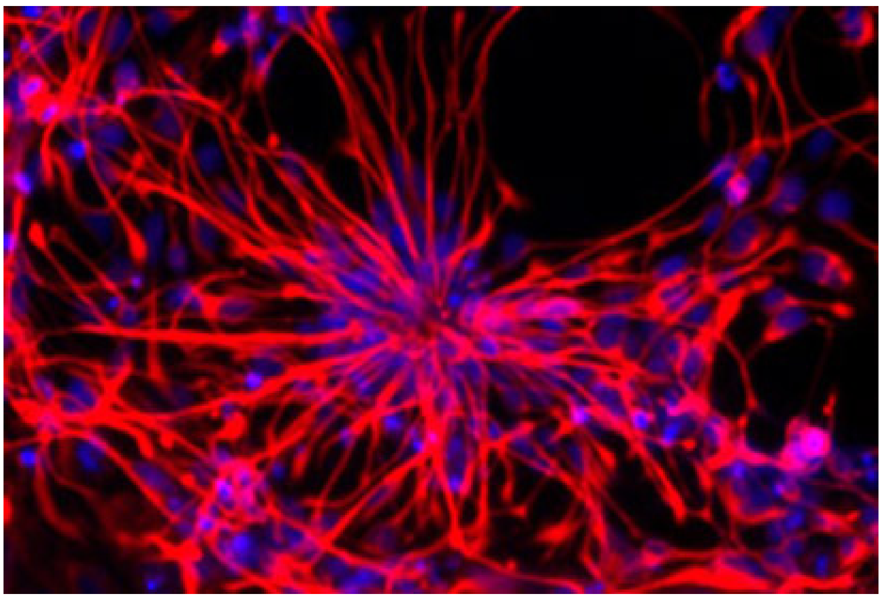
Physical cues help mature cells revert into embryonic-like stem cells

October 20 2013, by Sarah Yang



Pluripotent stem cells, created from human skin or mouse ear tissue, are shown here developing into neurons. Cell nuclei are shown in blue, and the red highlights a type of filament protein expressed in nerve cells. Credit: Song Li's Lab

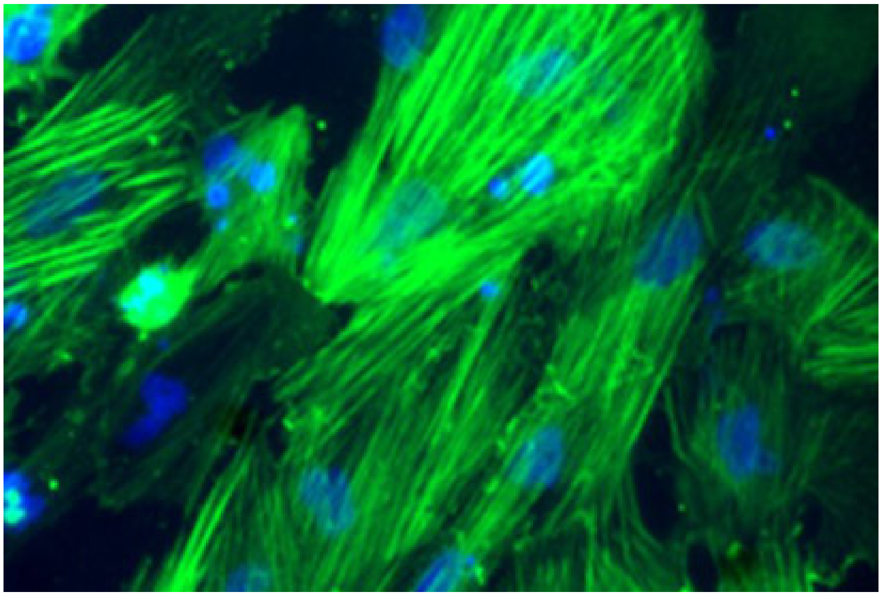
(Phys.org) —Bioengineers at the University of California, Berkeley, have shown that physical cues can replace certain chemicals when nudging mature cells back to a pluripotent stage, capable of becoming any cell type in the body.

The researchers grew fibroblasts – cells taken from human skin and mouse ears – on surfaces with parallel grooves measuring 10 micrometers wide and 3 micrometers high. After two weeks of culture in a special cocktail used to reprogram mature cells, the researchers found a four-fold increase in the number of cells that reverted back to an embryonic-like state compared with cells grown on a flat surface. Growing cells in scaffolds of nanofibers aligned in parallel had similar effects.

The study, published online today (Sunday, Oct. 20) in the journal *Nature Materials*, could significantly enhance the process of reprogramming adult cells into embryonic-like stem cells that can differentiate, or develop, into any type of tissue that makes up our bodies.

The 2012 Nobel Prize in Physiology or Medicine was awarded to scientists who discovered that it was possible to reprogram cells using biochemical compounds and proteins that regulate gene expression. These induced pluripotent stem cells have since become a research mainstay in regenerative medicine, disease modeling and drug screening.

"Our study demonstrates for the first time that the physical features of biomaterials can replace some of these biochemical factors and regulate the memory of a cell's identity," said study principal investigator Song Li, UC Berkeley professor of bioengineering. "We show that biophysical signals can be converted into intracellular chemical signals that coax cells to change."



Stem cells created by UC Berkeley researchers are shown here developing into muscle tissue. Smooth muscle actin protein is highlighted in green, and cell nuclei are shown in blue. Credit: Song Li's Lab

The current process for reprogramming cells relies on a formula that uses a virus to introduce gene-altering proteins into mature cells. Certain chemical compounds, including valproic acid, that can dramatically affect global DNA structure and expression are also used to boost the efficiency of the reprogramming process.

"The concern with current methods is the low efficiency at which cells actually reprogram and the unpredictable long-term effects of certain imposed genetic or chemical manipulations," said study lead author Timothy Downing, who did this research as a graduate student in the UC Berkeley-UC San Francisco Joint Graduate Program in Bioengineering. "For instance, valproic acid is a potent chemical that drastically alters the cell's epigenetic state and can cause unintended changes inside the cell. Given this, many people have been looking at different ways to improve various aspects of the reprogramming process."

Previous studies have shown that physical and mechanical forces can influence cell fate, but the effect on epigenetic state and cell reprogramming had not been clear.

The new study found that culturing cells on micro-grooved biomaterials improved the quality and consistency of the reprogramming process, and was just as effective as valproic acid.

"Cells elongate, for example, as they migrate throughout the body," said Downing, who is now a research scientist in Li's lab. "In the case of topography, where we control the elongation of a cell by controlling the physical microenvironment, we are able to more closely mimic what a cell would experience in its native physiological environment. In this regard, these physical cues are less invasive and artificial to the cell and therefore less likely to cause unintended side effects."

The researchers are studying whether growing cells on grooved surfaces could eventually replace valproic acid and perhaps other chemical compounds in the reprogramming process.

"We are also studying whether biophysical factors could help reprogram cells into specific cell types, such as neurons," said Jennifer Soto, UC Berkeley graduate student in bioengineering and another co-author of the study.

More information: Paper: dx.doi.org/10.1038/nmat3777

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