

## Body may be able to 'coach' transplanted stem cells to differentiate appropriately

November 19 2012

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Pluripotent stem cells are nature's double-edged sword. Because they can develop into a dizzying variety of cell types and tissues, they are a potentially invaluable therapeutic resource. However, that same developmental flexibility can lead to dangerous tumors called teratomas if the stem cells begin to differentiate out of control in the body.

To prevent this outcome, researchers must first give the cells a not-so-subtle shove toward their final developmental fate before transplanting them into laboratory animals or humans. But exactly how to do so can vary widely among laboratories. Now researchers at the Stanford University School of Medicine have used an experiment in mice to hit upon a way to possibly skip this fiddly step by instead relying mostly on signals within the body to keep the [stem cells](#) in line.

"Before we can use these cells, we have to differentiate, or 'coach,' them down a specific developmental pathway," said Michael Longaker, MD, the Deane P. and Louise Mitchell Professor in the School of Medicine. "But there's always a question as to exactly how to do that, and how many developmental doors we have to close before we can use the cells. In this study, we found that, with appropriate environmental cues, we could let the body do the work."

Allowing the body to direct differentiation could speed the U.S. [Food and Drug Administration](#)'s approval of using such [pluripotent stem cells](#), Longaker believes, by eliminating the extended periods of laboratory manipulation required during the forced differentiation of the cells.

Longaker, who co-directs Stanford's Institute for [Stem Cell Biology](#) and Regenerative Medicine, is the senior author of the research, which will be published online Nov. 19 in the [Proceedings of the National Academy of Sciences](#). Postdoctoral scholars Benjamin Levi, MD, and Jeong Hyun, MD, and research assistant Daniel Montoro are co-first authors of the work. Longaker is also a member of the Stanford Cancer Institute.

"Once we identify the key proteins and signals coaching the tissue within the body, we can try to mimic them when we use the stem cells," said Longaker. "Just as the shape of water is determined by its container, cells respond to external cues. For example, in the future, if you want to replace a failing liver, you could put the cells in a scaffold or microenvironment that strongly promotes liver cell differentiation and place the cell-seeded scaffold into the liver to let them differentiate in the optimal macroenvironment."

In Longaker's case, the researchers were interested not in the liver, but in bone formation. Longaker himself is a pediatric plastic and reconstructive surgeon who specializes in craniofacial malformations. "Imagine being able to treat children and adults who require craniofacial skeletal reconstruction, not with surgery, but with stem cells," he said.

The researchers removed a 4 millimeter circle of bone from the skulls of anesthetized laboratory mice—a defect just large enough to stymie the natural healing properties of the bone's endogenous stem cells. They then implanted in the damaged area a tiny, artificial scaffold coated with a protein called BMP-2 that they knew (from previous experiments) stimulated bone growth. Each scaffold was seeded with 1 million human stem cells. They then waited and watched for several months as the bone regrew.

"We found that the human cells formed bone and repaired the defect," said Longaker. "What's more, over time that human bone created by the

stem cells was eventually replaced by mouse bone as part of the natural turnover process. So the repair was physiologically normal."

The researchers credit the regrowth to the tandem nature of a macroenvironment of bone damage and a microenvironment of scaffolding coated with a bone-growth-triggering molecule.

The researchers tested the ability of both human embryonic stem cells and human induced pluripotent stem cells, or iPS cells, to heal the defects. (iPS cells are generated in the laboratory from fully differentiated cells like those found in skin, whereas embryonic stem cells are isolated from human embryos.) They found that the iPS cells seeded onto the BMP-2-containing scaffolds healed more than 96 percent of the defect within eight weeks of transplantation. Human embryonic stem cells were similarly successful, healing 99 percent of the defect within eight weeks.

In addition to repairing the defect, the technique also produced relatively few dangerous teratomas: Two out of 42 animals in the study developed the tumors. (Both teratomas occurred in animals that had received embryonic stem cells, rather than iPS cells.) In contrast, both types of stem cells readily formed teratomas when implanted under the kidney surface of an immunodeficient animal—a standard laboratory test to confirm stem cells' pluripotent potential.

"We still have work to do to completely eliminate teratoma formation," said Longaker, "but we are highly encouraged." He speculates that combining the technique with other strategies—perhaps by including other cell types to act as chaperones to the differentiating stem cells—may eventually overcome the problem.

"I want to see how broadly applicable this technique may be," said Longaker, who speculated that it may be useful to replace damaged

cartilage in joints during arthroscopy. "Cartilage doesn't heal itself, so perhaps you can add some cells that can form replacement tissue in this macroenvironment while you're already looking in the joint."

Provided by Stanford University Medical Center

Citation: Body may be able to 'coach' transplanted stem cells to differentiate appropriately (2012, November 19) retrieved 11 May 2024 from <https://medicalxpress.com/news/2012-11-body-transplanted-stem-cells-differentiate.html>

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