Pluripotent cells created by nuclear transfer can prompt immune reaction, researchers find

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Mouse cells and tissues created through nuclear transfer can be rejected by the body because of a previously unknown immune response to the cell's mitochondria, according to a study in mice by researchers at the Stanford University School of Medicine and colleagues in Germany, England and at MIT.

The findings reveal a likely, but surmountable, hurdle if such therapies are ever used in humans, the researchers said.

Stem cell therapies hold vast potential for repairing organs and treating disease. The greatest hope rests on the potential of pluripotent stem cells, which can become nearly any kind of cell in the body. One method of creating pluripotent stem cells is called somatic cell nuclear transfer, and involves taking the nucleus of an adult cell and injecting it into an egg cell from which the nucleus has been removed.

The promise of the SCNT method is that the nucleus of a patient's skin cell, for example, could be used to create pluripotent cells that might be able to repair a part of that patient's body. "One attraction of SCNT has always been that the genetic identity of the new pluripotent cell would be the same as the patient's, since the transplanted nucleus carries the patient's DNA," said cardiothoracic surgeon Sonja Schrepfer, MD, PhD, a co-senior author of the study, which will be published online Nov. 20 in *Cell Stem Cell*.

"The hope has been that this would eliminate the problem of the patient's immune system attacking the pluripotent cells as foreign tissue, which is a problem with most organs and tissues when they are transplanted from one patient to another," added Schrepfer, who is a visiting scholar at Stanford's Cardiovascular Institute. She is also a Heisenberg Professor of the German Research Foundation at the University Heart Center in Hamburg, and at the German Center for Cardiovascular Research.

Possibility of rejection

A dozen years ago, when Irving Weissman, MD, professor of pathology and of developmental biology at Stanford, headed a National Academy of Sciences panel on stem cells, he raised the possibility that the immune system of a patient who received SCNT-derived cells might still react against the cells' mitochondria, which act as the energy factories for the cell and have their own DNA. This reaction could occur because cells created through SCNT contain mitochondria from the egg donor and not from the patient, and therefore could still look like foreign tissue to the recipient's immune system, said Weissman, the other co-senior author of the paper. Weissman is the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research and the director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

That hypothesis was never tested until Schrepfer and her colleagues took up the challenge. "There was a thought that because the mitochondria were on the inside of the cell, they would not be exposed to the host's immune system," Schrepfer said. "We found out that this was not the case."

Schrepfer, who heads the Transplant and Stem Cell Immunobiology Laboratory in Hamburg, used cells that were created by transferring the nuclei of adult mouse cells into enucleated eggs cells from genetically different mice. When transplanted back into the nucleus donor strain,

the cells were rejected although there were only two single nucleotide substitutions in the mitochondrial DNA of these SCNT-derived cells compared to that of the nucleus donor. "We were surprised to find that just two small differences in the mitochondrial DNA was enough to cause an immune reaction," she said.

"We didn't do the experiment in humans, but we assume the same sort of reaction could occur," Schrepfer added.

Until recently, researchers were able to perform SCNT in many species, but not in humans. When scientists at the Oregon Health and Science University announced success in performing SCNT with human cells last year, it reignited interest in eventually using the technique for human therapies. Although many stem cell researchers are focused on a different method of creating pluripotent stem cells, called induced pluripotent stem cells, there may be some applications for which SCNT-derived pluripotent cells are better suited.

Handling the reaction

The immunological reactions reported in the new paper will be a consideration if clinicians ever use SCNT-derived stem cells in human therapy, but such reactions should not prevent their use, Weissman said. "This research informs us of the margin of safety that would be required if, in the distant future, we need to use SCNT to create pluripotent cells to treat someone," he said. "In that case, clinicians would likely be able to handle the immunological reaction using the immunosuppression methods that are currently available."

In the future, scientists might also lessen the immune reaction by using eggs from someone who is genetically similar to the recipient, such as a mother or sister, Schrepfer added.

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