More Than Skin Deep

Scientists discover ways to generate embryonic stem cells from skin tissue. **BY LAMONT WILLIAMS**

Take skin cells, tweak them a bit, and they can become heart cells for a patient with chronic heart disease or insulin-producing cells for a patient with diabetes. Such cell-based therapies in which stem cells give rise to specific types of cells to repair damaged cells or tissues, also referred to as regenerative medicine, are still in the future. But two recent studies conducted by groups based at NCRR-funded National Primate Research Centers (NPRCs) are helping to pave the way toward custom-made cells and tissues for patients.

"The field of regenerative medicine is an extremely important one," says John Harding, NCRR's director of primate resources. "It is potentially the way we are going to cure some diseases that are not curable by any other means at present. The advances at the Oregon and Wisconsin NPRCs will significantly accelerate this area of research."

The two recent breakthroughs rely on the fact that nearly every cell in the human body contains the full set of genes required for making every type of cell. During development, a fertilized egg develops into an embryo, which contains embryonic stem cells. These cells turn different sets of genes off while leaving others on, giving rise to heart, brain, skin, or other specialized cells in the body. In most cases, the specialized cells retain the full complement of genes even though not all of these genes are functional.

Researchers at the Oregon NPRC essentially persuaded one type of specialized cell—a skin cell—to revert back to its embryonic stem cell status. The method used, called somatic cell nuclear transfer, involved obtaining an egg cell of a female rhesus macaque *(Macaca mulatta)* and removing its nucleus. The researchers then transferred the nucleus of a skin cell from another adult macaque into the enucleated egg cell. The transfer allowed the egg cell to mature into an embryo containing embryonic stem cells, mimicking normal development. By providing or removing certain chemical signals, the researchers prompted the stem cells to develop into nerve, heart, liver, pancreatic, and other cells.

■ Shoukhrat Mitalipov and his colleagues at the Oregon National Primate Research Center (NPRC) have generated embryonic stem cells from rhesus macaque skin cells using somatic cell nuclear transfer. Research at NCRR-funded NPRCs has played an important role in the field of regenerative medicine.

This process could potentially be used to take skin cells from a patient suffering from disease and, using the process of somatic cell nuclear transfer, produce cells that will replace those damaged by disease. Because the replacement cells would originate from the patient,

PHOTO BY MICHAEL MCDERMOTT

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there would not be the risk of the cells being rejected by the patient's immune system. "Consider a patient with Parkinson's disease," says Shoukhrat Mitalipov, co-director of the Assisted Reproductive Technologies and Embryonic Stem Cell Core Laboratory at the Oregon NPRC in Beaverton, who leads the research. "In this person, there is a certain type of neuron that has been damaged, producing the patient's symptoms. This new technique may one day be used to create new neurons that can be placed into the patient to cure the condition."

Although federally funded researchers can only use this technique in animal models because it involves living eggs, such studies could provide important insights into the eventual success of cell-based therapies in humans. "Moving forward, the primate centers will be extremely valuable for regenerative medicine," says James Thomson, a professor at the University of Wisconsin School of Medicine and Public Health. "In this field, you need a model that is long lived like the primate to follow these diseases, which tend to be diseases of old age."

Thomson, a pioneer in stem cell research, directed the group at the Wisconsin NPRC that reported the first isolation of embryonic stem cell lines from a rhesus macaque in 1995. He then led his group to the first successful isolation of human embryonic stem cell lines in 1998. Last year, one week after the announcement of the Oregon team's success, Thomson's team, along with a team of Japanese scientists working independently, reported that human skin cells could be transformed into stem cells without the use of living egg cells or embryos.

Thomson and colleagues used viruses as laboratory tools to introduce four genes into the genome of human skin cells, causing the skin cells to become pluripotent stem cells. Although stem cells generated through this technique, called induced pluripotent stem (iPS) cells, appear to behave like ordinary embryonic stem cells, more tests are needed to precisely determine the properties of iPS cells. Thomson's team and other researchers are also working on finding ways to remove the "extra" genes once they are no longer needed.

If iPS cells prove to be like embryonic stem cells and are able to produce any type of cell in the body, they could be used to replace damaged cells and tissues using a patient's own cells. Because no human eggs or embryos would be used, the technique would circumvent the ethical and legal issues that surround the use of embryonic stem cells in therapy. But before any therapies can be used with patients, "more work in the primate centers needs to be performed showing that therapies based on iPS cells can be done and are safe," says Thomson.

■ Stem cell research pioneer James Thomson and colleagues at the University of Wisconsin have generated cells that appear to function like embryonic stem cells by "reprogramming" human skin cells. These cells could potentially be used to create different types of cells that can replace damaged cells in patients with diseases like diabetes or Parkinson's.

These advances, which have generated much excitement among stem cell researchers, build on many years of work developing the necessary tools and expertise at all NPRCs. "The base grants to the centers allowed the buildup of the intellectual and physical infrastructure needed to accomplish breakthroughs such as these," says Harding. And primate centers will undoubtedly continue to play an important role in regenerative medicine as more discoveries are made. ■

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ADDITIONAL READING:

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