Stem Cells Created From Somatic Cells

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Using a technique that has been used in scientific investigations for decades, scientists have turned back the clock on human adult cells and reprogrammed them to become stem cells. In addition to possibly leading to an alternative means of stem cell production in the future, the new approach may provide insight into the underlying developmental processes of stem cells and offer researchers a new tool for studying disease.

However, there is at least one huge technical hurdle standing in the way of using this technique for developing therapies to treat patients.

The team of scientists from Harvard University, in Cambridge, Mass, fused human embryonic stem cells with skin cells from an adult man and found that the adult cells reverted to an embryonic state (Cowan et al. Science. 2005; 309:1369-1373). Previously, other scientists used the same technique to reprogram adult mouse cells to an embryonic state (Tada et al. Curr Biol. 2001;11:1553-1558).

"Cell fusion has been around for almost a century, but this group applied this technique into the stem cell field," said Su-Chun Zhang, PhD, a stem cell researcher and professor of anatomy and neurology at the University of Wisconsin’s Waisman Center in Madison.

NEW APPROACH

With approval from the Harvard University committees responsible for reviewing animal, stem cell, and human research, the scientists genetically engineered human embryonic stem cells to carry a gene that makes the cells resistant to one antibiotic. The human stem cells were derived from embryos left over from in vitro fertilization (Cowan et al. N Engl J Med. 2004;350:1353-1356). They also inserted a gene for resistance to a second antibiotic into human adult skin cells. Then they mixed the two cell types in the presence of a chemical that causes cells to fuse. The resulting cells were grown in conditions that allow embryonic stem cells to grow but also contained the two antibiotics. The only surviving cells were the cells that had fused and now carried genes for resistance to both antibiotics. These cells were allowed to grow and were subjected to a battery of experiments that showed that they demonstrated all the characteristics of human embryonic stem cells.

The researchers also repeated their fusion experiment with human adult bone cells and human embryonic stem cells from a different stem cell line. “We were worried that this phenomenon would be particular to one embryonic stem cell line or one particular adult cell type,” said Kevin Eggan, PhD, a member of the Harvard team and assistant professor of molecular and cellular biology. But they found that a hybrid of these cell types also reverted to an embryonic state.

While this new technique might eventually offer an alternative to existing means of producing stem cell lines, this will require overcoming significant technical hurdles.

The hybrid cells produced by the fusion technique are tetraploid, containing DNA from both the embryonic stem cell and the adult somatic cell. To make them therapeutically useful, the scientists would have to develop a way to remove the embryonic DNA, which would be technically very difficult, Eggan said. An existing technique, somatic cell nuclear transfer, in which human embryonic stem cells are produced by transferring the nucleus of an adult somatic cell into an enucleated, unfertilized human oocyte, produces normal diploid cells that contain only the DNA from the adult somatic cell and could be used therapeutically. However, there are ethical concerns about using human oocytes that have prevented this technique from being widely embraced.

DEVELOPMENTAL CLUES

The immediate promise of this technique lies in providing clues about the
Skin Cancer’s Ranks Rise
Immunosuppression to Blame

Tracy Hampton, PhD

CHICAGO—Ever-growing numbers of individuals are at increased risk of developing skin cancer, and not just because of sun worship and the pursuit of the perfect tan. More people are susceptible now because of impaired immunity due to immunosuppressive drugs following organ transplantation or for various rheumatologic and dermatologic conditions. Also vulnerable are patients who have compromised immune surveillance due to such conditions as HIV and chronic lymphocytic leukemia (CLL), which increases their risk of developing cancer.

While such individuals present a challenge to physicians, their conditions can help shed light on the mechanisms involved and may therefore provide opportunities for therapeutic innovations.

TRANSPLANT RECIPIENTS

“Skin cancer is the most common malignancy in the posttransplant setting and affects the majority of patients eventually,” said Clark Otley, MD, of the Mayo Clinic and Mayo Medical School, in Rochester, Minn, during the annual meeting of the American Academy of Dermatology held here in July. With 30% and 70% of patients developing skin cancer (including squamous cell carcinoma, melanoma, and basal cell carcinoma) within 20 years of a solid organ allograft, it is vitally important to monitor these individuals and develop effective ways to decrease their risks.

Additionally, the fusion technique is easy, so it can be used to replicate numerous cells. And because it doesn’t rely on the limited supply of human oocytes, it might be used to produce stem cell lines for research on disease. For instance, researchers could produce hybrid cells that contain DNA from an individual with a disease and could study those cells to identify what’s going wrong.

“It’s helpful in a way because it provides a tool for research,” Zhang said. “You can provide different human stem cells with different genetic backgrounds.”

But Eggan and Zhang agree that many questions remain to be answered to understand the utility of cells produced through this technique. “We don’t know if cells produced this way are normal,” Zhang said.

An analysis of 93,934 renal transplantations from 1988 to 1996 revealed that the half-life for kidney grafts nearly doubled over that period of time (Hariharan et al. N Engl J Med. 2000;342:605-612). And after performing more than 1000 heart transplant operations between 1977 to 1999, the cardiac transplantation program at Columbia University, in New York City, reported that recipients had a 1-year survival rate of approximately 90% and a 5-year survival rate of approximately 75% (Edwards et al. Clin Transpl. 1999;249-261). As the number of organ allograft recipients who live for many years after transplantation continues to grow, it is likely that skin cancer incidences will be on the rise as well in the years to come.

It is thought that immunosuppressive drugs may accelerate the development of skin cancer in transplant recipients by being directly carcinogenic or by creating a state of compromised immune surveillance. The human papillomavirus may play a role as well, although to what extent is not clear. “This virus is present in keratinocytes, and immunosuppressive treatment induces its development,” said Brigitte Dréno, MD, PhD, of the Centre Hospitalier Universitaire, in Nantes, France.