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MIT researchers convert skin cells to stem cells

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In this month's issue of Cell Stem Cell, scientists at MIT's Whitehead Institute for Biomedical Research continue their groundbreaking work on pluripotent stem cells. The team headed by Rudolf Jaenisch shows that a specific sequence of biochemical manipulations can reprogram a skin cell into a pluripotent stem cell.

In 2006, research led by Shinya Yamanaka at Kyoto University, Japan, showed that skin cells from mice could be reprogrammed, or reverted, to a pluripotent stem cell (termed iPS, for induced pluripotent stem cell) using four key pluripotent-associated genes. Pluripotency is the condition in which a cell can become any cell type in the body, such as muscle, skin or neurons.

The cells derived from pluripotent cells are said to be differentiated. These cells are unable to become other cells in the body because the structure of their nuclei is restrictive and certain genes are turned off.

Yamanaka's work was the first to show that differentiated cells could become pluripotent cells, a feat once thought to be impossible. It opened a new door in the search to create patient-specific stem cells, which can be used for medical treatments.

However, as promising as this initial work was, there were problems. The reprogrammed cells were not fully pluripotent. Also, the four reprogramming genes were introduced into the cell using a virus. Furthermore, one of the four genes is known to be oncogenic, or cancer-causing.

Three groups headed by Yamanaka, Jaenisch and a team from UCLA remedied the first problem in the summer of 2007. They showed that these new iPS cells were fully pluripotent, having characteristics of true pluripotent stem cells.

Finally, in November 2007, Yamanaka, as well as a team from Wisconsin, reprogrammed human skin cells, taking the research one step closer to clinical applications.

Until now the research in this area has been poorly understood at the molecular level. Is reactivation of pluripotency a random process or does it require a specific sequence of molecular events? Furthermore, do the four genes required to start the process of reprogramming interfere with differentiation later on? Jaenisch and his team answered these questions.

To address the first question, the researchers created reprogramming genes under the control of a specific substance. This means that they could have the genes turned on in the presence of this substance and turned off in its absence. If the reprogramming genes were turned on, the cells went through the reprogramming process as expected.

To quantify the reprogramming process (which takes close to three weeks), the team took cells on different days and used a machine that sorts them. This machine separates cells based on very specific cell-surface markers. The team separated the cells undergoing reprogramming and looked for indications of reprogramming, such as certain proteins expressed.

Results showed that when expressing the reprogramming genes, a minimum of 16 days is required to fully reprogram skin cells to pluripotent cells, with one pluripotency marker arising first at three days, followed by another marker at nine days, and the fully reprogrammed cell at 16 days or later.

This final stage of reprogramming was also the time in which the expression of the four genes could be removed. Any time point before then, the cells could not be reprogrammed. The cells thus go through a sequential, not random, process of reprogramming.

Jaenisch then went on to answer the second question. Must the four reprogramming genes be turned off in order for the iPS cells to differentiate? Using the iPS cells derived from the previous experiment, the researchers injected the cells into mice, looking for the formation of a teratoma, or tumor, with every cell type present. This is a hallmark of pluripotent stem cells. Their iPS cells did form a teratoma.

Then they created another iPS cell that is unable to turn off its four reprogramming genes. Injection of this cell into mice revealed it was unable to form a teratoma, indicating the importance of silencing the four genes.

Jaenisch concludes that there is a specific sequence of events required for reprogramming a cell to a pluripotent state. Also, silencing of the four reprogramming genes is necessary for differentiation of the iPS. The results will help future researchers to define what a cell needs to reprogram itself without using a virus or cancer-causing genes.

With this new knowledge, research can proceed to create patient-specific stem cells, which may be used to cure diseases like diabetes, Parkinson's disease, muscular dystrophy and others.