Researcher discovers mechanism for changing adult cells into stem-like cells

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In 2006, Dr. Shimya Yaminaka of Kyoto University in Japan set the stem cell and regenerative medicine research world on fire when he successfully transformed differentiated mouse skin cells into cells that looked and behave like embryonic stem cells. Embryonic stem cells, the subject of much controversy when used in research, have the ability to differentiate into any type of tissue.

Yaminaka's creation of induced pluripotent stem cells [iPSCs] meant that in the future, research to improve human disease might be able to use iPSCs in lieu of embryonic stem cells. Since then, researchers around the world have been able to replicate his process. However, no one has been able to unlock the mechanism that allows cells to be regressed from differentiated to undifferentiated cells—until now.

University of Colorado Cancer Center researcher Chuan-Yuan Li, PhD, and his group have discovered that so-called "grim-reaper" caspase genes are the gatekeepers that can open the door to allow differentiated adult cells to regress to undifferentiated iPSCs.

"By doing experiments in which we added caspase inhibitor genes to the Yaminaka protocol, we discovered that when caspases are turned off, you cannot make IPSCs," says Li, professor of radiation oncology at the University of Colorado School of Medicine. "We were able to shut down the process almost completely."

The discovery is the cover article in the Oct. 8, 2010 issue of *Cell Stem*

Cell.

"For practical reasons, the discovery is important because even though the transformation to iPSCs is a straightforward process on surface, it is not very efficient, and this information can help increase efficiency," Li says. "It can also help with the problem of cells that don't complete the transformation process acting like cancer cells. And from a purely scientific perspective, it is fascinating to understand why the magic happens."

Li's group had been working on the roles of caspases in wound healing when Yaminaka published his initial iPSC work in mice. That got Li thinking about potential roles of caspases in iPSC generation.

"I thought maybe caspases could also induce iPS cells instead of the four transcriptional factors that Yamanaka used," he says. "If that was true, it would be very exciting."

For six months, his group tried different experiments using various caspase genes to coax human skin cells into iPS cells, but they had no success. Although caspases were not sufficient to make iPS cells, Li kept going with the idea that caspases were somehow involved.

They made their discovery when they introduced the caspase inhibitors into skin cells, which almost completely shut down the induction of iPS cells.

Caspases, Li says, appear to loosen up the built-in controls that make a cell differentiated or undifferentiated, just like a clutch allows a driver to switch gears while driving. Undifferentiated stem-like cells and differentiated cells from one person have the exact same genes. The difference between them is which genes are turned on or off.

In other words, he says, caspases could be the key to a kind of cellular reincarnation—taking a cell that, during human development, became a skin cell back to its original state to become any kind of cell.

"About twenty years ago, a scientist who was among the first to clone the caspase 3 gene named the gene Yama, the Hindu Lord of Death who was responsible for both killing a being and setting him on his way into his reincarnated life," Li said. "It is now becoming clear that caspases don't just kill, but they can change the cell's fate. They could be a mediator of epigenetic changes in multi-cellular organisms."

Provided by University of Colorado Denver