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UCLA Scientists Find Molecular Differences Between Embryonic Stem Cells And Reprogrammed Skin Cells

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UCLA researchers have found that embryonic stem cells and skin cells reprogrammed into embryonic-like cells have inherent molecular differences, demonstrating for the first time that the two cell types are clearly distinguishable from one another.

The data from the study suggest that embryonic stem cells and the reprogrammed cells, known as induced pluripotent stem (iPS) cells, have overlapping but still distinct gene expression signatures. The differing signatures were evident regardless of where the cell lines were generated, the methods by which they were derived or the species from which they were isolated, said Bill Lowry, a researcher with the Broad Stem Cell Research Center and a study author.

"We need to keep in mind that iPS cells are not perfectly similar to embryonic stem cells," said Lowry, an assistant professor of molecular, cell and developmental biology. "We're not sure what this means with regard to the biology of pluripotent stem cells. At this point our analyses comprise just an observation. It could be biologically irrelevant, or it could be manifested as an advantage or a disadvantage."

The study appears in the July 2, 2009 issue of the journal *Cell Stem Cell.*

The iPS cells, like embryonic stem cells, have the potential to become all of the tissues in the body. However, iPS cells don't require the destruction of an embryo.

The study was a collaboration between the labs of Lowry and UCLA researcher Kathrin Plath, who were among the first scientists and the first in California to reprogram human skin cells into iPS cells. The researchers performed microarray gene expression profiles on embryonic stem cells and iPS cells to measure the expression of thousands of genes at once, creating a global picture of cellular function.

Lowry and Plath noted that, when the molecular signatures were compared, it was clear that certain genes were expressed differently in embryonic stem cells than they were in iPS cells. They then compared their data to that stored on a National Institutes of Health data base, submitted by laboratories worldwide. They analyzed that data to see if the genetic profiling conducted in other labs validated their findings, and again

they found overlapping but distinct differences in gene expression, Lowry said.

"This suggested to us that there could be something biologically relevant causing the distinct differences to arise in multiple labs in different experiments," Lowry said. "That answered our first question: Would the same observation be made with cell lines created and maintained in other laboratories?"

Next, UCLA researchers wanted to confirm their findings in iPS cell lines created using the latest derivation methods. The cells from the UCLA labs were derived using an older method that used integrative viruses to insert four genes into the genome of the skin cells, including some genes known to cause cancer. They analyzed cell lines derived with newer methods that do not require integration of the reprogramming factors. Their analysis again showed different molecular signatures between iPS cells and their embryo-derived counterparts, and these signatures showed a significant degree of overlap with those generated with integrative methods.

To determine if this was a phenomenon limited to human embryonic stem cells, Lowry and Plath analyzed mouse embryonic stem cells and iPS lines derived from mouse skin cells and again validated their findings. They also analyzed iPS cell lines made from mouse blood cells with the same result

"We can't explain this, but it appears something is different about iPS cells and embryonic stem cells," Lowry said. "And the differences are there, no matter whose lab the cells come from, whether they're human or mouse cells or the method used to derive the iPS cells. Perhaps most importantly, many of these differences are shared amongst lines made in various ways."

Going forward, UCLA researchers will conduct more sophisticated analyses on the genes being expressed differently in the two cell types and try to understand what is causing that differential expression. They also plan to differentiate the iPS cells into various lineages to determine if the molecular signature is carried through to the mature cells. In their current study, Lowry and Plath did not look at differentiated cells, only the iPS and embryonic stem cells themselves.

Further study is crucial, said Mark Chin, a postdoctoral fellow and first author of the study.

"It will be important to further examine these cells lines in a careful and systematic manner, as has been done with other stem cell lines, if we are to understand the role they can play in clinical therapies and what effect the observed differences have on these cells," he said.

Source:
Kim Irwin
University of California - Los Angeles