New steps forward in cell reprogramming

August 10 2009

"When you work with mature cells, for some reason only a few of them actually reprogram into an iPS cell: Why is the reprogramming process so inefficient?" asked Konrad Hochedlinger, assistant professor of Stem Cell and Regenerative Biology. Photograph by B. D. Colen/Harvard News Office

(PhysOrg.com) -- Harvard Stem Cell Institute (HSCI) researchers at Massachusetts General Hospital (MGH) have substantially improved the odds of successfully reprogramming differentiated cells into induced pluripotent stem cells (iPS) by blocking the activity of the gene that instructs the cells to stop dividing.

Konrad Hochedlinger and colleagues at the MGH Center for Regenerative Medicine also found that reprogramming efforts are more likely to be successful if they target immature cells rather than their more mature counterparts for reprogramming.

Induced pluripotent cells are adult cells that have been reprogrammed back to an embryo-like state in which they have regained the potential to turn into any of the 220 cell types in the body, such as liver cells, skin cells, or heart cells. “This has been a main question and main interest in the field for a long time,” says Hochedlinger. “When you work with mature cells, for some reason only a few of them actually reprogram into an iPS cell: Why is the reprogramming process so inefficient?”

The team has devised two solutions for the problem of inefficiency, one of which involves selecting only certain cell types for reprogramming. The work is being published in two separate reports, one in the journal *Nature*, and the other in Nature Genetics.

Researchers know how to reprogram fully developed cells into iPS cells, yet the efficiency of the process remains very low - only about one in every 1,000 mature cells is successfully reprogrammed. Hochedlinger explained that because it’s been difficult to reprogram mature differentiated cells, he and his colleagues focused their effort on a population of relatively rare progenitor cells, cells heading down a particular developmental pathway, but not yet turned into the eventual cell type.

“By attempting to reprogram a population of progenitor cells, you have a way to increase efficiency,” says Hochedlinger. “This may be relevant when you think about upscaling iPS technology in a human setting. If you want to make iPS disease-specific cells from a limited amount of tissue material, you may want to specifically isolate these rare progenitor cells because you know the chance is much higher that they will give rise to an iPS cell compared with the mature cells which actually make the bulk of the tissue.”

Progenitor cells can give rise to a number of mature cell types within a given tissue type. For instance, blood progenitor cells give rise to all

types of blood cells. Cardiac progenitors give rise to a number of different types of cardiac cells. But cardiac progenitors do not develop into blood cells, and vice versa.

“The second solution we came up with was identifying molecules whose manipulation enhances the cell division cycle, the proliferation of the cells, and thereby also enhances the efficiency of the reprogramming,” Hochedlinger continues.

Normally adult cells have a limited number of cell division they can go through before they stop dividing. “Certain molecules turn on to tell the cell ‘stop dividing now,’” he says. “We find that if we inactivate the molecule, it makes the cell continue dividing. And we can increase the efficiency of reprogramming by making the cell grow indefinitely.”

The work is an important step in “fine-tuning” the science of creating iPS cells. It both takes advantage of progenitor cells’ ability to be reprogrammed, and also allows researchers to begin the process with a mature cell, where specific molecules are manipulated to obtain cell division and enhance the efficiency.

Producing iPS cells en masse will provide researchers with a way to study diseases in the laboratory, as well as provide targets for drug development, and, if the iPS cells prove to be biologically identical to human embryonic stem cells, they may provide material for cell transplants in diseases such as diabetes, Parkinson’s disease, and heart disease.

Provided by Harvard University (news : web)