Scientists create human embryonic stem cells with enhanced pluripotency

CAMBRIDGE, Mass. (May 3, 2010) – Whitehead Institute researchers have converted established human induced pluripotent stem (iPS) cells and human embryonic stem (ES) cells to a base state of greater pluripotency.

“This is a previously unknown pluripotent state in human cells,” says Jacob Hanna, a postdoctoral researcher in the lab of Whitehead Member Rudolf Jaenisch. “It’s the first time these cell types have approached the flexibility found in mouse ES cells.”

ES cells and iPS cells have attracted much attention because of their potential to mature into virtually any cell type in the body. Because ethical and legal issues have hampered human ES cell research, mouse cells have provided a more viable platform for ES cell studies. However, mouse and human ES cells differ in a number of significant ways, raising the very real possibility that breakthroughs in mouse stem cell science simply won’t be reproducible with human stem cells.

“I think this really opens things up, and gives us the possibility to define the biological properties of these new cells,” says Whitehead Member Rudolf Jaenisch. “For example, we can to study whether gene targeting, which is highly efficient in mouse ES cells but exceedingly inefficient in traditional human ES cells, is improved in the new 'naïve' human ES cells.”

Researchers have had a relatively easy time genetically manipulating and preventing differentiation (maturation beyond the base pluripotent state) in mouse ES and iPS cells. But human ES and iPS cells have different sets of expressed genes and depend on different signaling pathways for growth and differentiation than mouse ES and iPS cells, which makes the human cells more difficult to work with.

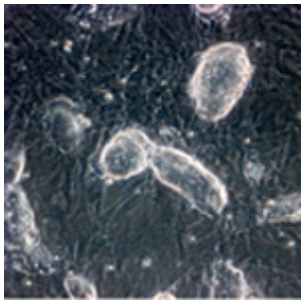
Because of these biological differences, researchers refer to mouse ES and iPS cells as “naïve” while human ES and iPS cells, which teeter on the verge of maturation, are more mature and are referred to as being “primed” for differentiation.

Hanna thought this “primed” state of human cells might be attributable to the way the human ES cell lines are created and stored. To generate ES cell lines, researchers remove cells from an early-stage embryo, called a blastocyst. Once removed from this ball of 80-100 cells, the ES cells are put into serum with other cells to keep the ES cells alive and prevent them from differentiating.

In creating iPS cells, researchers take cells from an adult and insert three to four genes into the cells’ genome. These genes reprogram

Whitehead Member Rudolf Jaenisch

Photo: John Soares/Whitehead



Whitehead researchers have converted established human induced pluripotent stem (iPS) cells and human embryonic stem (ES) cells to a base state of greater pluripotency, similar to that of mouse iPS and ES cells. The converted, more pluripotent human stem cells (above) more closely resemble the ball-like mouse stem cells, both biochemically and morphologically. Using cells in this more pluripotent state, researchers will now be able to conduct experiments with human ES cells under conditions that are equivalent to working with mouse ES cells. This will significantly enhance the ability to use human ES cells for the study of human diseases.

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the adult cells to an embryonic stem-cell-like state. Like ES cells, iPS cells are maintained in serum with other cells. Although human and mouse ES and iPS cells are created and handled in identical fashion, human cells inevitably default to the primed state, suggesting that perhaps some step in the process allows the human ES cells to move ever so slightly toward differentiation.

To determine whether ES and iPS cells could be made with traits similar to the analogous mouse cells, Hanna inserted two of the genes used to create iPS cells into established human ES and iPS cell lines. He also added growth factors into the cells' serum. After about three weeks, the human cells became like their mouse counterparts, both morphologically and biochemically.

"That was really exciting," says Jaenisch, who is also a professor of biology at MIT. "But the process required those inserted genes to be expressed, and that is not what he wanted. He wanted to do this without gene insertion."

Because the random insertion of genes can cause neighboring genes to be over- or under-expressed, potentially resulting in cancer or cell death, Hanna screened through hundreds of small molecules for candidates might mimic the function of the inserted genes. Finally, he found a cocktail of four molecules that converts established human ES and iPS cells to the naïve state characteristic of mouse ES cells.

Despite this discovery, we still know very little about human ES cells in this naïve state.

"I think this really opens things up, and gives us the possibility to define the biological properties of these new cells," says Jaenisch. "For example, we can to study whether gene targeting, which is highly efficient in mouse ES cells but exceedingly inefficient in traditional human ES cells, is improved in the new "naïve" human ES cells."

Not only is this line of research important for stem cell scientists, but it may also impact how human ES and iPS cells could be used therapeutically.

"Because the all of the differences between human ES cells and mouse ES cells, it's really important we understand what could be the basis of these differences before we really start proceeding into therapeutic application," says Hanna. "We want to really understand the biology of these cells and need to revisit a lot of the biology and differentiation potential of human ES and iPS cells."

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Written by Nicole Giese.

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Rudolf Jaenisch's primary affiliation is with Whitehead Institute for Biomedical Research, where his laboratory is located and all his research is conducted. He is also a professor of biology at Massachusetts Institute of Technology.

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