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**Professor Jaenisch: Induced Pluripotent Stem Cells – Great Potential but a Long Way to Go for Use in Therapy**

**"Stem cells generated from adult somatic cells have undisputed advantages for disease research and potentially one day even for individualized therapy. However, their widespread use may be further away in the future than is sometimes publicly predicted," said Professor Rudolf Jaenisch of the Whitehead Institute (Cambridge, MA, USA) in a statement to the press at the international conference "Stem Cells in Development and Disease", organized by the Max Delbrück Center for Molecular Medicine (MDC) in Berlin.**

Since 2006, several research groups have reprogrammed somatic cells into induced pluripotent stem (iPS) cells, which are similar in many properties to natural stem cells. "Besides the fact that here ethical issues and political debates are less important than for embryonic stem (ES) cells, iPS cells have the advantage that they are tailored to the particular patient and therefore – unlike ES cells – cannot be rejected by the immune system," Professor Jaenisch said. This could lead to a ‘revolution’ in transplantation medicine. Furthermore, iPS cells could also differentiate into certain cell types such as nerve or heart cells, so that a use in many areas of medicine is conceivable.

However, iPS cells also pose a number of problems, and many questions remain unanswered. To convert somatic cells into iPS cells, four gene regulators (the transcription factors Oct4, Sox2, Klf4 and c-Myc) are induced into skin cells using retroviruses as a transport vehicle. There they are expressed to a greater extent than normal. These ‘vehicles’ bear the risk of causing tumors. Now, by means of ‘molecular scissors’ it has become possible to cut out the viruses again from the pluripotent cells once their work is completed and/or to use other vectors instead of retroviruses.

"Furthermore,” Professor Jaenisch added, “we are looking for transcription factors which would improve the success score of reprogramming – still a random process – and would also help us find the best possible stem cells." He pointed out that only a minority of donor somatic cells can be reprogrammed to pluripotency. His research group at the Whitehead Institute has taken two approaches to solve this problem: First, the researchers inhibited the signaling pathway of the molecules p53/p21 (it slows down the activity of genes) and second, they overexpressed a marker termed Lin28 so that the cells proliferate faster. Both approaches accelerate the formation of iPS cells. “These results suggest that the number of cell divisions is a key parameter driving the epigenetic reprogramming of the somatic cell into pluripotency," Professor Jaenisch said.

**Targeted modification of genes in human embryonic stem cells**

Moreover, the targeted introduction of a DNA molecule into a cell is very inefficient and thus poses a major impediment to realizing the potential of both human ES cells and iPS cells. Using a new technique, it has now become possible to modify expressed and silent genes in human ES cells and in iPS cells. By means of enzymes (Zn finger mediated genome editing), a gene is induced into the cell, and in conjunction with this a DNA fragment at a specific locus is deleted, repaired or overexpressed.

To better understand the reprogramming process, it is crucial to take into consideration the heritable information not encoded in the [DNA](http://en.wikipedia.org/wiki/DNA) sequence – epigenetics. In different cells the "work" of (almost always identical) DNA is different, which leads to the activation of respectively different genes. "Epigenetics is therefore the key control mechanism – and the reprogramming of adult cells is no different than an epigenetic phenomenon," Professor Jaenisch explained. Understanding this phenomenon would mean finding the best "recipe" for producing induced pluripotent stem cells.

**Different stages of pluripotency**

Human and mouse ES cells are derived from blastocysts, an early development stage of the embryo (in humans: first week), but have very different biological properties. Previous molecular analyses suggest that pluripotent human ES cells resemble mouse ES cells from the epiblast stage, a more advanced stage of development. The Jaenisch research group has converted conventional human ES cells into a more immature stage, which corresponds very closely to the stage of the pluripotent mouse ES cells.

In contrast to conventional human ES cells, these epigenetically modified cells have properties which are quite similar to those of the mouse ES cells. The generation of such "naïve" human ES cells will enable the molecular analysis of the previously undefined pluripotent stage. This may open up new opportunities for patient-specific, disease-relevant research.

**Future prospects**

Professor Jaenisch’s research group has also succeeded in converting cells from patients with the non-inherited form of Parkinson’s disease into iPS cells. The aim of this research is first to elucidate the etiology and pathogenesis of neurodegenerative diseases (e.g. Alzheimer’s disease or ALS) in the laboratory and subsequently to find potential molecules for therapy.

Despite all the advances made in the production of iPS cells, in the near future researchers will still need human embryonic stem cells as comparison molecules. "Therefore, the ideological rejection of all research with ES cells does not seem to us to be justified,” Professor Jaenisch stressed. "That is why we need to better inform the public about our goals and the benefits of stem cell research. In any case, it is still a long way to the therapeutic use of reprogrammed adult stem cells."

Rudolf Jaenisch, b. 1942 in Wölfelsgrund, Germany

1967 MD, Univ. of Munich

1967 Max Planck Institute of Biochemistry, Munich

1970 Princeton (New Jersey)

1972 Salk Institute (La Jolla)

1977 University of Hamburg

1984 Whitehead Institute (Cambridge/USA)

Main research areas

Transgenetics (created the first transgenic mouse model in1974)

Epigenetics, regulation of gene expression

Stem cell research

Therapeutic cloning

Selected awards

2001 Peter Gruber Foundation Award in Genetics

2002 Robert Koch Prize

2006 Max Delbrück Medal

2009 Ernst Schering Prize

2010 Grand Federal Cross of Merit with star

2011 Wolf Prize in Medicine

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