A new shortcut for stem cell programming

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Scientists at the Life and Brain Research Center at the University of Bonn, Germany, have succeeded in directly generating brain stem cells from the connective tissue cells of mice.

These stem cells can reproduce and be converted into various types of brain cells. To date, only reprogramming in brain cells that were already fully developed or which had only a limited ability to divide was possible. The new reprogramming method presented by the Bonn scientists and submitted for publication in July 2011 now enables derivation of brain stem cells that are still immature and able to undergo practically unlimited division to be extracted from conventional body cells. The results have now been published in the current edition of the prestigious journal *Cell Stem Cell*.

The Japanese stem cell researcher Professor Shinya Yamanaka and his team produced stem cells from the connective tissue cells of mice for the first time in 2006; these cells can differentiate into all types of body cells. These induced pluripotent stem cells (iPS cells) develop via reprogramming into a type of embryonic stage. This result made the scientific community sit up and take notice. If as many stem cells as desired can be produced from conventional body cells, this holds great potential for medical developments and drug research. "Now a team of scientists from the University of Bonn has proven a variant for this method in a mouse model," report Dr. Frank Edenhofer and his team at the Institute of Reconstructive Neurobiology (Director: Dr. Oliver Brüstle) of the University of Bonn. Also involved were the epileptologists and the Institute of Human Genetics of the University of

Bonn, led by Dr. Markus Nöthen, who is also a member of the German Center for Neurodegenerative Diseases.

Edenhofer and his co-workers Marc Thier, Philipp Wörsdörfer and Yenal B. Lakes used connective tissue cells from mice as a starting material. Just as Yamanaka did, they initiated the conversion with a combination of four genes. "We however deliberately targeted the production of neural stem cells or brain stem cells, not pluripotent iPS multipurpose cells," says Edenhofer. These cells are known as somatic or adult stem cells, which can develop into the cells typical of the nervous system, neurons, oligodendrocytes and astrocytes.

The gene "Oct4" is the central control factor

The gene "Oct4" is a crucial control factor. "First, it prepares the connective tissue cell for reprogramming, later, however, Oct4 appears to prevent destabilized cells from becoming brain stem cells" reports the Bonn stem cell researcher. While this factor is switched on during reprogramming of iPS cells over a longer period of time, the Bonn researchers activate the factor with special techniques for only a few days. "If this molecular switch is toggled over a limited period of time, the brain stem cells, which we refer to as induced neural stem cells (iNS cells), can be reached directly," said Edenhofer. "Oct4 activates the process, destabilizes the cells and clears them for the direct reprogramming. However, we still need to analyze the exact mechanism of the cellular conversion."

The scientists at the University of Bonn have thus found a new way to reprogram cells, which is considerably faster and also safer in comparison to the iPS cells and embryonic stem cells. "Since we cut down on the reprogramming of the cells via the embryonic stage, our method is about two to three times faster than the method used to produce iPS cells," stresses Edenhofer. Thus the work involved and the costs are also much lower. In addition, the novel Bonn method is associated with a dramatically lower risk of tumors. As compared to other approaches, the Bonn scientists' method stands out due to the production of neural cells that can be multiplied to a nearly unlimited degree.

Low risk of tumor and unlimited self renewal

A low risk of tumor formation is important because in the distant future, neural cells will replace defective cells of the nervous system. A vision of the various international scientific teams is to eventually create adult stem cells for example from skin or hair root cells, differentiate these further for therapeutic purposes, and then implant them in damaged areas. "But that is still a long way off," says Edenhofer. However, the scientists have a rather urgent need today for a simple way to obtain brain stem cells from the patient to use them to study various neurodegenerative diseases and test drugs in a Petri dish. "Our work could form the basis for providing practically unlimited quantities of the patient's own cells." The current study was initially conducted on mice. "We are now extremely eager to see whether these results can also be applied to humans," says the Bonn scientist.

More information: Direct conversion of fibroblasts into stably expandable neural stem cells, *Cell Stem Cell*, DOI: 10.1016/j.stem.2012.03.003 In the printed edition at April 6th 2012.

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