Imperial Prize and Japan Academy Prize to:

Shinya YAMANAKA
Director, Center for iPS cell Research and Application, Kyoto University

for “The Generation of Induced Pluripotent Stem (iPS) Cells”

Outline of the work:

Professor Shinya Yamanaka succeeded in directly reprogramming somatic cells into pluripotent stem cells, which is considered a major scientific breakthrough. In 2006, he and his laboratory announced that they had generated embryonic-like stem cells by introducing four genes—Oct 3/4, Sox2, Klf4 and c-Myc—into mouse fibroblasts by retroviral vectors and culturing the cells for a few weeks. The resultant cells have the ability to differentiate into any type of functional cell and to grow vigorously—the typical morphology of embryonic stem (ES) cells. They also demonstrated similar gene expressions to those of ES cells. Prof. Yamanaka named these cells “induced pluripotent stem (iPS) cells.” The following year, his research group reported the generation of human iPS cells, using the same gene quartet as in the mouse.

Prof. Yamanaka and his team have further developed methods to generate safe iPS cells. Tumor formation was observed in chimeric mice made by using iPS cells and their progenies caused by the reactivated c-Myc gene delivered from retroviral vectors used in iPS cell generation. This posed a safety problem for using iPS cells in regenerative medicine. c-Myc is a known oncogene, so it carries a risk of causing cancer if its retrovirus were to be reactivated in vivo. To solve this problem, the Yamanaka lab re-modified the iPS-cell-generation protocol and successfully established mouse and human iPS cells by using only three of the four gene set excluding c-Myc.

Creating methods of deriving iPS cells without impairing the integrity of the genome will be vital for avoiding potential tumorigenicity. Retroviral integration alone may activate or inactivate other genes in the recipient genome, causing an unacceptable risk for use in human patients. In addressing this problem, Prof. Yamanaka’s team reported in October 2008 that they had developed a virus-free protocol for the generation of iPS cells. Using a pair of plasmid vectors, instead of retrovirus vectors, the group induced pluripotency in mouse fibroblast cells by introducing the four genes.

The next step he took was to increase the efficiency with which iPS cells can be generated. The success rate of generating iPS cells by the original protocol using the four transcription factors was less than one percent. Prof. Yamanaka’s lab showed that the loss of function of the transcription factor p53, known for its tumor suppressing activity, results in a dramatic jump in the success rate of reprogramming both mouse and human somatic cells. In addition, his group found that the efficiency of mouse and human iPS cell generation can be improved several times by culturing cells under low-oxygen conditions.

In a joint research project, Prof. Yamanaka’s team and Professor Hideyuki Okano’s group at Keio University found that the somatic cell origin may play a significant role in securing the safety of both mouse iPS cells and mouse iPS-derived functional cells, which they reported in July 2009. The two groups generated iPS cells from mouse iPS cell clones characterized by their origin cell type (embryonic and tail tip fibroblasts, liver and stomach cells) and differentiated them into neurospheres, which were transplanted into the brains of immunodeficient mice. As a result,
neurospheres made from embryonic fibroblast-derived iPSCs and stomach-derived iPSCs showed similarly low mortality and tumorigenicity. The study also showed that the absence or presence of retrovirally delivered c-Myc had no appreciable effect on the rate of tumor formation. These findings show the need for vigorous evaluation using human cells prior to any therapeutic application.

It was known that differentiated cells can be reprogrammed as some scientists had proven it experimentally using frogs or sheep. Prof. Yamanaka’s discovery—reprogramming somatic cells by using only four to three genes—shocked the stem-cell research community worldwide because his iPSC cell technique makes it possible to induce pluripotency in a comparatively simple and highly reproducible manner. Furthermore, as iPSC cells do not require the destruction of early stage embryos, needed in isolating ES cells, their use precludes ethical issues surrounding human ES cells. iPSC cells also circumvent risks of immune rejection when ES-derived functional cells are transplanted into a body. Therefore, the technology is expected to be used for understanding the mechanisms of various intractable diseases, drug screening and toxicology, and may be applied to cell transplant therapy in the future. Further studies on the mechanisms of reprogramming cells will also contribute to the advancement of basic science in cell biology.

References


