Molecular Basis during iPS Cell Generation and Its Application

Shinya Yamanaka

2010 Balzan Prize for Stem Cells: Biology and Potential Applications

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Period: 2011-2017

Shinya Yamanaka is Director of the Center for iPS Cell Research and Application (CiRA) at Kyoto University, Senior Investigator at the Gladstone Institute of Cardiovascular Disease in San Francisco, and Professor of Anatomy at the University of California, San Francisco. Yamanaka planned a five- to six-year research project on molecular mechanisms and application of induced pluripotent stem (iPS) cells at the Center for iPS Cell Research and Application (CiRA) at Kyoto University. CiRA hired one young faculty member, Dr. Saito, to promote the research to control cell fate using synthetic RNA-based gene manipulation technologies. His laboratory developed unique synthetic RNA molecules in order to detect and purify target cells derived from iPS cells and control the fate of target cells depending on intracellular environment. He was responsible for the research project aimed at developing new methods to control mammalian cell fate with high safety and purity using artificial RNA switches and circuits. These RNA systems detect specific protein and/or RNA expressed in target cells and then control gene expression.

Advances made in 2015 included the successful development of synthetic "microRNA switches", pointing to next-generation technology for control of gene expression and stem cell engineering. In their latest work, the Saito group developed a method that makes it possible to detect and purify target live cell populations derived from human iPS cells. In addition, the Saito group succeeded in constructing synthetic gene circuits that selectively control the cell fate by RNA-only delivery. Because these circuits are entirely RNA-based, they would be safer

to use in cells than their DNA-based counterparts and therefore available for a number of biomedical applications. Recently, the Saito group demonstrated their miRNA switch technology that can be used to regulate the CRISPR-Cas9 system that engineers the genome of target cells. The new biotechnology tool is called the "miR-Cas9 switch", in which the genome editing activity of Cas9 can be modulated through endogenous miRNA signatures in mammalian cells. They succeeded in distinguishing human iPS cells and differentiated cells for genome editing, which may be used for future in vivo genome editing.

In early 2013, Shinya Yamanaka decided to use the second part of his prize to spread iPS cell research over institutes other than CiRA, with Dr. Aoi at Kobe University to study recapitulation of several intractable diseases, including cancer, by iPS cell technology. In 2013, a new laboratory for the Aoi Group was built at the Kobe University graduate school of medicine. The basic arrangement of the study environment and the measures for regulations with which the iPS cell establishment or induction to various cell differentiation can be conducted have already reached completion. Until 2016, various projects for hepatology, gastroenterology, neurology, urology, dermatology, diabetology, endocrinology, haematology and oncology, in collaboration with more than ten clinical departments have been launched to cure intractable diseases.

Aoi's group also focuses on cancer stem cells, which have been suggested to be the potential for self-renewal and tumorigenesis in certain cancers. Inspired by iPS cell technology, Aoi's group successfully established a novel technology to induce cancer stem cell (CSC) properties in intestinal cancer cells by introducing defined factors and collecting the cells with CSC properties, which leads to a further understanding of cancer disease mechanisms and medical applications. Currently, in addition to working on generation and analyses of induced cancer stem cells from various types of human cancer cells such as lung cancer cells, they are also constructing various carcinogenesis models using several types of human iPS cell-derived cells.

Publications

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