Recent Progress in iPS Cell Research towards Regenerative Medicine

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Nobel Prize in Physiology or Medicine 2012
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Induced pluripotent stem cells (iPSCs) were originally generated from mouse and human fibroblasts by retroviral transduction of 4 genes: Oct3/4, Sox2, c-Myc, and Klf4. iPSCs are similar to embryonic stem cells (ESCs) not only in morphology and proliferation, but also gene expression, and pluripotency. However, unlike ESCs, iPSCs can be generated without destroying fertilized eggs. In addition to fibroblasts, iPSCs can be made using various somatic cells, such as hepatic cells, gastric epithelial cells, neural cells, dental pulp cells, peripheral blood cells, and cord blood cells. Furthermore, somatic cell donation may come from various genetically identified individuals, providing better opportunities for personalized applications in regenerative medicine. As a result, cell therapies, disease mechanisms, and new drug developments are being studied with iPSCs worldwide.

However, in the course of these studies, reactivation of integrated genes in iPSCs, tumor formation attributed to differentiation-resistant clones, and considerable variations in differentiation ability between iPSC clones have all been reported. These observations stress the importance of determining the best induction protocol and the best evaluation method for iPSC clones intended for future clinical applications. To address these issues, we aim to standardize iPSC technology; providing guidelines for cell sources and inducing factors, along with reliable methods for quality control.

Regarding the safety of iPSC derivation, we have reported an integration-free method using episomal vectors. In extended studies of iPSC-inducing factors, we discovered that p53 shRNA, CyclinD1, LIN28, L-Myc, and in particular, Glis1, which is strongly expressed in the unfertilized egg, may each substitute for the oncogene c-Myc. An optimized combination of factors and delivery methods will establish iPSCs with efficiencies and qualities suitable for clinical applications.

To determine quality, it is essential to establish strict evaluation methods that distinguish good iPSCs for transplantation. In iPSC differentiation to neural progenitor cells, we have found that some iPSCs are resistant to differentiation, eventually resulting in tumors. We have performed a series of comparative analyses of global gene expression, DNA methylation, and exon sequencing amongst 49 human iPSC and 10 human ESC lines, and related these results to differentiation potential. While there is no clear molecular signature to distinguish between ESCs and iPSCs, we have identified gene expression profiles that can be used as molecular markers to expose and avoid differentiation-resistant lines.

Now, we are integrating this knowledge with the goal of preparing iPSCs in accordance with Good Manufacturing Practice (GMP) in our cell-processing center at the Center for iPS Cell Research and Application (CiRA) at Kyoto University. Furthermore, setting a standard of clinical grade iPSCs will enable us to compile an iPSC stock from volunteers bearing specific human leukocyte antigens (HLA), and build a foundation to realize the promise of regenerative medicine.

Date
2 April 2013 (Tue)

Time
11.30am - 12.30pm

Venue
Auditorium, Matrix L2
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