Mini-Lecture 13

Recent Progress in iPS Cell Research - 자가 만능줄기세포의 도래

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Background: Recent discoveries in the reprogramming of somatic cells into pluripotent stem cells (induced pluripotent stem cell, iPS cell), by viral transduction of certain transcription factors, has opened a new-era of regenerative medicine. Transduction of defined factors has successfully achieved pluripotency. However, during the generation process of iPS cells, genetic manipulation and integration of certain factors may cause tumorigenicity, which limits further application. Accordingly, there is ongoing an extensive search for new technologies for reprogramming.

Methods and Results: We report that the delivery of ESC (embryonic stem cell)-derived proteins enables the reprogramming of adult somatic cells, converting them into pluripotent stem cells without the forced expression of ectopic transgenes. In a series of experiments, we used adult fibroblasts from both permissive strain (C57) and resistant or non-permissive strain (FVB) for ESC derivation. During the reprogramming process, gene expression profiles of protein-iPS cells assessed by RT-PCR and microarray were convertted from somatic to ESC-equivalent status. Epigenetic status of protein-iPS cells measured by bisulfite genomic sequencing and genomewide ChiP sequencing was also very similar to that of ESCs. We verified that protein-based reprogramming is neither by the contamination of protein donor ESC nor by DNAs/RNAs from donor ESC. Under embryoid body-based spontaneous differentiation protocol, protein-iPS cells expressed ectoderm (glial fibrillary acidic protein), mesoderm (α-smooth muscle actin and troponin T) and endoderm (α-fetoprotein) lineage markers. When cells were injected into NOD/SCID mice, well-differentiated teratomas were developed. Furthermore, protein-iPS cells were injected into blastocysts, we observed chimeric mice. Up until 40 weeks old, no tumor was grossly observed in chimeric mice, indicating that protein-based strategy can offer a safe and effective way for reprogramming. Finally, we performed a tetraploid blastocyst complementation experiment, which is considered the most stringent functional assay of pluripotency. We confirmed fetal animals have been derived from protein-iPS cells.

Conclusions and Significance: We demonstrate that a single transfer of ESC-derived proteins into primarily cultured adult somatic cells, rather than repeated transfer or prolonged exposure to materials, can achieve full reprogramming up to the pluripotent state. These results provide a safe and effective alternative strategy for reprogramming of adult somatic cells, and suggest that the described technique could be further developed to provide tailored- or patient-specific cell therapy.