10-YEAR ANNIVERSARY

Achieving pluripotency

Nuclear reprogramming — whereby the nucleus from a differentiated somatic cell is reprogrammed to a pluripotent embryonic-like state — was initially achieved by two methods: the fusion of somatic cells with embryonic stem (ES) cells, and nuclear transfer, in which the nucleus of a differentiated cell is injected into an enucleated, undifferentiated cell such as an oocyte. Both these methods require the availability of embryonic cells to generate pluripotent stem cells, which remains an ethical issue in addition to being technically challenging.

In 2006, Takahashi and Yamanaka revolutionized the stem cell field by showing that it is possible to convert adult somatic cells directly into pluripotent embryonic-like cells by expressing a limited number of transcription factors and culturing the transformed cells under ES cell-like conditions.

They selected 24 genes as candidate factors to induce pluripotency, based on their known role in the maintenance of ES cell identity, and introduced them into mouse fibroblasts harbouring a selective marker that is expressed only in ES cells. Although none of these factors alone could induce the expression of the marker, the 24 genes together did, generating some cells with the growth characteristics and morphology of ES cells, which they called induced pluripotent stem (iPS) cells. Next, they narrowed the set of factors necessary and sufficient to obtain iPS cells down to four: OCT3 (also known as POU5F1 or OCT4), Sry box-containing factor 2 (SOX2), Krüppel-like factor 4 (KLF4) and MYC. Cells expressing these four factors were able to induce the formation of teratomas with all three germ layers *in vivo* and embryoid bodies *in vitro*, showing the successful reprogramming of differentiated cells into pluripotent cells.

The following year, two other studies from the Yamanaka and Thompson groups showed that transcription factor-mediated reprogramming to a pluripotent state using just four factors can also be achieved in human cells.

iPS cells opened up an entirely new field of stem cell research and the potential for patient-specific therapies. Although the generation of iPS cells has low efficiency and the developmental potential of human iPS cells remains to be fully explored, they are already a key tool for the study of the molecular mechanisms underlying pluripotency.

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ORIGINAL RESEARCH PAPERS Takahashi, K. & Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**, 663–676 (2006) | Takahashi, K. *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* **131**, 861–872 (2007) | Yu, J. *et al.* Induced pluripotent stem cell lines derived from human somatic cells. *Science* **381**, 1917–1920 (2007)
FURTHER READING Nishikawa, S., Goldstein, R. A. & Nierras, C. R. The promise of human induced pluripotent stem cells for research and therapy. *Nature Rev. Mol. Cell Biol.* **9**, 725–729 (2008)

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