

## Differentiation and Integrity of Pluripotent Stem Cells

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### Editorial

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### Editorial note

Adult stem cells have limitations with their potency; contrary Embryonic Stem Cells (ESCs), they are not able to differentiate into cells from all three germ layers. As such, they are deemed multipotent.

However, reprogramming allows for the creation of pluripotent cells, induced Pluripotent Stem Cells (iPSCs), from adult cells. These are not adult stem cells, but somatic cells (e.g. epithelial cells) reprogrammed to give rise to cells with pluripotent capabilities. Using genetic reprogramming with protein transcription factors, pluripotent stem cells with ESC-like capabilities have been derived. The first demonstration of induced pluripotent stem cells was conducted by Shinya Yamanaka and his colleagues at Kyoto University [1]. They used the transcription factors Oct3/4, Sox2, c-Myc, and Klf4 to reprogram mouse fibroblast cells into pluripotent cells. Subsequent work used these factors to induce pluripotency in human fibroblast cells. Junying Yu, James Thomson, and their colleagues at the University of Wisconsin–Madison used a different set of factors, Oct4, Sox2, Nanog and Lin28, and carried out their experiments using cells from human foreskin. However, they were able to replicate Yamanaka's finding that inducing pluripotency in human cells was possible [2].

Induced pluripotent stem cells differ from embryonic stem cells. They share many similar properties, such as pluripotency and differentiation potential, the expression of pluripotency genes, epigenetic patterns, embryoid body and teratoma formation, and viable chimera formation, but there are many differences within these properties. The chromatin of iPSCs appears to be more "closed" or methylated than that of ESCs. Similarly, the gene expression pattern between ESCs and iPSCs, or even iPSCs sourced from different origins. There are thus questions about the "completeness" of reprogramming and the somatic memory of induced Pluripotent Stem Cells. Despite this, inducing somatic cells to be pluripotent appears to be viable [3].

As a result of the success of these experiments, Ian Wilmut, who helped create the first cloned animal Dolly the Sheep, has announced that he will abandon somatic cell nuclear transfer as an avenue of research.

iPSCs have helped the field of medicine significantly by finding numerous ways to cure diseases. Since human iPSCs has given the advantage to make vitro models to study toxins and pathogenesis.

Furthermore, induced pluripotent stem cells provide several therapeutic advantages. Like ESCs, they are pluripotent. They thus have great differentiation potential; theoretically, they could produce any cell within the human body (if reprogramming to pluripotency was "complete"). Moreover, unlike ESCs, they potentially could allow doctors to create a pluripotent stem cell line for each individual patient. Frozen blood samples can be used as a valuable source of induced pluripotent stem cells [4]. Patient specific stem cells allow for the screening for side effects before drug treatment, as well as the reduced risk of transplantation rejection. Despite their current limited use therapeutically, iPSCs hold create potential for future use in medical treatment and research.

Epigenetic factors are also thought to be involved in the actual reprogramming of somatic cells in order to induce pluripotency. It has been theorized that certain epigenetic factors might actually work to clear the original somatic epigenetic marks in order to acquire the new epigenetic marks that are part of achieving a pluripotent state. Chromatin is also reorganized in iPSCs and becomes like that found in ESCs in that it is less condensed and therefore more accessible. Euchromatin modifications are also common which is also consistent with the state of euchromatin found in ESCs.

Due to their great similarity to ESCs, iPSCs have been of great interest to the medical and research community. iPSCs could potentially have the same therapeutic implications and applications as ESCs but without the controversial use of embryos in the process, a topic of great bioethical debate. In fact, the induced pluripotency of somatic cells into undifferentiated iPS cells was originally hailed as the end of the controversial use of embryonic stem cells. However, iPSCs were found to be potentially tumorigenic, and, despite advances, were never approved for clinical stage research in the United States. Setbacks such as low replication rates and early senescence have also been encountered when making iPSCs, hindering their use as ESCs replacements [5].

Additionally, it has been determined that the somatic expression of combined transcription factors can directly induce other defined somatic cell fates (transdifferentiation); researchers identified three neural-lineage-specific transcription factors that could directly convert mouse fibroblasts (skin cells) into fully functional neurons. This result challenges the terminal nature of cellular differentiation and the integrity of lineage commitment; and implies that with the proper tools, all cells are totipotent and may form all kinds of tissue.

Some of the possible medical and therapeutic uses for iPSCs derived from patients include their use in cell and tissue transplants without the risk of rejection that is commonly encountered. iPSCs can potentially replace animal models unsuitable as well as in vitro models used for disease research.

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