Holding on to the memories

The reprogramming of differentiated somatic cells to a pluripotent embryonic stem (ES) cell-like state can be achieved by somatic cell nuclear transfer or by expressing a combination of four transcription factors — octamer-binding protein 4 (OCT4; also known as POU5F1), SRY box-containing factor 2, Krüppel-like factor 4 and MYC. Two studies now show that nuclear transfer ES (ntES) cells and transcription factor-induced pluripotent stem (iPS) cells show differences in differentiation potential, and that this might be due to iPS cells retaining DNA methylation and gene expression patterns of their tissue of origin.

Kim *et al.* tested the capacity of ntES cells, iPS cells derived from blood (B-iPSCs) and fibroblasts (F-iPSCs), and ES cells derived from fertilized embryos (fES cells) to differentiate into haematopoietic and osteogenic cells (a mesenchymal lineage that can be derived from fibroblasts). All stem cell lines expressed pluripotency markers such as OCT4

and Nanog, but showed differences in differentiation potential. Specifically, ntES cells derived from the nuclei of dermal fibroblasts and fES cells differentiated with similar efficiency to haematopoietic or osteogenic cells, whereas B-iPSCs produced primarily haematopoietic cells and F-iPSCs were more efficient in producing osteogenic cells. Similarly, Polo *et al.* found that genetically identical iPS cell lines generated from four different somatic cell lines had different and biased differentiation potentials, which reflect their cells of origin.

But what is the molecular basis of these variable differentiation capacities? As reprogramming involves the resetting of genome methylation, Kim *et al.* analysed the DNA methylation pattern of the different stem cell lines. They found that ntES cells and fES cells have the most similar methylation patterns, whereas F-iPSCs and B-iPSCs retain residual methylation marks specific to their tissue of origin. Similarly, Polo *et al.*

compared the transcriptional profiles of the four genetically identical iPS cell lines derived from different somatic cell types and found that they are distinguishable, but also express cell-specific markers related to their cell of origin. Importantly, these differences correlate with different levels of histone methylation, which may account for gene expression differences between iPS cells derived from different tissues.

Interestingly, the groups find that by either generating successive cultures of iPS cells or generating secondary and tertiary iPS cells by successive differentiation and reprogramming steps, iPS cells gradually lose their DNA methylation marks and specific expression patterns and equalize their differentiation potentials.

Together, these studies show that iPS cells retain an epigenetic memory relating to their cell of origin that restricts their differentiation potential, and that these epigenetic marks can be modulated. The mechanisms that control the maintenance or erasing of epigenetic memory in pluripotent stem cells remain to be determined.

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“ iPS cells retain an epigenetic memory ... that restricts their differentiation potential ”

ORIGINAL RESEARCH PAPERS Kim, K. *et al.* Epigenetic memory in induced pluripotent stem cells. *Nature* 19 Jul 2010 (doi:10.1038/nature09342) | Polo, J. M. *et al.* Cell type of origin influences the molecular and functional properties of mouse induced pluripotent stem cells. *Nature Biotech.* 28, 848–855 (2010)
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