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REPROGRAMMING

Your contacts reveal your past

Reprogramming differentiated cells into induced pluripotent stem cells (iPSCs) holds promise for generating patient-specific cells for regenerative medicine. However, transcriptomics and DNA-methylation analyses have revealed that iPSCs typically retain a subtle molecular 'memory' of their cell-type of origin, which then favours subsequent differentiation towards the original cell-type lineages. A new study shows that iPSCs also harbour chromosomal structural signatures of their cellular origin.

Krijger *et al.* used cells from the OSKM-inducible mouse model, in which the pluripotency factors OCT4, SOX2, KLF4 and MYC are expressed following doxycycline treatment. They induced pluripotency starting with four distinct mouse cell types — pre-B cells, bone-marrow-derived macrophages, neural stem cells and mouse embryonic fibroblasts — to generate parallel lines of early-passage (p3) iPSCs and then later-passage (p20) iPSCs after further *in vitro* culture. To characterize the conformational topology of chromosomes in these source cells and derived iPSCs, the investigators applied the chromosome conformation capture method Hi-C, which uses next-generation sequencing to report, on a genome-wide scale, physical contacts between chromosomal regions.

Analysis of the genome-wide contact maps revealed that reprogramming caused major, widespread alterations to chromosome structure. The founder cell types were highly distinct from each other in cluster analyses, whereas the iPSCs were highly similar regardless of their cell of origin or passage number, and they displayed a pluripotency-associated contact signature that was also shared by embryonic stem cells. Finer-scale analyses provided further support: reprogramming caused a convergence in the structure of local topologically-associated domains (TADs) and near-complete dissolution of cell-type-specific chromosomal loops while increasing looping and contacts between pluripotency-associated genes.

Despite the global convergence of chromosome structure towards a common pluripotency-associated conformation, the investigators found that iPSCs displayed subtle chromosome structure signatures in early-passage iPSCs that allowed their cell-type-of-origin to be determined. These distinguishing signatures involved intra-TAD connectivities and DNA-binding positions of the TAD-organizing protein CTCF. Intriguingly, although these signatures allowed the cell of origin to be determined, they were absent in the original source cell types. Thus, the authors propose that these chromatin structure signatures arise *de novo* during reprogramming, in contrast to the 'memory' nature of DNA methylation and transcriptomic signatures that are a retained remnant of their cellular history.

It will be interesting to dissect whether the cell-of-origin structural signatures have functional consequences, such as if they influence the differentiation potential of iPSCs.

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ORIGINAL ARTICLE Krijger, P. H. L. *et al.* Cell-of-origin-specific 3D genome structure acquired during somatic cell reprogramming. *Cell Stem Cell* http://dx.doi.org/10.1016/j.stem.2016.01.007 (2016)

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