

 STEM CELLS

Out for the count

As more methods are published on how to generate induced pluripotent stem (iPS) cells from differentiated, mature cells, so increases the need to carefully analyse the DNA content of these cells. A recent paper published in *Cell Stem Cell* indicates that chromosomal aberrations in human iPS cells are more common than previously thought.

Yoav Mayshar, Uri Ben-David and colleagues carried out a meta-analysis of global gene expression data in 66 human iPS cells and 38 human embryonic stem cells (HESCs) that were generated in 18 different studies. The rationale for using global gene expression analysis is the increasing evidence that genes that reside together on a chromosome show increased or decreased expression when a genomic alteration has occurred. To look for aneuploidy, gene expression levels in the HESCs and iPS cell data were compared with the median gene expression levels of a reference data set from a panel of pluripotent stem cells, and those that were expressed 1.5-fold or higher were subject to location enrichment analyses using two previously published software programs (Expander and EASE); and comparative genomic hybridization analysis was carried out using standard software (CGH-Explorer) to determine the spatial expression of the genes in the data sets.

The authors initially tested this approach on two human HESCs known to harbour trisomies in either

chromosome 17 or chromosome 21 and then assessed all 38 HESCs. They found chromosome aberrations in 12 of these lines, eight of which involved changes in whole chromosomes, and three of these were verified by karyotype analyses. Of the iPS cell data set, two iPS cells were known to have trisomy of both chromosome 1 and chromosome 9 and these were correctly identified. Another set of cells in the data set were known to have a small genetic deletion in chromosome 15, which CGH-Explorer also clearly detected. However, other events detected at low confidence using standard array CGH were not verified, leading the authors to suggest that their approach might not detect changes occurring in only a minority of cells in a population. Overall, the authors identified 19 aberrations in the iPS cells, nine of which were further confirmed by cytogenetic or DNA-based analyses, and the false-positive rates of these approaches were very low.

Interestingly, this meta-analysis confirmed that chromosomal changes can increase in culture over time. Indeed, in human iPS cells, trisomy of chromosome 12 is most frequently selected for, and both *NANOG* and *GDF3*, which are involved in maintaining pluripotency, reside on chromosome 12p and are overexpressed as a consequence. In addition, the expression of several genes that are involved in cell cycle regulation was evident in human iPS cells with genomic aberrations.



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These findings suggest that iPS cells need to be carefully monitored in culture for genomic changes if their biological properties are to be correctly interpreted. The genomic instability evident in some of these lines also needs to be understood to ensure that they can differentiate into their required tissue type efficiently and without tumorigenic consequences.

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ORIGINAL RESEARCH PAPER Mayshar, Y. et al. Identification and classification of chromosomal aberrations in human induced pluripotent stem cells. *Cell Stem Cell* 7, 521–531 (2010)

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