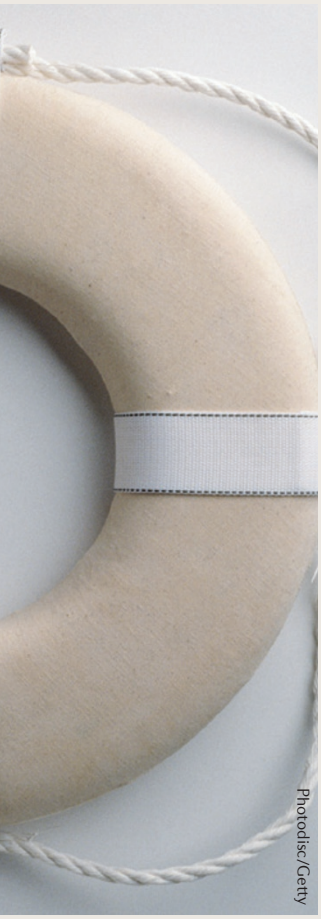
Nature Reviews Genetics | AOP, published online 4 February 2014; doi:10.1038/nrg3680

GENOME STABILITY

Chromosome correction through reprogramming



Photodisc/Getty

Pluripotent cells, such as embryonic stem cells and induced pluripotent stem cells (iPSCs), are known to display chromosomal instability relative to differentiated cells, which leads to frequent gains or losses of whole chromosomes. A new study now identifies a potentially valuable and therapeutically relevant consequence of this instability: for cells that contain a disease-associated chromosomal abnormality known as a ring chromosome, reprogramming to pluripotency can restore a normal chromosomal karyotype.

Ring chromosomes result from the intrachromosomal fusion of two ends of a chromosome, which typically results in the deletion of a multigenic locus from one of the former chromosome ends. Although rare, ring forms of various chromosomes are causes of a range of severe genetic diseases.

Patient-derived iPSCs are increasingly used as tractable model systems for disease studies, so Bershteyn *et al.* reprogrammed fibroblasts from a patient with Miller–Dieker syndrome (MDS) that was caused by a ring form of chromosome 17, denoted r(17). Crucially, the authors noticed that most of the iPSC clones (four of six) showed a numerically and structurally normal karyotype and proliferated efficiently, whereas the remaining clones retained r(17) and stopped growing. Interestingly, the normal karyotype did not result merely from linearization of the ring chromosome, as the previously deleted region of r(17) was restored. The repair mechanism seems to be specific to ring chromosomes, as reprogramming fibroblasts from other patients with MDS that was caused by similar deletions of chromosome 17 in non-ring form did not lead to a normal copy number of this region.

Further investigations provided insights into the mechanism of the ring chromosome correction. Cytogenetic analyses in populations of iPSCs showed cell-to-cell variability in chromosome content, including complete loss of r(17) to leave only the normal homologue. Additionally, in the karyotypically corrected cells, single-nucleotide polymorphism (SNP) microarrays revealed that the two copies of chromosome 17 were entirely homozygous. Overall, this indicates that the ring chromosome had been lost and had been replaced by an additional copy of its normal homologue to result in uniparental disomy (UPD). This correction seems to be driven by the proliferative advantage of karyotypically normal iPSCs relative to r(17) iPSCs; the proliferative defect caused by r(17) was greater in iPSCs than in fibroblasts, which suggests that iPSCs could be a particularly efficient system for purging ring chromosomes.

Finally, ring forms of chromosome 13 from other patient-derived fibroblasts were also corrected on reprogramming to iPSCs, which indicates that this mechanism might apply broadly to various ring chromosomes.

Such results imply that reprogramming to iPSCs can provide a mechanism for repairing a large-scale chromosomal defect that both corrects the loss-of-function of multiple genes and restores a normal karyotype. However, potential therapeutic applications will need to be carefully considered. UPD is itself linked to disease through the unmasking of recessive disease-associated alleles and through inappropriate biallelic expression or silencing of imprinted genes, and it is therefore not a perfect genetic correction. Furthermore, it is not yet known whether karyotypically corrected iPSCs that are derived from patients with ring chromosomes will have therapeutic potential in these patients, but this is an exciting avenue for further investigation.

Darren J. Burgess

ORIGINAL RESEARCH PAPER Bershteyn, M. *et al.* Cell-autonomous correction of ring chromosomes in human induced pluripotent stem cells. *Nature* http://dx.doi.org/10.1038/nature12923 (2014)