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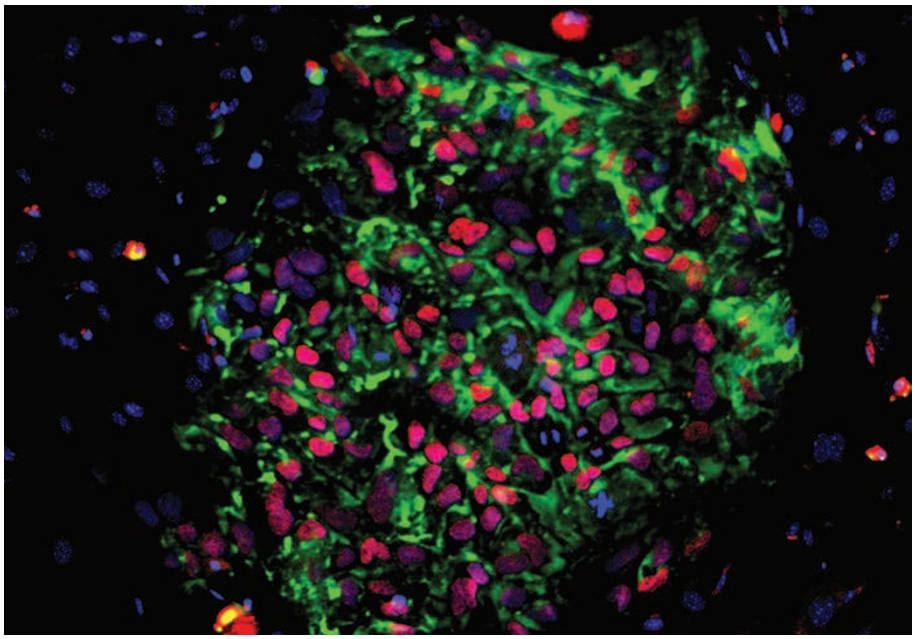

**Induced pluripotent stem cells retain 'memories' of the adult cells from which they are derived.**

MEDICINE

# Flaw in induced-stem-cell model

*Adult cells do not fully convert to embryonic-like state.*

**BY ELIE DOLGIN**

Medical researchers' hopes of replacing politically fraught embryonic stem (ES) cells with stem cells derived from adult tissues have suffered a setback. Induced pluripotent stem (iPS) cells, created by turning back the developmental clock on adult tissues, and ES cells display similar gene-expression patterns, and both can produce any of the various tissues in the human body. But patterns of epigenetic changes — alterations that affect gene expression without changing the DNA sequence — tell a different story about iPS cells, a team led by Joseph Ecker, a molecular geneticist at the Salk Institute in La Jolla, California, reports online in *Nature* this week[1].

"They are slightly different creatures," says Chad Cowan, a stem-cell biologist at Massachusetts General Hospital in Boston who was not involved in the work. The finding suggests that iPS cells may not be suitable substitutes for ES cells in modelling or treating disease.

Ecker and his colleagues analysed patterns of DNA methylation, a type of epigenetic change, across the genomes of 15 cell lines. These included four human ES cell lines, five iPS cell lines and the tissues from which they came, as well as differentiated cells made from both kinds of stem cells. "If you look with blinders on, they look fairly similar," says Ecker. "But if you zoom in you find different signatures of what an iPS cell is."

The researchers found that rather than being reset to an embryo-like state, methylation patterns near the tips and centres of chromosomes in the iPS cells resembled those in the adult tissues from which the iPS cells had been derived. This could constrain the types of tissues that the cells are capable of forming. "The reprogramming process, although fascinating, is a fundamentally different way of getting to pluripotency than deriving cells from [embryos]," says George Daley, a stem-cell expert at Children's Hospital Boston in Massachusetts. "We're still looking for reprogramming methods that return cells to the ES-cell-like state," he adds.

The finding that reprogrammed stem cells carry an epigenetic 'memory' dovetails with work published last year by Daley and others comparing mouse iPS and ES cells[2,3]. In mice, however, the methylation differences could be reset, either by continuing to culture the iPS cells or by differentiating the cells again to more specialized cell types. In the human cells, the epigenetic marks lingered even after the iPS cells had been coaxed to form new tissues.

Regardless of their epigenetic differences, neither iPS cells nor ES cells may turn out to be perfect models of tissues in the body. Both cell types seem to harbour genomic abnormalities. In separate work published last month[4], a team led by Jeanne Loring, a stem-cell researcher at the Scripps Research Institute in La Jolla, found that ES cells tended to contain duplicated chunks of DNA linked to genes associated with self-renewal, whereas iPS cells incorporated extra cancer-causing genes and fewer tumour-suppressor genes. These genomic differences between the two types of stem cells probably result from the culturing techniques used to derive and maintain them.

"When we culture cells outside a normal organism they can acquire features that may not be compatible with life once they go back into an organism," says Richard Young, a stem-cell biologist at the Whitehead Institute in Cambridge, Massachusetts.

The impact of such discrepancies remain unclear, says William Lowry, a stem-cell biologist at the University of California, Los Angeles. "The problem is that we don't know if any of these differences are going to be consequential." ■

1. Lister, R. *et al. Nature* doi:10.1038/nature09798 (2011).
2. Kim, K. *et al. Nature* **467,** 285–290 (2010).
3. Polo, J. M. *et al. Nature Biotechnol.* **28,** 848–855 (2010).
4. Laurent, L. C. *et al. Cell Stem Cell* **8,** 106–118 (2011).