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50 & 100 YEARS AGO

50 YEARS AGO

A significant milestone on the road to space flight was passed on August 20, when, for the first time, living animals were successfully brought back to earth after being in orbit in space, aboard the second Russian space-ship satellite [*Sputnik 5*]... The living creatures in the satellite included two dogs, 40 mice (21 black and 19 white) and 2 rats ... It is stated that the pulse and rate of respiration of the dogs were measured and their behaviour observed by television, the information being stored and telemetered back to earth. On the eighteenth revolution of the satellite its velocity was reduced by a retro-rocket and it descended through the atmosphere; all the animals and biological specimens are reported as being recovered in good condition.

From *Nature* 3 September 1960.

100 YEARS AGO

The argument lately arrived at by the representatives of Great Britain and the Congo has affected the settlement of a troublesome boundary dispute ... The original agreement ... was signed at Brussels on May 9, 1894. By this it was enacted:— "That the sphere of influence of the Independent Congo State shall be limited to the north of the German sphere in East Africa by a frontier following the thirtieth meridian ..." At the time this agreement was made the 30th meridian was shown on the maps as dividing Lake Edward into two approximately equal parts ... The actual event proved that the selection of this line had resulted in the maximum of inconvenience and loss. The true position of the meridian was found to be about half a degree east of its position as assumed in 1894, and a strict interpretation of the letter of the treaty would have involved our retirement from Lake Edward and from practically the whole of the Ruwenzori district. Such a contingency was obviously intolerable.

From *Nature* 1 September 1910.

other differentiated cell types, into broadly potent stem cells that resemble embryonic stem (ES) cells[10]. This achievement sets the stage for *in vitro* production of patient-specific and disease-specific cells for therapies and analyses of disease mechanisms.

Although many of the transcription factors that guide heart development have been identified, no single factor seems to be a cardiac master regulator. But a recent study[11] found that two transcription factors, Gata4 and Tbx5, in combination with Baf60c — a component of a protein complex that modifies DNA–protein fibres called chromatin — could induce differentiation of non-cardiac mesoderm from the embryo into beating cardiomyocytes. Such factors probably perform dual functions: the opening and rearrangement of chromatin, as has been shown for Gata4, and the induction of a self-maintaining program of gene expression that defines the differentiated state.

Ieda *et al.*[1] tested different combinations of 14 genes that encode transcription factors with known roles in heart development for their ability to convert neonatal mouse fibroblasts in culture into cardiomyocytes. With introduction into fibroblasts of as few as three factors (Gata4, Tbx5 and Mef2c) — which include the two already known to be effective for reprogramming embryonic cells[11] — some 25% of these cells expressed the cardiac-specific marker MHC and another marker of cardiomyocyte maturity, cTnT. However, these factors are involved in regulating a host of cardiac genes. It is therefore of paramount importance to determine whether the apparent cardiomyocyte traits that the authors observe reflect enforced expression of some cardiac genes or a truly self-maintaining cardiac program.

The authors[1] note that their reprogrammed cells resembled cardiomyocytes in several ways: they were beating cells, had identifiable myofilaments containing the α-actinin protein, and showed Ca^{2+} oscillations and action potentials similar to adult ventricular cardiomyocytes. Moreover, the overall gene-expression pattern in these cells was broadly very different from that of cardiac fibroblasts and similar, although not identical, to that of neonatal cardiomyocytes. Modifications of histone proteins and of DNA associated with select genes suggested both broad changes in chromatin and establishment of new, stable gene-expression states.

The induced cardiomyocytes were stable for at least a week in culture, even after the expression of the three transcription factors was turned off. What's more, when the authors injected fibroblasts that had been reprogrammed *in vitro* into the heart muscle of live animals, the cells differentiated *in situ* to form small isolated cardiomyocyte-like cells with myofilaments. It is not known, however, whether these new inhabitants of the heart were electrically coupled.

The cell type that underwent 'transdifferentiation' in Ieda and co-workers' experiments is highly relevant to the mechanism of nuclear reprogramming that they report. Solid organs such as the heart contain a variety of cell populations, and, to isolate fibroblasts from smooth muscle and endothelial cells, the authors selected a subpopulation of neonatal cardiac fibroblasts that expressed the cell-surface protein Thy1. Such cells are likely to be highly immature and even stem-cell-like — in the adult, Thy1 marks mesenchymal stem-like cells and their early descendants, which are known to have the potential for differentiation into several other cell types. Nonetheless, the efficiency of conversion Ieda *et al.* report suggests that their starting material is not a rare stem-cell subpopulation. Whether adult cardiac fibroblasts can be similarly converted to cardiomyocytes should be determined, because it could be of relevance for the use of this strategy in the clinic.

Using genetic lineage tracing, the authors show that conversion into cardiomyocytes does not proceed via formation of an immature mesodermal or cardiac progenitor. However, given the known limitations of the tagging system they used (the marker genes of interest were expressed only transiently or at low levels), this finding would need confirmation using other experimental approaches.

More work is required before this approach[1] sees use in heart repair. It is a fertile beginning, nonetheless, and adds significantly to the growing body of data suggesting that we might be able to short-circuit developmental programs and directly establish an entirely new and stable program for clinical use. As is the case for reprogramming of differentiated cells to an embryonic stem-cell-like state[12], the mechanism underlying such transdifferentiation may involve obligatory changes in senescence genes, in epithelial status, in expression of regulatory noncoding RNAs such as microRNAs, and in chromatin modifiers. Beyond clinical potential, therefore, this paper opens many doors to explore the nature of reprogrammed cellular states. ■

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1. Ieda, M. *et al. Cell* **142,** 375–386 (2010).
2. Gurdon, J. B. *Annu. Rev. Cell Dev. Biol.* **22,** 1–22 (2006).
3. Campbell, K. H. S., McWhir, J., Ritchie, W. A. & Wilmut, I. *Nature* **380,** 64–66 (1996).
4. Zhou, Q. & Melton, D. A. *Cell Stem Cell* **3,** 382–388 (2008).
5. Weintraub, H. *et al. Proc. Natl Acad. Sci. USA* **86,** 5434–5438 (1989).
6. Gehring, W. J. & Ikeo, K. *Trends Genet.* **15,** 371–377 (1999).
7. Vierbuchen, T. *et al. Nature* **463,** 1035–1041 (2010).
8. Zhou, Q., Brown, J., Kanarek, A., Rajagopal, J. & Melton, D. A. *Nature* **455,** 627–632 (2008).
9. Forsberg, M. *et al. Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1009412107 (2010).
10. Yamanaka, S. & Blau, H. M. *Nature* **465,** 704–712 (2010).
11. Takeuchi, J. K. & Bruneau, B. G. *Nature* **459,** 708–711 (2009).
12. Samavarchi-Tehrani, P. *et al. Cell Stem Cell* **7**, 64–77 (2010).