50 Years Ago

To many people nutrition means no more than the study of foods and their use by the living body. But with increasing evidence of widespread malnutrition throughout the world, and of a deteriorating situation in regard to world population and food supplies, much emphasis needs to be placed on the importance of work outside the laboratory on problems associated with providing people everywhere with an adequate diet. In many parts of the world an immediate problem is a means of conveying foods from one place to another. For example, fruit, the sale of which provides a livelihood for some people, may be rotting on the trees because there are no roads on which it can be transported to other people who might benefit by addition of fruit to their diet ... Lack of adequate means of distribution may seriously limit the use of fish, and while many people suffer the effects of protein malnutrition, fishermen not far away suffer economic disaster because they cannot get rid of harvest gluts.

From *Nature* 7 July 1962

100 Years Ago

Measurements of the temperature of flowing lava are so rare that some made by Prof. G. Platania during the eruption of Etna last September possess considerable interest … His observations were made with a Féry's radio-pyrometer on a stream of lava flowing from the lowest of a string of craters in the neighbourhood of M. Rosso, a few days before the eruption ceased. The temperatures, in parts where the lava was still red, ranged from 795° to a maximum of 940° C.

From *Nature* 4 July 1912

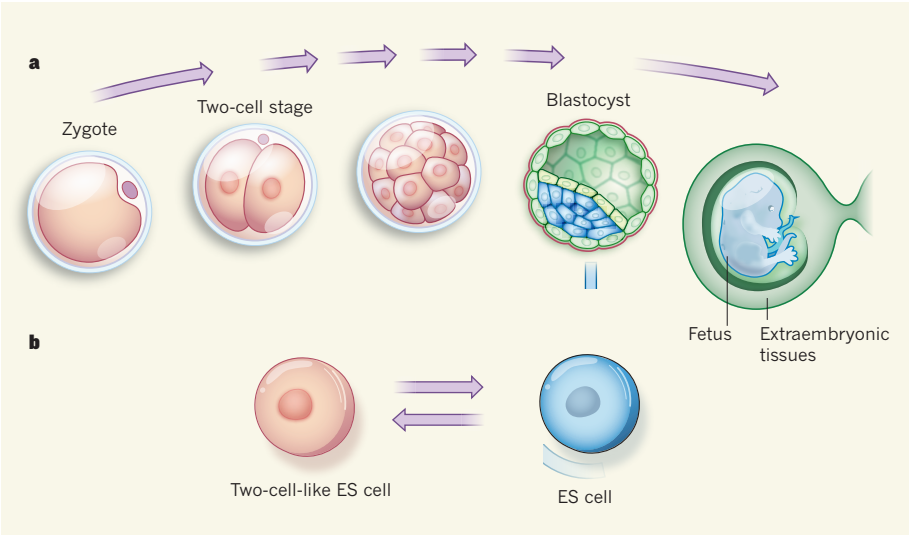

Figure 1 | A 'totipotent-like' state in embryonic stem cells. **a**, During the early development of a mouse embryo, many genes are transiently expressed after the first division of the fertilized egg (zygote). Macfarlan *et al.*[1] find that some of those genes contain virus-derived sequences that drive the genes' transient expression at the two-cell stage. Further cellular divisions result in the development of a blastocyst, a mass of cells that have defined fates: those in the inner cell mass give rise to the fetus, whereas the rest contribute to extraembryonic tissues such as the placenta. **b**, Embryonic stem (ES) cells, which are derived from the inner cell mass of blastocysts, self-renew in culture (curved arrow). The authors show that most, if not all, ES cells pass through a short-lived state during which they display features that are typical of the totipotent two-cell stage: unlike the rest of the ES cells in the culture, they lack expression of the proteins Oct4, Sox2 and Nanog, and have the ability to form cells of both the placenta and the fetus.

shared by all pluripotent stem cells.

Crucially, the researchers established that the rare ES cells, but not the rest of the ES cells in a culture, can contribute to both fetal and placental tissues, thereby fulfilling a key attribute of totipotency. However, it remains to be seen whether the two-cell-like ES cells have the potential to generate a complete, live organism.

What is the significance of the two-cell-like ES cells? To address this question, it is important to note that cells from two-cell embryos or early blastocysts represent transient states. Unlike ES cells, they do not self-renew but progress to the next developmental stage. Furthermore, both symmetrical and asymmetrical cell divisions follow the two-cell stage and establish which blastocyst cells will develop into the fetus and which will become extraembryonic tissues[9]. By contrast, ES cells self-renew through symmetrical divisions. So how can the two-cell-like ES cells generate extraembryonic tissues? A precise analysis of single ES cells is required to understand how they generate different cell types, and whether the cells' fate is determined stochastically or is a pre-programmed property of individual cells. For example, do key molecular determinants of different fetal and placental lineages become segregated into individual cells when they differentiate from two-cell-like ES cells?

The authors found that the two-cell-like cells, unlike the rest of the ES cells, did not produce the proteins Oct4, Sox2 and Nanog, which are typically associated with pluripotency, and instead expressed several genes that are commonly active in two-cell embryos. Notably, one of these genes encodes the protein Zscan4, which is required for the maintenance of telomeres (the ends of chromosomes, which are eroded every time DNA duplicates) and for genomic stability. Lack of Zscan4 leads to a gradual decline in the proliferative capacity of ES cells[10]. Macfarlan *et al.* observed that the rare ES cells also displayed a two-cell-like pattern of epigenomic marks — chemical modifications of DNA, and of DNA-bound proteins, that do not alter DNA sequence but affect gene expression.

Therefore, fluctuating patterns of gene expression might provide pluripotent stem cells with a window of opportunity to enter specific cell states. In particular, transition of ES cells through a two-cell-like state may be crucial for 'resetting' the epigenome, for the repair and maintenance of telomeres, and for refreshing the core genetic network underlying pluripotency. Future research, particularly at the single-cell level, may help to reveal why, and how, these cells go through such fluctuating states. It may also advance our knowledge of the mechanisms of cellular rejuvenation and reprogramming in early germ cells, which eventually develop into sperm and eggs. These cells are considered to be immortal, as they have the potential to generate a whole organism and therefore all subsequent generations. ■

Azim Surani *and* **Julia Tischler** *are at the Wellcome Trust Cancer Research UK Gurdon Institute, University of Cambridge, Cambridge CB2 1QN, UK.*
e-mail: a.surani@gurdon.cam.ac.uk