STEM CELLS

What doesn't kill you may reprogram you

Somatic cells in the mouse can be converted to a pluripotent state merely through exposure to a physical stimulus.

The cells of multicellular organisms are not static. Rather, they are plastic entities, flexible enough that their fate and function can be manipulated if only one can find the right way to do it. Cellular plasticity has recently come into keen focus with the discovery that differentiated somatic cells can be reprogrammed to pluripotency to yield induced pluripotent stem (iPS) cells.

Two recently published papers from groups at the RIKEN Center for Developmental Biology, Kobe, Japan, and Harvard Medical School, Boston, now mark a new phase in our understanding of the plasticity of cell fate (Obokata *et al.*, 2014a,b). Previous methods to reprogram cells have typically involved the forced overexpression of at least one transcription factor. The new studies, led by Haruko Obokata at RIKEN, instead show that reprogramming can be accomplished by exposing cells to a purely physical stimulus.

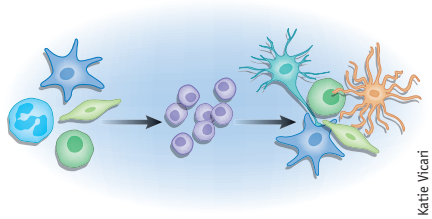
Starting with lymphocytes from the spleen of a one-week-old mouse, the researchers tested several physical stressors for their ability to turn on a fluorescent reporter of the *Oct4* (*Pou5f1*) gene, a known marker of pluripotency. Half an hour in mildly acidic conditions (the optimal pH is 5.4–5.8), they report, followed by culture in medium routinely used for mouse embryonic stem (ES) cells, results in the surprisingly robust appearance of Oct4-positive cells within a week, with a quarter to half of the surviving cells expressing the marker. The process is relatively fast, and the resulting cells express most other known markers of pluripotency and also fulfill functional criteria for this state.

Because Obokata and colleagues did some of their experiments using immune cells that had undergone genomic rearrangement at the T cell–receptor locus, they could trace these rearrangements to make sure that a true reprogramming event had occurred. They also could trigger low pH–induced fate conversion starting with cells from many other tissues of the neonatal mouse.

The researchers name the cells that emerge 'stimulus-triggered acquisition of pluripotency', or STAP, cells. Although STAP cells have many of the defining features of pluripotency, including the ability to contribute to all lineages of a chimeric mouse, they differ from conventional ES or iPS cells in some respects: primarily, they do not proliferate well and cannot be maintained in culture under standard conditions. But if the culture conditions are modified, Obokata and colleagues report, STAP cells either can yield ES-like pluripotent stem cells that then grow in culture or can be nudged along a different developmental path to resemble trophoblast stem cells (which build the placenta *in vivo*).

Are stimulus-triggered methods likely to supersede transcription factor–mediated reprogramming to pluripotency? Perhaps the most exciting aspect of iPS cells is the ability to derive them from the cells of any human being, including individuals known to harbor mutations relevant for disease. Such cells and their derivatives can then be used to study human disease and phenotypic variation with precise control and in the relevant cell types. How important STAP turns out to be will therefore depend on whether STAP cells and their derivatives can be generated starting from human cells and, moreover, whether this will apply to adult donor cells as well.

A particularly appealing aspect is that STAP does not require genetic modification of cells. Since the initial reports of reprogramming to pluripotency, which used integrating viral vectors to introduce the reprogramming factors into cells, there has been much effort to develop methods that do not permanently modify the genome, either with non-integrating DNA vectors or by moving away from DNA-based factor delivery entirely. If stimulus-triggered reprogramming does work efficiently for fate conversions in adult human cells, it could in principle be a way forward.


Katie Vicari

Somatic cells can be rendered pluripotent without reprogramming factors.

It remains to be seen, however, whether the variability that has plagued existing human iPS cell lines will also impede the flexible application of stimulus-triggered lines. Furthermore, this exciting new approach to cellular reprogramming does not eliminate the continuing challenge of how to differentiate the resulting pluripotent cells efficiently and scalably into mature and functional cell types.

At the more fundamental level, the work of Obokata and colleagues raises perhaps more questions than answers: What are the inhibitory mechanisms that prevent such fate conversions from happening more frequently *in vivo*? Do STAP cells have an embryonic counterpart during normal development? And what exactly is going on when cells reprogram in this way? But what is clear is that on both the technology development and fundamental research fronts, the discovery of stimulus-triggered reprogramming will prompt many lines of inquiry.

Natalie de Souza

RESEARCH PAPERS

Obokata, H. *et al.* Bidirectional developmental potential in reprogrammed cells with acquired pluripotency. *Nature* **505**, 676–680 (2014a).

Obokata, H. *et al.* Stimulus-triggered fate conversion of somatic cells into pluripotency. *Nature* **505**, 641–647 (2014b).