STEM CELLS

An alternative to induced pluripotency?

Two groups report the derivation of human pluripotent stem cell lines from embryos derived by somatic cell nuclear transfer using adult cells as donors.

There are two ways to convert a somatic cell into a stable pluripotent cell. One may reprogram the somatic cell to induced pluripotency by the introduction of a defined set of transcription factors. Or one may carry out a somatic cell nuclear transfer (SCNT)—in which the somatic cell is fused to an enucleated egg, which effects the reprogramming—and then derive pluripotent stem cells from the resulting embryo.

Reprogramming to induced pluripotent stem cells has often seemed, in recent years, to eclipse SCNT: it is relatively easy, does not require special cells or expertise, and has been shown, time and again, in a multitude of laboratories, to work. Furthermore, until just last year, SCNT had not been demonstrated to yield diploid pluripotent stem cells in human. Now, two research groups, one at the New York Stem Cell Foundation (NYSCF) and the other at the CHA University, Seoul, report the refinement of existing methods to achieve the derivation of human pluripotent stem cells from SCNT embryos made with adult, not fetal, donor cells.

The lead author of one of the studies, Dieter Egli at NYSCF, speculates that one reason it has taken so long to optimize conditions in the human system is because the human embryo can develop for quite long (up to the eight-cell stage) purely fueled by maternal products. Yet many reagents that have been empirically determined to improve nuclear transfer must be added early, during the first cell cycle. Thus, "it's hard [when things don't work] to trace back what went wrong before," Egli says.

His group identified four methodological elements for successful SCNT with human cells. First, it is important to preserve plasma-membrane integrity during the initial fusion step and prevent calcium levels in the oocyte from rising too high at this stage (though it must rise later, during activation). Second, the oocyte must be efficiently activated, which may be achieved in several ways—indeed, the different groups use different methods—but must, according to Egli, keep the meiotic kinases in the oocyte inactive. Third, as has been reported before in animal SCNT, the addition of inhibitors of histone deacetylase facilitates reprogramming. And finally, as in the work of Shoukhrat Mitalipov and colleagues at Oregon Health & Science University, who first reported SCNT using human fetal donor cells, an optimized medium that includes fetal bovine serum is critical for derivation of pluripotent stem cell lines from the SCNT blastocyst. "All these improvements work together," says Egli. "I would not leave out a single one."

The group headed by Young Chung and Dong Ryul Lee, at CHA University, essentially followed the protocols that have been reported previously for SCNT with fetal donors but added a longer (2-hour instead of 30-minute) activation step after fusion. The researchers were thus able to derive pluripotent stem cells from SCNT embryos made with cells from a 35- or 75-year-old donor (Chung *et al.*, 2014). Egli and colleagues reported pluripotent stem cell lines using cells from a 32-year-old diabetic donor (Yamada *et al.*, 2014). The overall efficiency of stem cell derivation, Egli says, is 5–10% but varies with the egg donor.

The advent of SCNT with adult human donor cells means that, for the first time, there is a technical alternative to reprogramming by induced pluripotency for the derivation of tailored cells from any healthy or diseased person; practical barriers, such as the need for human oocytes and special expertise, still remain. Nevertheless, comparisons of isogenic induced pluripotent and SCNT embryonic stem cells will surely prove illuminating about changes due to the particular reprogramming method and, therefore, about which method is best suited to produce cells for which application.

Natalie de Souza

RESEARCH PAPERS

Chung, Y.G. *et al.* Human somatic cell nuclear transfer using adult cells. doi:10.1016/j.stem.2014.03.015 (17 April 2014).

Yamada, M. *et al.* Human oocytes reprogram adult somatic nuclei of a type 1 diabetic to diploid pluripotent stem cells. doi:10.1038/nature13287 (28 April 2014).