STEM CELLS

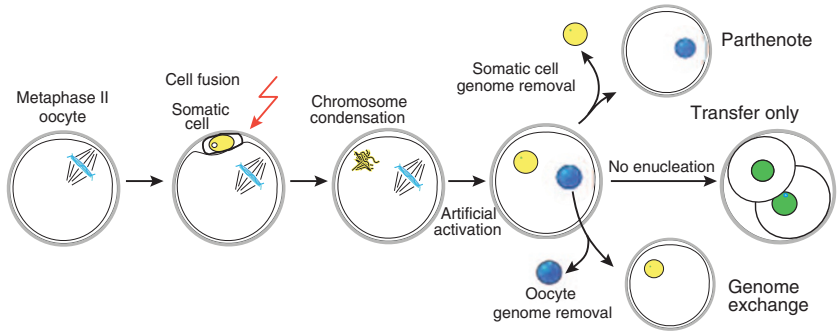
Human oocytes: still in the game

Retaining the recipient oocyte genome after human somatic cell nuclear transfer permits development to the blastocyst stage and derivation of triploid human embryonic stem cell lines.

In many animal species—sheep, pig, monkey and cat, to name a few—transfer of a somatic cell nucleus to an enucleated oocyte results in reprogramming of the donor cell genome to a totipotent state. There have been reports that this is possible in the human system, too, but the numbers of successful attempts are vanishingly small, and somatic cell nuclear transfer–derived human embryonic stem cell (hESC) lines have not been reported. Such hESC lines are exciting in principle because they would harbor the genome of the person who donated the somatic cell and could prove invaluable for both basic research—on disease, for instance—and also eventually for therapy. But it has remained an open question whether this strategy for deriving individual-specific hESC lines is even feasible. A recent report from researchers at the New York Stem Cell Foundation (NYSCF) and Columbia University indicates that it is.

Dieter Egli moved to the NYSCF at an opportune time. The American Society for Reproductive Medicine and the International Society for Stem Cell Biology had just endorsed the notion that, if properly conducted and reviewed, it is acceptable to financially compensate women who donate oocytes for research. Before this, only donation for reproductive purposes was remunerated, with the result that sufficient oocytes could not be obtained for research. Under the new guidelines, researchers at the NYSCF gave women who had already made the decision to donate the additional option to donate for either research or reproduction; as a consequence they obtained 270 human oocytes from 16 donors, with which they conducted their experiments.

But having the oocytes in hand was not enough. The researchers—Egli, Scott Noggle and colleagues—observed time and again that replacement of the oocyte genome with that of a somatic cell led to developmental arrest at the 6–10-cell stage. In contrast, *in vitro*–fertilized oocytes or haploid oocytes that had been parthenogenetically activated did not arrest and went on to form blastocysts. Oocytes from which the genome had been removed and then put back also did not arrest. Even oocytes in which the somatic cell genome was added and then removed, without removing the oocyte genome, went on to generate blastocysts. The researchers also observed that the developmental arrest coincided with inhibition of transcription from the donor cell genome. It appeared that, in the genome-exchange situation, the oocyte could not reprogram the donor nucleus.



Can human oocytes reprogram somatic cells? The schematic shows three preparations tested for donor-cell reprogramming and development. Reprinted from *Nature*.

To test whether removal of the oocyte genome was the culprit, the researchers asked whether or not reprogramming would proceed if they did not remove the oocyte genome after somatic cell nuclear transfer. To their surprise, the resulting embryos did not arrest, went on to develop into blastocysts and could be used for the derivation of ESC lines. The resulting hESC lines are triploid, in each case harboring the haploid oocyte as well as the diploid donor genomes, but otherwise meet standard criteria for pluripotent stem cells.

"We are now in the fortunate position to be able to do controlled experiments," says Egli. In particular, he and his colleagues should be able to study what is being removed from the oocyte during extraction of its genome and to determine whether it is possible to remove the genome in such a way that developmental arrest is avoided. This could lead to the derivation of normal, diploid hESCs. Furthermore, it will be interesting to compare the existing triploid ESCs with induced pluripotent stem cells (iPSCs) generated from the same donors. Do these ESCs also have genomic lesions, acquired during the reprogramming process as has been reported for iPSCs?

Egli and colleagues already have hints that, compared to previous reports on reprogramming to induced pluripotency, the human oocyte can more rapidly and effectively remove epigenetic memory of the donor cell type. They compared allele-specific expression of several genes and found that loci across the genome were on average expressed at levels in proportion to their copy number. Both pluripotency-associated genes and fibroblast-associated genes did not deviate from this pattern.

Will studies such as these help us to understand how the oocyte reprograms so much more efficiently than exogenous factors? Will this lead to an improvement of methods to generate human iPSCs? Are the cells generated by these different procedures equivalent? Only time will tell, but knowing that the human oocyte can reprogam somatic cells in the laboratory is an important first step.

Natalie de Souza

RESEARCH PAPERS
Noggle, S. *et al.* Human oocytes reprogram somatic cells to a pluripotent state. *Nature* **478**, 70–75 (2011).