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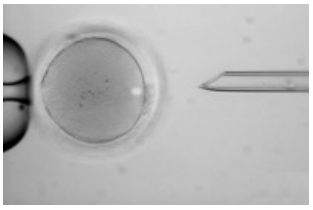
Exchange of DNA Between Egg Cells May Help Prevent Mitochondrial Diseases

by Gretchen Vogel on 24 October 2012, 5:01 PM | 2 Comments

With the help of modified in vitro fertilization (IVF) techniques, researchers are a step closer to finding a way to prevent mitochondrial diseases that can cause a range of potentially fatal disorders. These techniques were previously shown to work in monkeys, but now scientists report that they have successfully transferred DNA from one human egg cell containing mutant mitochondria to another without those mutations, thus producing embryos that can develop for several days and give rise to embryonic stem cells. The technique is not very efficient, however, and it is not ready to try in patients.

ENLARGE IMAGE



Poised. Researchers use a micropipette to remove the nuclear DNA from a human oocyte.

Credit: Oregon Health Sciences University

Mutations in the mitochondria, organelles that produce a cell's energy and carry their own DNA, can cause a range of symptoms, including heart failure, dementia, and blindness. The severity and onset of symptoms can vary, but they tend to affect tissue with high energy demands, such as heart, muscle, and brain. There is no way to treat the condition. Because mitochondrial DNA (mtDNA) in embryos primarily comes from the oocyte, or egg cell, several groups of researchers have been working to find ways to prevent the condition using modified IVF techniques, which would allow women who carry the mutations a chance to conceive children with healthy mitochondria.

One technique that has worked in monkeys is called spindle transfer. Researchers remove the nuclear DNA—which accounts for the vast majority of the genetic information—from an unfertilized egg cell that carries mutant mitochondria. Then, they transfer the DNA into an egg from a healthy donor, from which the nuclear DNA has also been removed. The result is an egg carrying the nuclear DNA from the patient and the healthy mitochondria of the donor egg. In 2009, Shoukhrat Mitalipov, a reproductive biologist at Oregon Health & Science University, West Campus, in Beaverton, and colleagues showed that the technique could produce healthy baby macaques. Today, they report online in *Nature* that they have used the technique with human oocytes, showing that it can produce normal-looking embryos.

It doesn't work as well as it did in monkeys, however. Only about half of the manipulated egg cells developed normally after being fertilized, significantly fewer than with standard IVF techniques. The researchers were able to derive embryonic stem cell lines from six of the spindle-transfer embryos. By analyzing the stem cells' mitochondria, they were able to find out whether any mitochondria were transferred along with the nuclear DNA. They found that less than 1% of the mtDNA in the resulting cells originated from the DNA donor cell, a rate that Mitalipov says is probably sufficient to prevent disease.

The technique has raised ethical questions, as the resulting offspring carry genetic material from three different sources: the nuclear DNA from the mother and father, along with the mitochondrial DNA from the egg donor.

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Because any female children born after the technique would pass the donated mtDNA to their children, the technique is a kind of germline gene therapy. The term refers to any genetic changes that would pass on to future generations, and experts agree that it requires extra scrutiny. Nevertheless, a prominent ethics group in the United Kingdom said earlier this year that the technique is justified as a way to prevent an otherwise untreatable disease.

The new result is promising, says Mary Herbert, a reproductive biologist at Newcastle University in the United Kingdom who also works on techniques to prevent mitochondrial disease. However, she says, the success rate is worryingly low. Before the technique could be used to treat patients, she says, researchers need to know much more about the potential health of the resulting embryos. She and her colleagues are working to develop assays that can better judge how embryos produced with such techniques compare to those from conventional IVF techniques. "It's an ethical imperative," she says, that potential patients have enough information to weigh the benefits against the possible risks of using the technique.

Mitalipov says that he and his colleagues are in contact with the U.S. Food and Drug Administration to determine what information would be required before clinical trials could go ahead.

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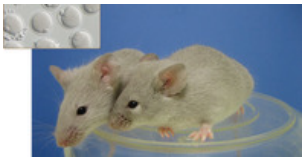

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So, to avoid the three parent issue. Can't we generate an oocyte from the fathers iPS cells, then shuffle the nuclear DNA and fertilize?

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Not sure you can reprogram a male cell (which has both an X and a Y chromosome, compared to the two X chromosomes in female cells) into an oocyte. It would also require the process of generating oocytes from iPS cells to be well established, using methods that don't require the use of viral transgenes. Even if those requirements were met, I can imagine that the rate of success would be even lower than it is with the three parent method..

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