Research sheds light on new strategy to treat infertility

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New research from Oregon Health & Science University describes the science behind a promising technique to treat infertility by turning a skin cell into an egg that is capable of producing viable embryos.

Researchers at OHSU documented in vitro gametogenesis, or IVG, in a mouse model through the preliminary steps of a technique that relies upon transferring the nucleus of a skin cell into a donated egg whose nucleus has been removed. Experimenting in mice, researchers coaxed the skin cell's nucleus into reducing its chromosomes by half, so that it could then be fertilized by a sperm cell to create a viable embryo.

The study is published in the journal *Science Advances*.

"The goal is to produce eggs for patients who don't have their own eggs," said senior author Shoukhrat Mitalipov, Ph.D., director of the OHSU Center for Embryonic Cell and Gene Therapy.

The technique could be used by women of advanced maternal age or for those who are unable to produce viable eggs due to previous treatment for cancer or other causes. It also raises the possibility of men in same-sex relationships having children who are genetically related to both parents.

Rather than attempting to differentiate induced pluripotent stem cells, or iPSCs, into sperm or egg cells, OHSU researchers are focused on a technique based on somatic cell nuclear transfer, in which a skin cell nucleus is transplanted into a donor egg stripped of its nucleus. In 1996, researchers famously used this technique to clone a sheep in Scotland named Dolly.

In that case, researchers created a clone of one parent. In contrast, the OHSU study described the result of a technique that resulted in embryos with chromosomes contributed from both parents. The process involves three steps:

- Researchers transplant the nucleus of a mouse skin cell into a mouse egg that is stripped of its own nucleus.
- Prompted by cytoplasm—liquid that fills cells—within the donor egg, the implanted skin cell nucleus discards half of its

chromosomes. The process is similar to meiosis, when cells divide to produce mature sperm or egg cells. This is the key step, resulting in a haploid egg with a single set of chromosomes.
- Researchers then fertilize the new egg with sperm, a process called in vitro fertilization. This creates a diploid embryo with two sets of chromosomes—which would ultimately result in healthy offspring with equal genetic contributions from both parents.

OHSU researchers previously demonstrated the proof of concept in a study published in January 2022, but the new study goes further by meticulously sequencing the chromosomes.

The researchers found that the skin cell's nucleus segregated its chromosomes each time it was implanted in the donor egg. In rare cases, this happened perfectly, with one from each pair of matching egg and sperm chromosomes.

"This publication basically shows how we achieved haploidy," Mitalipov said. "In the next phase of this research, we will determine how we enhance that pairing so each chromosome-pair separates correctly."

Laboratories around the world are involved in a different technique of IVG that involves a time-intensive process of reprogramming skin cells to become iPSCs, and then differentiating them to become egg or sperm cells.

"We're skipping that whole step of cell reprogramming," said co-author Paula Amato, M.D., professor of obstetrics and gynecology in the OHSU School of Medicine. "The advantage of our technique is that it avoids the long culture time it takes to reprogram the cell. Over several months, a lot of deleterious genetic and epigenetic changes can happen."

Although researchers are also studying the technique in human eggs and early embryos, Amato said it will be years before the technique would be ready for clinical use.

"This gives us a lot of insight," she said. "But there is still a lot of work that needs to be done to understand how these chromosomes pair and how they faithfully divide to actually reproduce what happens in nature."

More information: Aleksei Mikhalchenko et al, Induction of somatic cell haploidy by premature cell division, *Science Advances* (2024). DOI: 10.1126/sciadv.adk9001. www.science.org/doi/10.1126/sciadv.adk9001

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