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Study shows how mitochondrial genes are passed from mother to child

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Research conducted at the Oregon National Primate Research Center at Oregon Health & Science University helps answer some long-standing questions about how certain disease-causing gene mutations are inherited.

The research specifically focused on gene mutations in cell mitochondria that can cause several diseases, including forms of cancer, diabetes, infertility and neurodegenerative diseases. With this new information, we now better understand how and when these mutations are passed to children to improve diagnosis and prevention. The research will be published online in the journal *Cell Reports* on Thursday May 3.

Shoukhrat Mitalipov, Ph.D., who previously developed a method for preventing the passing of mitochondrial genetic mutations from mother to infant in 2009, directed the research.

This latest breakthrough, which was conducted in rhesus macaque monkeys because of their similarity to humans, demonstrates the specific stage of early embryonic development when genetic mutations are passed from mother to fetus. This stage, referred to by scientists as "the bottleneck," occurs when an early embryo called blastocyst, transitions into a fetus.

To conduct the research, Mitalipov and colleagues needed to design a way to mark and track specific mitochondrial genes as they transitioned from egg, through fertilization, to embryo and then to fetus. This was

accomplished by combining two separate mitochondrial genomes into one egg cell. More specifically, one-half of an egg cell from a species of Indian-continent rhesus macaque monkey was merged with one-half of an egg cell from a Chinese-continent monkey. Because these animal species have distinct mitochondrial gene sequences (like breeding two distinct species of dogs), their genetics could be tracked closely.

The microscopic manipulation of splitting and uniting two halved egg cells takes specialized skills and expertise, which the Mitalipov lab has developed over a period of several years. A link to a video explaining this process can be found in the multimedia section of this press release.

By studying the development of these joined and then fertilized eggs, scientists were surprised to see that eggs transitioned from containing a 50/50 split of genetics to a fetus that contained a nearly 100 percent either Indian or Chinese-based genome.

"We discovered that during early development, each individual cell in the eight-cell embryo would contain varying percentages of the Indian and Chinese rhesus genes. Some would be a 50/50 split. But others would be 90/10 and so on," explained Mitalipov. "When these percentages were combined as a whole embryo, the average genetic split between the two species was about equal as initially created. However, later during the transition from a blastocyst to fetus, the genetics would swing one way or another. The resulting offspring would have always a genome that is predominantly Chinese or Indian. Our study tells us precisely when this mitochondrial gene switch occurs and how this can lead to disease."

This finding raises significant questions about validity of currently methods for genetic diagnosis in early embryos, when a woman is known to carry a mitochondrial gene mutation may pass a disease to her children.

"The current pre-implantation genetic diagnosis method is to examine genetic disease risk is by taking one cell from an early eight-cell embryo, and then looking for mutations in that one particular cell. This is done to predict if the remaining embryo is mutation-free," explained Mitalipov.

"The problem with this approach is that you may choose a cell that may not have mutations. But that does not mean the remaining cells in an embryo are mutation-free. Our research suggests that such approach could be flawed because diagnosis takes place prior to the stage when an offspring's mitochondrial genetics is truly established."

With this new information and with additional data gathered through further research, Mitalipov and colleagues believe that new methods for genetic diagnosis for mitochondrial disease should be located. The research also demonstrates that the Mitalipov lab's previously developed method for preventing the passing of mitochondrial mutations from mother to child is highly successful.

Provided by Oregon Health & Science University

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