Medical Xpress

Scientists advise caution with regard to artificial insemination method

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Already a few dysfunctional mitochondria (in yellow on top of the picture) could cause a disease by overgrowing functional ones (in blue). Credit: Iain Johnston

The approval of a new treatment method by which three parents will be able to beget a child is being discussed since a few years in Great Britain and will possibly become a reality in two years. The method is supposed to help in eliminating the mother's genetic defects already in the test tube. The defect lies in so-called mitochondria, the "power houses" of cells. To get rid of defective mitochondria the nucleus of one egg cell has to be transferred to another egg cell bearing intact mitochondria. Scientists at the Vetmeduni Vienna show for the first time that even a few defective mitochondria dragged along in the transfer could cause diseases. The results were published in *Cell Reports*.

Mitochondria are cell organelles located within animal and human cells. They produce energy for the organism, possess their own genetic material - mitochondrial DNA (mtDNA) - and are transmitted exclusively by the mother. Depending on their activity and tasks, different numbers of mitochondria are present in a cell - usually a few hundred to a thousand per body cell.

Inherited mitochondrial disorders or so-called mitochondropathies occur in about one of 10,000 humans throughout the world. Diseases such as diabetes, stroke, cardiac defects, epilepsy, or muscle weakness may originate from mitochondrial defects. Inherited mitochondrial disorders have been incurable so far. Therefore, efforts are now being made to enable women with this disease to bear healthy children by means of nuclear transfer.

Mitochondria multiply at different rates

Jörg Burgstaller, a scientist and member of Gottfried Brem's research group at the Vetmeduni Vienna, has been working for several years on the genetics of mitochondria. It was known before that different types of mitochondria within a cell can proliferate at different rates. However, it was not known whether this is a singular phenomenon or if these cases

occur more frequently.

Burgstaller investigated this in four newly bred mouse models which carried different mixtures of mitochondria whose DNA were related to each other to a differing extent. This meant no health problem for the mice since all mtDNAs are were fully functional.

The outcome was: the more distantly two types of mitochondria within an egg cell were related, the more frequently a growth advantage was noted in favor of one of the two types of mitochondria. When two different mtDNAs were equally common in cells of an organ at the time of birth, one type was completely lost after a while. One mitochondria variant had thus achieved a growth advantage compared to the other variant and superseded the latter. This effect was almost non-existent in genetically very similar mitochondria within the cells; the ratio between the two types of mitochondria was not altered in that case.

The effect is of significance in reproduction medicine

Burgstaller's results may have effects on the planned introduction of the so called "Three-Parent Baby" in Great Britain. Experts take the cell nucleus of one human egg cell whose mitochondria have a defect and place it in an egg cell with "healthy" mitochondria. The baby resulting from this procedure has three parents, namely the mother whose cell nucleus is used, the mother whose mitochondria are involved, and the father whose sperm inseminated the egg cell.

However, this method raises the following problem: in every nuclear transfer, a small number of defective mitochondria are transferred into the healthy egg cell. "So far it was believed that this minimal 'contamination' is of no consequence for the baby. However, our data show that the effect may have dramatic consequences on the health of the offspring. If the mitochondria of both mothers are genetically very

different, it may have the same effects seen in the mouse model," says Burgstaller who developed the theory together with co-author Joanna Poulton, Professor of Mitochondrial Genetics at the John Radcliffe Hospital in Oxford. "One mitochondrial type may be able to assert itself against the other. If the assertive one happens to carry the defective mtDNA, the benefit of the therapy would be jeopardized."

The solution to the "Three-Parent Baby"-problem

Burgstaller and his colleagues suggest the following solution to the problem: the mtDNA of both mothers, i.e. the donor of the nucleus and the donor of the mitochondria, should be analyzed in advance and aligned to each other. So called "machting haplotypes" could prevent the dangerous effect. In the future the effect may even be utilized in a targeted manner to suppress defective mtDNA.

More information: "mtDNA Segregation in Heteroplasmic Tissues Is Common In Vivo and Modulated by Haplotype Differences and Developmental Stage," Joerg Patrick Burgstaller, Iain G. Johnston, Nick S. Jones, Jana Albrechtová, Thomas Kolbe, Claus Vogl, Andreas Futschik, Corina Mayrhofer, Dieter Klein, Sonja Sabitzer, Mirjam Blattner, Christian Gülly, Joanna Poulton, Thomas Rülicke, Jaroslav Piálek, Ralf Steinborn and Gottfried Brem, *Cell Reports*. DOI: 10.1016/j.celrep.2014.05.020

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