NEWS IN FOCUS

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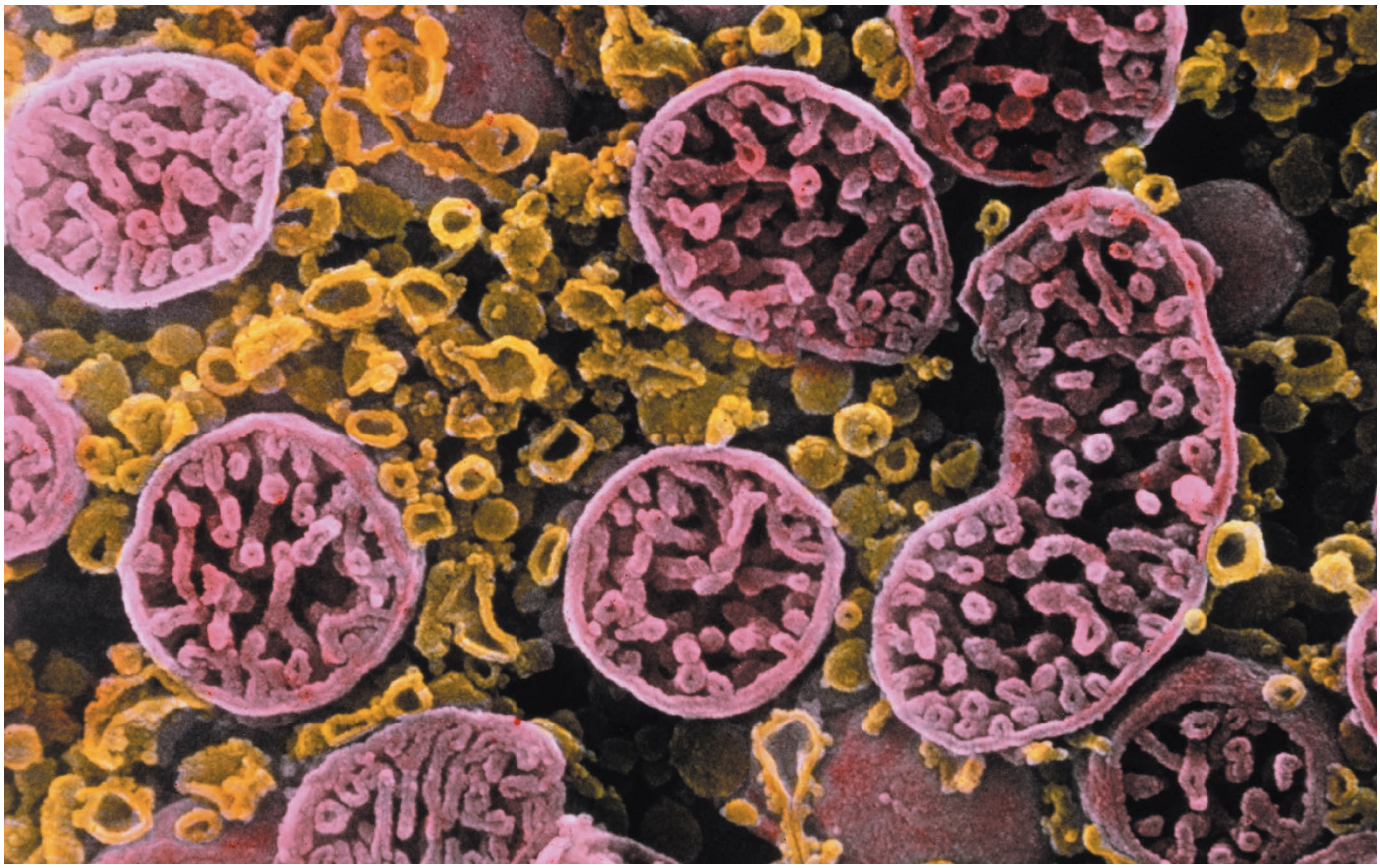

Mitochondria (shown in pink) are the cell's energy-producing structures and can contain harmful genetic mutations.

REPRODUCTIVE MEDICINE

Three-person embryos may not expel harmful genes

Technique to stop children inheriting mutated mitochondria has potential to backfire.

BY EWEN CALLAWAY

A gene-therapy technique that aims to prevent mothers from passing on harmful genes to children through their mitochondria — the cell's energy-producing structures — might not always work.

Mitochondrial replacement therapy involves swapping faulty mitochondria for those of a healthy donor. But if even a small number of mutant mitochondria remain after the transfer — a common occurrence — they can outcompete healthy mitochondria in a child's cells and potentially cause the disease that the therapy was designed to avoid, experiments suggest.

"It would defeat the purpose of doing mitochondrial replacement," says Dieter Egli, a stem-cell scientist at the New York Stem Cell Foundation Research Institute who led the work. Egli says that the finding could guide ways to surmount this hurdle, but he recommends that the procedure not be used in the meantime.

The UK government last year legalized mitochondrial replacement therapy, although the country's fertility regulator has yet to give the green light to its use in the clinic. In the United States, a panel convened by the National ▶

Academies of Sciences, Engineering, and Medicine has this year recommended that clinical trials of the technique be approved if preclinical data suggest that it is safe.

As many as 1 in 5,000 children are born with diseases caused by harmful genetic mutations in the DNA of their mitochondria; the diseases typically affect the heart, muscles and other power-hungry organs. Children inherit all their mitochondria from their mothers.

To prevent a mother who has harmful mitochondrial mutations from passing them to her children, the proposed remedy is to transplant the nuclear DNA of her egg into another, donor egg that has healthy mitochondria (and has been emptied of its own nucleus). The resulting embryo would carry the mitochondrial genes of the donor woman, and the nuclear DNA of the father and mother. These are sometimes called three-person embryos.

Current techniques can't avoid dragging a small number of the mother's mitochondria into the donor egg, totalling less than 2% of the resulting embryo's total mitochondria. This isn't enough to cause health problems. But researchers have worried that the proportion of faulty, 'carried-over' mitochondria may rise as the embryo develops. The UK Human Fertilisation and Embryology Authority (HFEA) — which will oversee clinical applications of mitochondrial replacement — has called for research into this possibility.

Egli's study offers some clarity (M. Yamada *et al. Cell Stem Cell* http://doi.org/bhsj; 2016). His team used eggs from women with healthy mitochondria, but otherwise followed a procedure similar to the real therapy: transplanting nuclear DNA from one set of egg cells into another woman's egg cells. The team converted these eggs into embryos using two copies of the maternal genome instead of sperm (to discount any role for paternal DNA), extracted stem cells from the embryos and grew the cells in dishes in the lab. The embryos, on average, had just 0.2% of carried-over mitochondrial DNA (mtDNA), and the resulting embryonic stem cells at first harboured similarly minuscule levels. But one stem-cell culture showed a dramatic change: as the cells grew and divided, levels of the carried-over mtDNA jumped from 1.3% to 53.2%, only to later plummet back down to 1%. When the team split this cell line into different dishes, sometimes the donor egg's mtDNA won out, but in others, the carried-over mtDNA dominated.

"I don't think it would be a wise decision to go forward with this uncertainty."

COMPETING DNA

Exactly how the carried-over mitochondria rose to dominance is unclear. Egli suspects that the resurgence happened because one mitochondrion copied its DNA faster than the others could, which he says is more likely to occur when large DNA-sequence differences exist between the two populations of mitochondria.

Iain Johnston, a biomathematician at the University of Birmingham, UK, says that this theory makes sense. He was part of a team that found that, in mice with mitochondria from lab strains and distantly related wild populations, one mitochondrial lineage tended to dominate (J. P. Burgstaller *et al. Cell Rep.* **7,** 2031–2041; 2014). If mitochondrial replacement does reach the clinic, Johnston says that donors should be chosen such that their mitochondria closely match those of the recipient mother.

But Mary Herbert, a reproductive biologist at the University of Newcastle, UK, who is part of a team pursuing mitochondrial replacement, says that mitochondria behave very differently in embryonic stem cells than in normal human development. Levels of mutant mitochondria can fluctuate wildly in stem cells. "They are peculiar cells, and they seem to be a law unto themselves," she says. She calls the biological relevance of the latest report "questionable", and thinks that data from embryos cultured for nearly two weeks in the laboratory will provide more useful information than Egli's stem-cell studies.

An HFEA spokesperson says that the agency is waiting for further experiments on the safety and efficacy of mitochondrial replacement (including data from Herbert's team) before approving what could be the world's first mitochondrial replacement in humans.

Egli hopes that the HFEA considers his team's data. He thinks that the problem can be surmounted, for instance, by improving techniques to reduce the level of carried-over mitochondria or matching donors so that their mitochondria are unlikely to compete. Until this is shown for sure, he advocates caution. "I don't think it would be a wise decision to go forward with this uncertainty." ■

EARTH SCIENCE

Carbon-sensing satellite system faces high hurdles

Space agencies plan an advanced fleet, but technical and political challenges abound.

BY JEFF TOLLEFSON

Today just two satellites monitor Earth's greenhouse-gas emissions from space. But if the world's leading space agencies have their way, a flotilla of such probes could be launched beginning in 2030. The ambitious effort would help climate scientists to improve their forecasts — and it could also help to verify whether countries are upholding their commitments to reduce greenhouse-gas emissions.

But researchers will need to clear a daunting array of political and technical hurdles if they are to get the system — estimated to cost several billion dollars — off the ground. Competition for satellite launch slots is stiff: last year, for instance, the European Space Agency shelved plans for an advanced carbon-dioxide-monitoring probe in favour of a mission to measure plant growth. And scientists must still prove that satellite measurements of gases such as CO_2 and methane can match the accuracy of data from observatories on Earth.

"We have a small fleet of satellites that are being launched, but these are all just scientific experiments," says David Crisp, science team leader for NASA's Orbiting Carbon Observatory-2 (OCO-2). "What we are trying to do now is just figure out how to monitor greenhouse gases from space."

Scientists have access to data from a pair of pioneering satellites: OCO-2, which launched in 2014 and measures CO_2, and Japan's Greenhouse Gases Observing Satellite (GOSAT), which launched in 2009 and tracks CO_2 and methane. NASA and the Japan Aerospace Exploration Agency are working to calibrate the instruments against each other and with a network of ground-based monitoring stations.

Both probes have a margin of error of about 0.5%, Crisp says. His team wants to reduce that to just 0.25% for the OCO-2 measurements.