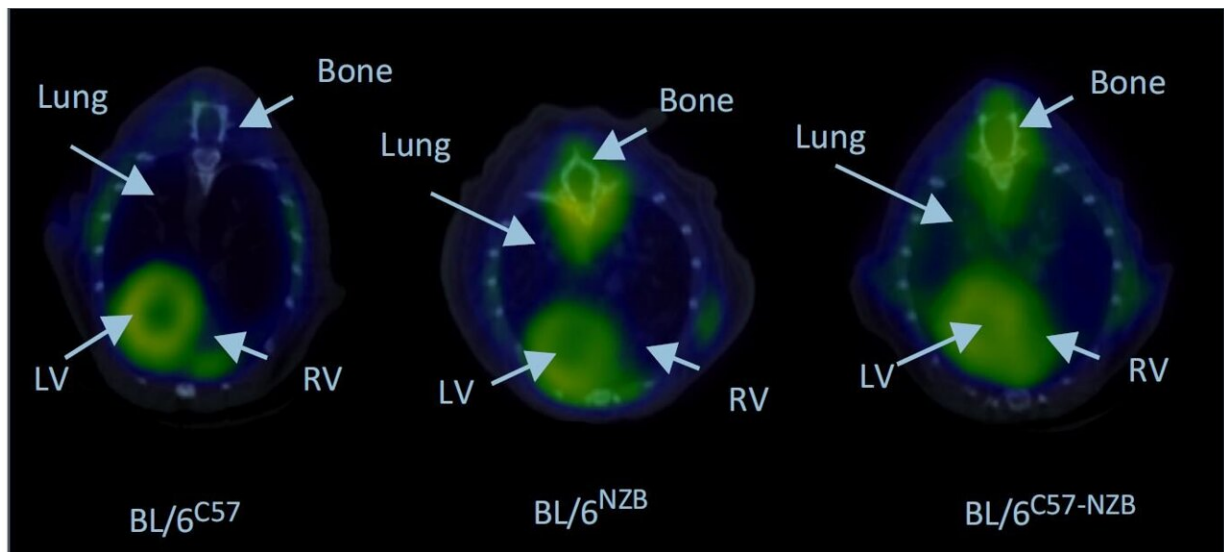


Study highlights the risks of mitochondrial therapeutic interventions

March 16 2022



Representative [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (PET/CT) images showing that DNPH alters cardiac glucose uptake, predominantly in the right ventricle and lung. Credit: CNIC

Research carried out at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) has demonstrated that mixing mitochondrial DNAs (mtDNAs) of different origins can have damaging effects over the medium and long term. mtDNA is a component of the genetic material that is transmitted exclusively from mothers to their children.

The study, published in *Circulation*, provides invaluable information

about how to identify and avoid possible risks associated with mitochondrial therapeutic interventions. The most popular of these methods include the injection of mitochondria from a [donor egg](#) into the egg of a woman with fertility problems and [mitochondrial replacement therapy](#) aimed at preventing the transmission of disease-causing mutations to descendants, popularly known as "three-parent children." Mitochondrial replacement therapy has already been approved in the United Kingdom.

The new study shows that, while most cells do not tolerate the presence of two mitochondrial genetic variants and progressively eliminate one of the two mtDNAs, some major organs are unable to do this, including the heart, lungs, and skeletal muscle.

For lead researcher Dr. José Antonio Enríquez, who heads the Functional Genetics of the Oxidative Phosphorylation System (GENOXPHOS) group at the CNIC, the findings have major implications for treatments involving the transfer of donor mitochondria because they show that "animals generated through these procedures appear healthy early in life but go on to suffer in later life from heart failure, pulmonary hypertension, loss of muscle mass, frailty, and premature death."

In the body, most of the DNA is contained in the [cell nuclei](#). In humans, this is where approximately 20,000 genes of the genome are located. However, another 37 genes are located outside the nucleus. "These genes are located in cellular compartments called mitochondria and constitute the mitochondrial DNA," explained Dr. Enríquez.

Nuclear DNA is transmitted from parents to their offspring, with the mother and father contributing 50% shares that mix when an egg is fertilized by a sperm.

In contrast, mtDNA is inherited only from the mother because the sperm mitochondria are destroyed in the interior of the fertilized egg.

Uniparental transmission of mtDNA is found in almost all organisms. In addition, mtDNA is present in multiple copies per cell, and these copies are all essentially identical, a phenomenon known as homoplasmy.

The presence of more than one mtDNA genetic variant in the cell is called heteroplasmy. Although very rare, heteroplasmy sometimes occurs naturally as a result of mtDNA mutations and can cause several diseases. New therapeutic approaches proposed in recent years and aimed at preventing disease or treating infertility can generate a new form of heteroplasmy in people.

"This new form of heteroplasmy, involving distinct non-mutated mtDNA variants, is produced when an individual's cells contain both the original recipient mtDNA and the donor mtDNA transferred during the intervention. In the GENOXPHOS group at the CNIC, we have been investigating whether this breaching of a natural biological barrier has detectable physiological effects," said Dr. Enríquez.

The researchers show that the selection between mtDNA variants coexisting in the same cell depends on their impact on cell metabolism and can be modulated by variations in gene function, drug actions, and dietary changes. "All of these factors help to determine the preference for one type of mitochondrial genome over another," they write.

"The question as to why mtDNA is transmitted to descendants from only one parent has yet to be answered, but until now the issue had no health implications," said first author Dr. Ana Victoria Lechuga-Vieco. "The new medical therapies that breach this biological barrier can generate, intentionally or non-intentionally, mixtures of mtDNA from more than one individual in the same cell."

Before the publication of the new study, "we did not know what impact this mtDNA mixing had for the individual," said Dr. Enríquez.

To address this question, the GENOXPHOS group generated mice with a single nuclear genome but with all their cells simultaneously containing two distinct mtDNA variants. "This mouse strain was fertile, and [young animals](#) showed no related disease," explained Dr. Lechuga-Vieco.

But long-term analysis over the full lifetime of these mice showed that the coexistence of two mtDNA variants in the same cell compromised mitochondrial function.

"We observed that cells rejected the presence of two mitochondrial genomes, and most of them progressively eliminated one of the mtDNA variants. Surprisingly, however, major organs like the heart, lungs, and skeletal muscle were unable to do this," explained Dr. Lechuga-Vieco.

"Organs that could eliminate one of the mtDNA variants, like the liver, recovered their mitochondrial metabolism and cellular health, but those that could not progressively deteriorated as the animals aged," continued Dr. Enríquez.

Thus the animals, which appeared healthy in their youth, in later life suffered from heart failure, pulmonary hypertension, loss of muscle mass, frailty, and premature death.

The researchers conclude that the dangerous effects of mitochondrial therapeutic interventions identified in the new study show the need for caution in the selection of the donor mtDNA genotype.

As the authors state in their article, the results of the *Circulation* study also imply that "Even the most promising method, for the replacement of oocyte mitochondria carrying known pathological mtDNA mutations,

may fail to achieve 100% replacement."

The study shows that recipient cells have a high capacity to select and amplify the original, pre-existing mtDNA variant, which may have been undetectable before transfer of the donor mtDNA. The procedure thus has the potential to result in a mix of mtDNA from two individuals in descendent cells. "The same problem arises with oocyte rejuvenation by microinjection of donor cytoplasm," pointed out Dr. Enríquez.

Similarly, added Dr. Enríquez, "A similar risk can arise when purified donor mitochondria are used to treat damaged [cells](#) implicated in cardiopulmonary or neurological diseases."

Dr. Enríquez stressed that these risks do not mean that mitochondrial replacement therapy should be abandoned. In the same way as blood transfusions and organ transplants require careful control of compatibility between recipient and donor, Dr. Enríquez recommends that any therapeutic strategy that risks the mixing of healthy mtDNA variants from two individuals should "ensure full compatibility between the donor and recipient mitochondrial genomes."

More information: Ana Victoria Lechuga-Vieco et al, Heteroplasmy of Wild Type Mitochondrial DNA Variants in Mice Causes Metabolic Heart Disease With Pulmonary Hypertension and Frailty, *Circulation* (2022). [DOI: 10.1161/CIRCULATIONAHA.121.056286](https://doi.org/10.1161/CIRCULATIONAHA.121.056286)

Provided by Centro Nacional de Investigaciones Cardiovasculares Carlos III (F.S.P.)

Citation: Study highlights the risks of mitochondrial therapeutic interventions (2022, March 16) retrieved 4 May 2024 from

<https://medicalxpress.com/news/2022-03-highlights-mitochondrial-therapeutic-interventions.html>

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