Gene discovery in fruit flies could help search for new treatments for mitochondrial disease

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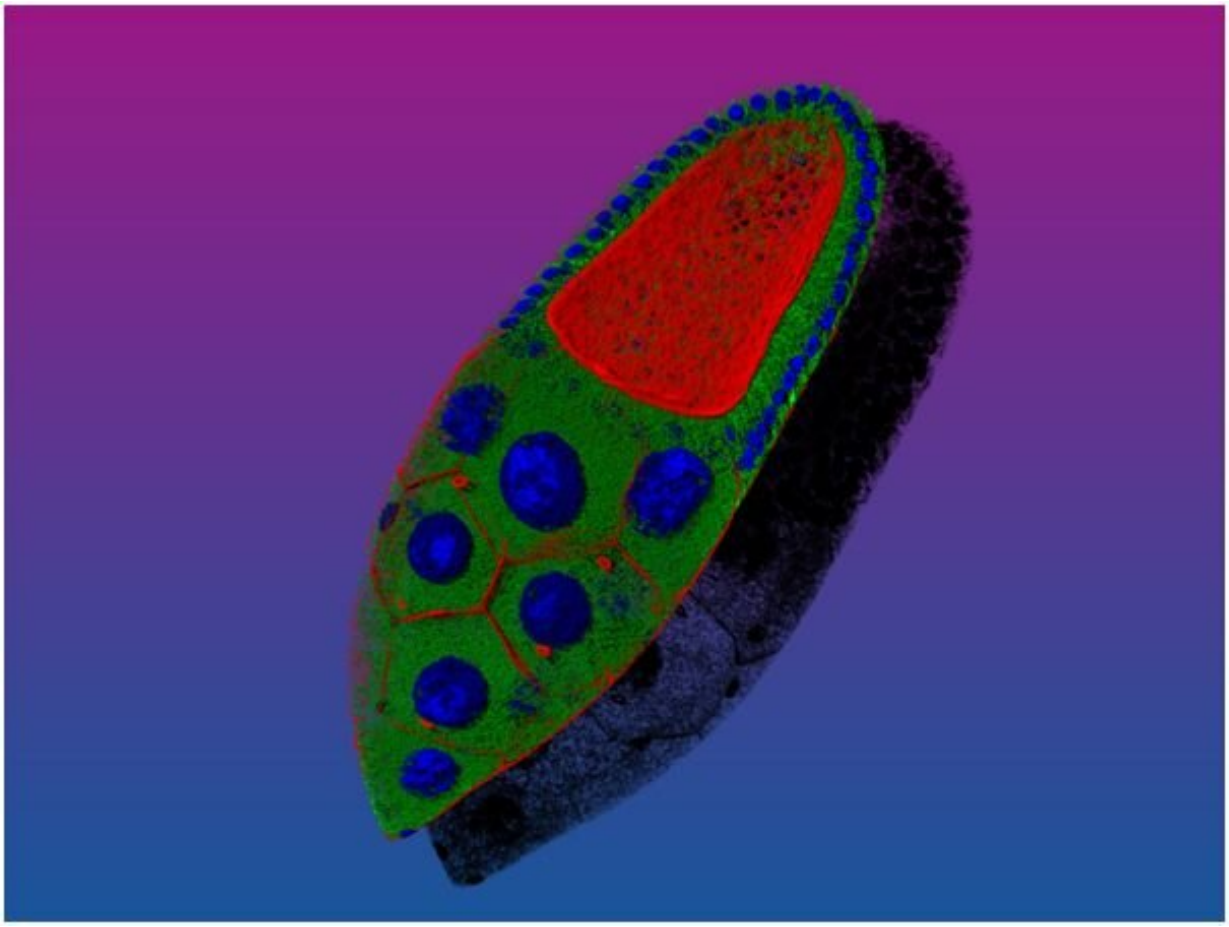

Picture 1 showing a Drosophila egg chamber stained for nuclear DNA (blue), actin (red), and mitochondria (green). The image is a 3-D reconstruction of around 80 confocal images. The egg chamber is an appropriate picture because mtDNA inheritance is maternal in humans and flies. Credit: University of

Scientists have identified a protein in fruit flies that can be targeted to reverse the effects of disease-causing mutations in mitochondrial genes. The discovery could provide clues about how to counteract human mitochondrial diseases, for which there is currently no cure.

Mitochondria, the powerhouses of the cell, are rod-shaped structures that generate almost all of the energy required by cells to perform their activities. Mitochondria carry their own DNA—mitochondrial DNA—which encodes 13 proteins essential for producing energy. This is distinct from the DNA in the cell nucleus—'nuclear DNA'—which encodes the blueprint for the whole organism. While nuclear DNA is derived half from each parent when an egg is fertilised by a sperm, mitochondrial DNA (mtDNA) is inherited solely from the mother, through the egg.

A typical cell has two copies of the nuclear DNA, but often contains hundreds or even thousands copies of mtDNA. During development and ageing as mtDNA continues to replicate, mutations can occur to some of the copies. This means that individuals will carry a mixture of mutated and healthy mitochondrial genomes, which constantly compete with each other to alter their relative abundance.

Some of these mutations are potentially harmful. Often, these harmful mutations are present in low abundance when they first arise, and their proportion remains low in many healthy individuals. However, in some people, they increase in abundance over time.

When the proportion of harmful mutations goes beyond 60-80% of all the mtDNA copies in a cell, there is not enough energy to support the

normal cellular activities, and disease symptoms will emerge. These disease symptoms can be further passed on to the next generation if mutant mitochondrial genomes are also present in high percentages in the mother's eggs.

To date, over 350 mutations in mtDNA have been reported to cause a spectrum of mitochondrial diseases that affect at least 1 in 5,000 individuals in the UK. Some of these conditions are fatal and there are currently no cures.

Researchers at the Wellcome Trust/ Cancer Research UK Gurdon Institute, University of Cambridge, have devised a model in the fruit fly to examine how the abundance of mutated mtDNA changes over time. This competition between healthy and mutated mitochondrial genomes is a fundamental feature of development and could be influenced by the nuclear DNA, but little is known about how.

The scientists created 'three-parent flies' which inherit some of their mtDNA from a second mother. This is done under the microscope using tiny tools where mitochondria from the second mother are transferred to fertilised fly eggs carrying genetic information from their original mother and father. The flies carry two competing mitochondrial genomes, one healthy and one mutated, that are normally balanced and co-transmitted to subsequent generations. However, a change in the nuclear DNA can tip the balance in favour of one mitochondrial genome at the expense of the other.

Using these three-parent flies in a 'genetic screen' allowed the scientists to measure the influence of every individual nuclear gene on the competition between healthy and diseased mitochondrial genomes.

The study identified multiple nuclear genes that could limit the harmful mitochondrial genome being passed on during development or to the

next generation. One of these genes codes for a protein called mtDNA polymerase. Reducing the amount of mtDNA polymerase increases the percentage of healthy mtDNA from 20% to 75% in just one generation. This increase eradicated disease symptoms and the new flies were much healthier.

There is no equivalent mouse model or human cell line in which scientists can perform such a genome-wide genetic screen to look at the effect of nuclear genes on the manifestation of mitochondrial disease. This model, using three-parent flies, is designed to help understand why mutant mtDNA may cause problems of different severity among different people and between different tissues in the body. The new results show that reducing the activity of a nuclear gene can almost eliminate the harmful mtDNA mutations and could potentially be used to reverse mitochondrial disease symptoms. This could provide a target for drugs to treat mtDNA-linked diseases.

"To achieve this dramatic change in the proportion of healthy mitochondrial DNA, we're not changing an individual's nuclear DNA," says lead author Dr. Hansong Ma, Group Leader at the Gurdon Institute. "All we are doing is reducing how much of certain proteins is produced. This could be achieved using drugs. Our fruit flies will help us rapidly screen potential drugs compounds."

The study is published in *Current Biology*.

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