How egg cells choose their best powerhouses to pass on

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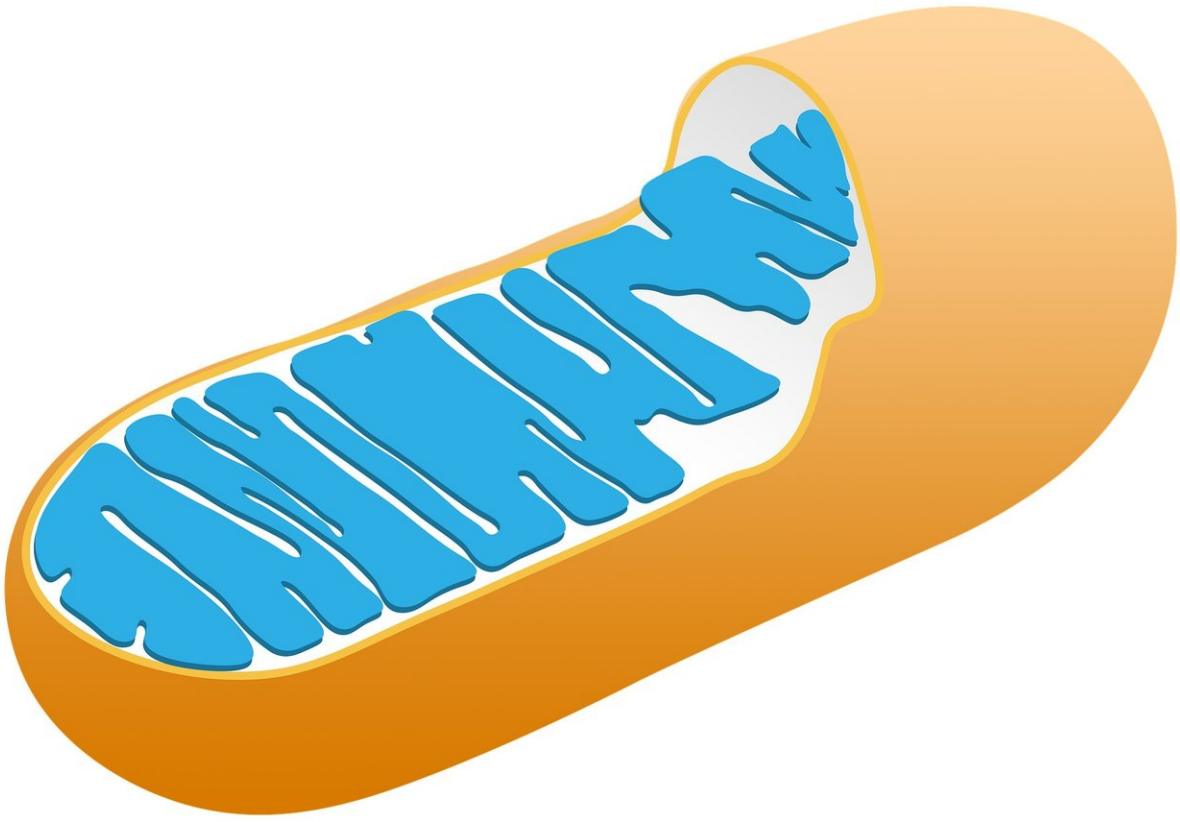

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Developing egg cells conduct tests to select the healthiest of their energy-making machines to be passed to the next generation. A new study in fruit flies, published online May 15 in *Nature*, shows how the testing is done.

The work focuses on mitochondria, the cellular machines that turn the sugars, fats and proteins we eat into energy used by the body's millions of cells. Led by researchers at NYU School of Medicine and the University of Toronto, the research team used a direct imaging technique to watch for the first time as maternal reproductive cells carefully choose which mitochondria to pass on.

"Our results confirm the theory that egg cells execute mitochondrial selection," says senior study author Ruth Lehmann, Ph.D., a Howard Hughes Medical Institute Investigator, Chair of the Department of Cell Biology, and Director of the Skirball Institute of Biomolecular Medicine, at NYU Langone Health. "The findings set the stage for new approaches to the treatment of mitochondrial diseases, which include myopathies that cause muscle weakness, neurological problems, and forms of diabetes."

Mitochondria are special among cellular machines in that they have their own DNA, called mitochondrial (mt) DNA. Unlike the much larger DNA sets (genomes) residing in the nuclei of cells, mtDNA is only passed on through the mothers' egg cells.

MtDNA is also more prone than nuclear DNA to develop random changes or mutations in its DNA code that build up as a person ages, but that also occur during the development of reproductive cells to cause

inherited diseases in roughly one in 4,300 children born in the United States.

Seeing Selection

A longstanding problem faced by the field was its inability to distinguish "good" mitochondria from bad, which hindered efforts to understand how mitochondria were sorted and inherited, says Lehmann.

For this reason, the current study was conducted in fruit flies (Drosophila melanogaster) designed to carry a mix of good (functional) and bad (mutant) mitochondria bearing fluorescent labels that set them apart. Having many cellular features, including mitochondrial selection, in common with humans, this fly species has served over time as a key model organism in the study of biological principles.

To protect their function, mitochondria are connected into long interconnected tubes that each contain many mtDNA molecules, researchers say. Within these tubes, mitochondria that, due to genetic flaws, fail to make any of the 13 proteins important for energy production (such as Adenosine-Tri-Phosphate (ATP)) can still survive by "borrowing" functional proteins made from other healthy DNA copies in the same tube.

By visualizing the process by which fly egg cells select mitochondria, the research team revealed that this process is triggered by a carefully timed drop in levels of Mitofusin, a protein that enables mitochondria to fuse. In the face of dropping Mitofusin levels, mitochondria were seen to separate into fragments such that each fragment on average contained many fewer complete sets of mitochondrial DNA. This forced each mitochondrion to stand on its own in terms of energy production, with the fragmented mitochondria containing mutant mtDNA not producing ATP as well.

Based on this competition, bad mitochondria are eliminated, say the authors, and the pool of mitochondria in mature egg cells becomes better able to support a healthy embryo.

By watching the fluorescent probes, the research team revealed the timeframe during which bad mitochondria were eliminated during the development of egg-making cells (oocytes) in flies. The newfound timing in turn revealed the sorting mechanism, because selection only took place during the developmental stage at which mitochondria were fragmented. The study further determined that faulty mitochondria were removed through mitophagy, a process known to label waste products for destruction, and involving the proteins Atg1 and BNIP3.

Not only was a Mitofusin drop and a fragmentation phase necessary for selection against faulty mitochondria in female reproductive cells, say the authors, but it also triggered selection when artificially induced in non-reproductive cells where it does not occur naturally. This finding set the stage for studies already underway that are exploring whether inducing mitochondrial fragmentation, by blocking fusion briefly, in bodily tissues can be used like a "DNA cleanser" for diseases caused by mtDNA changes that accumulate with age.

More information: Mitochondrial fragmentation drives selective removal of deleterious mtDNA in the germline, *Nature* (2019). DOI: 10.1038/s41586-019-1213-4 , www.nature.com/articles/s41586-019-1213-4

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