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How mitochondrial gene defects impair respiration, other major life functions

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Researchers are delving into abnormal gene function in mitochondria, structures within cells that power our lives. Mitochondria are the place where energy is generated from the most basic molecules of food. Because this function is essential to life, defects in mitochondria may affect a wide range of organ systems in humans and animals.

Some names of mitochondrial disorders are Leigh's disease, MELAS syndrome and complex I deficiency. These are often severe and progressive conditions that attack brain, muscles and numerous other parts of the body.

Mitochondrial diseases are individually very rare, but because hundreds of them exist, they collectively have a large impact, affecting at least 1 in 5,000 people, and perhaps more, who often remain undiagnosed. In addition to a wide array of diseases originating in the mitochondria itself, malfunctioning mitochondria also contribute to complex disorders like Parkinson's disease, Alzheimer's disease, epilepsy and diabetes, among others.

For such crucial biological actors, much remains unknown about exactly how mitochondria function. A new study, published Aug. 12 in the online journal PLoS One, sheds light on mitochondrial biology.

Using genetic engineering, researchers interrupted the activity of individual genes directly involved in the production of energy within mitochondria. "If we knock down the function of specific system

components, what happens?" said study leader Marni J. Falk, M.D., who directs the Mitochondrial-Genetics Disease Clinic at The Children's Hospital of Philadelphia. "Our ultimate goal is to translate the knowledge into targeted therapies, that is, effective ways to intervene. But first we need to understand the underlying disease mechanisms."

Falk's team made use of a simple model organism often studied in biology, Caenorhabditis elegans, which is a small worm called a nematode. Because mitochondria arose very early in evolution and play such fundamental roles in multicellular organisms, learning the details of how mitochondria function in C. elegans provides useful clues to understanding their function in humans.

Falk and colleagues studied a biological pathway that occurs within mitochondria, called the respiratory chain. They specifically focused on the largest component of that chain, complex I, which contains 45 subunits and is the most common culprit in human mitochondrial disease.

Her team studied the nuclear genes for 28 different complex I subunits that are very similar between humans and C. elegans, as well as two genes that help assemble the subunits into a functioning complex. By using a technique called RNA interference to knock out the function of each gene, they were able to determine how gene defects may contribute to mitochondrial diseases.

The study team found that one subset of genes impairs the ability of mitochondria to consume oxygen, called respiratory capacity, in C. elegans. Another group affects how the worms react to anesthesia. "Some children with mitochondrial complex I disease are hypersensitive to anesthesia, so this new understanding may be important in guiding their clinical management," said Falk.

Because mitochondrial diseases in humans comprise a large number of different disorders showing a wide range of severity, understanding the differences in contributions from different genes within the respiratory chain may help researchers better understand why mitochondrial dysfunction causes specific problems in people. Even better, says Falk, such research points to genes that might be targeted in potential treatments.

Dr. Falk's team continues to work to explore the many different consequences of mitochondrial respiratory chain dysfunction in animal models, and ways in which these consequences might themselves be treated. This work helps to suggest specific genes that may be the cause of mitochondrial disease in individual patients, as well as clarify the biology of how specific genes may cause disease. "Such work might one day benefit patients by pointing to specific drugs that alleviate secondary problems that arise when the respiratory chain cannot do its job," added Falk.

Source: Children's Hospital of Philadelphia (news : web)