

Mitochondrial DNA mutations can cause degenerative heart and muscle disease

A single change in the DNA of mitochondria – the cellular power plants that generate energy in all human cells – has been found to cause degenerative heart and muscle disease, according to University of California, Irvine researchers.

The study provides new insights into age-related disease and further proof that the mitochondria play a central role in human health. Study results appear in the Feb. 15 issue of *Science*.

Douglas Wallace, director of the Center for Molecular and Mitochondrial Medicine and Genetics at UC Irvine and study leader, says the findings also address a core dilemma facing efforts to cure and treat inherited degenerative diseases, including chronic heart and muscle disease.

“While these diseases traditionally have been assumed to result from mutations in the genes encoded by DNA in the cell’s nucleus,” he said, “most common degenerative diseases frequently do not exhibit inheritance patterns wholly consistent with our understanding of these nuclear DNA genetics. Our demonstration that mutations in the mitochondrial DNA can also cause the same diseases means that both nuclear and mitochondrial DNA genes that affect mitochondrial function can contribute to disease risk.”

A complete understanding of the importance of mitochondrial defects caused by either mitochondrial or nuclear DNA mutations could lead to treatments effective for age-related diseases that affect millions worldwide, Wallace added.

To prove the importance of mitochondrial DNA mutations for health, the UC Irvine researchers generated a relatively mild mitochondrial DNA mutation in mouse cells, which reduced a key enzyme of mitochondrial energy production by 50 percent.

They then used female mouse embryonic stem cells to create mice in which this mitochondrial DNA energy deficiency mutation was inherited through the female germ line, which is the reproductive cells and other genetic material passed to offspring. Mice harboring the mutant mitochondrial DNA appeared normal early in life, but by one year they developed marked muscle and heart disease, similar to disease that can develop in humans.

“Consequently, mitochondrial DNA mutations and their related energy defects are sufficient to cause age-related disease,” said Wallace, the Donald Bren Professor of Biological Sciences and Molecular Medicine and a National Academy of Sciences member. “Therefore, mitochondrial energy deficiency may be a common factor in these diseases.”

Weiwei Fan, Katrina Waymire, Navneet Narula, Peng Li, Christophe Rocher, Pinar Coskun, Mani Vannan, Jaget Narula and Grant MacGregor of UC Irvine also participated in this study, which is supported by the National Institutes of Health and the California Institute of Regenerative Medicine.

About mitochondria: Mitochondria exist in all human cells and have their own DNA. They generate energy by burning the calories that we eat with the oxygen that we breathe, much like a coal-burning power plant. In addition to energy, mitochondrial combustion generates “smoke” in the form of oxygen radicals. These oxygen radicals damage the mitochondrial DNA giving it a very high mutation rate, both in the tissues of our bodies and also in the cells of the female germ line.

Since the mitochondrial DNA is outside of the cell’s nucleus and not associated with its DNA, it is

inherited exclusively from the mother and is present in thousands of copies per cell.

As the mitochondrial DNA of our cells accumulates damage with age, the blueprints required to sustain energy production are lost, the body's equivalent of a brownout. The resulting age-related decline in cellular energy production ultimately leads to tissue and organ failure and the development of clinical disease or illness. Thus the accumulation of mtDNA damage may explain aging and the delayed-onset and progressive course of age-related diseases and aging.

Source: University of California - Irvine

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