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Researchers at UT Southwestern discover new function for old enzyme

DALLAS – Feb. 3, 2005 – In a step toward understanding the early evolution of the cell, researchers at UT Southwestern Medical Center have discovered that an enzyme important in the production of energy also protects the mitochondria, the energy factory itself.

The enzyme, called aconitase, is a well-known component of the pathway in cells that produces energy. But in a study using baker's yeast, Dr. Ronald Butow, professor of molecular biology, has shown a new function for the enzyme – keeping the mitochondrial genome intact.

The study is available online and in the Feb. 4 edition of the journal *Science*.

Mitochondria are the powerhouses of cells and create energy for all cellular processes. It is thought that mitochondria are descended from bacteria that originally took up residence in early cells. Through elements of a little-understood symbiotic relationship between the bacteria and the cell, the bacteria lost their independence and evolved into an organelle that provides energy for the cell. The relationship between mitochondria and the cell make each vital to the other's survival, and may explain a key biological event – the development of an efficient energy producer to fuel the evolution of more complex life forms.

Because of their supposed microbial origins, mitochondria have their own DNA, which is separate from the DNA in the cell nucleus. Cells that have lost their mitochondrial DNA do not pass on working mitochondria when they divide. Without working mitochondria, cells cannot produce energy efficiently. Events that lead to mitochondrial DNA defects are associated with neuromuscular diseases and premature aging disorders in humans.

"Mitochondrial DNA was discovered in the 1960s, and we still do not know much about how it is organized, packaged or inherited," said Dr. Butow. "What is really amazing is that we very recently discovered proteins associated with mitochondrial DNA that were thought to only have metabolic functions, and that aconitase, one of these proteins, is essential for mitochondrial DNA maintenance and inheritance, a new function independent of its normal enzyme activity."

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To determine the region of aconitase that keeps mitochondrial DNA intact, Dr. Butow's group made mutations in parts of the enzyme that are important for its catalytic activity. In spite of these mutations, aconitase still functions in the maintenance of mitochondrial DNA. The researchers concluded that aconitase's role in protecting the mitochondrial genome is independent of its role in making energy, giving a new face to the long-known enzyme.

Genes in the cell's nucleus code for aconitase, and once made, the protein is shuttled to the mitochondria to serve its functions. According to Dr. Butow, aconitase may participate in an internal cell communication system known as retrograde signaling. Retrograde signaling serves as a status-check in cells, where the mitochondria signal to the nucleus if something is wrong and when things are better again. By protecting the mitochondrial DNA, aconitase may be part of the "A-OK" signal after the cell experiences stress.

The role of aconitase in stabilizing the mitochondrial genome may be an evolutionary adaptation where the mitochondria co-opts a nuclearly encoded protein to ensure survival of its genome, said Dr. Butow. "The cell takes care of the nucleus, because that is where its genome is," he said, "but the mitochondrial genome is not looked after. It has to take care of itself."

Other UT Southwestern researchers who participated in the study are lead author Dr. Xin Jie Chen, assistant professor of molecular biology, and Xiaowen Wang, research assistant in molecular biology. Dr. Brett A. Kaufmann, a former graduate student at UT Southwestern now with the Montreal Neurological Institute, also contributed.

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