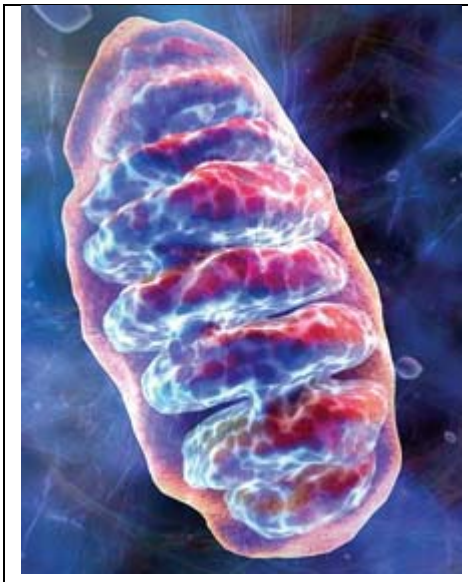
Technology Review
PUBLISHED BY MIT

Friday, September 21, 2007

# A Fountain of Youth in Mitochondria?

A recently discovered cell survival switch could be key to increasing longevity.
By Emily Singer

Cranking up an enzyme in a cell's powerhouse--the mitochondria--makes the cell resilient to stress and death, according to a study published today in the journal *Cell*. The findings could provide a new set of targets for drugs to treat the diseases related to aging, including Alzheimer's and diabetes. Scientists say that the research might also point to the long-sought source of caloric restriction's life-extending benefits.



**Youthful mitochondria:** The mitochondrion, shown here, is a tiny cellular structure that turns chemical fuel into cellular energy.

Boosting certain enzymes within the mitochondria protects the cell against stress and death, and may provide new drug targets for diseases related to aging.

Harvard biologist David Sinclair describes his research and the importance of age-related therapeutics

"Now we have a way of making drugs that can keep cells from dying and prevent diseases such as Alzheimer's," says David Sinclair, a biologist at Harvard Medical School, in Boston, who led the work. The findings broaden the focus of Sirtris Pharmaceuticals, a company based in Cambridge, MA, and cofounded by Sinclair, which is developing compounds that target the sirtuins, a class of enzymes previously linked to longevity. (See "The Enthusiast."). Thus far, the company has focused on a molecule that targets SIRT1, an enzyme that also boosts mitochondrial health but is found outside the mitochondria. "SIRT1 is the tip of the iceberg," says Sinclair. "Other sirtuins are also important for treating the diseases of aging."

Mitochondria are tiny energy factories within each cell that convert chemical fuel into energy. A growing body of evidence suggests that mitochondrial function plays a vital role in aging and age-related ailments, such as Alzheimer's, Parkinson's, heart disease, and type 2 diabetes. For example, mitochondria in older people are less efficient than those in younger people--a change that may underlie insulin resistance, a precursor to diabetes.

In the study, Sinclair and his collaborators genetically engineered cells to express higher levels of a mitochondrial enzyme called NAMPT, and then subjected those cells to toxic chemicals. They found that cells with higher enzyme levels were better protected against these chemicals and more resistant to cell death. The researchers also found that as long as the cells' mitochondria were healthy, the cells could stay alive, regardless of the state of the rest of the cell. "That means the mitochondria are the gatekeepers of cell survival," says Sinclair.

Boosting levels of the NAMPT enzyme increases amounts of a chemical known as NAD, a key cofactor in many metabolic reactions. NAD is also crucial for the function of sirtuins, which have previously been

linked to longevity. (See "The Fountain of Health."). The cell survival benefits seen in the current study appear to be dependent on two of these enzymes: SIRT3 and SIRT4, which could provide new targets for drugs to prevent diseases of aging, says Sinclair. "If you can find a drug that activates the SIRT3 enzyme, you can keep cells alive when they would otherwise die, such as in a neurodegenerative disorder."

Sinclair also suggests that this mechanism underlies the longevity benefits of caloric restriction. Decades of research has shown that a diet that provides adequate nutrition but severely limits caloric intake increases longevity in flies, worms, and mice, and seems to protect against the diseases of aging. "We know that caloric restriction keeps the mitochondria healthy, and we think we have uncovered a major mechanism of how caloric restriction works," says Sinclair. "It's exciting because it involves the mitochondria, the energy apex of the cell."

Source: http://www.technologyreview.com/biomedicine/19413/#afteradbody