Scientists discover new survival mechanism for stressed mitochondria

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Scientists at The Scripps Research Institute (TSRI) have discovered a natural mechanism that cells use to protect mitochondria, the tiny but essential "power plants" that provide chemical energy for cells throughout the body. Damage to mitochondria is thought to be a significant factor in common neurodegenerative disorders, cancer and even the aging process. The TSRI researchers' discovery could lead to new methods for protecting mitochondria from such damage, thereby improving human health.

"The mechanism that we've identified potentially gives us another way to treat the many disorders that involve mitochondrial dysfunction," said R. Luke Wiseman, the Arlene and Arnold Goldstein Assistant Professor in TSRI's Department of Molecular & Experimental Medicine.

Wiseman was the senior author of the new study, which appears in the December 3, 2013 issue of the journal *Cell Metabolism*.

Power Plants of the Cell

Mitochondria are microscopic reactors that burn oxygen to make ATP, the basic unit of chemical energy in cells. As such, they are the major consumers of the oxygen we breathe.

But the oxygen molecules concentrated within mitochondria are highly reactive, tending to modify proteins in unwanted ways, changing them into abnormal shapes and often causing them to become dysfunctional

and clump together. If this misfolding and aggregation gets out of control—induced by factors including genetic mutations, aging and environmental toxins such as pesticides—the result can be the failure of mitochondria and cell death.

To help protect themselves from excess protein misfolding and aggregation, cells have evolved signaling pathways that protect mitochondria during stress. These pathways primarily function by increasing the production of mitochondrial "chaperone" molecules that help keep proteins within mitochondria folded properly and protease enzymes that can cut up misfolded and aggregated mitochondrial proteins.

"These signaling pathways that regulate mitochondrial 'proteostasis' mechanisms, as we call them, have so far been poorly characterized in mammalian cells, but on the whole, they seem very important for cellular survival under stress," said Wiseman.

Reducing the Burden

In the new study, Wiseman and members of his laboratory, including first authors Kelly Rainbolt and Neli Atanassova focused on a third mechanism of mitochondrial proteostasis regulation: the reduced "import" of proteins into mitochondria.

"We predicted that reducing the population of newly imported proteins entering mitochondria would reduce the burden on mitochondrial chaperones and proteases during cellular stress," said Rainbolt.

The team started by examining a protein complex, TIM23, which works as one of the chief importers of proteins into the inner section, or matrix, of mitochondria. TIM23 contains a core subunit called Tim17, which—uniquely in mammals—has two almost-identical variants,

Tim17A and Tim17B, that incorporate into distinct complexes. The researchers used an environmental toxin, arsenite, to induce a general stress response in cultured mammalian cells and monitored alterations in Tim17A and Tim17B.

The results showed that Tim17A levels in the cells' mitochondria fell sharply in response to arsenite, while Tim17B levels were unaffected. Intriguingly, the authors found that the decrease in Tim17A was induced downstream of an established biologic signaling pathway that protects cells during stress. The decrease in Tim17A occurred not only because Tim17A production was reduced, but also because Tim17A was degraded more rapidly than usual. The team soon found that a mitochondrial protease, YME1L, is responsible for the stress-induced degradation of Tim17A.

"The capacity for an established, protective biologic signaling pathway to induce Tim17A degradation indicated to us that Tim17A degradation is likely a protective mechanism to promote mitochondrial proteostasis in response to pathologic insults," said Rainbolt.

In fact, the scientists showed that reducing Tim17A protein levels increased cellular survival in response to stresses that directly challenge mitochondrial proteostasis and function.

Since alterations in mitochondrial proteostasis mechanisms are common to many human diseases, including cancer and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, Wiseman notes that the identification of new cellular mechanisms regulating mitochondrial proteostasis, such as Tim17A degradation, suggests potential new therapeutic approaches to attenuate mitochondrial dysfunction in these diseases.

More information: "Stress-Regulated Translational Attenuation

Adapts Mitochondrial Protein Import Through Tim17A Degradation," *Cell Metabolism*, 2013.

Provided by The Scripps Research Institute

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