Scientists fill in a piece of the copper transport puzzle

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Researchers have identified the protein that carries copper into mitochondria, where copper is required for the functioning of the cell's energy conversion machinery. The discovery, published in the Feb. 9 issue of the *Journal of Biological Chemistry*, fills in a piece of the puzzle of how copper is distributed and used in the cell.

Humans acquire copper in trace amounts from food. Despite its low levels, copper is essential for the functioning of numerous important enzymes, for example some of those involved in synthesizing collagen and neurotransmitters. Notably, copper is required for building cytochrome c oxidase, known as COX, a large protein complex in mitochondria that forms the last step of the electron transport chain, which harvests energy for the production of ATP, the energy currency of the cell.

Paul Cobine of Auburn University and his collaborator Scot Leary at the University of Saskatchewan have been working for more than 10 years on understanding how copper is used to assemble COX. One of the basic questions was: How does copper get across the membranes in mitochondria?

"To get (copper) to the correct address (in the cell) without interfering with other proteins, or disrupting other targets that have a high chance of binding copper, is a herculean delivery effort," Cobine said. "This is akin to finding your way to an exit in a crowded bar without touching the other people or getting redirected. Then after finding the exit you must

make sure you go through the right door."

In the new paper, the researchers used multiple lines of evidence to arrive at an answer: Copper is transported within mitochondria by a protein called SLC25A3. This discovery was surprising because SLC25A3 was already known to transport phosphate, a negatively charged ion, whereas copper ions carry a positive charge. The researchers speculate that the copper ions may need to bind to another partner, forming a negatively charged complex, for SLC25A3 to be able to transport it. How the transporter distinguishes between its very different types of cargo is the next question the researchers want to address.

Previously known mutations in the gene encoding SLC25A3 are responsible for poorly understood genetic disorders involving dysfunctional heart and muscle fibers, leading to enlarged hearts and low muscle tone. As these tissues require large amounts of energy, it seems plausible that the symptoms these patients experience could be related to insufficient copper transport in mitochondria.

"(These symptoms) all sound like they could be related to both ATP production and cytochrome c oxidase," Cobine said.

With the discovery of the copper transport pathway within mitochondria, the health effects of copper can be studied in more detail because researchers will be able to distinguish the effects of copper on COX from the other pathways that it's involved in.

"If we don't deal with copper properly throughout our life, what are the metabolic diseases that (could) come up?" Cobine asks. "Now we have the ability to look at what happens when you lose mitochondrial copper at different (developmental) stages."

More information: Aren Boulet et al, The mammalian phosphate carrier SLC25A3 is a mitochondrial copper transporter required for cytochromecoxidase biogenesis, *Journal of Biological Chemistry* (2017). DOI: 10.1074/jbc.RA117.000265

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