Mitochondrial mystery: Investigating cells' power packs fuels understanding of rare, and common, diseases

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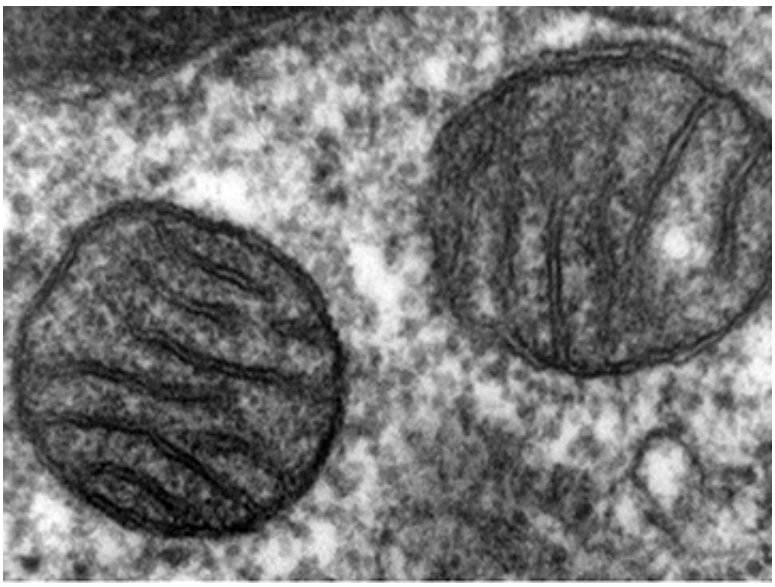

Finding what may be the final protein that allows mitochondria to absorb vital calcium promises to not only further explain how these cellular powerhouses work but also open the door for investigating links to rare and common diseases. Credit: Wikimedia Commons

(Medical Xpress)—Mitochondria, the powerhouses of our cells, would have been good models for the "Got Milk?" campaign; they have an insatiable thirst for calcium.

"It's an incredibly strong phenomenon. When you give mitochondria a

pulse of calcium, they just take in all of it," said Vamsi Mootha, professor of systems biology at Harvard Medical School and professor of medicine at Massachusetts General Hospital.

Taking in and sending out calcium appears to be one way mitochondria coordinate their activity with the rest of the cell. Cells may send calcium signals to mitochondria to turbocharge energy production during exercise. Absorbing and selectively releasing calcium may also allow mitochondria to fine-tune cellular signals that influence the release of neurotransmitters, muscle contraction, insulin release, gene activity and cell growth.

On the flip side, mitochondria that overindulge in calcium can burst and trigger cell death. Calcium buildups in mitochondria have been documented in common age-related conditions such as neurodegenerative disease, type 2 diabetes and muscle atrophy.

Although researchers noticed decades ago that mitochondria soak up calcium like sponges, they couldn't understand how it happens—or the role the process may play in disease—until they identified all the players.

Enter Mootha and his team of biologists, computer scientists, biochemists and clinicians. In the last 10 years they have systematically catalogued every protein that makes up mitochondria (they have found more than 1,000) and figured out which ones are involved in calcium intake (about five).

Now, they report in *Science Express* that they have found what they believe is the last link in the calcium transport chain: a protein called EMRE ("EM-ray").

The finding promises to not only further explain how mitochondria work but also open the door for investigating how the shuttling of calcium may

or may not contribute to disease—including rare mitochondrial illnesses that kill within the first months of life. Mootha and his clinical collaborators have long been engaged in trying to improve diagnostics and care for such children.

"As always with basic research, it's difficult to anticipate what the disease relevance may be, if any," said Mootha, who received a MacArthur Fellowship or "genius grant" in 2004. "But because we see an overload of calcium in so many pathologic states, we have strong reason to believe that understanding this channel is going to provide insight into these disease processes."

How mitochondria suck it up

A few years ago, Mootha's lab used a combination of comparative genomics and computation to identify the main components of what they call the calcium uniporter—that is, the molecules that transport calcium, and only calcium, from the cell body through the mitochondria's membrane.

The researchers determined mitochondria can't take in calcium without a key protein they named MCU, which sits in the inner membrane and forms a pore, as well as two related proteins they named MICU-1 and MICU-2, which act like sensors at the entry of the pore. A duplicate copy of MCU, called MCUb, has also been recently reported. But they suspected there was more to the story.

Since the team had reached "the limits of computation," Yasemin Sancak, a post-doctoral researcher in Mootha's lab and first author of the current paper, applied biochemical techniques to human cells in a lab dish to uncover any remaining players.

She found just one more distinct protein, EMRE, which she believes

serves two functions: linking the MICU-1/MICU-2 sensor to the MCU pore, and keeping the channel open to calcium when necessary.

"Because proper calcium transport is associated with rare inborn errors of metabolism as well as virtually every common age-associated pathology, we think knowing these components may provide insights into disease or even opportunities for targeting mitochondria for therapeutics," said Sancak.

The team also conducted an evolutionary analysis and discovered that EMRE is a much newer protein than its partners.

"MCU and MICU-1/MICU-2 were a part of the earliest mitochondria during the birth of eukaryotes. It's an ancient pathway. EMRE is special because it was born with animals," said Mootha.

"We think this means animals need more complex calcium regulation than simpler organisms," added Sancak.

In sickness and in health

While one part of Mootha's lab tries to understand the basics of how mitochondria work, another is investigating the links between mitochondrial dysfunction and disease.

One group Mootha hopes to eventually help are infants and children who suffer from rare mitochondrial disorders. Born with a defect in either nuclear DNA (which makes the 1,000 mitochondria-related proteins his team catalogued) or the mitochondria's own DNA (which makes just 13 proteins), such children typically die within a few months or years after birth.

"Some of the children will develop blindness, others neurodegeneration,

others cardiomyopathy, others will have a GI tract that stops moving. At present, we don't know how these defects within the machinery of the mitochondria give rise to the diverse spectrum of pathology," said Mootha, who has been spending more time in the lab than seeing such patients in recent years in part because there is little he can do for them without advancing research.

"These diseases are devastating, and we have poor diagnostic tools and no effective therapies," he said.

Combining their 1,000-protein catalog with the plummeting cost of gene sequencing has allowed his team to identify more than a dozen genes so far that are responsible for mitochondrial diseases and begin making specific diagnoses in patients. Other doctors and scientists around the world are following their lead.

Now another portion of his lab is able to focus on developing therapies for the children.

Whether calcium signaling has anything to do with these disorders has yet to be determined, said Mootha, although he suspects it will turn out to play a role.

"One of our hypotheses is that defects in mitochondria cause a secondary alteration in some of the calcium signaling, which might give rise to some of the pathology," he said. "There's no genetic evidence yet that calcium is important in these disorders. It gets back to the point that now that we know these components, we can sequence some of these patients' genes and ask, hey, is this what the cause of the disease is?"

The same holds true for the far more common conditions that have been associated with mitochondrial dysfunction, such as neurodegeneration and type 2 diabetes.

"Right now we don't know what's chicken and what's egg. Are the cells dying and as a consequence the mitochondria are swelling up with calcium? Or are mitochondria swelling up with calcium and driving the pathology?" said Mootha. "One of the things we'll be able to do now is genetically perturb the conduit for bringing calcium into mitochondria and pursue these questions with rigor."

More information: www.sciencemag.org/content/ear … nce.1242993.abstract

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