Mitochondria channel calcium

Mitochondria take up Ca^{2+} in response to certain stimuli, which upregulates aerobic metabolism and sensitizes cells to apoptosis, but the identity of the mitochondrial calcium uniporter (MCU) had remained elusive. De Stefani *et al.* now reveal that this long sought-after Ca^{2+} channel is a 40 kDa protein of the mitochondrial inner membrane.

As a uniporter regulator called mitochondrial calcium uptake 1 (MICU1; also known as CBARA1) was recently identified in the MitoCarta database (an inventory of mammalian mitochondrial genes), the authors searched this database for the actual MCU. They narrowed down the list of candidates to one protein, which they termed MCU, the tissue expression of which is ubiquitous and correlates with that of MICU1. Importantly, cell fractionation experiments and immuno-electron microscopy revealed that MCU localizes to mitochondria, along with mitochondrial markers, and more detailed experiments showed that it is found in the inner mitochondrial membrane.

To confirm that MCU has a role in mitochondrial Ca^{2+} uptake, the authors expressed small interfering RNA (siRNA) against MCU in HeLa cells and treated them with histamine, an inositol-1,4,5-trisphosphate-generating agonist that causes Ca^{2+} release from the endoplasmic reticulum. Mitochondrial Ca^{2+} uptake was significantly reduced in cells expressing MCU siRNA. In the converse experiment, overexpression of MCU caused an increase in mitochondrial Ca^{2+} uptake in response to histamine, sensitizing cells to apoptosis. Together, these data suggest that MCU is the mitochondrial Ca^{2+} channel.

Finally, to confirm the channel activity of MCU, the authors generated recombinant MCU protein, inserted it into lipid bilayers and tested its electrophysiological properties in response to Ca^{2+}. The results were in agreement with the characteristics previously reported for the unknown uniporter. For example, the MCU was inhibited by ruthenium red, which is known to inhibit Ca^{2+}uptake by isolated mitochondria. Furthermore, mutation of two negatively charged residues in the presumed pore-forming region of MCU abolished its channel activity.

As the authors explain, the identification of the mitochondrial Ca^{2+} channel means that "Informative animal models can now be generated and new drugs developed to influence processes regulated by mitochondrial Ca^{2+} signals, such as aerobic metabolism and cell death."

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ORIGINAL RESEARCH PAPER De Stefani, D. *et al.* A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter. *Nature* 19 Jun 2011 (doi:10.1038/nature10230)

> "MCU is the mitochondrial Ca^{2+} channel."

ADDENDUM

Calcium: Mitochondria channel calcium
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It has come to our attention that Baughman *et al.* reported similar findings in parallel to those discussed in this Research Highlight, identifying the core component of the elusive mitochondrial calcium uniporter (MCU), which they termed MCU, through genomic, physiological, biochemical and pharmacological approaches. We apologize to the authors of this paper for the omission.

ORIGINAL RESEARCH PAPER
Baughman, J. M. *et al.* Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter. *Nature* 19 Jun 2011 (doi:10.1038/nature10234)