CELL BIOLOGY

A sensor for calcium uptake

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Mitochondria — the cell's power plants — increase their energy production in response to calcium signals in the cytoplasm. A regulator of the elusive mitochondrial calcium channel has now been identified.

Various stimuli generate signalling by calcium ions, a mechanism that has wide-ranging roles in biology, triggering secretion, contraction and differentiation, among other processes. Many of these processes are energy-intensive, necessitating increased production of the energy molecule ATP by cellular organelles called mitochondria. Thus, when cytoplasmic calcium signals are generated, calcium ions also enter mitochondria, where they enhance the activity of many metabolic enzymes and thereby increase ATP production[1,2]. But how does Ca^{2+} enter mitochondria? Reporting on page 291 of this issue, Perocchi *et al.*[3] describe a protein that acts as a gatekeeper for the channel that transports Ca^{2+} into mitochondria — the first regulator of this channel to be identified.

The regulation of cytoplasmic and mitochondrial Ca^{2+} levels is tightly linked. Increased cytoplasmic levels of Ca^{2+} stimulate rapid uptake of the ion by mitochondria, and oscillations in Ca^{2+} levels in mitochondria can be observed in response to those in the cytoplasm[1]. When cytoplasmic Ca^{2+} levels are particularly high, mitochondria can act as a Ca^{2+} buffer, taking up and storing large amounts of the ion. Mitochondria thus modulate the dynamics of cytoplasmic Ca^{2+} signals and protect cells from Ca^{2+} overload, while simultaneously promoting longer-term increases in their own metabolic activity. In addition, excessive Ca^{2+} uptake by mitochondria activates pathways that lead to programmed cell death.

The delivery of cytoplasmic Ca^{2+} into mitochondria presents a special challenge. Unlike Ca^{2+} channels such as the IP_3 receptor in the endoplasmic reticulum (ER) — a cellular organelle that releases this ion into the cytoplasm — the mitochondrial uptake system works in the opposite direction, against the Ca^{2+} concentration gradient. Years of work have revealed that Ca^{2+} influx into mitochondria is driven by the presence of a strong negative electrical potential across the mitochondrial inner membrane, rather than by ATP-dependent pumping (which is used to transport Ca^{2+} from the cytoplasm into the ER). Moreover, various studies have shown that cells have physical junctions, created by connector proteins, that hold the ER and mitochondrial membranes in close proximity, being separated by only 10–30 nanometres of aqueous space. At these junctions, local Ca^{2+} concentrations may reach much higher levels than elsewhere, allowing mitochondria to directly take up Ca^{2+} ions released from the ER[4] (Fig. 1).

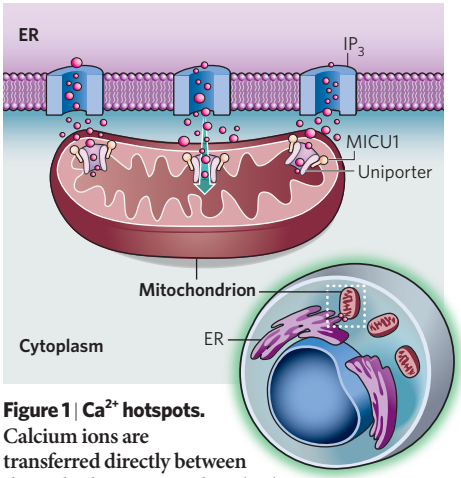

Figure 1 | Ca^{2+} hotspots. Calcium ions are transferred directly between the endoplasmic reticulum (ER) and mitochondria at junctions between the two organelles. This transfer is mediated by the IP_3 receptor in the ER membrane and the Ca^{2+} uniporter in the inner mitochondrial membrane. Although IP_3 receptors and uniporters are probably distributed all over their respective organelles, uniporters at junctions can be preferentially activated owing to the high local Ca^{2+} concentrations present. Perocchi *et al.*[3] identify MICU1 as a Ca^{2+}-sensitive regulator of the mitochondrial uniporter.

This unique mitochondrial Ca^{2+}-uptake channel has been termed the uniporter. It is located in the inner mitochondrial membrane — the outer membrane is freely permeable to Ca^{2+}. The uniporter is highly sensitive to Ca^{2+} concentrations, which suggests that not only is this ion transported through the channel, but it also functions as a regulator that can strongly increase the channel's activity. Once the ER is no longer releasing Ca^{2+} and cytoplasmic Ca^{2+} levels are again low, Ca^{2+} is moved out of the mitochondria and back into the cytoplasm by a Na^+/Ca^{2+} exchanger (NLCX)[5] in the membrane, and possibly by an ion-exchange mechanism mediated by a Ca^{2+}/H^+ exchanger (LETM1)[6].

The molecular identities of most Ca^{2+} regulatory proteins are known, but the mitochondrial Ca^{2+} uniporter has remained an enigma. To identify the uniporter and its immediate regulators, Perocchi *et al.*[3] performed a highly focused genetic screen, considering only candidate genes that met three criteria.

First, the authors obtained their shortlist of candidates by using a catalogue of mitochondrial proteins that they had produced earlier[7] and selecting proteins of the inner mitochondrial membrane — the site of the uniporter's action. Second, they made use of evolutionary knowledge. Research in diverse organisms has established that uniporter activity is present in vertebrates and in a highly divergent branch of protozoa known as kinetoplastids, but is absent from the mitochondria of the yeast *Saccharomyces cerevisiae*. Perocchi and colleagues therefore focused on genes encoding mitochondrial proteins that are present in vertebrates and kinetoplastids, but not in yeast. Finally, they considered only genes that are broadly expressed across mammalian cell types. Combined use of these filters left just 13 candidate genes.

From RNA interference experiments performed to identify genes necessary for Ca^{2+} uptake, Perocchi *et al.* singled out the gene encoding a protein that they name MICU1 (for mitochondrial Ca^{2+} uptake 1). The authors find that MICU1 triggers Ca^{2+} influx into mitochondria when the ion binds to two sites, known as EF hands. These EF hands provide an appealing explanation for the strong regulation of the uniporter by Ca^{2+}. Although MICU1 could in principle be the uniporter itself, a sequence analysis shows that it probably has only one transmembrane region. As ion channels typically contain many such regions, MICU1 is more likely to be the Ca^{2+} sensor that regulates uniporter activity.

If proven correct, Perocchi and co-workers' identification of the Ca^{2+} sensor is a significant advance, because it provides a path to identifying the uniporter channel itself, as well as being a starting point for mechanistic studies. For example, how do the EF hands of MICU1 'gate' the activity of the channel? Also, previous work suggests that the Ca^{2+} sensing responsible for mitochondrial Ca^{2+} uptake occurs at the ER–mitochondrion junctions, and so the present study offers experimental possibilities for studying Ca^{2+} signalling at these junctions.

Perocchi and colleagues' work provides a compelling example of the power of comparative genomics. With the number of sequenced genomes of various organisms steadily increasing, and a wealth of data available on the phenotypic properties of different organisms, similar strategies may provide an effective route to discovering the missing molecular components of crucial cellular processes. ■

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