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Getting metals into mitochondria

Scientists consider mitochondria, an organelle within cells, as a power plant. But mitochondria are also a site for metallurgy. There iron enters heme, the compound that binds oxygen in hemoglobin and certain other proteins, or helps form iron-sulfur proteins, crucial for metabolic functions in mitochondria and cells; manganese helps manage the oxygen that contributes to power generation. Because no one had previously found a route for iron and manganese to enter mitochondria, some scientists had proposed that these metals freely access the organelle. We thought this idea was unlikely because mitochondria handle iron and oxygen so near each other they could interact to form toxic, highly reactive molecules. Hence iron entry into mitochondria should be carefully controlled to minimize risk.

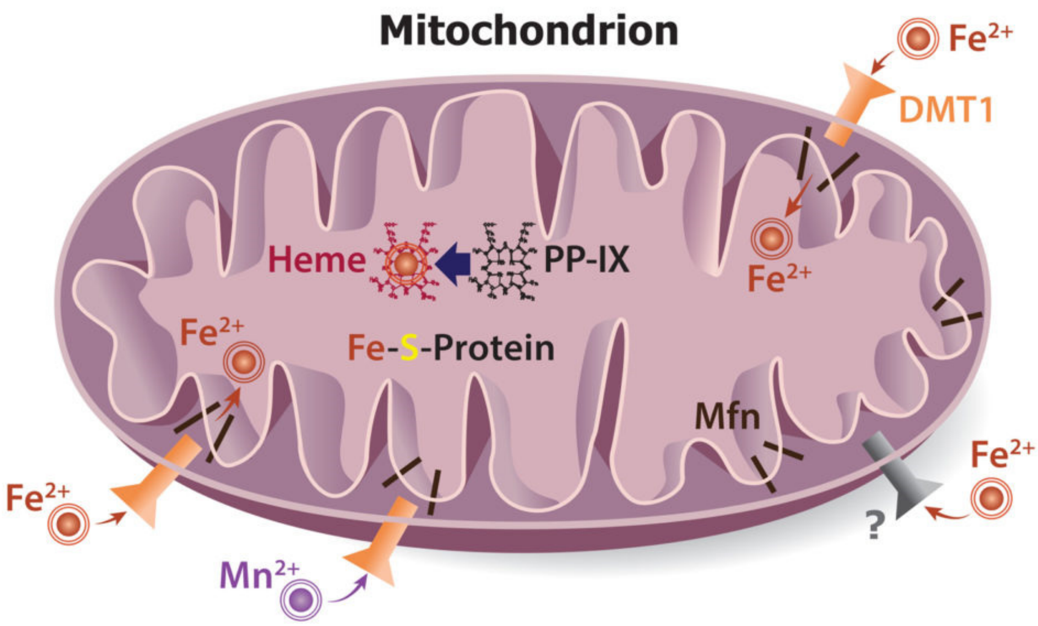

Fig. 1. Metallurgy and the mitochondrion. Mitochondria have an outer membrane and an inner one. DMT1 penetrates the outer membrane where it enables manganese (Mn2+) and iron (Fe2+) entry; while the unidentified transporter (?) also contributes to Fe2+ import. Yet another transporter, mitoferrin (Mfn) gets Fe2+ into the central part of the organelle where it combines with protoporphyrin-IX (PP-IX) to form Heme or attaches to an iron sulfur protein. Association of Mfn on the inner membrane with DMT1 on the outer is hypothetical, not experimentally proven.

We already knew that a metal transporter called DMT1 is the major intestinal iron transporter where it can also transport manganese (and some other metals). DMT1 is also present on the outer cell membrane of many cells where it again helps govern metal entry into cells. DMT1 can also move from there to the membrane of intracellular vesicles where DMT1 participates in iron entry as part of a process called the transferrin cycle. When we found that DMT1 associated with several known mitochondrial proteins, we suspected DMT1 could also be located in that organelle. So DMT1 on the mitochondrial membrane might regulate entry of metals into the organelle.

Fortunately, we had cell lines engineered to increase DMT1 under certain experimental conditions and could show that levels of DMT1 found on mitochondria also reflected that increase. Isolated mitochondria from the cells with low and high levels of DMT1 revealed that manganese entry into the mitochondria was almost entirely dependent on the level of DMT1. Iron entry was more complex. There was dependency on the level of DMT1, but it ultimately became clear that mitochondria had another regulated mode of iron transport where the transporter has yet to be identified. Two different known DMT1 inhibitors blocked DMT1's contribution to iron or manganese into mitochondria. Both metals' import also responded to pH just as DMT1 does, namely low pH promoting uptake and high pH reducing import; and the binding of iron was that expected for DMT1.

We showed that mitochondria isolated from rat kidney cortex, where there is a naturally high level of DMT1, took up iron in a similar fashion as in cell lines. Similarly, renal mitochondria took up manganese if they came from normal (+/+) rats but failed to do so if they came from Belgrade (-/-) rats where the DMT1 gene from both parents has mutated to lose function. Those from +/- rats, where only one gene of the DMT1 gene pair is mutated, had intermediate incorporation of the metal. There is also a high level of DMT1 in mitochondria of red blood cell precursors where lots of iron influx is needed to make the heme of hemoglobin so hemoglobin can bind oxygen. Therefore DMT1 controls manganese entry into mitochondria, but another as yet unknown transport system as well as DMT1 facilitates iron entry. It provides some satisfaction to learn that nature does provide a way for cells to manage the import of metals into mitochondria and part of that process is a familiar transporter, DMT1, used by nature to allow iron and manganese entry into the gut. So often when we learn the answer to a question, however, we get another question and here the next question is – what is the other transport system that allows rapid import of iron into mitochondria?

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Publications

A role for divalent metal transporter (DMT1) in mitochondrial uptake of iron and manganese.
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Mitochondria represent another locale for the divalent metal transporter 1 (DMT1).
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