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Review

Mitochondrial iron homeostasis and its dysfunctions in neurodegenerative disorders

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ABSTRACT

Synthesis of the iron-containing prosthetic groups—heme and iron–sulfur clusters—occurs in mitochondria. The mitochondrion is also an important producer of reactive oxygen species (ROS), which are derived from electrons leaking from the electron transport chain. The coexistence of both ROS and iron in the secluded space of the mitochondrion makes this organelle particularly prone to oxidative damage. Here, we review the elements that configure mitochondrial iron homeostasis and discuss the principles of iron-mediated ROS generation in mitochondria. We also review the evidence for mitochondrial dysfunction and iron accumulation in Alzheimer's disease, Huntington Disease, Friedreich's ataxia, and in particular Parkinson's disease. We postulate that a positive feedback loop of mitochondrial dysfunction, iron accumulation, and ROS production accounts for the process of cell death in various neurodegenerative diseases in which these features are present.

Contents

Abbreviations: ABC, ATP-binding cassette; AβOs, Aβ oligomers; AD, Alzheimer's disease; APP, amyloid precursor protein; DHBA, dihydroxybenzoic acid; CALG, calcein green; DMT1, divalent metal transporter 1; FA, Friedreich's ataxia; FPN1, ferroportin 1; IRP1, iron-regulatory protein 1; HD, Huntington's disease; Htt, Huntingtin; ISC, iron–sulfur cluster; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Mtfrn, mitoferrin; LIP, labile iron pool; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PHFs, tau paired helical filaments; ROS, reactive oxygen species; RPA, rhodamine B[(1,10-phenanthroline-5-yl)aminocarbonyl]benzyl ester; SNc, substantia nigra pars compacta; TfR1, transferrin receptor 1.

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1. The key role of mitochondria in iron metabolism

Iron is an essential cofactor in many fundamental biological processes, including DNA synthesis and repair, oxygen transport, cellular respiration, metabolism of xenobiotics, and hormonal synthesis (Gutteridge and Halliwell, 2000). The mitochondrion plays a key role in iron metabolism because it is the cellular location for the synthesis of iron–sulfur clusters (ISCs), prosthetic groups that are vital for cell function (Dailey and Meissner, 2013; Stehling et al., 2013).

The most common ISCs are 2Fe–2S and 4Fe–4S, which are formed by iron atoms tetrahedrally coordinated with bridging sulfides. These ISCs are bound to proteins, most often through cysteine and histidine residues. In the electron transport chain, 12 ISCs transport electrons from complex I to complex III, and 5 heme-containing proteins transport electrons through complexes III and IV (Rouault and Tong, 2008). Examples of other proteins with ISCs are ferrochelatase, which is involved in the addition of iron to porphyrin IX for heme synthesis, enzymes of the citric acid cycle such as mitochondrial aconitase and succinate dehydrogenase, replicative DNA polymerase, and ribonucleotide reductase, an enzyme that catalyzes the formation of deoxyribonucleotides from ribonucleotides. For a comprehensive listing of ISC-containing proteins, refer to http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Iron-Sulfur+Proteins. Defects in the synthesis of ISCs result in varied disease states that include Erythropoietic protoporphyria, Myopathy, Friedreich's ataxia, Microcytic anemia, X-linked sideroblastic anemia and Cerebellar ataxia (Lill, 2009). The process of ISC synthesis is complex and the understanding of its regulatory mechanisms is in progress. The readers are referred to recent reviews for detailed description of the components and mechanism of ISC synthesis (Beilschmidt and Puccio, 2014; Lill et al., 2014; Maio and Rouault, 2014; Rouault, 2012; Stehling et al., 2013).

Among the various ISC-containing proteins, cytoplasmic iron regulatory protein 1 (IRP1), a cytoplasmic aconitase that contains a 4Fe–4S cluster and becomes active as IRP1 when the cluster dissociates from the protein (Haile et al., 1992; Shand and Volz, 2013), is of particular interest for this review. IRP1 is sensitive to a variety of oxidative stress signals that can either activate or inhibit it. Hydrogen peroxide (Sureda et al., 2005), nitric oxide (Stys et al., 2011), and peroxinitrite (Soum and Drapier, 2003) induce complete ISC dissociation, resulting in IRP1 activation. In contrast, superoxide only partially disassembles the 4Fe–4S cluster and abrogates both aconitase and iron regulatory element (IRE)-binding activity (Gehring et al., 1999). The activation of IRP1 by oxidative insults may be involved in neuronal death in disorders associated to increased reactive oxygen species (ROS) production, since activation of IRP1 may lead to increased iron uptake and a vicious cycle of more iron and more ROS-mediated damage (see below).

2. Mitochondrial iron homeostasis

Under homeostatic conditions, incoming iron reaches the cytoplasm where it is either taken up by ferritin for safe storage or is incorporated into mitochondria, a process likely carried out via multiple mechanisms (Fig. 1). The best-known pathway is inward iron transport mediated by mitoferrin, a protein located in the inner mitochondrial membrane (1). As discussed below, Fe^{2+} is the most likely iron species transported by mitoferrin, given its predominance in the reductive environment of the cytoplasm. Alternative mechanisms of iron delivery have been reported, although their details are only descriptive. An alternative mechanism is the delivery of iron to mitochondria by chaperone- or siderophore-mediated processes (2). Evidence obtained in yeast supports a model of delivery of cytosolic iron to mitochondria by a complex consisting of glutaredoxin 3 and Bovine lymphocyte antigen (BolA)-like proteins. Yeast cells lacking glutaredoxin 3 show impaired iron transfer to mitochondria and impaired ISC and heme synthesis (Muhlenhoff et al., 2010; Philpott, 2012). An alternative molecule possibly involved in mitochondrial iron delivery is the mammalian siderophore 2,5-dihydroxybenzoic acid (2,5-DHBA). Knockdown of 3-OH butyrate dehydrogenase, the enzyme that catalyzes 2,5-DHBA formation, results in 2,5-DHBA depletion, elevated levels of cytoplasmic iron, and depletion of mitochondrial iron (Devireddy et al., 2010). Further work by Cabantchik's group provided evidence for a fluid-phase endocytic mechanism of non-transferrin-bound iron (Shvartsman and Ioav Cabantchik, 2012; Shvartsman et al., 2007). In this model, endocytic vesicles containing extracellular non-transferrin-bound iron deliver iron to mitochondria without passing through the cytosolic LIP (3). Another mechanism of mitochondrial iron delivery without passing iron through the cytosolic LIP is the so-called transferrin "kiss-and-run" model (4), which proposes that iron released from transferrin in the endosome is delivered via direct interaction of endosomes with mitochondria (Sheftel et al., 2007). In this model, iron delivery to mitochondria is only mildly affected by cytosolic iron chelators.

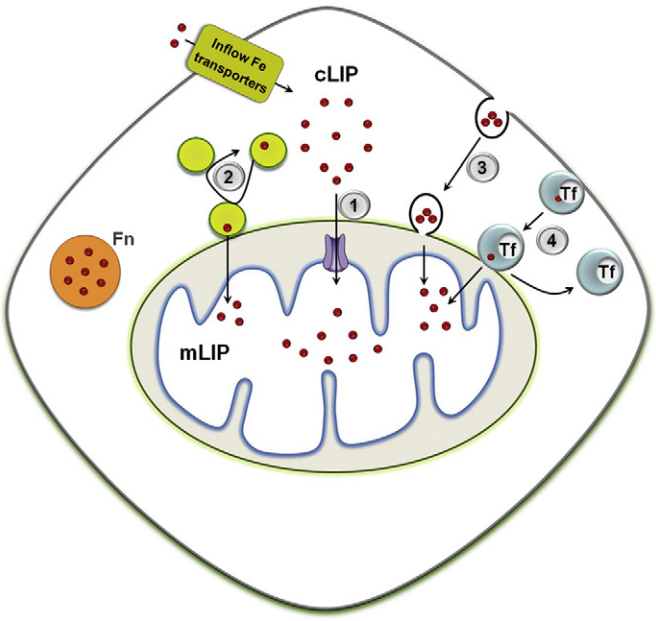

Fig. 1. Multiple routes of iron entrance into mitochondria. Iron entrance into mitochondria may be achieved by multiple mechanisms. The best-known pathway is the inward transport mediated by mitoferrin (pathway 1 (Paradkar et al., 2009)), a protein located in the inner mitochondrial membrane. A second mechanism is the delivery of iron to mitochondria through a chaperone- or siderophore-mediated process (pathway 2 (Muhlenhoff et al., 2010; Philpott, 2012)). A third model proposes the entrance of iron into the cell by fluid-phase endocytosis with subsequent delivery to mitochondria without passing through the cytosolic labile iron pool (cLIP) (pathway 3 (Shvartsman and Ioav Cabantchik, 2012)). A fourth mechanism proposes that iron released from transferrin (Tf) in the endosome is delivered through a direct interaction of endosomes with mitochondria (pathway 4 (Sheftel et al., 2007)). The relative importance of these iron delivery systems remains to be established. mLIP: mitochondrial labile iron pool. Fn: ferritin.

Although the relative contributions of these iron delivery mechanisms have not been determined, mitoferrin-mediated iron transport seems to be the predominant transport system. In addition, this type of transport is apparently regulated, because mitoferrin dysregulation is observed in pathological conditions of mitochondrial iron accumulation (Huang et al., 2009).

2.1. Mitochondrial iron homeostasis and the mitochondrial LIP

Mitochondria contain redox-active iron, as demonstrated by the presence of a redox-active mitochondrial LIP (Petrat et al., 2002b), which can potentially damage molecules that are susceptible to oxidation. Given the constitutive presence of ROS such as superoxide and H_2O_2, iron levels within the mitochondrion must be tightly regulated. An iron shortage affects numerous processes in which iron is a cofactor including the electron transport chain, whereas an excess of redox-active iron promotes the generation of the noxious hydroxyl radical.