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Review

Mitochondrial iron homeostasis and its dysfunctions in neurodegenerative disorders

Natalia P. Mena, Pamela J. Urrutia, Fernanda Lourido, Carlos M. Carrasco, Marco T. Núñez *

Department of Biology, Faculty of Sciences, Universidad de Chile, Santiago, Chile
Research Ring on Oxidative Stress in the Nervous System, Universidad de Chile, Santiago, Chile

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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.

* Corresponding author at: Biología, Facultad de Ciencias, Universidad de Chile, Las Palmeras 3425, Santiago 7800024, Chile. Tel.: +56 2 29787360.
E-mail address: mnunez@uchile.cl (M.T. Núñez).

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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.

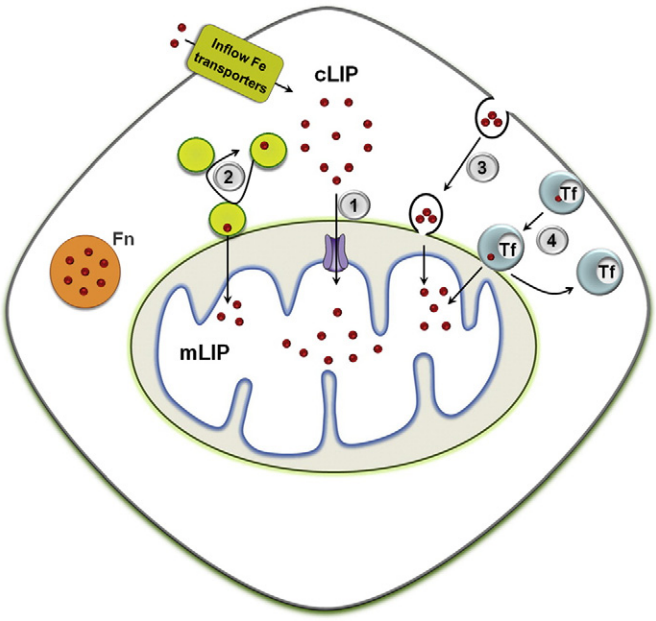

Fig. 1. Multiple routes of iron entrance into mitochondria. Iron entrance into mitochondria may be achieved by multiple mechanisms. The best-known pathway is the inward transport mediated by mitoferrin (pathway 1 (Paradkar et al., 2009)), a protein located in the inner mitochondrial membrane. A second 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.

The mechanisms by which mitochondria regulate their iron content and the possible interplay between cytoplasmic and mitochondrial iron are emerging but highly relevant subjects for understanding the mechanisms of mitochondrial dysfunction in neurodegenerative processes.

Extracellular iron is readily incorporated into both the cytosolic and mitochondrial LIPs, with the incorporation into mitochondria apparently preferential over incorporation into the cytosol (Fig. 2A, compare curves for CALG and RPA) (Shvartsman et al., 2007). Moreover, iron incorporation into mitochondria is minimally affected by the cytosolic chelator 5,5′-dimethyl-BAPTA, a compound that greatly impairs incorporation of iron into the cytosolic LIP. Iron incorporation into mitochondria as a function of the extracellular iron concentration is saturable (Fig. 2B) (Mazariegos et al., 2006). Incubation of HepG2 cells with different concentrations of iron results in the entry of iron into mitochondria until a steady-state level is reached (~10 μM; Fig. 2B′).

These studies suggest that the mitochondrion tightly regulates its uptake of iron. In addition, incorporation of iron into mitochondria is apparently preferential over incorporation of iron into the cytosolic LIP. Although the mechanisms responsible for this homeostasis and the apparent preference for mitochondria are unknown, the above observations underline the fundamental relevance of mitochondrial iron homeostasis for normal cell function.

3. Mitochondrial iron transporters

Fig. 3 shows the main mitochondrial proteins involved in iron flux. Below, we review the transporters that mediate iron flux and iron-containing groups across mitochondrial membranes.

3.1. Mitoferrin

The zebrafish mutant frascati shows decreased mitochondrial iron content and profound hypochromic anemia. The cause for these conditions was traced to a mutation in a gene for the mitochondrial solute carrier family 25 (SLC25) called mitoferrin (Shaw et al., 2006). The phenotype of frascati is restricted to developing red blood cells, because other cell types show no evidence of decreased mitochondrial iron. In mammalian cells, the mitoferrin-1 paralog, mitoferrin-2, is expressed ubiquitously. Knockdown of mitoferrin-1 or mitoferrin-2 results in decreased ISC and heme synthesis as a consequence of decreased mitochondrial iron content (Paradkar et al., 2009). Mitoferrin-1 and mitoferrin-2 levels are regulated post-translationally. The half-life of mitoferrin-1 protein is increased in developing red blood cells, resulting in its accumulation in mitochondria. In contrast, the half-life of mitoferrin-2 is low and does not accumulate in developing red blood cells or other cells (Paradkar et al., 2009). Mitoferrin-2 may require association with other proteins to mediate iron transport. In a cell model of erythroblast differentiation, mitoferrin-1 forms a functional complex with ferrochelatase, the terminal enzyme in heme synthesis, and the ATP-binding cassette transporter B10 (ABCB10), a mitochondrial inner membrane transporter whose expression is induced during erythropoiesis (Chen et al., 2009, 2010). The formation of a complex consisting of mitoferrin-1 and ferrochelatase optimizes iron delivery to ferrochelatase for efficient heme synthesis.

Little is known about the involvement of mitoferrin-2 in brain iron dyshomeostasis, although initial evidence points to its participation in mitochondrial iron accumulation. Mitoferrin-2 mRNA expression is upregulated in a mouse model of Friedreich's ataxia (FA) (Huang et al., 2009), a situation that is replicated in SHSY-5Y cells following treatment with the Parkinsonian toxin 1-methyl-4-phenylpyridinium iodide (MPP+) (Carroll et al., 2011); in this latter case, however, a paradoxical decrease in mitoferrin-2 protein was observed.

The species of iron transported by mitoferrins is unknown, although Fe^{2+} is most likely, given its predominance in the reductive environment of the cytoplasm. Studies with the mitoferrin yeast homologs Mrs3p and Mrs4p revealed that inner mitochondrial membrane vesicles

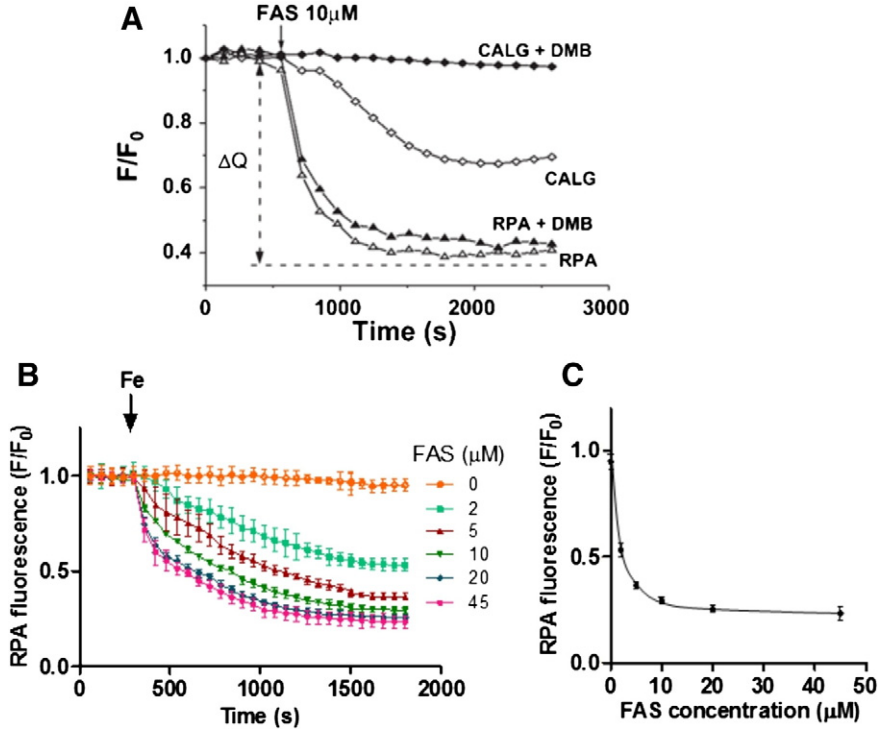

Fig. 2. The size of the mitochondrial LIP is regulated. A) H9c2 cells preloaded with the iron sensors rhodamine B-[(1,10-phenanthrolin-5-yl)aminocarbonyl]benzyl ester (RPA, (mitochondria) and calcein green (CALG, cytosol) were challenged with 10 μM ferrous ammonium sulfate (FAS) in the presence or absence of the intracellular chelator 5,5-dimethyl-BAPTA (DMB). Note that changes in mitochondrial LIP (RPA fluorescence) are not affected by DMB, whereas changes in cytosolic LIP (CALG fluorescence) are highly affected. ΔQ: delta of fluorescence quenching. Data are from Shvartsman et al. (2007). B) HepG2 cells loaded with the mitochondrial iron sensor RPA, the fluorescence of which is quenched upon iron binding, were challenged with different concentrations of FAS, and changes in RPA fluorescence were detected as a function of time. This figure was modified from Mazariegos et al. (2006). C) Plot of RPA fluorescence changes as a function of FAS concentration. Data were derived from B. The saturation of the mitochondrial LIP becomes evident at concentrations of FAS above 10 μM.

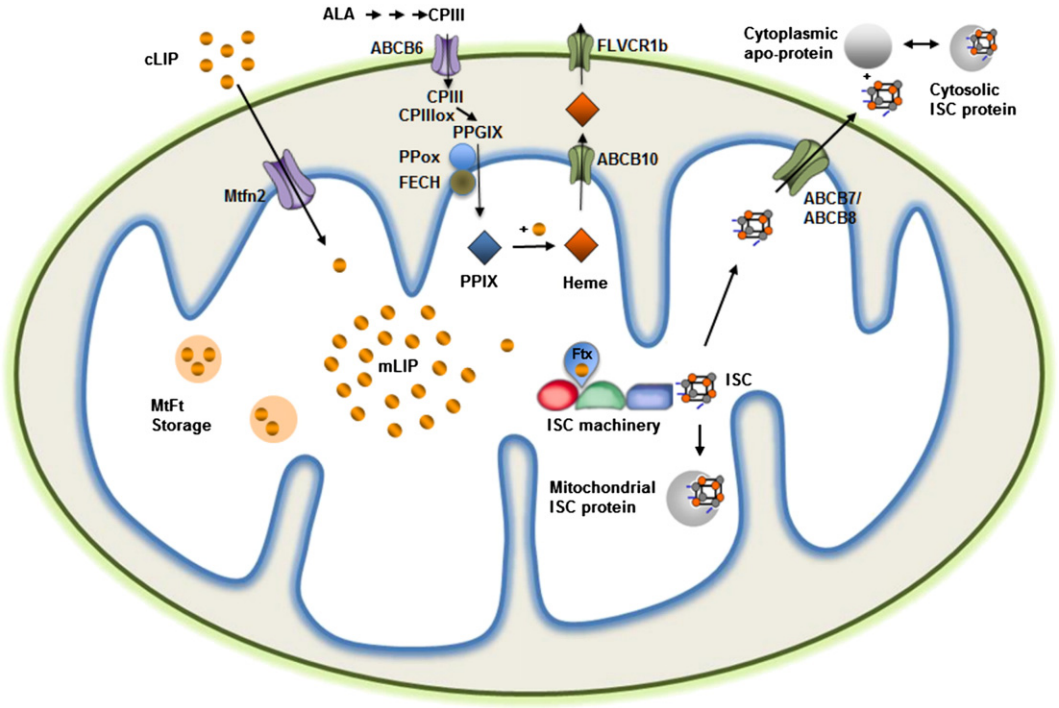

Fig. 3. Mitochondrial iron metabolism. Fe^{2+} from the cytosolic labile iron pool (cLIP) is imported into mitochondria by the Mtfrn2 transporter and becomes part of the mitochondrial LIP (mLIP). In the mitochondrial matrix, iron can (1) be stored in mitochondrial ferritin (FtMt), (2) bind to frataxin (Ftx), a chaperone that delivers iron to the ISC assembly machinery, or (3) bind to protoporphyrin IX to form heme. Newly formed ISCs are either incorporated as cofactors to mitochondrial apoproteins, for example proteins of the electron transport chain machinery, or are transported by ABCB7 and ABCB8 to the cytoplasm where they are incorporated into ISC-requiring apoproteins. The first step in heme biosynthesis occurs in the mitochondrial matrix with the formation of D-aminolevulinic acid (ALA), which is transported to the cytoplasm via an unknown mechanism. In the cytoplasm, ALA is converted by a series of reactions into coproporphyrin III (CPIII) that is transported back into the intermembrane space by the ABCB6 transporter. The enzyme CPIII oxidase catalyzes the decarboxylation of CPIII to yield protoporphyrinogen IX (PPGIX), which is converted to protoporphyrin IX (PPIX) by protoporphyrinogen oxidase (PPox), an enzyme located in the inner mitochondrial membrane. Heme is formed by the addition of Fe^{2+} to protoporphyrin IX, a reaction that is catalyzed by ferrochelatase (FECH), which is also located in the inner mitochondrial membrane. After synthesis, heme is transported into the intermembrane space, probably by ABCB10, and into the cytoplasm by FLVCR1b.

show rapid uptake of Fe^{2+} in response to iron starvation, whereas vesicles from the double deletion strain mrs3/4Delta show no measurable Fe^{2+} uptake. Interestingly, Cu^{2+} is transported at rates similar to Fe^{2+}, whereas Zn^{2+} and Cd^{2+} are not substrates (Froschauer et al., 2009).

Mitoferrin-2 may also be involved in the aging process. Iron accumulation in mitochondria and increased mitochondrial oxidative damage have been observed as a function of age (Atamna, 2004; Mallikarjun et al., 2014; Seo et al., 2008), although no evidence for the participation of mitoferrin has been demonstrated. In contrast, treatment of *Caenorhabditis elegans* with RNA interference for mitoferrin results in a 50–80% increase in lifespan, accompanied by decreased body size and reduced fecundity (Ren et al., 2012). These results indicate the importance of mitochondrial iron accumulation during aging and the possible participation of mitoferrin-2 in this process.

Taken together, these studies point to mitoferrin as the main way of iron entrance to mitochondria. Although there is no direct evidence at present, most probably mitoferrin expression and activity are regulated by the iron requirements of mitochondria. The role of mitoferrin in the process of mitochondrial iron accumulation observed in neurodegenerative diseases like PD, HD and FA, remains to be elucidated.

3.2. ISC transport

The transport of ISCs from mitochondria to the cytoplasm is mediated by the inner mitochondrial membrane transporter ABCB7 (yeast ATM1), in a process that requires reduced glutathione (Bekri et al., 2000; Lill et al., 2014; Pondarre et al., 2006). In humans, loss-of-function mutations in *ABCB7* results in a sideroblastic anemia condition called X-chromosome-linked sideroblastic anemia, in which patients show iron accumulation in mitochondria (Pondarre et al., 2007; Sato et al., 2011). Mice lacking ABCB7 show iron accumulation in mitochondria and decreased amounts of cytoplasmic proteins containing ISCs, without changes in mitochondrial proteins containing ISCs (Pondarre et al., 2006). In addition, silencing of *ABCB7* in HeLa cells causes mitochondrial iron accumulation (Cavadini et al., 2007), and disruption of *ABCB7* in *C. elegans* induces oxidative stress and cell death (Gonzalez-Cabo et al., 2011). These results strongly support the view that ABCB7 transports mitochondrial ISCs into the cytoplasm. No information is available regarding the putative regulation of ABCB7 expression in relation to ISC demand. ABCB7 may not work alone. Cardiac deletion of ABCB8 in mice results in acute mitochondrial iron accumulation, mitochondrial damage, and cardiomyopathy (Ichikawa et al., 2012). Iron accumulation is due to decreased iron export from isolated mitochondria. In addition, ABCB8 deletion leads to decreased activity of cytosolic, but not mitochondrial, iron–sulfur-containing enzymes. Thus, ABCB8, like ABCB7, mediates ISC export from mitochondria (Ichikawa et al., 2012). What regulates ABCB7/ABCB8 expression, how they are inserted in the inner mitochondrial membrane and whether there are other eventual components of the ISC export machinery are questions that require further research.

3.3. Relationship between ISC synthesis and cell iron status

Evidence presented here (Fig. 2) suggests that in iron supply terms, mitochondria have preference over cytoplasm, which eventually makes ISC synthesis more resilient to iron deficiency. Scanty but convincing evidence suggests that iron overload affect mitochondrial GSH levels. In neuroblastoma cells, iron overload decreases the GSH/GSSG ratio (Nunez et al., 2004), and decreased mitochondrial reduced glutathione was reported in a rat model of mitochondrial iron overload (Pardo Andreu et al., 2009). Thus, decreased mitochondrial GSH should be a consequence of iron overload. No direct evidence has been reported

about the putative effect of iron overload on ISC synthesis. Nevertheless, decreased mitochondrial GSH content caused by iron overload should decrease both ISC synthesis (Grx5) and export (ABCB7/Atm1).

3.4. Transport of heme precursors

The mitochondrion also is the cellular locus for the synthesis of heme. The incorporation of iron into protoporphyrin IX mediated by ferrochelatase accounts for the last step of heme synthesis. The link between iron deficiency and decreased heme synthesis is firmly established (Yannoni and Robinson, 1976). In contrast, the role of mitochondrial iron overload on heme synthesis has been less explored. In a rat model of human hereditary hemochromatosis, the activity and protein levels of the heme synthesis enzyme 5-aminolevulinate dehydrase (or porphobilinogen synthase) were significantly reduced, suggesting that iron-loading may produce a decrease in heme synthesis (Bonkovsky et al., 1987).

The identification of mitochondrial transporters for heme and porphyrin precursors has been hampered partially because of the complexities of heme biosynthesis, which takes place initially in mitochondria, continues in the cytoplasm, and finishes in mitochondria (Ajioka et al., 2006; Dailey and Meissner, 2013; Fleming and Hamza, 2012; Nilsson et al., 2009; Severance and Hamza, 2009) (Fig. 3). The first step in heme synthesis takes place in the mitochondrial matrix with the condensation of succinyl-CoA and glycine by aminolevulinic acid synthase to generate D-aminolevulinic acid. The mechanism of D-aminolevulinic acid export across the mitochondrial outer membrane into the cytoplasm is unknown. In the cytoplasm, D-aminolevulinic acid is converted to coproporphyrin III (CPIII), which is transported back into the mitochondrial intermembrane space, possibly via ABCB6; this transporter interacts with heme and porphyrins and transports CPIII from the cytoplasm into mitochondria (Krishnamurthy et al., 2006), where it is converted to protoporphyrinogen III and then to protoporphyrin IX. Heme is formed by the addition of Fe^{2+} to protoporphyrin IX by ferrochelatase, an enzyme associated with the inner membrane.

The nature of the proteins that transport heme out of mitochondria has been demonstrated only recently. After synthesis, heme is transported into the mitochondrial intermembrane space probably by M-ABC2, later named ABCB10 (Zhang et al., 2000). Evidence from immature erythroid precursors shows that newly formed heme is transported from the intermembrane space into the cytoplasm by feline leukemia virus subgroup C receptor 1b (FLVCR1b), an isoform of Flvcr1 that transports heme out of the cell (Chiabrando et al., 2012). Overexpression of *Flvcr1b* in K562 cells promotes heme synthesis and erythroid differentiation, whereas its silencing causes mitochondrial heme accumulation and termination of erythroid differentiation (Chiabrando et al., 2012).

To identify unknown transporters that may be involved in mitochondrial iron acquisition, a large-scale computational search was performed to identify mitochondrial proteins that are consistently coexpressed with the core machinery of heme biosynthesis. The study identified SLC22A4, SLC25A39, and TMEM14C as putative mitochondrial iron transporters. Moreover, knockdown of all three putative transporters in zebrafish results in profound anemia as indicated by the lack of hemoglobinized cells (Nilsson et al., 2009). Further research is needed to elucidate the nature and mechanism of transport of heme and its precursors.

4. Iron toxicity and ROS production by mitochondria

4.1. Redox-active iron and the generation of ROS

Redox-active iron is defined as an iron ion with the capacity to engage in one-electron exchange reactions, either by oxidation ($Fe^{2+} \rightarrow Fe^{3+}$) or reduction ($Fe^{3+} \rightarrow Fe^{2+}$). The iron atom has octahedral coordination chemistry. Seminal work by Graf and associates demonstrated that the availability of only one of the six coordination sites is sufficient to render the iron atom redox active, namely capable of catalyzing the production of hydroxyl radicals by Fenton chemistry (Graf et al., 1984). Increased levels of iron promote neurotoxicity through hydroxyl radical formation, glutathione consumption, protein aggregation, lipid peroxidation, nucleic acid modification, and reduced DNA repair activity (Farina et al., 2013; Jomova et al., 2010; Mitra et al., 2014; Nunez et al., 2004).

A small but relevant fraction of cytosolic iron (range 0.2–1.5 μM) is weakly complexed to low-molecular weight substrates such as phosphate, citrate, glutathione, carbohydrates, nucleotides, polypeptides, and other molecules (Epsztejn et al., 1997; Kakhlon and Cabantchik, 2002; Kruszewski, 2003; Petrat et al., 2002a). The Fe(II)–glutathione complex is the predominant component of this pool (Hider and Kong, 2011). This weakly complexed iron is known as the cytosolic "labile iron pool" (LIP). In this pool, iron is redox-active, cycling between the Fe^{2+} and Fe^{3+} forms, although the Fe^{2+} form is prevalent given the reductive intracellular environment.

The concept of the LIP to describe a pool of "loosely bound" iron was introduced by Greenberg and Wintrobe in 1946 (Greenberg and Wintrobe, 1946). Later, this pool was termed "chelatable iron", based on methodological approximations to detect cellular iron pools using fluorescent chelators such as calcein and RPA (Kakhlon and Cabantchik, 2002; Petrat et al., 2002a). In cultured neuroblastoma cells, the LIP represents about 3% of the total cellular iron under basal culture conditions, but this percentage increases 3- to 4-fold, to μM concentrations, after exposure of cells to high extracellular iron concentrations (Nunez et al., 2004; Nunez-Millacura et al., 2002). In cell models, iron overload results in increased lipid peroxidation, protein modifications, and DNA damage, consistent with the production of ROS that eludes neutralization by the cell's antioxidant systems (Mello-Filho and Meneghini, 1991; Sochaski et al., 2002; Zoccarato et al., 2005).

Increases in cellular redox-active iron are directly associated with increased ROS and with changes in the intracellular reduction potential (Kruszewski, 2003; Nunez et al., 2004). In the presence of H_2O_2, Fe^{2+} generates the hydroxyl radical (Fenton reaction). The resulting Fe^{3+} can be reduced back to Fe^{2+} either by the superoxide radical or by cellular reductants such as glutathione or ascorbate, allowing further generation of hydroxyl radicals (for thermodynamic parameters, see Nunez et al., 2012). The hydroxyl radical is considered one of the most reactive species in biological systems because its reaction rate is only limited by its diffusion (rate constant range, 10^9–10^{12} mol^{-1} s^{-1}). This molecule induces irreversible damage to DNA, RNA, proteins, and lipids. Indeed, the hydroxyl radical is believed to be the etiological agent for several diseases and may be involved in the natural process of aging (Davies, 2005; Lipinski, 2011).

4.2. ROS production by mitochondria

Mitochondria play a central role in ROS generation, a process closely associated with ATP production (Boveris and Cadenas, 1975; Cadenas and Davies, 2000; Han et al., 2001; Romano et al., 2014). Oxygen captures electrons "leaking" from the electron transport chain forming superoxide, which permutates into hydrogen peroxide and molecular oxygen in a reaction catalyzed by mitochondrial superoxide dismutase. Notably, this reaction is both spontaneous and fast, with rate constants for the noncatalyzed and superoxide dismutase 2-catalyzed reactions of 5×10^5 mol^{-1} s^{-1} and 1.6×10^9 mol^{-1} s^{-1}, respectively. In vivo, the concentration of superoxide is estimated to be between 10^{-10} and 10^{-11} M and that of H_2O_2 to be 1000 times higher, between 10^{-7} and 10^{-8} M (Goldstein and Czapski, 1990). The preservation of mitochondrial iron homeostasis is essential for maintaining minimal hydroxyl radical production while concurrently supporting optimal heme and ISC synthesis.

Mitochondrial DNA is particularly susceptible to oxidative damage. It is continually exposed to ROS that are generated by the mitochondrial electron transport chain, but unlike nuclear DNA, mitochondrial DNA is

not protected by histones and is not readily repaired (Chen and Butow, 2005; Croteau and Bohr, 1997; Druzhyna et al., 2008; Ma et al., 2009).

5. Mitochondrial dysfunction in neurodegenerative diseases

Mitochondria are not only intrinsic sources of ROS, but they also play a vital role in the regulation of intracellular Ca^{2+} and apoptotic processes. In recent years, increasing attention has been given to the role of mitochondrial dysfunction in the pathogenesis of various neurodegenerative disorders (Fernandez-Checa et al., 2010; Filosto et al., 2011; Lim et al., 2008). Here we review the relationship between iron accumulation and mitochondrial dysfunction in the development of the most prevalent neurodegenerative diseases associated with iron accumulation in the brain.

5.1. Relationship between mitochondrial iron accumulation and neurodegeneration

Iron accumulates with age in the healthy human brain and is most prominent after 50 years of age (Bartzokis et al., 2007; Drayer et al., 1986; Hallgren and Sourander, 1958; Martin et al., 1998; Schipper, 2012; Schroder et al., 2013). As discussed above, a cause–effect relationship between iron and oxidative damage has been established, because increased redox-active iron contributes to oxidative damage as a consequence of hydroxyl radical generation through the Fenton reaction. Neurons are particularly sensitive to ROS and ATP imbalances because of their unique elongated morphology and their dependence on ATP to propagate electrical signals, maintain ionic gradients, and facilitate anterograde and retrograde transport along axons (Andrews et al., 2005; Fang et al., 2012; Morris and Hollenbeck, 1993; Su et al., 2013; Summers et al., 2014).

Increasing evidence points to disrupted iron homeostasis as an important factor in neurodegeneration (Enns, 2003; Gogvadze et al., 2009; Jellinger, 2009; Mandemakers et al., 2007; Sas et al., 2007). Knowledge about the mechanisms that link iron accumulation with the loss of mitochondrial function is emerging (Horowitz and Greenamyre, 2010). Several reports in recent decades have described brain mitochondrial dysfunction in neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and other neurodegenerative disorders that include a less investigated group of disorders, known as NBIA (Neurodegeneration with Brain Iron Accumulation), which are characterized by the presence of high brain iron, particularly within the basal ganglia (Kurian and Hayflick, 2013, Schneider and Bhatia, 2013). Concurrently, increasing evidence pointed to increased levels of iron in specific regions of the brain in AD and PD (Enns, 2003; Gogvadze et al., 2009; Jellinger, 2009; Mandemakers et al., 2007; Sas et al., 2007). The persistence of a high-iron phenotype in affected areas, together with the known capacity of iron to generate damaging ROS, is the basis of the "metal-based neurodegeneration hypothesis", which posits that redox-active metals (Fe, Cu, Mn) present in specific brain regions generate ROS that cause peroxidation of membrane phospholipids. This, in turn, leads to the formation of reactive aldehydes that react with proteins to produce misfolded aggregates that overwhelm the ubiquitin/proteasome protein degradation system and accumulate in intracellular inclusion bodies (Crichton et al., 2011; Kell, 2010; Nunez et al., 2012).

Given the constitutive presence of ROS derived from electron transport activity, mitochondrial iron levels must be tightly regulated, as a shortage of iron affects a myriad of processes in which iron is a cofactor. On the other hand, an excess of redox-active iron promotes the generation of cytotoxic hydroxyl radicals. Knowledge of the mechanisms by which mitochondria regulate their iron content and the possible interplay between cytoplasmic and mitochondrial iron are highly relevant topics of incipient investigation.

Whether mitochondrial iron accumulation is a founding event or a consequence of upstream events in a particular disease is a matter of debate. Here we hypothesize that the iron accumulation process is downstream of other primary causes but that the consequences of iron accumulation are germane to neuronal death.

5.2. Mitochondrial dysfunction and iron accumulation in AD

Mitochondrial dysfunction is a hallmark of amyloid-β (Aβ)-induced neuronal toxicity in AD. Mitochondrial dysfunction may induce the formation of Aβ-containing senile plaques and neurofibrillary tangles, the two pathological hallmarks of the disease (Gu et al., 2012; Moreira et al., 2006; Swerdlow and Khan, 2009). One possible cause for mitochondrial dysfunction is the incomplete translocation and accumulation of the amyloid precursor protein (APP) in the mitochondrial membrane (Anandatheerthavarada et al., 2003). Upon translocation to mitochondria, APP is efficiently cleaved by the gamma-secretase complex, forming the Aβ peptide (Ankarcrona and Hultenby, 2002; Hansson et al., 2004). Aβ interacts directly with Aβ-binding alcohol dehydrogenase, promoting the release of cytochrome C and increasing ROS production (Lustbader et al., 2004). Moreover, Aβ interferes with the mitochondrial membrane potential upon interaction with cyclophilin D, a component of the mitochondrial permeability transition pore. The Aβ–cyclophilin D interaction results in ROS production that in turn induces cyclophilin D translocation from the external to internal mitochondrial membrane, triggering the opening of the mitochondrial permeability transition pore (Du et al., 2008; Lustbader et al., 2004).

Recent evidence has revealed that Aβ oligomers, which are recognized as one of the most toxic forms of the Aβ peptide, interfere with mitochondrial dynamics (Hefti et al., 2013; Sanmartin et al., 2012). Overexpression of Aβ in M17 cells affects the expression of different proteins involved in mitochondrial fission and fusion, such as DLP1, Fis1, and OPA1 (Wang et al., 2008). Alterations in mitochondrial dynamics induced by Aβ overexpression result in mitochondrial fragmentation, reduced mitochondrial membrane potential, and mitochondrial dysfunction, as evidenced by increased generation of ROS and reduced ATP production (Wang et al., 2008).

Initial studies have revealed iron, copper, and zinc accumulation in areas with extensive lesions and pathology of senile plaques (Ding et al., 2009; Goodman, 1953; House et al., 2008; Lovell et al., 1998; Smith et al., 1997; Zhu et al., 2009). The cellular distribution of iron accumulation has not been fully resolved. Increased levels of iron in both neurons and microglia have been shown, suggesting that in these cells, some aspect of iron metabolism is disrupted, resulting in an increased capacity to import or a decreased capacity to export iron (Antharam et al., 2012; Benkovic and Connor, 1993; Lovell et al., 1998). Not only total iron but also redox-active iron is enriched in both neurofibrillary tangles and senile plaques in the cerebral cortex of AD postmortem specimens, suggesting hydroxyl radical-mediated damage in these areas (Smith et al., 1997).

Several proteins of the iron homeostasis machinery show altered levels and have been associated with AD pathology (Bush, 2013). For example, increased levels of the iron importer DMT1 has been observed in the cortex and hippocampus of AD transgenic models (Zheng et al., 2009), whereas levels of the iron storage protein ferritin are increased in reactive microglia present both in and around senile plaques (Connor et al., 1992). Similarly, AD brains show decreased levels of the iron exporter ferroportin 1 (Fpn1) (Crespo et al., 2014; Raha et al., 2013) and ferroxidase activity of APP (Duce et al., 2010) together with reduced levels of ceruloplasmin (Connor et al., 1993), which are required for the release of iron from cells. All these changes in iron homeostasis proteins clearly point to an iron accumulation phenotype, with an evident risk for the development of metal-based neurodegeneration.

APP mRNA has a functional ferritin-like IRE; hence, an increase in intracellular iron level enhances APP mRNA translation via the IRE/IRP system (Rogers et al., 2002). Thus, an unwanted consequence of iron accumulation may be increased Aβ formation via increased APP level. Aβ is a redox-active protein with autoaggregation and oligomerization properties that are enhanced by interactions with metal ions such as

zinc, copper, and iron (Huang et al., 2004). In particular, Fe^{3+} enhances the formation of amyloid fibrils containing Aβ1–42 and Aβ25–35 (House et al., 2004; Monji et al., 2002). Taken together, these data indicate that increased intracellular iron may be linked to increased Aβ oligomer toxicity.

Several reports have linked the formation of neurofibrillary tangles with increased cellular iron (Bouras et al., 1997; Egana et al., 2003; Good et al., 1992; Sayre et al., 2000). Indeed, iron interacts with hyperphosphorylated tau, an interaction that contributes to the formation of neurofibrillary tangles (Guo et al., 2013; Smith et al., 1997). Treatment of Fe^{3+}–paired helical filament (PHF) aggregates from AD brains with the reducing agent β-mercaptoethanol results in solubilization of both reduced iron and PHFs, indicating that PHFs in association with Fe^{3+} constitute the insoluble pool of PHFs (Yamamoto et al., 2002).

The interaction between tau and APP is necessary for APP trafficking to the plasma membrane. Tau knockout mice develop age-dependent brain atrophy, iron accumulation, and neuronal loss in the substantia nigra pars compacta (SNc) with concomitant cognitive deficits and Parkinsonism (Lei et al., 2012). Consistent with the role of APP as an iron export ferroxidase, tau knockout also induces iron retention in primary neuronal cultures. Soluble tau is also found in the SNc of PD patients. These data suggest that soluble tau is a participant in cellular iron efflux.

The above data strongly support the view that mitochondrial dysfunction and increased intracellular iron are instrumental for both increased Aβ oligomerization and the formation of PHFs. In turn, the formation of PHFs may result in decreased soluble tau and iron accumulation.

5.3. Mitochondrial dysfunction and iron accumulation in Huntington disease (HD)

HD is a genetic disorder caused by a defect on chromosome 4 in which a CAG repeat in exon 1 of the gene for Huntingtin (Htt) is present many more times than in unaffected individuals (36–120 repeats vs. 10–28 repeats, respectively) (Beal and Ferrante, 2004; Gatchel and Zoghbi, 2005; Imarisio et al., 2008). Clinical symptoms of HD include a progressive increase in involuntary movements called chorea, cognitive deterioration, neuropsychiatric symptoms, and premature death. Mutant Htt induces a selective loss of neurons in the basal ganglia—the part of the brain that controls movement, emotion, and cognitive ability. Furthermore, patients with HD exhibit weight loss, which may be related to impaired mitochondrial ATP synthesis (Djousse et al., 2002).

Decreased energy metabolism has been proposed as a mechanism by which mutant Htt mediates neuronal death (Acuna et al., 2013; Browne and Beal, 2004; Chaturvedi and Beal, 2008). Various mechanisms have been proposed to explain the energy deficit in the HD brain, including decreased glucose metabolism, impaired mitochondrial ATP production, impaired mitochondrial calcium homeostasis, abnormal mitochondrial trafficking, and impaired mitochondrial biogenesis (Benchoua et al., 2006; Brennan et al., 1985; Browne, 2008; Gu et al., 1996; Lim et al., 2008; Milakovic and Johnson, 2005; Mochel and Haller, 2011; Powers et al., 2007; Tabrizi et al., 1999).

Mitochondrial dysfunction is often associated with the pathogenesis of HD. Analysis of postmortem brains from patients with advanced disease shows deficits in the activity of complexes I, II and III (Brennan et al., 1985; Browne et al., 1997; Damiano et al., 2010; Milakovic and Johnson, 2005; Parker et al., 1990). However, similar in vitro studies with samples from presymptomatic and early-stage (grade 1) patients showed no impairment in striatal or cortical complexes I–IV, indicating that respiratory chain impairment is a late event in the development of the disease (Guidetti et al., 2001; Oliveira, 2010).

The exact nature and causes of mitochondrial dysfunction in HD remain unknown. Several studies have determined that mutant Htt physically associates with mitochondria. Mutant Htt-STHdhQ111 is found in the mitochondrial outer membrane in striatal cells obtained from patients with HD and from HD model transgenic mice (Choo et al., 2004; Panov et al., 2002). Postmortem brain tissue from HD patients shows an increase in the expression of mitochondrial fission proteins Drp1 and Fis1 and decreased expression of fusion proteins mitofusin and OPA1. In addition, wild-type Htt interacts with Drp1, increasing its enzymatic activity (Johri et al., 2011; Kim et al., 2010; Shirendeb et al., 2011; Song et al., 2011; Wang et al., 2009). Mutant Htt can impair mitochondrial function via several mechanisms: (1) by binding to Drp1 more tightly than wild-type Htt, disrupting the balance of mitochondrial fission–fusion dynamics in favor of fission, (2) by decreasing anterograde and retrograde axonal transport of mitochondria, and (3) by binding to peroxisome proliferator-activated receptor coactivator-1α (PGC-1α) protein, which reduces its transcription factor activity, resulting in the reduced expression of PGC-1α target genes that are involved in mitochondrial biogenesis and antioxidant defenses (Shirendeb et al., 2012), reviewed in Johri et al. (2013). The net result of these mitochondrial impairments is reduced ATP production, which may initially result in neuronal dysfunction followed by neuron death.

Iron accumulation does not seem to be a founding event in HD but may be an early event in the pathological cascade. In particular, iron accumulates in the basal ganglia of both HD patients and murine models of HD (Bartzokis and Tishler, 2000; Bartzokis et al., 1999; Chen et al., 1993; Dexter et al., 1992; Simmons et al., 2007; van den Bogaard et al., 2013). Iron levels are especially high in myelinating oligodendrocytes (Vonsattel et al., 2011) and in microglia (Simmons et al., 2007), the latter of which respond to oxidative stimuli by releasing inflammatory cytokines (Baeuerle and Henkel, 1994; Sen and Packer, 1996). Premature myelin breakdown and subsequent remyelination with increased oligodendrocyte and iron levels may contribute to HD pathogenesis (Bartzokis et al., 2007), since the increased levels of iron may result in increased production of hydroxyl radicals, promoting damage to neighboring neurons (Sapp et al., 2001; Singhrao et al., 1999; van den Bogaard et al., 2013).

Htt appears to be required for transferrin receptor 1 (TfR1)-mediated iron uptake. Knockdown of Htt during early development in zebrafish results in a hypochromic blood phenotype associated with increased TfR1 transcripts that is suggestive of cellular iron starvation (Lumsden et al., 2007). Because erythroid cells acquire iron via transferrin endocytosis, these results suggest a role for Htt in supporting iron uptake by transferrin-mediated endocytosis. Furthermore, treatment of mouse embryonic stem cells with the iron chelator desferrioxamine results in upregulation of Htt, an observation that strongly suggests the involvement of Htt in normal iron homeostasis (Hilditch-Maguire et al., 2000). Arguably, perturbation of the normal role of Htt in iron uptake by polyglutamine tract expansion may contribute to the iron accumulation that is observed in HD pathology.

Taken together, the above evidence supports a role for mutant Htt in the induction of mitochondrial dysfunction, which is probably an early event. Iron accumulation is likely a later event in HD-associated neurodegeneration, although both processes may develop through both sequential and parallel paths.

5.4. Mitochondrial dysfunction and iron accumulation in idiopathic PD

PD is a neurodegenerative disorder characterized by a cardinal clinical triad: bradykinesia, rigidity, and tremor (Hirsch et al., 2013). Symptoms in PD result from the loss of dopaminergic neurons in the SNc, the loss of innervation to the striatum, and the subsequent release of dopamine (Booij et al., 1997; Iranzo et al., 2010; Kaufman and Madras, 1991).

Abundant evidence points to the involvement of mitochondrial dysfunction in the pathophysiology of PD. Initial observations emerged in the 1980s when four college students developed marked Parkinsonism after an intravenous injection of illicit drugs. Further analysis of the substances injected revealed the existence of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Once injected, MPTP crosses the brain–blood barrier and is metabolized by astrocytes to yield MPP+. After uptake mediated by the dopamine transporter, MPP+ causes

death specifically of dopaminergic neurons by inhibiting mitochondrial complex I (Gautier et al., 2014; Heikkila et al., 1984; Langston et al., 1984; Nicklas et al., 1985).

Reduced activity of mitochondrial complex I is a common characteristic in PD brain tissue. The activity and the number of complex I subunits are decreased in postmortem SNc tissue from idiopathic PD patients (Bindoff et al., 1989; Mizuno et al., 1989; Parker et al., 1989; Schapira et al., 1989). Rotenone, a selective inhibitor of complex I, has been linked epidemiologically to PD in association with the use of rotenone-based pesticides in farming (Betarbet et al., 2000; Kamel, 2013; Pezzoli and Cereda, 2013). Moreover, reduced complex I activity and an increased susceptibility to MPP+ are observed in cybrids containing mitochondrial DNA from PD patients (Chaturvedi and Flint Beal, 2013; Gu et al., 1998; Swerdlow et al., 1996; Swerdlow et al., 2001), suggesting mitochondrial DNA-encoded defects in PD.

Mitochondrial complex I is a major source of ROS. Using complex I subunit-specific immunocapture antibodies, the protein oxidation pattern of complex I subunits in brain mitochondria from PD patients was reproduced by incubating isolated brain mitochondria with NADH in the presence of rotenone but not by the addition of an exogenous oxidant. In addition, complex I activity correlates inversely with the complex I protein oxidation status (Keeney et al., 2006).

Increased iron in damaged areas is another common characteristic of PD brains. Early studies noted increased iron content in the SNc of postmortem brain tissue from PD patients (Dexter et al., 1987; Rojas et al., 1965; Sofic et al., 1988). Increased iron and ferritin were traced to the microglia, astrocytes, and dopaminergic neurons in the SNc (Jellinger et al., 1990; Snyder and Connor, 2009; Zhang et al., 2006). These results were confirmed by nuclear magnetic resonance studies (Berg et al., 1999; Gorell et al., 1995) and repeated in the mouse MPTP model (He et al., 2003). Additional studies using magnetic resonance imaging showed an association between iron accumulation and disease progression (Schuff, 2009).

Some reports have failed to confirm increased iron in PD patients. For a comprehensive recount of the conflicting results on iron content in the SNc of PD patients, the reader is referred to a recent review (Friedman and Galazka-Friedman, 2012). A Mössbauer spectroscopy study that determined total iron in the SNc from PD patients compared with controls found no differences in mean iron concentrations between the two groups (Galazka-Friedman et al., 2012). In the same study, detection of non-ferritin-bound labile iron with atomic absorption spectroscopy revealed a 2.4-fold increase in this iron in the SN of PD compared with controls. Although these concentrations are 2000 times lower than the concentration of total iron, the authors hypothesize that the higher concentrations of this non-ferritin-bound iron found in PD brains may enhance oxidative damage mediated by the Fenton reaction (Galazka-Friedman et al., 2012).

Supporting a role for iron in disease development, pharmacological approaches aimed at iron chelation show prevention of MPTP-induced dopaminergic neuronal death in mice (Kaur et al., 2003). Similarly, treatments that chelate iron decrease neurodegeneration caused by 6-hydroxydopamine (6-OHDA) in rats (Youdim et al., 2004).

Dopaminergic neurons of the SNc contain neuromelanin, which acts as an intracellular iron buffer (Zecca et al., 2004). Neuromelanin is a dark polymer formed by oxidized metabolites of dopamine and a peptide component that contributes ~15% of the mass (Zecca et al., 2002). Neuromelanin has high- and low-affinity binding sites for Fe^{3+} (Double et al., 2003). Ferritin is poorly expressed in melanized dopaminergic neurons of the SN compared with neurons in other parts of the brain (Snyder and Connor, 2009), and thus neuromelanin is the main iron storage moiety in these neurons. The high-affinity sites are thought to be protective as they sequester iron in a redox-inactive form, whereas iron bound to the low-affinity sites is redox-active (Gerlach et al., 2008). Thus, under low to moderate iron loads, iron is safely bound to high-affinity sites, but when the high-affinity binding capacity of neuromelanin is surpassed, iron binds to low-affinity binding sites in a redox-active form.

Iron accumulation in the SNc of PD patients may be due to increased expression of DMT1. Studies from our laboratory and others, indicated that expression of the + IRE isoform of DMT1 is increased in the SN of PD patients, an observation that was replicated in the PD models of MPTP and 6-OHDA intoxication. The increase in DMT1 was accompanied by iron accumulation and increased oxidative stress (Salazar et al., 2006; Salazar et al., 2008; Song et al., 2007; Zhang et al., 2009).

Levels of the iron export transporter FPN1 are decreased in animal models of PD and have the same effect of promoting iron accumulation. In rats, the levels of FPN1 and the ferroxidase hephaestin, which are both involved in iron export from cells, were decreased compared with the control 1 day after 6-OHDA treatment. In a cell culture system, silencing of FPN1, but not of hephaestin, results in increased cellular iron levels and increased ROS generation (Wang et al., 2007).

The causes for the changes in DMT1 and FPN1 levels in SNc dopaminergic neurons are unknown but may be linked to mitochondrial dysfunction and increased ROS. An endogenous source of free radicals unique to dopaminergic neurons is derived from the nonenzymatic oxidation of dopamine to aminochrome, the precursor of neuromelanin in dopaminergic neurons. Aminochrome can undergo a one-electron reduction to form the leukoaminochrome o-semiquinone radical (Arriagada et al., 2004; Zoccarato et al., 2005). We found that treatment of SH-SY5Y neuroblastoma cells with low concentrations of aminochrome results in inhibition of complex I, increased level of the +IRE isoform of DMT1, and decreased level of FPN1. Consistent with these findings, cells treated with aminochrome show increased iron uptake and accumulation (Aguirre et al., 2012). All these effects are absent when cells are incubated with aminochrome in the presence of the antioxidant *N*-acetylcysteine. These results suggest that the catabolism of dopamine generates redox-active derivatives that inhibit mitochondrial complex I through oxidative modifications and modify the levels of iron transporters in a way that leads to iron accumulation.

In a recent study, we found that inhibition of complex I results in decreased synthesis of ISCs and increased IRP1 mRNA binding activity along with increased cytosolic LIP (Mena et al., 2011). The finding that inhibition of complex I results in increased IRP1 activity is consistent with previous observations showing that IRP1 activity is increased in postmortem tissue of PD patients and in the ipsilateral ventral mesencephalon of 6-OHDA-treated rats (Salazar et al., 2006). Thus, IRP1 activation may be the link between inhibition of complex I and iron accumulation, two hallmarks of idiopathic PD.

5.5. Mitochondrial dysfunction and iron accumulation in FA

FA is an autosomal recessive mitochondrial disorder characterized by progressive cardiologic and neurological degeneration that affects mainly the dorsal root ganglia, the spinal cord, and the cerebellum (Harding, 1981; Hughes et al., 1968; Koeppen and Mazurkiewicz, 2013; Lamarche et al., 1984). FA is usually caused by a homozygous GAA repeat expansion mutation in intron 1 of *FXN* (Campuzano et al., 1996; Pandolfo, 2002; Rotig et al., 1997). The effect of the GAA expansion mutation is reduced expression of frataxin, a mitochondrial protein that acts as an iron chaperone in mitochondrial heme and ISC synthesis (Al-Mahdawi et al., 2008; Campuzano et al., 1996; Vaubel and Isaya, 2013; Yoon and Cowan, 2004). In addition to decreased ISC synthesis, frataxin insufficiency results in mitochondrial iron accumulation, extensive oxidative damage, loss of myelinated fibers, and subsequent cell death (Chantrel-Groussard et al., 2001; Gakh et al., 2006; Koeppen, 2011; Koeppen et al., 2009; Wong et al., 1999).

Mitochondrial iron accumulation in FA has been demonstrated mostly in the heart and several other systemic tissues (Bradley et al., 2000; Delatycki et al., 1999; Michael et al., 2006; Puccio et al., 2001), whereas evidence for iron accumulation in neuronal mitochondria is conspicuously absent. Using cardiac tissue from a conditional *frataxin* knockout mouse, Huang and collaborators demonstrated that frataxin

deficiency leads to downregulation of proteins involved in four mitochondrial iron utilization pathways: ISC synthesis, mitochondrial iron storage, heme synthesis, and increased expression of the mitochondrial iron importer mitoferrin-2 (Huang et al., 2009). In addition, frataxin deficiency leads to an increased level of TfR1, ferritin, and heme oxygenase 1 and to a decreased level of FPN1 (Huang et al., 2009; Whitnall et al., 2012). Thus, frataxin deficiency leads to a false iron deficiency signal, with increased capacities for cellular iron uptake (increased TfR1) and retention (decreased FPN1) and decreased iron storage (ferritin). Although the cause of these changes in protein levels is unknown, they may be mediated by a low cytosolic iron signal resulting from increased mitochondrial uptake (mitoferrin-2) and/or by increased IRP1 activity as the result of decreased ISC synthesis (Mena et al., 2011).

A study by Rouault's group showed that *frataxin* mRNA expression is dependent on cytoplasmic iron levels, decreasing with iron depletion, and increasing with metal accumulation (Li et al., 2008). These findings are interesting because they suggest the possibility of a cycle in which the mitochondrial iron overload and the associated cytosolic iron depletion further decrease frataxin expression (Li et al., 2008).

In summary, a decreased expression of frataxin is considered the main initiator of FA disease pathology. Frataxin deficiency is widely associated with decreased synthesis of ISCs, although information is still emerging (Bayot et al., 2011; Martelli and Puccio, 2014; Pastore and Puccio, 2013; Richardson et al., 2010). Nevertheless, decreased frataxin level clearly results in decreased ISC synthesis, mitochondrial dysfunction, iron accumulation, and increased oxidative damage, conditions that ultimately lead to cell death. A critical question still unanswered is the mechanisms by which mutated frataxin participates in the induction of mitochondrial iron accumulation. Further knowledge in this subject will be valuable for the design of new therapeutic approaches that may consider the use of mitochondria-targeted iron chelators.

5.6. Possible therapeutic approaches

Iron chelation has been suggested as an effective therapy for the treatment of PD and other diseases with a NBIA component, as detailed in several recent reviews (Hayflick and Hogarth, 2011; Jomova et al., 2010; Oshiro, et al., 2011; Ward, et al., 2012). In particular, 8-OH quinoline-based chelators (clioquinol, M30) and hydroxyl-substituted pyridinones (deferiprone) are regarded increasingly as putative candidates for the treatment of neurodegenerative diseases with an iron accumulation component (Pandolfo and Hausmann, 2013; Tardiff et al., 2012; Youdim, 2012). Clioquinol and its successor PBT1 and M30 belong to this new generation of chelators that have proved effective for the treatment of experimental PD and AD (Bush, 2013; Kupershmidt et al., 2012; Regland et al., 2001; Youdim et al., 2004). Clioquinol, and its successor PBT1, has been described as a zinc and copper chelator, although through its 8-OH quinoline moiety it is also an iron chelator. Clioquinol dissolves amyloid deposits in vitro and in vivo, probably by redistribution of Zn, Cu and Fe (Bareggi and Cornelli, 2012). In a pilot Phase 2 trial with AD patients, the clioquinol group presented minimal deterioration compared to the placebo group. Plasma zinc levels rose and plasma Aβ42 levels declined in the clioquinol group, whereas both increased in the placebo group (Ritchie et al., 2003). However, analysis of two randomized double-blind trials of clioquinol administered to patients with AD showed no evidence as to whether clioquinol/PBT1 has any benefit for AD patients (Sampson et al., 2014).

Deferiprone treatment has shown promising results. In a double-blind, placebo-controlled clinical trial using a delayed start (DS) strategy, early-stage PD patients (12-month treatment with DFP) responded significantly earlier and sustainably to treatment in both substantia nigra iron deposits and Unified Parkinson's Disease Rating Scale motor indicators of disease progression compared to the DS group (last 6 month of treatment with DFP) (Devos et al., 2014).

In mice, M30 was found to prevent the loss of TH-positive neurons induced by post-intranigral injection of the proteasome inhibitor lactacystin (Zhu et al., 2009) and a 6-month treatment of aged mice with M30 significantly reduced cerebral iron accumulation, accompanied by a marked decrease in cerebral β-amyloid plaques (Kupershmidt et al., 2012).

In summary, there is mixed evidence on the benefits of an iron chelation therapy for the treatment of neurodegenerative diseases

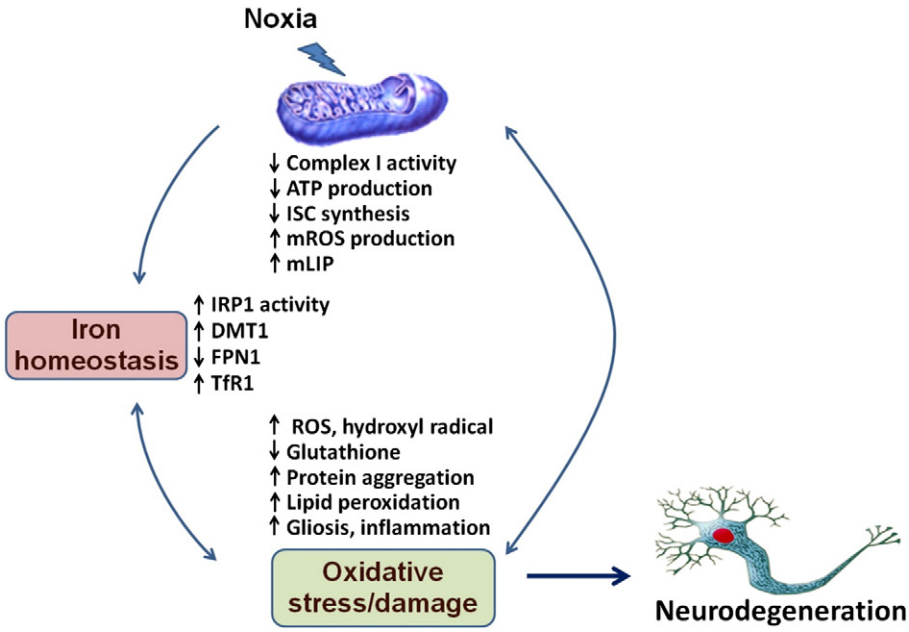

Fig. 4. We propose that inhibition of mitochondrial complex I by endogenous and/or exogenous toxins results in a vicious cycle of mitochondrial dysfunction, iron accumulation, and oxidative damage. In this scheme, complex I dysfunction results in decreased ISC synthesis, activation of IRP1, increased DMT1, Mtfn2, and TfR1 levels, and subsequent iron accumulation. With time, the ever-increasing ROS production by iron and mitochondrial dysfunction overcomes the antioxidant response, inducing oxidative damage and finally neuronal death. mROS: mitochondrial ROS.

with an iron accumulation component. Nevertheless, this seems to be a route worthy to pursue. The synthesis of second generation chelators, effective at lower concentrations and targeted to specific cell types may result in safer and more specific iron chelation strategies.

6. Concluding remarks

The mitochondrion is the main producer of ROS in the cell, making this organelle especially susceptible to oxidative damage. The mitochondrion is also the place for the synthesis of ISCs and heme prosthetic groups, a condition that generates intensive traffic of iron into and out of this organelle. Knowledge of the mechanisms that regulate mitochondrial iron content is emerging. Preliminary evidence shows that iron entrance into mitochondria is regulated and that mitochondria have higher requirements for iron than the cytosol.

Mitochondrial dysfunction, iron accumulation, and oxidative stress are hallmarks of several neurodegenerative diseases such as PD, AD, HD and FA. The molecular relationships among these three phenomena are beginning to be revealed. Fig. 4 summarizes the main ideas described in this review. We propose that mitochondrial dysfunction results in increased ROS production, decreased ISC synthesis, IRP1 activation, and iron accumulation. In turn, iron accumulation is the cause of hydroxyl radical-mediated damage (lipid peroxidation, protein aggregation, etc.). As reviewed here, the initial event that engage this cycle seems to be particular for each neurodegenerative disorder and may or may not have a genetic component. Nevertheless, mitochondria dysfunction seems to be a founding event and iron dyshomeostasis and oxidative damage downstream events.

These three phenomena—mitochondria dysfunction, iron accumulation and oxidative damage—generate a positive feedback loop of increased iron accumulation and oxidative stress. Intervention at some of these three levels, for instance mitochondrial dysfunction or iron dyshomeostasis, should reduce accumulative oxidative damage, thus generating a new therapeutic approach for the treatment of neurodegenerative diseases.

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