REDOX EXPERIMENTAL MEDICINE

N Teferi *et al.* | 2023:1 | e230004

REVIEW

Mitochondrial dysfunction, iron accumulation, and ferroptosis in Parkinson's disease

Nahom Teferi[1], **Meron Challa**[2], **Timothy Woodiwiss**[1], **Bryan Allen**[3] and **Michael Petronek**[3]

[1]Department of Neurosurgery, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA
[2]University of Iowa Carver College of Medicine, Iowa City, Iowa, USA
[3]Department of Radiation Oncology, Free Radical and Radiation biology, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA

Correspondence should be addressed to N Teferi: nahom-teferi@uiowa.edu

Abstract

Iron accumulation and ferroptosis have long been implicated in the pathogenesis and neuronal loss of Parkinson's disease. With the growing discovery of genes associated with Parkinson's disease and mitochondrial function, there is emerging evidence of the convergent role of mitochondrial dysfunction, subsequent reactive oxygen species generation and ensuing iron accumulation working in concert to facilitate neuronal loss and injury in Parkinson's disease. This subsequently leads to a vicious cycle where mitochondrial dysfunction may stimulate iron accumulation and inflammation as part of a synergistic feed-forward cycle resulting in neuronal death after the antioxidant cellular defense systems are overwhelmed. We reviewed the existing literature on mitochondrial and iron homeostasis and described the potential intersections of the disease mechanisms leading to iron accumulation, ferroptosis and dopaminergic cell death, ultimately culminating in the onset and progression of Parkinson's disease.

Keywords

- mitochondrial dysfunction
- iron accumulation
- ferroptosis
- Parkinson's disease

Redox Experimental Medicine (2023) **2023**, e230004

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and affects approximately 1–2 persons per 1000 of the general population globally (Tysnes & Storstein 2017). It is characterized by progressive loss of dopaminergic neurons in parts of the substantia niagra pars compacta (SNpc) resulting in the loss of dopaminergic inputs in the caudate and putamen, subsequently leading to the characteristic motor symptoms associated with the disease (bradykinesia, resting tremor, and rigidity). The slow degradation of dopaminergic neurons of SNpc is associated with the gradual accretion of iron (Fe) often leading to depletion of dopamine in the striatum, loss of neuromelanin (NM), and increased aggregation of α-synuclein within Lewy bodies (Dauer & Przedborski 2003).

There have been multiple reports in the literature which have shown the presence of increased Fe accumulation in the substantia nigra (SN) of patients with PD (Dexter *et al.* 1987, Eid *et al.* 2017). Fe is the most abundant transition metal in the human body and has many essential functions in the brain and nervous system, such as oxygen transport and mitochondrial respiration, protein and DNA synthesis, myelination, dendrite development, and neurotransmitter biosynthesis (Fraga *et al.* 2005, Zheng & Monnot 2012). Excess Fe accumulation tends to affect dopaminergic neurons more as the essential neuronal pigment, NM, primarily synthesized in these neurons, requires Fe catalysis in its synthesis (Edwards *et al.* 2000).

The current understanding of Fe metabolism in PD is that Fe accumulation leads to excessive production

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-23-0004

of reactive oxygen species (ROS), resulting in protein, DNA, and phospholipid oxidation. These reactions can ultimately lead to structural and functional damage in the SN (Youdim *et al.* 1989). Ferroptosis has also recently been shown to play a role in PD pathogenesis (Zhao *et al.* 2019*b*) and multiple altered gene products associated with brain Fe metabolism have also been noted in PD, further reinforcing the connection between PD and Fe metabolism (Rhodes & Ritz 2008). Furthermore, α-syn aggregation has also been shown to trigger ROS generation accompanied by oxidative damage in a Fe-dependent manner, leading to cell death (Angelova *et al.* 2020). This has led to growing interest in the connection between excess Fe and mitochondrial dysfunction as an important initiating factor in the onset of PD (Malpartida *et al.* 2020). As many PD initiation model systems utilize the inhibition of mitochondrial electron transport chain (ETC) complex I (e.g. rotenone), there may be a critical connection between mitochondrial-derived ROS and Fe accumulation that has yet to be fully appreciated. Here we review the sources and potential mechanisms of Fe accumulation in PD while contextualizing the current understanding within a juxtaposition of mitochondrial dysfunction, ROS accumulation, and Fe metabolic disruptions resulting in the eventual dopaminergic neuronal cell death associated with the onset of PD.

Iron metabolism

Cytosolic iron metabolism

Following absorption from the digestive track, Fe is bound to transferrin (Tf), a protein that binds two ferric (Fe^{3+}) ions for transport in the circulatory system. Depending on the amount of intracellular Fe content, cells are able to regulate the expression of Tf receptors (TfR) on their cell membrane and hence control the amount of Fe uptake. After binding to TfR, the Tf–TfR complex is then endocytosed into the cell in vacuoles, where the acidic milieu facilitates the release of Fe ions from the complex (Piñero & Connor 2000, Torti & Torti 2013). Following complex dissociation, Fe in the form of ferrous (Fe^{2+})is then shuttled into the cytosol by divalent metal transporter–1 (DMT1) (Torti & Torti 2013). Fe^{2+}, after transport into the cytoplasm, can then be directed into three major pathways. It can undergo storage for later utilization in ferritin (Ft), be used in the biosynthesis of Fe–S clusters, heme-proteins, and other Fe-containing proteins or remain in a redox-active labile Fe state in the cytosol (commonly referred to as the 'labile iron pool' or LIP) (Hentze *et al.* 2010).

The LIP within the cytosol is highly regulated and correlates well with the total Fe content within the cell, despite comprising only ≈2–5% of the total Fe of the cell (Chutvanichkul *et al.* 2018). The LIP is in a constant state of flux because it can serve as a significant, detrimental catalyst of oxidative distress as free, redox-active Fe can readily react with O_2 and H_2O_2 to generate superoxide $O_2^{\bullet-}$ and $HO^{\bullet}$, respectively (Kakhlon & Cabantchik 2002, Kruszewski 2003). The LIP content in the cytosol is primarily regulated via storage in Ft or export through ferroportin (Fpn-1) during Fe overload states. Under Fe-depleted conditions, Fe uptake can be stimulated by enhanced TfR expression (Shi *et al.* 2008, Hilton *et al.* 2012, Frey *et al.* 2014). Due to the critical nature of intracellular Fe homeostasis in maintaining a delicate balance between essential cellular function and avoiding oxidative distress, the LIP serves as a central modulator of iron metabolism. The LIP directly alters the expression of different Fe regulatory proteins (e.g. Ft, TfR, and Fpn-1) (Cairo & Pietrangelo 2000). These proteins exist within a rapid-response network with protein turnover half-lives that exist on the order of minutes to ensure homeostasis and avoid oxidative distress. For example, in HeLa cells, the TfR internalization half-life has been shown to be approximately 5 min (Bleil & Bretscher 1982). The rapid turnover of these key regulatory proteins is achieved through post-transcriptional regulation. There are hair-loop structures known as Fe response elements (IREs) in the mRNA of these proteins, which serve as binding sites for iron-responsive proteins (IRP1/2) (Bleil & Bretscher 1982). IRP1 is a cytoplasmic aconitase enzyme that contains a $[4Fe\text{-}4S]^{2+}$ cluster, while IRP2 is regulated primarily by proteasomal degradation *via* the $[2Fe\text{-}2S]^{+}$ containing FBXL5. Thus, IRP1/2 are both sensitive and responsive to homeostatic deviations in labile iron.

IRP, a cytosolic aconitase enzyme, primarily exists in a reduced state with a complete $[4Fe\text{-}4S]^{2+}$ cluster (Hentze *et al.* 2010). This allows for the aconitase function of the enzyme. However, in the absence of Fe or the presence of ROS (e.g. $O_2^{\bullet-}$ and H_2O_2), the cluster can be oxidized to a $[3Fe\text{-}4S]^{+}$ cluster state, that occurs under low LIP Fe conditions. In this state, the aconitase function of IRP1 as a citric acid intermediate is lost and it primarily binds to IREs of iron regulatory proteins facilitating translation of TfR mRNA, while blocking translation of Ft and Fpn-1 (Cairo & Pietrangelo 2000). This serves to increase Fe uptake into the cytosol while reducing the export of Fe from the cytosol into

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-23-0004

the bloodstream. Under Fe overload conditions, IRP1 primarily exists in the reduced state with a complete $[4Fe\text{-}4S]^{2+}$ cluster, allowing the enzyme to fulfill its aconitase function. This leaves the IREs of TfR, Ft, and Fpn-1 unbound, facilitating the degradation of TfR mRNA while enhancing the translation of Ft and Fpn-1 mRNAs and subsequently decreasing LIP levels (Cairo & Pietrangelo 2000). The converse is true under Fe depletion conditions, where IRP1 has an incomplete $[3Fe\text{-}4S]^{+}$ cluster that renders the aconitase function inactive and allows IRP1 to bind to IREs. In addition to the Fe responsiveness, the $[4Fe\text{-}4S]^{2+}$ cluster of aconitase/IRP1 contains a non-cysteine bound, solvent-exposed Fe ion which can readily react with ROS (e.g. $O_2^{\bullet-}$, H_2O_2, $HO_2^{\bullet}$) leading to an oxidized cluster (Lushchak *et al.* 2014), suggesting that ROS may be a critical modulator of the IRP1 function. Similar to the Fe responsiveness of IRP1, IRP2 is regulated through degradation by ubiquitination by an Fe-responsive ligase complex, which is controlled by the O_2-responsive [2Fe-2S]+ of FBXL5 (Takahashi-Makise *et al.* 2009, Hentze *et al.* 2010, Wang *et al.* 2020). Thus, IRP1/2 are key Fe regulators for the maintenance of LIP homeostasis and can be modulated by ROS. However, the redox sensitivity of the IRP2 degradation pathway remains unclear. While the function of this rapid-response post-transcriptional homeostatic mechanism has been studied extensively, the biological consequence of its modulation remains an active area of research (Lushchak *et al.* 2014).

Mitochondrial iron metabolism

Mitochondria, canonically considered the primary energy source of the cell, play an important role not only in adenosine triphosphate (ATP) production but also in Fe metabolism. In addition to housing the TCA cycle and ETC, the mitochondria serve as the hub of Fe-dependent biosynthetic functions (Petronek *et al.* 2021). Important Fe-containing proteins (e.g. Fe-S clusters) are synthesized in the mitochondria. Because the IRP-IRE system is directly controlled by Fe-S clusters, it appears that mitochondrial Fe regulation is essential for maintaining global, cellular Fe homeostasis. However, the regulation of mitochondrial Fe content is not well elucidated. Fe transporter proteins, mitoferrin-1 and 2 (Mfrn-1/2), are thought to be responsible for shuttling Fe across the inner mitochondrial membrane (IMM) (Muckenthaler *et al.* 2017). It is hypothesized that mitochondrial Fe content regulates the translation of Mfrn proteins, similar to the modulation of TfR expression by LIP (Paradkar *et al.* 2009, Troadec *et al.* 2011); however, the mechanism(s) remain elusive.

Iron and Parkinson's disease

Fe and genetics of PD

While the etiology of PD is likely multifactorial, there are several genes (over 20 to date) thought to be involved in familial PD that have been discovered since the late 1990s (Table 1). These genes are located in ~18 chromosomal loci, commonly denoted by PARK, to signify association with PD (Klein & Westenberger 2012). In most of these loci, the causative gene has not been clearly identified or the mutation in the gene is considered a risk factor for developing PD rather than the driver mutation (Klein & Westenberger 2012). However, there are six genes that have been shown to be clearly linked to heritable forms of the disease (Table 1). Most of these genes are inherited in an autosomal recessive mode of inheritance (PRKN, PINK1, DJ-1, and ATP13A2), with mutations in SNCA and LRRK2 genes responsible for autosomal-dominant forms of the disease (Klein & Westenberger 2012).

Alterations of Fe metabolism have been found to be among those associated with genetic mutations in PD patients. There is evidence that the Fe content in the SNpc of patients with PARK2 mutation, the most commonly identified mutation in patients with juvenile PD, is increased when compared to individuals with sporadic forms of the disease (Roth *et al.* 2010). The E3 ubiquitin ligase PARK2 negatively regulates DMT1, an essential Fe transport protein, by ubiquitination (Roth *et al.* 2010). Thus, it can be inferred that decreased levels of the parkin protein would increase Fe cellular content and Fe-mediated toxicity. SNCA and LRRK2 gene mutations are thought to result in PD through toxic gain of function mutations resulting in the formation of misfolded α-synuclein proteins with subsequent accumulation of toxic oligomers, fibrils, and protofibrils altering mitochondrial morphology, ETC function, and autophagy (Klein & Westenberger 2012). Similarly, the PINK1 gene mutation is thought to result in loss of function mutation altering the function of the PINK1 protein, which is a mitochondrial membrane protein kinase with a critical role in the mitochondrial quality control pathway (Ge *et al.* 2020). Under normal conditions, the PINK1 protein on the outer mitochondrial membrane is undetectable. During times of stress, such as impaired mitochondrial electron transport, oxidative stress, and proteotoxicity, PINK1 accumulates

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-23-0004

Table 1 PD-associated genes and influences on ETC function.

Gene	Mitochondrial effect	Mechanism	References
SNCA		Mutant monomers or oligomers	Chinta *et al.* (2010)
	Abnormalities in mitochondrial morphology Complex I activity ↓ UPS and ALP dysfunction		
PRNK		Protein turnover	Palacino *et al.* (2004), Casarejos *et al.* (2006), Dehay *et al.* (2013)
	ETC enzyme activities ↓ Protein levels of several subunits of complexes I and IV ↓ Mitochondrial integrity ↓ UPS and ALP dysfunction		
PINK1		Phosphorylation	Park *et al.* (2006), Gautier *et al.* (2008), Dibble *et al.* (2009), Esteve-Rudd *et al.* (2010), Liu *et al.* (2011), Shim *et al.* (2011)
	UPS dysfunction ETC enzyme activities ↓ ATP production ↓ Mitochondrial fission ↓ Disruption of mitochondrial morphology ALP dysfunction		
DJ-1		Chaperone	Irrcher *et al.* (2010), Shim *et al.* (2011), Heo & Rutter (2012)
	Complex I and II activities ↓ ATP production, O(2) consumption, and mitochondrial membrane potential ↓ Defect in mitochondrial morphology Defect in the assembly of complex I		
LRRK2		Unknown, probably regulating mitophagy	Saha *et al.* (2009), Mortiboys *et al.* (2010), Niu *et al.* (2012), Chen *et al.* (2012), Dehay *et al.* (2013)
	ATP production and mitochondrial membrane potential ↓ Defects in fission/fusion dynamics ALP dysfunction		
ATP13A2	ALP dysfunction	Unknown	Usenovic *et al.* (2012), Dehay *et al.* (2013)

ALP, autophagy–lysosome pathway; ATP, adenosine triphosphate; UPS, ubiquitin–proteasome system.

on the outer mitochondrial membrane and is able to directly phosphorylate Parkin in the cytosol and increase its ubiquitin ligase activity. This is critical for the initiation of autophagic clearance of damaged mitochondria by lysosomes, also known as mitophagy (Youle & Narendra 2011, Ko & Tan 2023). However, PD patients can have a loss of function PINK1 mutation, resulting in decreased Parkin recruitment. This leads to the accumulation of damaged/abnormal mitochondria and makes neurons more susceptible to oxidative stress and ubiquitinated inclusion bodies (e.g. Lewy bodies) and subsequent neurodegeneration (Klein & Westenberger 2012, Ge *et al.* 2020, Ko & Tan 2023).

DJ-1 and ATP13A2 mutations are both loss of function mutations with truncation and misfolding of proteins involved in antioxidant and neuroprotective functions, respectively. In addition, altered proteins from these genes are also noted to be involved in mitochondrial disruption with increased fragmentation, dysregulation of endoplasmic reticulum-mitochondrial interactions, elevated numbers of mitochondrial DNA mutations, increased ROS production, and ensuing disruption of mitophagy (Ramirez *et al.* 2006, Malgieri & Eliezer 2008, Ge *et al.* 2020).

Mitochondrial dysfunction, iron accumulation, neuroinflammation and ferroptosis in neuronal loss in Parkinson's disease

Mitochondria are a primary energy source for neurons. This organelle generates ATP through oxidative phosphorylation, processed by ETC embedded in the inner mitochondrial membrane (IMM). The ETC is composed of transmembrane complexes I, II, III, IV, and

V and two electron carriers, the ubiquinone (following absorption from the digestive tract, i.e. CoQ) and cytochrome c (cyt c). For ATP production, electrons are transferred from NADH and FADH2 to oxygen via the transport chain, coupled with the generation of a proton gradient across IMM (Zhao *et al.* 2019*a*). However, when the ETC is impaired, the mitochondria can be a primary source of ROS generation, namely superoxide ($O_2^{\bullet-}$) (Zhao *et al.* 2019*a*). Complexes I–III all contain Fe-S clusters that serve to facilitate electron transport and when impaired, can result in insufficient electron transfer to O_2 leading to an accumulation of $O_2^{\bullet-}$ and disrupted mitochondrial membrane potential (Zhao *et al.* 2019*a*). The pathophysiologic mechanism that associates mitochondrial dysfunction and Fe accumulation in PD is not fully elucidated, though logical hypotheses can be generated based on the standard models for the generation of PD. Prior models of dopaminergic neuroblastoma cells treated with mitochondrial complex I inhibitors, such as rotenone or MPP+ (1-methyl-4-phenylpyridinium), have shown increased ROS production, Fe accumulation, and mitochondrial Fe uptake (Lee *et al.* 2009, Mena *et al.* 2011). Because MPP+ and rotenone are complex I inhibitors routinely used for the induction of PD, this could provide significant insight into the physiochemical mechanisms driving PD initiation. ETC complex I functions as an electron transport protein, allowing for an electron transfer from NADH to ubiquinone through a covalently bound flavin mononucleotide and 7–10 Fe-S clusters (Gnandt *et al.* 2016). There is a stepwise construction of the Fe-S clusters that connect the NADH oxidation site to the quinone reduction site, which serves to regulate the electron tunneling rate through the complex. For example, rotenone inhibits the electron transfer from the Fe-S clusters to ubiquinone, leading to a build-up of electrons that can be put back onto O_2 to generate $O_2^{\bullet-}$ (Fig. 1) (Horgan *et al.* 1968) and MPP+ is believed to function in the same fashion (Richardson *et al.* 2007). Similarly, it has been shown that aged mice have significantly decreased complex I activity associated with neurodegeneration (Pollard *et al.* 2016). Thus, it can be reasonably inferred that increased steady-state levels of $O_2^{\bullet-}$ play a significant role in PD initiation through the age-associated degeneration of complex I (Sandhu & Kaur 2003, Kruse *et al.* 2016, Tyrrell *et al.* 2020), but further mechanistic work is required to elucidate this hypothesis.

As discussed earlier, over 20 PD-related genes have been discovered and although familial PD cases are not common, they can also provide insights into the pathogenesis of PD. Many of the PD-causing genes affect

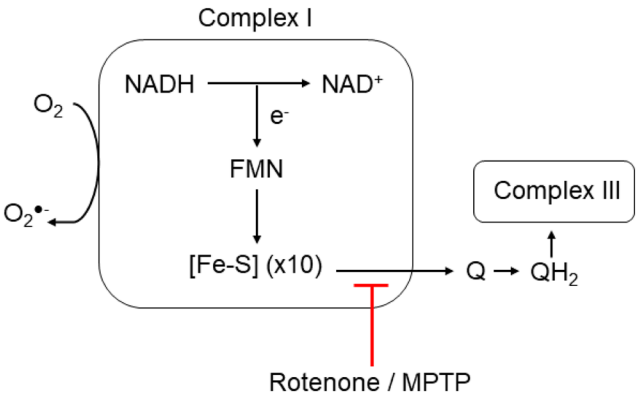

Figure 1
Transfer of an electron through electron transport chain complex I to generate a reduced quinone is impaired by traditional PD inducers. ETC complex I oxidizes NADH to shuttle an electron through a flavin mononucleotide and a series of Fe-S clusters to semiquinone to generate a reduced quinone. Rotenone and MPP+/MPTP Fe impair the transfer of the electron to the semiquinone from the Fe-S clusters, leading to the build-up of electrons and the generation of $O_2^{\bullet-}$.

quality control systems of mitochondria, lysosomal regulation, or lipid/protein homeostasis and thus directly or indirectly influence ETC function (Tyrrell *et al.* 2020) (Table 1). Due to mutations in genes like *PINK1*, *PRNK*, ATP production by mitochondria is directly or indirectly affected with subsequent reduced turnover and altered post-translational modifications of ETC proteins, impaired assembly or instability of mitochondrial complexes, abnormal protein aggregation, and dysregulated lipid metabolism. In addition to preventing mitophagy, enhancing α-Syn aggregation, and apoptosis, impaired ETC proteins also contribute to excessive ROS generation and PD pathogenesis.

Mitochondria also have a key role in Fe metabolism in association with the synthesis of Fe-S clusters and heme proteins that are vital for cell function. There are 12 protein subunits in the ETC that contain Fe-S clusters and 8 proteins that contain heme in their active centers (Rouault & Tong 2005); thus, Fe homeostasis and ETC function are intimately connected. Additionally, rotenone's suppression of complex I reduces the activity of enzymes with Fe-S clusters, such as mitochondrial and cytoplasmic aconitases (Rouault & Tong 2005). This is unsurprising as $O_2^{\bullet-}$ can react with the $[4Fe\text{-}4S]^{2+}$ cluster of aconitase leading to cluster oxidation, the release of the solvent-exposed Fe^{2+} site, and aconitase inactivation (Gardner 2002). The reduction in cytoplasmic aconitase activity is associated with an increase in Fe regulatory IRP1 mRNA binding activity and an increase in the mitochondrial labile Fe pool (Talbot & Brand 2005). Since IRP1 activity post-transcriptionally regulates the

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-23-0004

expression of Fe import proteins (e.g. TfR), inhibition of aconitase function by $O_2^{\bullet-}$ accumulation may result in a false Fe deficiency signal resulting in unnecessary and detrimental Fe accumulation. Hence, the inhibition of mitochondrial complex I in PD, due to mutations in PD genes Parkin, Pink 1, DJ-1 or LRRK2, may result in increased oxidative stress and increased Fe accumulation (Fig. 2).

While mitochondrial and ETC dysfunction is critical for the initiation of PD, neuroinflammation is believed to be responsible for the progression of symptoms (Hirsch & Hunot 2009, Urrutia *et al.* 2014, Troncoso-Escudero *et al.* 2018). Neuroinflammation has been shown to be strongly associated with neuronal loss in several neurodegenerative disorders including PD. Inflammation, often resulting in the generation of large amounts of proinflammatory cytokines and recruitment of glial and peripheral immune cells, triggers a cascade of events with further increased production of reactive nitrogen species, ROS, and mitochondrial dysfunction resulting in increased disruption of Fe metabolism and Fe accumulation with subsequent progression of neurodegeneration (Hirsch & Hunot 2009, Urrutia *et al.* 2014).

As Fe builds up over time, it can catalyze further ROS accumulation through reactions of O_2 and H_2O_2 (Emerit *et al.* 2001) that can further disrupt ETC complexes creating a positive feedback loop of further mitochondrial dysfunction and Fe accumulation leading to α-synuclein aggregation, proteasomal dysfunction, changes in mitochondrial fission/fusion dynamics, opening of the mitochondrion permeability pore, increased cytoplasmic cyt c, and activation of cell death pathways including apoptosis and eventual neuronal loss (Urrutia *et al.* 2014).

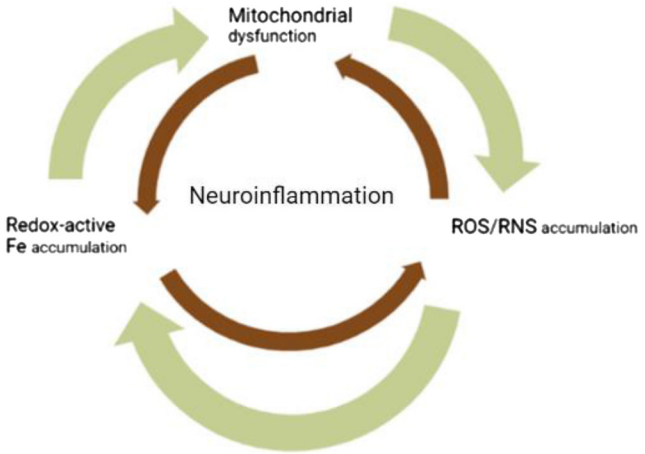

Figure 2
Mitochondrial dysfunction and iron accumulation and an ensuing positive feedback cascade with the generation of ROS. Mitochondrial disruptions, particularly ETC complex I inhibition, frequently lead to the generation of $O_2^{\bullet-}$ which can result in increased steady-state levels of ROS (including but not limited to $O_2^{\bullet-}$ and H_2O_2). The increased levels of ROS may be able to impair IRP1/2 activity *via* Fe-S cluster disruptions and increasing freely reactive (i.e. labile) Fe causing a Fe metabolic shift toward enriched Fe uptake through TfR and DMT1. The enhanced Fe accumulation further enriches the labile iron pool which can further catalyze ROS production. This feed-forward cascade may be critical in the accumulation of oxidative damage and eventual neuronal cell death.

Ferroptosis in Parkinson's disease

Ferroptosis is an Fe-dependent form of regulated cell death characterized by oxidative changes in the intracellular microenvironment with subsequent severe lipid peroxidation and toxic lipid peroxide accumulation (Galluzzi *et al.* 2018). It is well established that Fe is a critical catalyst in the propagation step of the lipid peroxidation cascade, as Fe can catalyze alkoxyl radical formation from phospholipid hydroperoxides in the following equation:

$$PLOOH + Fe^{2+} \rightarrow PLO^{\bullet} + OH^{-} + Fe^{3+}$$

The newly formed alkoxyl radical (PLO•) can then produce new chains of lipid peroxidation via an epoxy peroxyl radical (Wilcox & Marnett 1993, Marnett & Wilcox 1995, Rice-Evans *et al.* 1995). These lipid peroxides and hydroperoxides can then result in the rapid oxidation of membrane phospholipids triggering ferroptosis (Stockwell *et al.* 2017). Increased intracellular levels of lipid peroxides also alter the teritary structures of proteins, nucleic acids, and other intracellular metabolites (Ayala *et al.* 2014) (Gaschler & Stockwell 2017).

The main cascade of events involved in ferroptosis-mediated cell death includes increased intracellular labile Fe content, generation of lipid peroxides and superoxides, and subsequent depletion of the glutathione/glutathione peroxidase system (Reichert & de Freitas 2020). The enzyme glutathione peroxidase 4 (GPx4) is responsible for reducing lipid peroxides to lipid alcohols and is the main regulator of ferroptosis (Seibt *et al.* 2019). Major class of ferroptosis inducers, like RSL3, work through interaction with the seleno-cyteine active site of GPx4 subsequently blocking its enzymatic activity (Yang *et al.* 2016). The GPx4 enzyme was also found to be essential for the survival of parvalbumin-positive interneurons, prevention of seizures, and protection against ferroptosis in animal models (Ingold *et al.* 2017). After ferroptosis is triggered, it initiates a chain of events that include activation of inflammatory pathways, oxidation of neurotransmitters, failure of neuronal communication, degeneration of myelin sheath, and astrocyte dysregulation, leading to cell

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-23-0004

death in glial cells, neurons, and Schwann cells (Thapa *et al.* 2022).

Do Van *et al*. first described the role of ferroptosis in PD (Do Van *et al.* 2016). PD models, both *in vitro* and *in vivo*, have since shown evidence of dopaminergic cell death due to ferroptosis. More recently, the role of α-synuclein as an initiator of ferroptosis has been described (Angelova *et al.* 2020). α-Synuclein, a protein abundantly expressed in the nervous system and known to be a main component of Lewy bodies, has been widely studied in PD. It has been shown that the pathogenic effects of α-synuclein are strongly correlated with the pathophysiology of PD (Do Van *et al.* 2016). Recent literature shows that the aggregation of α-synuclein (a common pathological finding in PD) leads to the generation of ROS with ensuing lipid peroxidation in a Fe-dependent manner. This later results in increased calcium influx and consequent neuronal loss and cell death (Angelova *et al.* 2020). This hypothesis has further been supported by the use of ferroptosis inhibitors like ferrostatin to suppress neuronal death (Miotto *et al.* 2020). Several studies suggest the modulation of ferroptosis as a therapeutic target in neurodegenerative diseases (Cardoso *et al.* 2017, Guiney *et al.* 2017, Weiland *et al.* 2019). Interestingly, it has also been shown that the non-oxidized form of dopamine is a strong inhibitor of ferroptotic cell death. Dopamine reduced erastin-induced Fe^{2+} iron accumulation, glutathione depletion, and also increased the stability of GPx4 (Wang *et al.* 2016). Thus, there is a growing body of literature supporting ferroptosis as a central mechanism in PD development.

Fe and neuromelanin

NM is a pigment present in different neurons of the human central nervous system and is particularly abundant in dopaminergic neurons of the SNpc and in the noradrenergic neurons of locus cerelus (Zecca *et al.* 2004, 2008). NM is accumulated in dopaminergic neurons of the SNpc because it is synthesized following an Fe chemical reaction with a dopamine semiquinone derivative (Gerlach *et al.* 2003). Similarly, NM in the locus coeruleus originates from noradrenaline with a similar chemical mechanism (Mouton *et al.* 1994, Zucca *et al.* 2023). This is consistent with the observed NM accumulation and subsequent degeneration of the locus coeruleus in PD (Braak *et al.* 2003).

NM pigment appears as a black and insoluble molecule composed of different components: melanin, proteins, lipids, and metal ions (mainly Fe). NM pigment is located within cytoplasmic organelles, with variable sizes ranging from 0.5 to 3.0 μm, surrounded by a double membrane, together with lipid bodies and proteins (Sulzer *et al.* 2008, Zecca *et al.* 2008). NM pigment concentration increases with aging, beginning its formation and accumulation early in life (Zecca *et al.* 2002). Though the exact role of NM in pigmented neurons is uncertain, other melanins provide a protective function by reducing the harm caused by free radicals. Experimental evidence suggests that NM may exhibit this characteristic by direct absorption of free radical species or *via* its ability to chelate transition metals. Up to 20% of the total Fe contained in the SN from normal subjects is bound within NM. NM is able to bind Fe in two different sites. Most of the available Fe, under normal conditions, is bound to NM at high-affinity sites, although under Fe overload conditions, these sites of NM become saturated, and the Fe will also bind to the low-affinity sites (Double *et al.* 2003). When Fe is bound to the low-affinity sites of NM, it is sequestered in its reactive form, it can recycle faster and potentially have an adverse role by promoting redox reactions and oxidative stress, contributing to neuronal damage observed in PD (Gerlach *et al.* 2003). The overloading of NM with Fe and other metals in neurons may trigger inflammatory and degenerative processes aggravating the underlying pathological condition (Korytowski *et al.* 1995). Furthermore, the level of redox activity detected in NM-Fe aggregates was significantly increased (+69%) in Parkinsonian patients and was highest in patients with the most severe neuronal loss (Faucheux *et al.* 2003).

Fe and alpha synuclein (α-synuclein)

The primary neuropathological hallmark of PD is the presence of α-synuclein-positive Lewy body (Spillantini *et al.* 1997). Although many studies have shown α-synuclein aggregation to be an important cause in the onset and progression of PD, the exact pathological mechanisms remain largely unknown. α-Synuclein has been shown to bind divalent metals like Fe in both the Fe^{2+} and Fe^{3+} states (Binolfi *et al.* 2006) with the Fe^{3+} form suggested to be more potent as it accelerates the rate of α-synuclein fibril formation and aggregation (Uversky *et al.* 2001). A correlation was noted between efficiency in stimulating fibrillation and inducing a conformational change with an increase in ion charge (Uversky *et al.* 2001). The potential for ligand bridging by polyvalent metal ions is proposed to be an essential factor in the metal-induced conformational changes of α-synuclein (Levin *et al.* 2011).

More recently, studies have also suggested a prion-like effect of α-synuclein, as it can be transmitted from one cell

to another (Kordower *et al.* 2008, Li *et al.* 2008). Although distinct processes are involved in the pathogenesis of neurodegeneration and prion disorders, both share the common feature of Fe accumulation raising concerns about the possible role of Fe overload in facilitating the propagation of neuropathogenic and prion proteins (Xiao *et al.* 2018). This is thought to be due to the role of Fe in causing lysosomal dysfunction, a common feature contributing to many neurodegenerative disorders and prion disease (Seibler *et al.* 2018, Root *et al.* 2021). Prior studies have demonstrated enhanced α-synuclein aggregation and transmission with deficiency of either β-glucocerebrosidase 1 or cathepsin D (both lysosomal protein hydrolases) (Bae *et al.* 2014, 2015), suggesting that normal lysosomal function is important for clearance of aggregated α-synuclein and propagation inhibition. Fe accumulation leads to the deposition of large amounts of Fe within lysosomes and as a result, high levels of Fe-catalyzed oxidative damage, compromising lysosomal membrane integrity (Terman & Kurz 2013) (Kurz *et al.* 2011). In addition, Fe has been shown to inhibit autophagosome-lysosome fusion through decreased expression of nuclear transcription factor EB, a master transcriptional regulator of autophagosome-lysosome fusion. Interestingly, the mRNA of α-synuclein has also been shown to contain IREs indicating that its translation is responsive to Fe metabolic changes (Friedlich *et al.* 2007, Lingor *et al.* 2017). Elevated mitochondrially derived ROS leading to enhanced IRP1 activity could theoretically enhance α-synuclein protein translation as an adaptive response. These findings indicate a key connection between Fe metabolism and α-synuclein aggregation in the pathogenesis of PD. It suggests that their interaction can result in a vicious cycle, in which Fe stimulates increased α-synuclein accumulation resulting in hastened α-synuclein synthesis, aggregation, and transmission, leading to PD progression; an effect that can be exacerbated by mitochondrially derived ROS.

Fe deposition in PD animal models

As previously discussed, Fe demonstrably affects, and is affected by, the aberrant peptide aggregation of α-synuclein observed in PD. Changes in Fe at the cellular and sub-cellular scale are reflected in detectable disease-related changes in the regional distribution of Fe in the brain (Riederer *et al.* 1992). Within the brain, most of the Fe is sequestered within Ft, a 450 kDa protein found in every cell type, with each protein capable of storing up to 4500 Fe ions. Ft levels are typically closely coupled to Fe levels, such that increased Fe leads to increased Ft production. However, in the SN of PD patients, there is evidence of a loss of this coupling such that Fe is increased, but Ft levels are decreased (Dexter *et al.* 1992). As IRP1 activation typically represses Ft translation, these results further support the hypothesis of an overstimulated Fe response system in PD (Martina *et al.* 1998).

Several studies in animal PD models have been conducted to investigate whether the changes in Fe content of the SN in PD patients are a primary or secondary event. Mochizuki *et al.* injected 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPP+) into the caudate and putamen in cynomolgus monkeys to create a hemi-Parkinsonian model. Post-mortem microscopic cross-sectional examination of the monkeys' basal ganglia structures was notable for a marked increase in Fe staining in the ipsilateral MPP+-lesioned side, especially in the SN. Similar changes, however, were not seen in other basal ganglia structures such as the pallidum, caudate, and putamen (Mochizuki *et al.* 2020). Furthermore, other studies have shown the changes in Fe content in the SN following MPP+ injections are correlated with dopaminergic cell death progression (He *et al.* 2003). They showed that apoptosis begins to occur in the injected SN, day 1 after MPP+ injection with the number of tyrosine hydroxylase positive neurons decreasing significantly starting a week later with subsequent onset of PD symptoms in a delayed fashion (He *et al.* 2003). Fe content was also significantly increased in the ipsilateral SN from 4.5 to 18 months after MPP+ injection, and the Fe increase was significantly correlated to the extent of dopaminergic cell death (He *et al.* 2003). Interestingly, it has been noted that the loss of dopaminergic neurons precedes Fe accumulation in the MPP+-lesioned monkeys. This supports the hypothesis that Fe accumulation may not be the primary event, but the increased Fe may contribute to the progression of nigral degeneration (Dashtipour *et al.* 2015) (Riederer *et al.* 1989). Furthermore, there is also evidence in the literature that PD motor scores, disability, rigidity, and freezing of gait scores have a positive correlation with Fe accumulation levels in the SN of PD patients (Martin-Bastida *et al.* 2017*b*, Naduthota *et al.* 2017). Clinically, this is significant as assessment of Fe levels may be useful for monitoring PD progression.

Fe chelation as a treatment PD

Given the strong link between Fe accumulation and the progression of PD symptoms, Fe chelation remains a viable therapeutic option in slowing PD progression.

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-23-0004

There are several Fe chelators that are currently in clinical use. Deferoxamine (DFO) was the first chelator that was shown to prevent the toxic effects of the NM–Fe complex on nigrostriatal co-culture clonogenics (Mochizuki *et al.* 1993). Further preclinical studies in animal PD models showed that treatment with DFO was able to improve behavioral deficits and increase the survival of dopaminergic neurons in the SN and striatum (Guo *et al.* 2016). However, these results were not clinically translatable as DFO had poor oral bioavailability ($t_{1/2} \approx$ 20–30 min) and poor brain penetrance (Ward *et al.* 2021). This led to the development of a newer class of Fe chelators which were orally bioavailable. Fe chelators like deferiprone, desferrithiocin, and deferasirox have increasingly been used in clinical Fe chelation studies with relative success (Bergeron *et al.* 2014).

Following successful studies with deferiprone on animal PD models and results that showed Fe chelation might be an effective therapeutic approach for PD (Dexter *et al.* 1999), two clinical trials were performed utilizing oral deferiprone in PD patients (Devos *et al.* 2014, Martin-Bastida *et al.* 2017*b*). In both studies, patients receiving 30 mg/kg/day showed a decrease in SN Fe content quantitated by MRI and improved Unified Parkinson's Disease Rating Scale (UPDRS) scores. The UPDRS evaluates various aspects of PD including non-motor and motor experiences of daily living and motor complications (Devos *et al.* 2014, Martin-Bastida *et al.* 2017*a*). Interestingly, in the study by Martin-Bastida *et al.*, patients with high values of inflammatory markers such as IL-6 showed a poor response to Fe chelation (Martin-Bastida *et al.* 2017*a*). This may indicate that once inflammatory pathways have been activated Fe is trapped within the macrophages of the reticuloendothelial system, and perhaps also in the glial cells of the brain, preventing chelators from accessing previously chelatable Fe pools. Most patients tolerated oral deferiprone well, with ~14% of patients in both studies developing agranulocytosis and neurotpenia.

Despite the relative safety of oral chelators like deferiprone, there exists a concern for the effects of long-term Fe chelation therapy, even at the relatively low doses used in these studies, in interfering with Fe homeostasis in the brain, particularly in oligodendrocytes (Ward *et al.* 2021). Mature oligodendrocytes involved in myelination have the highest Fe concentrations of all brain cells. Fe has been proposed to be involved in myelin production, not only as a co-factor for cholesterol and lipid biosynthesis but also via its requirement for oxidative metabolism (Connor & Menzies 1996). To this end, newer drugs to reduce the impact of Fe accumulation and free radical-mediated neurodegeneration in PD, without directly affecting Fe metabolism, are currently being developed. These include the development of drugs with dual properties of radical scavenging and moderate Fe chelation properties to induce disease modification by slowing the process of neurodegeneration (Youdim *et al.* 2014, Bar-Am *et al.* 2016).

Conclusion

The underlying characteristics of PD include mitochondrial dysfunction, Fe accumulation, and ROS generation with α-synuclein accumulation, leading to ferroptosis and neuronal loss, particularly in the SNpc. Given the interconnectivity of mitochondrial dysfunction, Fe accumulation, oxidative stress, and inflammation, it is likely that the initiation of any one of these factors will induce or enhance the others through a positive feedback loop, ultimately resulting in apoptotic neuronal cell loss and death (Fig. 3). Given the toxic effects of Fe overload on glial cells and the proven efficacy of Fe chelators in rescuing neurodegeneration in different animal models, further therapeutic options would be a multifaceted approach

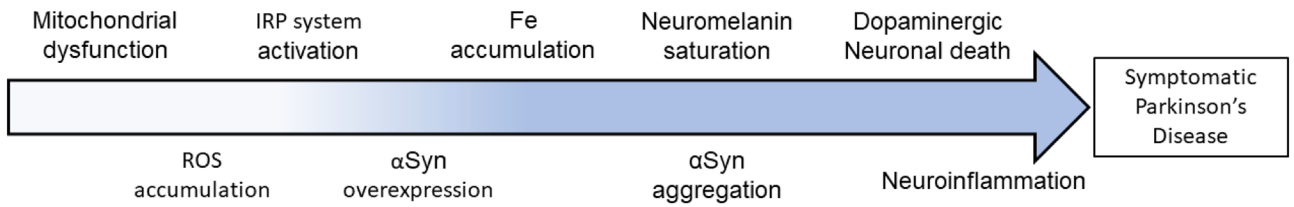

Figure 3
Hypothetical timeline showcasing the intersection of mitochondrial dysfunction and iron accumulation in the dopaminergic (DA) neurons of the SN pars compacta leading to the symptomatic presentation of Parkinson's disease. In this model, mitochondrially derived ROS leads to iron-responsive protein (IRP) system activation. IRP activation can theoretically lead to enhanced αSyn expression and Fe accumulation within the DA neurons of the SNpc. The increased iron concentration saturates the iron-binding sites of neuromelanin, and the increased labile iron pool is able to catalyze αSyn aggregation as a pathological intermediate. Eventually, this process leads to various forms of neuronal cell death, including ferroptosis. This DA neuronal cell death subsequently activates neuroinflammatory pathways and glial scarring in the SNpc which ultimately results in the symptomatic onset of Parkinson's disease.

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-23-0004

using medications with anti-inflammatory, antioxidant, and Fe chelation capabilities. Further understanding of the pathophysiological processes driving PD progression may pave the way forward in halting ferroptosis-mediated neuronal loss, neuroinflammation, and neurodegeneration in PD.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not for-profit sector.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author contribution statement

Conception and design: N Teferi, M Petronek; Collection and assembly of reference articles: N Teferi, M Gudeta, T Woodiwiss; Data analysis and interpretation: N Teferi, M Gudeta, T Woodiwiss; Manuscript writing: N Teferi, B Allen, M Petronek; Final approval of manuscript: All authors.

References

Angelova PR, Choi ML, Berezhnov AV, Horrocks MH, Hughes CD, De S, Rodrigues M, Yapom R, Little D, Dolt KS, *et al.* 2020 Alpha synuclein aggregation drives ferroptosis: an interplay of iron, calcium and lipid peroxidation. *Cell Death and Differentiation* **27** 2781–2796. (https://doi.org/10.1038/s41418-020-0542-z)

Ayala A, Muñoz MF & Argüelles S 2014 Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxidative Medicine and Cellular Longevity* **2014** 1–31. (https://doi.org/10.1155/2014/360438)

Bae EJ, Yang NY, Song M, Lee CS, Lee JS, Jung BC, Lee HJ, Kim S, Masliah E, Sardi SP, *et al.* 2014 Glucocerebrosidase depletion enhances cell-to-cell transmission of α-synuclein. *Nature Communications* **5** 4755. (https://doi.org/10.1038/ncomms5755)

Bae EJ, Yang NY, Lee C, Kim S, Lee HJ & Lee SJ 2015 Haploinsufficiency of cathepsin D leads to lysosomal dysfunction and promotes cell-to-cell transmission of α-synuclein aggregates. *Cell Death and Disease* **6** e1901. (https://doi.org/10.1038/cddis.2015.283)

Bar-Am O, Amit T, Youdim MB & Weinreb O 2016 Neuroprotective and neurorestorative potential of propargylamine derivatives in ageing: focus on mitochondrial targets. *Journal of Neural Transmission* **123** 125–135. (https://doi.org/10.1007/s00702-015-1395-3)

Bergeron RJ, Wiegand J, McManis JS & Bharti N 2014 Desferrithiocin: a search for clinically effective iron chelators. *Journal of Medicinal Chemistry* **57** 9259–9291. (https://doi.org/10.1021/jm500828f)

Binolfi RM, Bertoncini CW, Bertoncini CW, Ceolin M, Zweckstetter M, Griesinger C, Jovin TM & Fernández CO 2006 Interaction of alpha-synuclein with divalent metal ions reveals key differences: a link between structure, binding specificity and fibrillation enhancement. *Journal of the American Chemical Society* **128** 9893–9901. (https://doi.org/10.1021/ja0618649)

Bleil JD & Bretscher MS 1982 Transferrin receptor and its recycling in HeLa cells. *EMBO Journal* **1** 351–355. (https://doi.org/10.1002/j.1460-2075.1982.tb01173.x)

Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN & Braak E 2003 Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging* **24** 197–211. (https://doi.org/10.1016/s0197-4580(02)00065-9)

Cairo G & Pietrangelo A 2000 Iron regulatory proteins in pathobiology. . *Biochemical Journal* **352** 241–250. (https://doi.org/10.1042/bj3520241)

Cardoso BR, Hare DJ, Bush AI & Roberts BR 2017 Glutathione peroxidase 4: a new player in neurodegeneration? *Molecular Psychiatry* **22** 328–335. (https://doi.org/10.1038/mp.2016.196)

Casarejos MJ, Menéndez J, Solano RM, Rodríguez-Navarro JA, García de Yébenes J & Mena MA 2006 Susceptibility to rotenone is increased in neurons from parkin null mice and is reduced by minocycline. *Journal of Neurochemistry* **97** 934-946. (https://doi.org/10.1111/j.1471-4159.2006.03777.x)

Chen CY, Weng YH, Chien KY, Lin K-J, Yeh T-H, Cheng, Y-P, Lu C-S & Wang H-L 2012 (G2019S) LRRK2 activates MKK4-JNK pathway and causes degeneration of SN dopaminergic neurons in a transgenic mouse model of PD. *Cell Death and Differentiation 19* 1623-1633. (https://doi.org/10.1038/cdd.2012.42)

Chinta SJ, Mallajosyula JK, Rane A & Andersen JK 2010 Mitochondrial α-synuclein accumulation impairs complex I function in dopaminergic neurons and results in increased mitophagy in vivo. *Neuroscience Letters* **486** 235-239. (https://doi.org/10.1016/j.neulet.2010.09.061)

Chutvanichkul B, Vattanaviboon P, Mas-Oodi S, U-Pratya Y & Wanachiwanawin W 2018 Labile iron pool as a parameter to monitor iron overload and oxidative stress status in β-thalassemic erythrocytes. *Cytometry. Part B, Clinical Cytometry* **94** 631–636. (https://doi.org/10.1002/cyto.b.21633)

Connor JR & Menzies SL 1996 Relationship of iron to oligodendrocytes and myelination. *Glia* **17** 83–93. (https://doi.org/10.1002/(SICI)1098-1136(199606)17:2<83::AID-GLIA1>3.0.CO;2-7)

Dashtipour K, Liu M, Kani C, Dalaie P, Obenaus A, Simmons D, Gatto NM, Zarifi M, Gatto NM, *et al.* 2015 Iron accumulation is not homogenous among patients with Parkinson's disease. *Parkinson's Disease* **2015** 1–8. (https://doi.org/10.1155/2015/324843)

Dauer W & Przedborski S 2003 Parkinson's disease: mechanisms and models. *Neuron* **39** 889–909. (https://doi.org/10.1016/s0896-6273(03)00568-3)

Dehay B, Martinez-Vicente M, Caldwell GA, Caldwell KA, Yue Z, Cookson MR, Klein C, Vila M & Bezard E 2013 Lysosomal impairment in Parkinson's disease. *Movement Disorders 28* 725-732. (https://doi.org/10.1002/mds.25462)

Devos D, Moreau C, Devedjian JC, Kluza J, Petrault M, Laloux C, Jonneaux A, Ryckewaert G, Garçon G, Rouaix N, *et al.* 2014 Targeting chelatable iron as a therapeutic modality in Parkinson's disease. *Antioxidants and Redox Signaling* **21** 195–210. (https://doi.org/10.1089/ars.2013.5593)

Dexter DT, Wells FR, Agid F, Agid Y, Lees AJ, Jenner P & Marsden CD 1987 Increase nigral iron content in postmortem parkinsonian brain. *Lancet* **330** 1219–1220. (https://doi.org/10.1016/s0140-6736(87)91361-4)

Dexter DT, Jenner P, Schapira AH & Marsden CD 1992 Alterations in levels of iron, ferritin, and other trace metals in neurodegenerative diseases affecting the basal ganglia. The Royal Kings and Queens Parkinson's Disease Research Group. *Annals of Neurology* **32**(Supplement) S94–S100. (https://doi.org/10.1002/ana.410320716)

Dexter DT, Ward RJ, Florence A, Jenner P & Crichton RR 1999 Effects of desferrithiocin and its derivatives on peripheral iron and striatal

dopamine and 5-hydroxytryptamine metabolism in the ferrocene-loaded rat. *Biochemistry and Pharmacology* **58** 151–155. (https://doi.org/10.1016/s0006-2952(99)00079-9)

Dibble LE, Addison O & Papa E 2009 The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. *Journal of Neurologic Physical Therapy* **33** 14-26. (https://doi.org/10.1097/NPT.0b013e3181990fcc)

Do Van B, Gouel F, Jonneaux A, Timmerman K, Gelé P, Pétrault M, Bastide M, Laloux C, Moreau C, Bordet R, *et al.* 2016 Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC. *Neurobiology of Disease* **94** 169–178. (https://doi.org/10.1016/j.nbd.2016.05.011)

Double KL, Gerlach M, Schünemann V, Trautwein AX, Zecca L, Gallorini M, Youdim MBH, Riederer P & Ben-Shachar D 2003 Iron-binding characteristics of neuromelanin of the human substantia nigra. *Biochemistry and Pharmacology* **66** 489–494. (https://doi.org/10.1016/s0006-2952(03)00293-4)

Edwards RH, Greene LA & Zecca L 2000 Neuromelanin biosynthesis is driven by excess cytosolic catecholamines not accumulated by synaptic vesicles. *PNAS* 24 **97** 11869–11874.

Eid R, Arab NTT & Greenwood MT 2017 Iron mediated toxicity and programmed cell death: a review and a re-examination of existing paradigms. *Biochimica et Biophysica Acta. Molecular Cell Research* **1864** 399–430. (https://doi.org/10.1016/j.bbamcr.2016.12.002)

Emerit J, Beaumont C & Trivin F 2001 Iron metabolism, free radicals, and oxidative injury. *Biomedicine and Pharmacotherapy* **55** 333–339. (https://doi.org/10.1016/s0753-3322(01)00068-3)

Esteve-Rudd J, Campello L, Herrero MT, Cuenca N & Martín-Nieto J 2010 Expression in the mammalian retina of parkin and UCH-L1, two components of the ubiquitin-proteasome system. *Brain Research* **1352** 70-82. (https://doi.org/10.1016/j.brainres.2010.07.019)

Faucheux BA, Martin ME, Beaumont C, Hauw JJ, Agid Y & Hirsch EC 2003 Neuromelanin associated redox-active iron is increased in the substantia nigra of patients with Parkinson's disease. *Journal of Neurochemistry* **86** 1142–1148. (https://doi.org/10.1046/j.1471-4159.2003.01923.x)

Fraga CG 2005 Relevance, essentiality and toxicity of trace elements in human health. *Molecular Aspects of Medicine* **26** 235–244. (https://doi.org/10.1016/j.mam.2005.07.013)

Frey AG, Nandal A, Park JH, Smith PM, Yabe T, Ryu MS, Ghosh MC, Lee J, Rouault TA, Park MH, *et al.* 2014 Iron chaperones PCBP1 and PCBP2 mediate the metallation of the dinuclear iron enzyme deoxyhypusine hydroxylase. *PNAS* **111** 8031–8036. (https://doi.org/10.1073/pnas.1402732111)

Friedlich AL Tanzi RE, Rogers JT, Rogers JT 2007 The 5′-untranslated region of Parkinson's disease α-synuclein messengerRNA contains a predicted iron responsive element. *Molecular Psychiatry* **12** 222–223. (https://doi.org/10.1038/sj.mp.4001937)

Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, *et al.* 2018 Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death and Differentiation* **25** 486–541. (https://doi.org/10.1038/s41418-017-0012-4)

Gardner PR 2002 Aconitase: sensitive target and measure of superoxide. *Methods in Enzymology* **349** 9–23. (https://doi.org/10.1016/s0076-6879(02)49317-2)

Gaschler MM & Stockwell BR 2017 Lipid peroxidation in cell death. *Biochemical and Biophysical Research Communications* **482** 419–425. (https://doi.org/10.1016/j.bbrc.2016.10.086)

Gautier CA, Kitada T & Shen J 2008 Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. *PNAS* **105** 11364-11369(https://doi.org/10.1073/pnas.0802076105)

Ge P, Dawson VL & Dawson TM 2020 PINK1 and Parkin mitochondrial quality control: a source of regional vulnerability in Parkinson's disease. *Molecular Neurodegeneration* **15** 20. (https://doi.org/10.1186/s13024-020-00367-7)

Gerlach M, Double KL, Ben-Shachar D, Zecca L, Youdim MB & Riederer P 2003 Neuromelanin and its interaction with iron as a potential risk factor for dopaminergic neurodegeneration underlying Parkinson's disease *Neurotoxicity Research* **5** 35–44. (https://doi.org/10.1007/BF03033371)

Gnandt E, Dörner K, Strampraad MFJ, de Vries S & Friedrich T 2016 The multitude of iron-sulfur clusters in respiratory complex I. *Biochimica et Biophysica Acta* **1857** 1068–1072. (https://doi.org/10.1016/j.bbabio.2016.02.018)

Guiney SJ, Adlard PA, Bush AI, Finkelstein DI & Ayton S 2017 Ferroptosis and cell death mechanisms in Parkinson's disease. *Neurochemistry International* **104** 34–48. (https://doi.org/10.1016/j.neuint.2017.01.004)

Guo C, Hao LJ, Yang ZH, Chai R, Zhang S, Gu Y, Gao HL, Zhong ML, Wang T, Li JY, *et al.* 2016 Deferoxamine-mediated up-regulation of HIF-1α prevents dopaminergic neuronal death via the activation of MAPK family proteins in MPTP-treated mice. *Experimental Neurology* **280** 13–23. (https://doi.org/10.1016/j.expneurol.2016.03.016)

Haacke EM, Cheng NY, House MJ, Liu Q, Neelavalli J, Ogg RJ, Khan A, Ayaz M, Kirsch W & Obenaus A 2005 Imaging iron stores in the brain using magnetic resonance imaging. *Magnetic Resonance Imaging* **23** 1–25. (https://doi.org/10.1016/j.mri.2004.10.001)

He Y, Thong PS, Lee T, Leong SK, Mao BY, Dong F & Watt F 2003 Dopaminergic cell death precedes iron elevation in MPTP-injected monkeys. *Free Radical Biology and Medicine* **35** 540–547. (https://doi.org/10.1016/s0891-5849(03)00385-x)

Hentze MW, Muckenthaler MU, Galy B & Camaschella C 2010 Two to tango: regulation of Mammalian iron metabolism. *Cell* **142** 24–38. (https://doi.org/10.1016/j.cell.2010.06.028)

Heo JM & Rutter J 2011 Ubiquitin-dependent mitochondrial protein degradation. *International Journal of Biochemistry and Cell Biology 43* 1422-1426. (https://doi.org/10.1016/j.biocel.2011.06.002)

Hilton RJ, David Andros N & Watt RK 2012 The ferroxidase center is essential for ferritin iron loading in the presence of phosphate and minimizes side reactions that form Fe(III)-phosphate colloids. *Biometals* **25** 259–273. (https://doi.org/10.1007/s10534-011-9500-z)

Horgan DJ, Ohno H & Singer TP 1968 Studies on the respiratory chain-linked reduced nicotinamide adenine dinucleotide dehydrogenase. XV. Interactions of Piericidin with the Mitochondrial Respiratory Chain. *The Journal of Biological Chemistry* **243** 5.

Hirsch CH & Hunot S 2009 Parkinson's disease: a target for neuroprotection? *Lancet Neurology* **8** 382–397.

Ingold I, Berndt C, Schmitt S, Doll S, Poschmann G, Roveri A, Peng X, Freitas FP, Aichler M, Jastroch M, *et al.* 2017 Selenium utilization by GPX4 was an evolutionary requirement to prevent hydroperoxide-induced ferroptosis. *Free Radical Biology and Medicine* **112** 24. (https://doi.org/10.1016/j.freeradbiomed.2017.10.023)

Irrcher I, Aleyasin H, Seifert EL, Hewitt S J, Chhabra S, Phillips M, Lutz AK, Rousseaux MWC, Bevilacqua L, Jahani-Asl A et al. 2010 Loss of the Parkinson's disease-linked gene DJ-1 perturbs mitochondrial dynamics. *Human Molecular Genetics* **19** 3734-3746. (https://doi.org/10.1093/hmg/ddq288)

Kakhlon O & Cabantchik ZI 2002 The labile iron pool: characterization, measurement, and participation in cellular processes(1). *Free Radical Biology and Medicine* **33** 1037–1046. (https://doi.org/10.1016/s0891-5849(02)01006-7)

Klein C & Westenberger A 2012 Genetics of Parkinson's disease. *Cold Spring Harbor Perspectives in Medicine* **2** a008888. (https://doi.org/10.1101/cshperspect.a008888)

Ko TK & Tan DJY 2023 Is disrupted mitophagy a central player to Parkinson's disease pathology? *Cureus* **15** e35458. (https://doi.org/10.7759/cureus.35458)

Kordower JH, Chu Y, Hauser RA, Freeman TB & Olanow CW 2008 Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nature Medicine* **14** 504–506. (https://doi.org/10.1038/nm1747)

Korytowski W, Sarna T & Zareba M 1995 Antioxidant action of neuromelanin: the mechanism of inhibitory effect on lipid

peroxidation. *Archives of Biochemistry and Biophysics* **319** 142–148. (https://doi.org/10.1006/abbi.1995.1276)
Kruse SE, Karunadharma PP, Basisty N, Johnson R, Beyer RP, MacCoss MJ, Rabinovitch PS & Marcinek DJ 2016 Age modifies respiratory complex I and protein homeostasis in a muscle type-specific manner. *Aging Cell* **15** 89–99. (https://doi.org/10.1111/acel.12412)
Kruszewski M 2003 Labile iron pool: the main determinant of cellular response to oxidative stress. 2003. *Mutation Research* **531** 81–92.
Kurz T, Eaton JW & Brunk UT 2011 The role of lysosomes in iron metabolism and recycling. *International Journal of Biochemistry and Cell Biology* **43** 1686–1697. (https://doi.org/10.1016/j.biocel.2011.08.016)
Lee DW, Kaur D, Chinta SJ, Rajagopalan S, Andersen JK 2009 A disruption in iron-sulfur center biogenesis via inhibition of mitochondrial dithiol glutaredoxin 2 may contribute to mitochondrial and cellular iron dysregulation in mammalian glutathione-depleted dopaminergic cells : implications for Parkinson's disease *Antioxidants and Redox Signaling* **11** 2083–2094. (https://doi.org/10.1089/ARS.2009.2489)
Levin J, Högen T, Hillmer AS, Bader B, Schmidt F, Kamp F, Kretzschmar HA, Bötzel K & Giese A 2011 Generation of ferric iron links oxidative stress to α-synuclein oligomer formation. *Journal of Parkinson's Disease* **1** 205–216. (https://doi.org/10.3233/JPD-2011-11040)
Li JY, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Björklund A, *et al.* 2008 Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nature Medicine* **14** 501–503. (https://doi.org/10.1038/nm1746)
Lingor P, Carboni E & Koch JC 2017 Alpha-synuclein and iron: two keys unlocking Parkinson's disease. *Journal of Neural Transmission* **124** 973–981. (https://doi.org/10.1007/s00702-017-1695-x)
Liu W, Acín-Peréz R, Geghman KD, Manfredi G, Lu B & Li C 2011 Pink1 regulates the oxidative phosphorylation machinery via mitochondrial fission. *PNAS* **108** 12920-12924. (https://doi.org/10.1073/pnas.1107332108)
Lushchak OV, Piroddi M, Galli F & Lushchak VI 2014 Aconitase post-translational modification as a key in linkage between Krebs cycle, iron homeostasis, redox signaling, and metabolism of reactive oxygen species. *Redox Report: Communications in Free Radical Research* **19** 8–15. (https://doi.org/10.1179/1351000213Y.0000000073)
Malgieri G & Eliezer D 2008 Structural effects of Parkinson's disease linked DJ-1 mutations. *Protein Science* **17** 855–868. (https://doi.org/10.1110/ps.073411608)
Malpartida AB, Williamson M, Narendra DP, Wade-Martins R & Ryan BJ 2020 Mitochondrial dysfunction and mitophagy in Parkinson's disease: from mechanism to therapy. *Trends in Biochemical Sciences* **46** 329–343. (https://doi.org/10.1016/j.tibs.2020.11.007)
Marnett LJ & Wilcox AL 1995 The chemistry of lipid alkoxyl radicals and their role in metal-amplified lipid peroxidation. *Biochemical Society Symposium* **61** 65–72. (https://doi.org/10.1042/bss0610065)
Martina M, Gray NK & Hentze MW 1998 IRP-1 binding to ferritin mRNA prevents the recruitment of the small ribosomal subunit by the cap-binding complex eIF4F, *Molecular Cell* **2** 383–388. (https://doi.org/10.1016/s1097-2765(00)80282-8)
Martin-Bastida A, Lao-Kaim NP, Loane C, Politis M, Roussakis AA, Valle-Guzman N, Kefalopoulou Z, Paul-Visse G, Widner H, Xing Y, *et al.* 2017*a* Motor associations of iron accumulation in deep grey matter nuclei in Parkinson's disease: a cross-sectional study of iron-related magnetic resonance imaging susceptibility. *European Journal of Neurology* **24** 357–365. (https://doi.org/10.1111/ene.13208)
Martin-Bastida A, Ward RJ, Newbould R & Piccini P 2017*b* Brain iron chelation by deferiprone in a phase 2 randomised double-blinded placebo controlled clinical trial in PD *Scientific Reports* **7** 1398.
Mena NP, Bulteau AL, Salazar J, Hirsch EC, Núñez MT 2011 Effect of mitochondrial complex I inhibition on Fe-S cluster protein activity. *Biochemical and Biophysical Research Communications* **409** 241–246. (https://doi.org/10.1016/j.bbrc.2011.04.137)
Miotto G, Rossetto M, Di Paolo ML, Orian L, Venerando R, Roveri A, Vučković AM, Bosello Travain V, Zaccarin M, Zennaro L, *et al.* 2020 Insight into the mechanism of ferroptosis inhibition by ferrostatin-1. *Redox Biology* **28** 101328. (https://doi.org/10.1016/j.redox.2019.101328)
Mochizuki H, Nishi K & Mizuno Y 1993 Iron–melanin complex is toxic to dopaminergic neurons in a nigrostriatal co-culture. *Neurodegeneration* **2** 1–7.
Mochizuki H, Choong CJ & Baba K 2020 Parkinson's disease and iron. *Journal of Neural Transmission* **127** 181–187. (https://doi.org/10.1007/s00702-020-02149-3)
Mortiboys H, Johansen KK, Aasly JO & Bandmann O 2010 Mitochondrial impairment in patients with Parkinson disease with the G2019S mutation in LRRK2. *Neurology* **75** 2017-2020. (https://doi.org/10.1212/WNL.0b013e3181ff9685)
Mouton PR, Pakkenberg B, Gundersen HJG & Price DL 1994 Absolute number and size of pigmented locus coeruleus neurons in young and aged individuals. *Journal of Chemical Neuroanatomy* **7** 185–190. (https://doi.org/10.1016/0891-0618(94)90028-0)
Muckenthaler MU, Rivella S, Hentze MW & Galy B 2017 A red carpet for iron metabolism. *Cell* **168** 344–361. (https://doi.org/10.1016/j.cell.2016.12.034)
Naduthota RM, Honnedevasthana AA, Lenka A, Saini J, Geethanath S, Bharath RD, Christopher R, Yadav R, Gupta AK & Pal PK 2017 Association of freezing of gait with nigral iron accumulation in patients with Parkinson's disease. *Journal of the Neurological Sciences* **382** 61–65. (https://doi.org/10.1016/j.jns.2017.09.033)
Niu J, Yu M, Wang C & Xu Z 2012 Leucine-rich repeat kinase 2 disturbs mitochondrial dynamics via Dynamin-like protein. *Journal of Neurochemistry 122* 650-658. (https://doi.org/10.1111/j.1471-4159.2012.07809.x)
Palacino JJ, Sagi D, Goldberg MS, Krauss S, Motz C, Wacker M, Klose J & Shen J 2004 Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *Journal of Biological Chemistry* **279** 18614-18622. (https://doi.org/10.1074/jbc.M401135200)
Paradkar PN, Zumbrennen KB, Paw BH, Ward DM & Kaplan J 2009 Regulation of mitochondrial iron import through differential turnover of mitoferrin 1 and mitoferrin 2. *Molecular and Cellular Biology* **29** 1007–1016. (https://doi.org/10.1128/MCB.01685-08)
Park J, Lee SB, Lee S, Kim Y, Song S, Kim S, Bae E, Kim J, Shong M, Kim J-M et al. 2006 Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin. *Nature* **441** 1157-1161. (https://doi.org/10.1038/nature04788)
Petronek MS, Spitz R, Buettner GR & Allem BG 2019 Linking cancer metabolic dysfunction and genetic instability through the lens of iron metabolism. *Cancers (Basel)* **11** 1077.
Piñero DJ & Connor JR 2000 Iron in the brain: an important contributor in normal and diseased states. *Neuroscientist* **6** 435–453. (https://doi.org/10.1177/107385840000600607)
Pollard AK, Craig EL & Chakrabarti L 2016 Mitochondrial Complex 1 activity measured by spectrophotometry is reduced across all brain regions in ageing and more specifically in neurodegeneration. *PLoS One* **11** e0157405. (https://doi.org/10.1371/journal.pone.0157405)
Ramirez A, Heimbach A, Gründemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat AL, Roeper J, *et al.* 2006 Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. *Nature Genetics* **38** 1184–1191. (https://doi.org/10.1038/ng1884)
Reichert CO & de Freitas FA 2020 Ferroptosis mechanisms involved in neurological diseases. *International Journal of Molecular Sciences* **8765** 21.
Rhodes SL & Ritz B 2008 Genetics of iron regulation and the possible role of iron in Parkinson's disease *Neurobiology of Disease* **32** 183–195. (https://doi.org/10.1016/j.nbd.2008.07.001)
Rice-Evans C, Halliwell B, Lunt GG, Marnett LJ & Wilcox AL 1995 The chemistry of lipid alkoxyl radicals and their role in metal-amplified lipid peroxidation. *Biochemical Society Symposium* **61** 65–72.

Richardson JR, Caudle WM, Guillot TS, Watson JL, Nakamaru-Ogiso E, Seo BB, Sherer TB, Greenamyre JT, Yagi T, Matsuno-Yagi A, *et al.* 2007 Obligatory role for complex I inhibition in the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Toxicological Sciences* **95** 196–204. (https://doi.org/10.1093/toxsci/kfl133)

Riederer P, Sofic E, Rausch WD, Schmidt B, Reynolds GP, Jellinger K & Youdim MB 1989 Transition metals, ferritin, glutathione, and ascorbic acid in parkinsonian brains. *Journal of Neurochemistry* **52** 515–520. (https://doi.org/10.1111/j.1471-4159.1989.tb09150.x)

Riederer P, Dirr A, Goetz M, Sofic E, Jellinger K & Youdim MB 1992 Distribution of iron in different brain regions and subcellular compartments in Parkinson's disease. *Annals of Neurology* **32**(Supplement) S101–S104. (https://doi.org/10.1002/ana.410320717)

Root J, Merino P, Nuckols A, Johnson M & Kukar T 2021 Lysosome dysfunction as a cause of neurodegenerative diseases: lessons from frontotemporal dementia and amyotrophic lateral sclerosis. *Neurobiology of Disease* **154** 105360. (https://doi.org/10.1016/j.nbd.2021.105360)

Roth JA, Singleton S, Feng J, Garrick M & Paradkar PN 2010 Parkin regulates metal transport via proteasomal degradation of the 1B isoforms of divalent metal transporter 1. *Journal of Neurochemistry* **113** 454–464. (https://doi.org/10.1111/j.1471-4159.2010.06607.x)

Rouault TA & Tong WH 2005 Iron-sulphur cluster biogenesis and mitochondrial iron homeostasis. *Nature Reviews. Molecular Cell Biology* **6** 345–351. (https://doi.org/10.1038/nrm1620)

Saha S, Guillily MD, Ferree A, Lanceta J, Chan D, Ghosh J, Hsu CH, Segal L, Raghavan K, Matsumoto K et al. 2009 LRRK2 modulates vulnerability to mitochondrial dysfunction in Caenorhabditis elegans. *Journal of Neuroscience 29* 9210-9218. (https://doi.org/10.1523/JNEUROSCI.2281-09.2009)

Sandhu SK & Kaur G 2003 Mitochondrial electron transport chain complexes in aging rat brain and lymphocytes. *Biogerontology* **4** 19–29. (https://doi.org/10.1023/a:1022473219044)

Seibler P, Burbulla LF, Dulovic M, Zittel S, Heine J, Schmidt T, Rudolph F, Westenberger A, Rakovic A, Münchau A, *et al.* 2018 Iron overload is accompanied by mitochondrial and lysosomal dysfunction in WDR45 mutant cells. *Brain* **141** 3052–3064. (https://doi.org/10.1093/brain/awy230)

Seibt TM, Proneth B & Conrad M 2019 Role of GPX4 in ferroptosis and its pharmacological implication. *Free Radical Biology and Medicine* **133** 144–152. (https://doi.org/10.1016/j.freeradbiomed.2018.09.014)

Shi H, Bencze KZ, Stemmler TL & Philpott CC 2008 A cytosolic iron chaperone that delivers iron to ferritin. *Science* **320** 1207–1210. (https://doi.org/10.1126/science.1157643)

Shim JH, Yoon SH, Kim KH, Han JY, Ha JY, Hyun DH, Paek SH, Kang UJ, Zhuang X & Son JH 2011 The antioxidant Trolox helps recovery from the familial Parkinson's diseasespecific mitochondrial deficits caused by PINK1- and DJ-1- deficiency in dopaminergic neuronal cells. *Mitochondrion* **11** 707-715. (https://doi.org/10.1016/j.mito.2011.05.013)

Spillantini MG, Schmidt ML, Lee VMY, Trojanowski JQ, Jakes R & Goedert M 1997 α-synuclein in Lewy bodies. *Nature* **388** 839–840. (https://doi.org/10.1038/42166)

Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, Fulda S, Gascón S, Hatzios SK, Kagan VE, *et al.* 2017 Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell* **171** 273–285. (https://doi.org/10.1016/j.cell.2017.09.021)

Sulzer D, Mosharov E, Talloczy Z, FA, Simon JD, Zecca L 2008 Neuronal pigmented autophagic vacuoles: lipofuscin, neuromelanin, and ceroid as macroautophagic responses during aging and disease *Journal of Neurochemistry* **106** 24–36. (https://doi.org/10.1111/j.1471-4159.2008.05385.x)

Takahashi-Makise N, Ward DM & Kaplan J 2009 On the mechanism of iron sensing by IRP2: new players, new paradigms. *Nature Chemical Biology* **5** 874–875. (https://doi.org/10.1038/nchembio.261)

Talbot DA & Brand MD 2005 Uncoupling protein 3 protects aconitase against inactivation in isolated skeletal muscle mitochondria. *Biochimica et Biophysica Acta* **1709** 150–156. (https://doi.org/10.1016/j.bbabio.2005.07.001)

Terman A & Kurz T 2013 Lysosomal iron, iron chelation, and cell death. *Antioxidants and Redox Signaling* **18** 888–898. (https://doi.org/10.1089/ars.2012.4885)

Thapa K, Khan H, Kaur A & Kaur G 2022 Therapeutic Insights on Ferroptosis in Parkinson's disease. *European Journal of Pharmacology* **930** 175133. (https://doi.org/10.1016/j.ejphar.2022.175133)

Torti SV & Torti FM 2013 Iron and cancer: more ore to be mined. *Nature Reviews. Cancer* **13** 342–355. (https://doi.org/10.1038/nrc3495)

Troadec MB, Warner D, Wallace J, Thomas K, Spangrude GJ, Phillips J, Khalimonchuk O, Paw BH, Ward DM & Kaplan J 2011 Targeted deletion of the mouse Mitoferrin1 gene: from anemia to protoporphyria. *Blood* **117** 5494–5502. (https://doi.org/10.1182/blood-2010-11-319483)

Troncoso-Escudero P, Parra A, Nassif M & Vidal RL 2018 Outside in: Unraveling the Role of Neuroinflammation in the Progression of Parkinson's Disease. *Frontiers in Neurology* **9** 860. (https://doi.org/10.3389/fneur.2018.00860)

Tyrrell DJ, Blin MG, Song J, Wood SC, Zhang M, Beard DA & Goldstein DR 2020 Age-associated mitochondrial dysfunction accelerates atherogenesis. *Circulation Research* **126** 298–314. (https://doi.org/10.1161/CIRCRESAHA.119.315644)

Tysnes OB & Storstein A 2017 Epidemiology of Parkinson's disease. *Journal of Neural Transmission* **124** 901–905. (https://doi.org/10.1007/s00702-017-1686-y)

Urrutia PJ, Mena NP & Núñez MT 2014 The interplay between iron accumulation, mitochondrial dysfunction, and inflammation during the execution step of neurodegenerative disorders. *Frontiers in Pharmacology* **5** 38. (https://doi.org/10.3389/fphar.2014.00038)

Usenovic M, Knight AL, Ray A, Wong V, Brown KR, Caldwell GA, Caldwell KA, Stagljar I & Krainc D 2012 Identification of novel ATP13A2 interactors and their role in α-synuclein misfolding and toxicity. *Human Molecular Genetics* **21** 3785-3794. (https://doi.org/10.1093/hmg/dds206)

Uversky VN, Li J & Fink AL 2001 Metal-triggered structural transformations, aggregation, and fibrillation of human α-synuclein: a possible molecular link between Parkinson′ s disease and heavy metal exposure. *Journal of Biological Chemistry* **276** 44284–44296. (https://doi.org/10.1074/jbc.M105343200)

Wang JY, Zhuang QQ, Zhu LB, Zhu H, Li T, Li R, Chen SF, Huang CP, Zhang X & Zhu JH 2016 Meta-analysis of brain iron levels of Parkinson's disease patients determined by postmortem and MRI measurements. *Scientific Reports* **6** 36669. (https://doi.org/10.1038/srep36669)

Wang H, Shi H, Rajan M, Canarie ER, Hong S, Simoneschi D, Pagano M, Bush MF, Stoll S, Leibold EA, *et al.* 2020 FBXL5 regulates IRP2 stability in iron homeostasis via an oxygen-responsive [2Fe2S] cluster. *Molecular Cell* **78** 31–41.e5. (https://doi.org/10.1016/j.molcel.2020.02.011)

Ward RJ, Dexter DT, Martin-Bastida A & Crichton RR 2021 Is chelation therapy a potential treatment for Parkinson's disease? *International Journal of Molecular Sciences* **22**. (https://doi.org/10.3390/ijms22073338)

Weiland A, Wang Y, Wu W, Lan X, Han X, Li Q & Wang J 2019 Ferroptosis and its role in diverse brain diseases. *Molecular Neurobiology* **56** 4880–4893. (https://doi.org/10.1007/s12035-018-1403-3)

Wilcox AL & Marnett LJ 1993 Polyunsaturated fatty acid alkoxyl radicals exist as carbon-centered epoxyallylic radicals: a key step in hydroperoxide-amplified lipid peroxidation. *Chemical Research in Toxicology* **6** 413–416. (https://doi.org/10.1021/tx00034a003)

Xiao Y, Chen X, Huang S, Li G, Mo M, Zhang L, Chen C, Guo W, Zhou M, Wu Z, *et al.* 2018 Iron promotes α-synuclein aggregation and transmission by inhibiting TFEB-mediated autophagosome-lysosome

fusion. *Journal of Neurochemistry* **145** 34–50. (https://doi.org/10.1111/jnc.14312)
Yang WS, Kim KJ, Gaschler MM, Patel M, Shchepinov MS, Stockwell BR 2016 Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. *PNAS* **113** E4966–E4975. (https://doi.org/10.1073/pnas.1603244113)
Youdim MB Ed. 1988 *Brain iron: neurochemical and behavioural aspects*. London: Taylor & Francis Group.
Youdim MB, Kupershmidt L, Amit T & Weinreb O 2014 Promises of novel multi-target neuroprotective and neurorestorative drugs for Parkinson's disease. *Parkinsonism and Related Disorders* **20** (Supplement 1) S132–S136. (https://doi.org/10.1016/S1353-8020(13)70032-4)
Youle RJ & Narendra DP 2011 Mechanisms of mitophagy. *Nature Reviews. Molecular Cell Biology* **12** 9–14. (https://doi.org/10.1038/nrm3028)
Zecca L, Bellei C, Costi P, Albertini A, E, Casella L, Gallorini M, Bergamaschi L, Moscatelli A, Turro NJ, *et al.* 2008 New melanic pigments in the human brain that accumulate in aging and block environmental toxic metals. *PNAS* **105** 17567–17572. (https://doi.org/10.1073/pnas.0808768105)
Zecca L, Fariello R, Riederer P, Sulzer D & Gatti A 2002 The absolute concentration of nigral neuromelanin, assayed by a new sensitive method, increases throughout the life and is dramatically decreased in Parkinson's disease. *FEBS Letters* **510** 216–220. (https://doi.org/10.1016/s0014-5793(01)03269-0)
Zecca L, Stroppolo A, Gatti A, Tampellini D, Toscani M, Gallorini M, Giaveri G, Arosio P, Santambrogio P, Fariello RG, *et al.* 2004 The role of iron and copper molecules in the neuronal vulnerability of locus coeruleus and substantia nigra during aging. *PNAS* **101** 9843–9848. (https://doi.org/10.1073/pnas.0403495101)
Zhao RZ, Jiang S, Zhang L & Yu ZB 2019*a* Mitochondrial electron transport chain, ROS generation and uncoupling (Review). *International Journal of Molecular Medicine* **44** 3–15. (https://doi.org/10.3892/ijmm.2019.4188)
Zhao Z, Bao X-Q & Dan Z 2019*b* Mechanisms of ferroptosis and its involvement in Parkinson's disease. *Acta Pharmaceutica Sinica* 399–406.
Zheng W & Monnot AD 2012 Regulation of brain iron and copper homeostasis by brain barrier systems: implication in neurodegenerative diseases. *Pharmacology and Therapeutics* **133** 177–188. (https://doi.org/10.1016/j.pharmthera.2011.10.006)
Zucca FA, Capucciati A, Bellei C, Sarna M, Sarna T, Monzani E, Casella L & Zecca L 2023 Neuromelanins in brain aging and Parkinson's disease: synthesis, structure, neuroinflammatory, and neurodegenerative role. *IUBMB Life* **75** 55–65. (https://doi.org/10.1002/iub.2654)

Received 28 February 2023
Accepted 9 May 2023
Available online 9 May 2023
Version of Record published 2 June 2023