The Role of the Antioxidant Response in Mitochondrial Dysfunction in Degenerative Diseases: Cross-Talk between Antioxidant Defense, Autophagy, and Apoptosis

Michael L.-H. Huang, Shannon Chiang, Danuta S. Kalinowski, Dong-Hun Bae, Sumit Sahni, and Des R. Richardson

Molecular Pharmacology and Pathology Program, Department of Pathology and Bosch Institute, Medical Foundation Building (K25), University of Sydney, Sydney, New South Wales 2006, Australia

Correspondence should be addressed to Michael L.-H. Huang; michael.huang@sydney.edu.au, Shannon Chiang; shannon.chiang@sydney.edu.au, and Des R. Richardson; d.richardson@sydney.edu.au

Received 13 November 2018; Revised 18 January 2019; Accepted 11 February 2019; Published 7 April 2019

Guest Editor: Livia Hool

Copyright © 2019 Michael L.-H. Huang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The mitochondrion is an essential organelle important for the generation of ATP for cellular function. This is especially critical for cells with high energy demands, such as neurons for signal transmission and cardiomyocytes for the continuous mechanical work of the heart. However, deleterious reactive oxygen species are generated as a result of mitochondrial electron transport, requiring a rigorous activation of antioxidative defense in order to maintain homeostatic mitochondrial function. Indeed, recent studies have demonstrated that the dysregulation of antioxidant response leads to mitochondrial dysfunction in human degenerative diseases affecting the nervous system and the heart. In this review, we outline and discuss the mitochondrial and oxidative stress factors causing degenerative diseases, such as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, Huntington’s disease, and Friedreich’s ataxia. In particular, the pathological involvement of mitochondrial dysfunction in relation to oxidative stress, energy metabolism, mitochondrial dynamics, and cell death will be explored. Understanding the pathology and the development of these diseases has highlighted novel regulators in the homeostatic maintenance of mitochondria. Importantly, this offers potential therapeutic targets in the development of future treatments for these degenerative diseases.

1. Mitochondria and Oxidative Stress

Mitochondria are the major energy-producing organelle of the cell via the process of oxidative phosphorylation (OXPHOS). In addition to this important role, mitochondria are also involved in a myriad of biological functions, from the generation of vital cellular metabolites such as iron-sulfur clusters (ISCs) and heme [1] to the regulation of cell death [2, 3]. However, as a consequence of active oxidative metabolism, in particular complex I and III of the electron transport chain, mitochondria are also a major source of reactive oxygen species (ROS) in cells [3, 4], with superoxide anions, hydroxyl radicals, and hydrogen peroxide being the predominant forms of ROS [5]. Apart from its well-known role in cytotoxicity, the generation of ROS has important signaling functions, with their levels being regulated by a suite of cellular antioxidants [2].

When the rate of ROS production exceeds cellular antioxidant capacity, the ensuing oxidative stress damages vital components of the cell, resulting in oxidation of membranes, proteins, and nucleic acids. Within the mitochondrion, ROS can potentiate profound damage to mitochondrial energy production by causing mitochondrial DNA (mtDNA) damage and subsequent defects in mtDNA-encoded subunits of the respiratory complex I and III [6]. Furthermore, ROS can readily interact with ISCs within subunits of complex I, II, and III to disrupt their function [6]. The exquisite dependence of neurons and cardiomyocytes on mitochondria for ATP production also means these cells are particularly susceptible to mitochondrial ROS [4, 7]. As such, the
accumulation of oxidative damage within cells leads to death and is a driver of aging as well as neurodegenerative and cardiodegenerative diseases [3, 8].

2. Mitochondrial DNA

The mtDNA encodes 22 transfer RNAs, two ribosomal RNAs, and 13 essential proteins of oxidative phosphorylation, the quintessential machinery responsible for ATP production [9]. Due to limited mtDNA repair enzymes, absence of protective histone molecules, and the susceptibility of mtDNA to oxidative damage, mtDNA is prone to mutations, which drives further mitochondrial dysfunction and potentiates a vicious cycle of mtDNA damage [4, 7, 10]. Mutations in mtDNA also accumulate with aging [11] or are inherited in a number of human mitochondrial diseases [12]. The importance of maintaining mtDNA integrity in age-related diseases is demonstrated by mice that lack a mutation in the mtDNA polymerase-γ (Polg), which disables the mtDNA proofreading activity of the enzyme [10]. As a result, Polg mutant mice accumulate mtDNA mutations during mtDNA replication [10] and carry an average of 9 point mutations per 10 kb in cytochrome b, versus 1 mutation per 10 kb in control mice [10]. The mutant mice develop pathologies associated with aging, including weight loss, osteoporosis, kyphosis, alopecia, cardiomyopathy, anemia, and sarcopenia [10].

3. Mitochondria and Antioxidant Defense

As the mitochondrion is an active site of cellular redox homeostasis and a major source of ROS, it is not surprising that the homeostasis of this organelle can be regulated by the master regulator of cellular antioxidant defense, NRF2, a transcription factor [13, 14]. The nuclear factor erythroid-derived 2-related factor 2 (NRF2) is a well-known transcription factor and a master regulator of a variety of antioxidant and detoxifying enzymes [15]. NRF2 heterodimerizes with small musculoaponeurotic fibrosarcoma (sMAF) proteins to enable specific binding to its target DNA sequence known as the antioxidant response element (ARE) [15, 16]. The binding of NRF2 to ARE leads to the transcriptional activation of ARE-containing genes; these include major phase II detoxifying enzymes in the glutathione, thioredoxin, and peroxiredoxin antioxidant systems (reviewed in [17]).

The expression of NRF2 is tightly regulated via the proteasomal system [17]. The best known mechanism of NRF2 regulation involves the Kelch-like ECH-associated protein 1 (KEAP1) which is the substrate adapter protein for the Cul3-RBX1 E3 ubiquitin ligase complex, which responds to electrophilic and/or oxidative signals [17]. In addition, there is a KEAP1-independent mechanism of NRF2 regulation involving glycogen synthase kinase-3β (GSK3β) that likely responds to receptor-mediated signal transduction [17]. This mechanism involves phosphorylation of nuclear NRF2 by GSK3β, leading to the recruitment of another E3-ubiquitin ligase adapter, β-TrCP [18, 19], or via the Src kinase, the Fyn-mediated nuclear NRF2 export process [20, 21].

An additional mechanism of NRF2 activation involves p62-dependent autophagic degradation of KEAP1 [22–25]. This process could involve the competitive binding of p62, which is reportedly induced by NRF2 activity [23], to the NRF2-binding site on KEAP1, thereby preventing KEAP1-mediated NRF2 degradation [23–25]. Therefore, increased phosphorylated p62-mediated autophagy increases NRF2 activity, which in turn increases p62 activity [23, 26].

In addition, NRF2 has been shown to directly affect mitochondrial homeostasis via its regulation of nuclear respiratory factor 1 (NRF1) through the 4 AREs in the NRF1 promoter and thereby promote mitochondrial biogenesis [14]. Other studies have also demonstrated that NRF2 is able to indirectly activate another major driver of mitochondrial biogenesis, the peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) via heme oxygenase-1 (HO-1)/carbon monoxide signaling [13, 27]. As such, NRF2 is essential for mitochondrial function, with regulation of NRF2 expression strongly and positively modulating mitochondrial membrane potential, ATP production, and efficiency of oxidative phosphorylation [15, 28].

Recently, NRF2 has also been identified to be associated with mitochondria through a complex of KEAP1 and the mitochondrial outer membrane serine/threonine protein phosphatase, PGAM5 [29, 30]. This NRF2-KEAP1-PGAM5 complex has been reported to play a role in mitochondrial retrograde trafficking. A decrease in NRF2 or PGAM5 expression results in decreased mitochondrial motility, which is particularly important for the transport of mitochondria along the neuronal axon [29]. Furthermore, PGAM5 is also a binding protein of the antiapoptotic protein, BCL-2-related protein, PGAM5 [31]. A decrease in PGAM5 may lead to KEAP1-mediated BCL-2 XL degradation, which thereby promotes apoptosis [32]. In particular, considering the reduction of NRF2 or PGAM5 in aging and human degenerative disease states [32–35], this NRF2-KEAP1-PGAM5 ternary interaction may be an important mechanism in the development of human diseases.

4. Mitochondrial Homeostasis and Dynamics

The maintenance of mitochondrial homeostasis is critical for proper functioning of the cell. Hence, mitochondria have a network of dynamic processes that tightly regulate its homeostasis and life cycle, namely, mitochondrial fusion and fission, mitochondrial biogenesis (Figure 1) [36–38]. Mitochondrial fusion and fission mediate mitochondrial quality control through regulation of its turnover via mitochondrial biogenesis and elimination [37, 39].

4.1. Mitochondrial Fusion. Mitochondrial fusion is a dynamic process in which two or more mitochondria fuse together in an attempt to reduce mitochondrial stress that could be
induced by senescent or damaged proteins and ROS (Figure 1) [39, 40]. This process enables damaged mitochondria to repair their function and prevent the accumulation of mtDNA mutations [39]. Mitochondrial fusion requires a spatially coordinated fusion of the outer and inner mitochondrial membranes that are different in electrophysiological properties, structure, and composition [40]. Notably in mammals, fusion of the outer and inner mitochondrial membranes is facilitated by members of the membrane-anchored dynamin family, mitofusin (MFN) 1 and 2, and the single dynamin family member, OPA1, respectively [36, 41, 42].

4.2. Mitochondrial Fission. When mitochondrial fusion is unable to restore mitochondrial homeostasis in disease conditions, the dynamic nature of the mitochondrial network shifts towards mitochondrial fission which leads to the removal of damaged mitochondria (Figure 1) [39]. Mitochondrial fission compartmentalizes damaged mitochondrial components into daughter organelles that are to be removed and targeted for elimination [39]. In mammals, mitochondrial fission involves the cytoplasmic protein, dynamin-related protein 1 (DRP1), which forms a ring structure to encircle and constrict at a site on the outer mitochondrial membrane upon its interaction with fission protein 1 (FIS1), which compartmentalizes damaged mitochondrial components into daughter mitochondria for elimination via mitophagy. Decreased ATP levels and membrane potential (ΔΨ) and increased ROS generation are features of damaged mitochondria. These dysfunctional mitochondria are detected by phosphatase and tensin homologue deleted on chromosome 10- (PTEN-) induced putative kinase 1 (PINK1) and recruits Parkin, which initiates mitophagy and the subsequent formation of the autophagosome to degrade targeted mitochondria. Damaged mitochondria can also induce apoptosis through the permeabilization of the mitochondrial membrane, leading to the release of cytochrome c that can activate caspase-mediated apoptosis, as well as the release of proapoptotic proteins such as apoptosis-inducing factor (AIF).
the elimination of irreversibly damaged mitochondria through an autophagic process known as mitophagy [39, 44]. The mechanism of mitophagy has been attributed to a number of key molecules, particularly phosphatase and tensin homologue deleted on chromosome 10- (PTEN-) induced putative kinase 1 (PINK1) and Parkin which were identified in models of Parkinson’s disease (PD) [45–47]. PINK1 is a serine/threonine kinase that specifically targets mitochondria while Parkin is an E3 ubiquitin ligase, with mutations in either genes resulting in the early-onset autosomal recessive form of PD [46, 48]. The initiation of mitophagy involves the targeting of damaged mitochondria by PINK1 that recruits and activates Parkin via its phosphorylation at Ser65 on the N-terminal ubiquitin-like domain (Figure 2) [49, 50]. PINK1 also phosphorylates ubiquitin at Ser65 leading to structurally distinctive properties, which allows for interactions with ubiquitin-binding proteins specific for mitophagy [49–51]. The phosphorylation of Parkin and ubiquitin by PINK1 leads to the recruitment and subsequent formation of ubiquitin chains on outer mitochondrial membrane proteins, such as MFN1 and/or MFN2 (Figure 2) [49]. The ubiquitination of MFN results in the inhibition of mitochondrial fusion and the recruitment of autophagy receptors to promote mitophagy (Figure 2) [45, 49, 52]. Therefore, the interaction between PINK1 and Parkin is critical for the initiation and regulation of mitophagy.

However, PINK1-independent mechanisms may exist as demonstrated by a recent study where PINK1 deficiency does not inhibit basal mitophagy in multiple high energy-demanding tissues, including neural tissue and the heart [53]. Over the past decade, a number of mitochondrial-localized mitophagic markers that interact with the autophagosomal protein, microtubule-associated protein 1A/1B-light chain 3 (LC3), have also been identified [49, 54–56]. These include FUNDC1, BNIP3, NIX, optineurin, and NDP52, which also potentiate mitophagy through their LC3-interacting regions (LIR) in both a PINK1-dependent and independent manner [49, 54–56]. A recent addition to this list of mitophagic markers is AMBRA1 [57]. AMBRA1 mediates the mitochondrial localization of the ubiquitin ligase HUWE1 and potentiates MFN2 ubiquitination and degradation but also the recruitment of autophagosome via the AMBRA1 LIR motif [57].

4.4. Mitochondrial Biogenesis. In addition to the removal and processing of mitochondrial stress, there is a need for the restoration of mitochondrial deficits by producing new mitochondria through mitochondrial biogenesis. This results in the replication of mtDNA and the synthesis and assembly of mitochondrial components. The transcription coactivator, PGC1α, regulates mitochondrial biogenesis by activating a group of transcription factors, such as NRF1, and the mitochondrial transcription factor A (TFAM) [58]. These two transcription factors mediate the transcription of nuclear DNA and mtDNA, respectively [58].

Together, the dynamic processes of mitochondrial fusion and fission, mitophagy, and biogenesis act to restore normal mitochondrial function and morphology in the presence of mitochondrial stress and damage, thus maintaining mitochondrial homeostasis.
5. Mitochondria and Apoptosis

Apoptosis is an active mechanism of programmed cell death in response to stress-inducing or regulatory signals. This process is tightly regulated to facilitate the growth, development, and replication or replacement of cells to maintain a normal cellular life cycle. Impairment of mitochondrial function and structure destabilizes the cell and initiates a signaling cascade for apoptosis [59]. There are a number of mechanisms by which mitochondria induce and mediate the process of programmed cell death in mammals. This often involves the permeabilization of the mitochondrial membrane with the release of cytochrome c and proapoptotic proteins that causes a cascade of apoptotic signaling to execute apoptosis. Mitochondrial mechanisms for apoptosis can be caspase-dependent or -independent (for more detail, see [8, 60–62]).

Cytochrome c is an essential component of the respiratory chain that facilitates the transfer of electrons from complex III to complex IV [62]. Mitochondrial dysfunction, mitochondrial membrane permeabilization, and oxidative stress can disrupt the electron transport chain and affect cytochrome c function [8]. In response, mitochondria release cytochrome c to the cytosol to trigger downstream activation of caspases and the formation of a caspase-activated complex, the apoptosome, which leads to apoptosis with the degradation of cellular components (Figure 3) [60]. The release of cytochrome c is mediated by protein members of the B-cell lymphoma 2 (BCL2) family, such as BAK and BAX, the mitochondrial permeability transition pore (MPTP), and mitochondrial lipids to execute apoptosis (Figure 3) [8]. Additionally, cytochrome c activates caspase-3 and -9 in the cytosol via forming the apoptosome complex by binding to and activating the apoptotic protease factor 1 (Apaf1) [63]. It

Figure 3: Mitochondrial caspase-dependent and caspase-independent mechanisms of apoptosis. Mitochondrial dysfunction leads to the permeabilization of its membranes, which is the first step towards apoptosis. Membrane permeabilization of the outer mitochondrial membrane is driven by the mitochondrial permeability transition pore (MPTP), members of the BCL2 protein family (i.e., BAK/BAX), and mitochondrial lipids such as cardiolipin. More specifically, cardiolipin is associated with BAX recruitment to the outer mitochondrial membrane that triggers membrane permeabilization. For the caspase-dependent mechanism of apoptosis, mitochondrial cytochrome c is released to trigger the formation of the apoptosome complex by binding to, and activating, the apoptotic protease activating factor 1 (Apaf1). This in turn, activates caspase-9 and -3, which leads to the release of CAD from its inhibitor, ICAD, resulting in apoptosis induction. The caspase-independent mechanism of apoptosis involves the mitochondrial release of proapoptotic proteins such as apoptosis-inducing factor (AIF) into the cytosol, whereby it can either directly interact with DNA or potentiate mitochondrial oxidative stress through its release to induce apoptosis.
is well established that the activation of caspase-3, in turn, liberates the caspase-activated deoxyribonuclease (CAD) from its inhibitor, ICAD, which results in apoptotic features of DNA fragmentation and chromatin condensation (Figure 3) [8, 64, 65].

Oxidized lipids also play an important role in the induction of apoptosis [66, 67]. Cardiolipin is the mitochondria-specific lipid whose oxidation results in mitochondrial membrane permeability and the recruitment of the proapoptotic protein, BAX (Figure 3) [66, 68, 69]. Cytochrome c is normally associated with cardiolipin in the inner mitochondrial membrane [70, 71]. The oxidation of cardiolipin results in both mitochondrial membrane permeabilization and cytochrome c dissociation and release [70–72].

Alternatively, following mitochondrial dysfunction, oxidative stress, or a decrease in ATP levels, a caspase-independent mechanism of mitochondrial-associated apoptosis may also be induced [60]. This involves permeabilization of the outer and inner mitochondrial membranes, whereby the mitochondria releases proapoptotic proteins, such as apoptosis-inducing factor (AIF), into the cytosol to regulate apoptosis (Figure 3) [60]. The translocation of AIF from the mitochondria to the cytosol occurs in a BCL2-controlled manner in which cytosolic AIF can travel further into the nucleus where it causes DNA fragmentation and chromatin condensation (Figure 3) [73, 74]. Furthermore, the mitochondrial release of AIF can also increase oxidative stress due its potential role in maintaining ROS levels generated by the respiratory chain (Figure 3) [73].

Previous studies on diabetic neuronal injury have also shown a mitochondrial profile of decreased mitochondrial membrane potential and BCL2 expression, accompanied by ROS generation and increased expression of proapoptotic proteins [75]. Similar mitochondrial alterations that mediate apoptosis are found in cardiac aging and pulmonary hypertension (for reviews: [76, 77]). In many of these diseases, mitochondrial oxidative stress appears to be a key feature of mitochondrial dysfunction that drives apoptosis in disease progression.

6. Iron Homeostasis and Mitochondrial Dysfunction

Iron is the most abundant transition metal in mammalian cells and is essential for myriad biological processes, including oxygen transport, cellular respiration, and DNA synthesis/repair [78]. The mitochondrion is a major site of iron metabolism, particularly the synthesis of heme (Fe-protoporphyrin IX) and ISCs that are essential cofactors required by the electron transport chain [1]. In terms of the delivery of iron into the mitochondrion, the only known iron transport protein that imports iron across the inner mitochondrial membrane is mitoferrin (MFRN) [79–81].

Two MFRNs exist: MFRN1 is erythroid-specific, while MFRN2 is ubiquitously expressed with low expression in erythroid cells [79]. Other potential mechanisms of iron delivery to the mitochondria have recently come to light. These involve glutaredoxin 3 [82, 83], or endocytic mechanisms (i.e., the “kiss and run” hypothesis) of targeted mitochondrial iron delivery via direct endosomal-mitochondrial contact that results in the metal ion bypassing the cytosol [84, 85]. Other mitochondrial proteins may also be involved in mitochondrial iron import. An example is the inner mitochondrial membrane ATP-binding cassette (ABC) transporter ABCB10, which physically interacts with MFRN1 to stabilize MFRN1 and increase mitochondrial iron import into the erythron [86].

7. Mitochondrial Dysfunction in Neurodegenerative Diseases

Neurons have a high metabolic load that is demonstrated by the fact that although the brain only accounts for 2% of human body mass, it consumes 20% of the body’s resting ATP production [87]. Studies over the past decade have demonstrated that neurodegenerative disorders manifest common pathological events associated with mitochondria. These include mitochondrial dysfunction [3], oxidative stress, autophagic dysfunction, and apoptosis [88]. In fact, defects and mutations within the genome are often pathological causes of many degenerative diseases that alter mitochondrial function.

7.1. Alzheimer’s Disease (AD). Alzheimer’s disease (AD) is the most common neurodegenerative disease, with an estimated 46.8 million AD patients worldwide [89]. AD is clinically characterized by progressive cognitive decline associated with senile plaques composed of β-amyloid (Aβ) peptide and neurofibrillary tangles composed of hyperphosphorylated tau [90]. In fact, mitochondrial dysfunction is a characteristic of Aβ-induced neurotoxicity in AD [90]. It has been reported that the amyloid precursor protein (APP) could translocate and accumulate in the mitochondrial membrane [90], where it may be cleaved by γ-secretase forming the toxic Aβ peptide [91, 92]. Subsequently, the Aβ peptide interacts with a number of mitochondrial proteins, which disrupts mitochondrial membrane potential and promotes apoptosis via cytochrome c release (Figure 4) [93, 94].

The pathogenesis of AD likely involves oxidative damage to mtDNA [95]. When AD patient mtDNA is inserted into mtDNA-deficient cells, the resulting cybrids showed respiratory enzyme defects and elevated ROS production and free radical scavenging enzyme activities that were seen in AD patient brains [95]. Regulatory regions in mtDNA from AD brains showed increased mutations relative to controls [96]. These mutations lead to an average 50% reduction in mtDNA transcription and mtDNA copy number, potentiating mitochondrial dysfunction (Figure 4) [96]. The ensuing ROS generation due to mitochondrial dysfunction in AD is well documented and leads to activation of the NFE2L2 pathway [97, 98]. Pharmacological targeting of NFE2L2 was found to elicit neuroprotection in Aβ-induced hippocampal neuron injury and appeared to involve the activation of the NFE2L2 downstream target, HO-1 [97, 98]. Additionally, pharmacological targeting of KEAP1 and GSK3β that regulate NFE2L2 activity resulted in neuroprotection in a mouse model of tauopathy [99].
It has been reported that Aβ disrupts mitochondrial fusion, resulting in mitochondrial fragmentation [100, 101]. In AD brains, increased Aβ production and its interaction with DRP1 are crucial factors causing mitochondrial fragmentation and neuronal damage (Figure 4) [102]. Conversely, reduced DRP1 expression or inhibition of DRP1 with a mitochondrial division inhibitor (mdivi1) restored pathologic Aβ- or tau-mediated mitochondrial fragmentation, mitochondrial dysfunction, and synaptic depression in neurons [103]. Furthermore, inhibition of DRP1 decreased β-secretase 1 (BACE1) expression and Aβ deposition in the brain of AD mice, leading to a concomitant increase in cognitive function [104, 105].

The loss of synapses in AD brains correlates strongly with a cognitive decline [106, 107]. A recent study demonstrated that the loss and dysregulation of synaptic mitochondria may be an important pathogenic factor in AD progression [108]. The synapse is a region of high energy demand and requires constant trafficking of mitochondria to this region [109]. As tau is involved in stabilizing microtubules required for anterograde transport of mitochondria (Figure 4) [109], tau hyperphosphorylation destabilizes microtubules and impairs mitochondrial anterograde transport [110, 111]. Moreover, oligomeric Aβ has also been shown to impair mitochondrial motility in hippocampal neurons without destabilizing microtubules [112–114]. This latter effect may potentially involve NFE2L2 and KEAP1’s role in mitochondrial motility [29], since depletion of NFE2L2 inhibits mitochondrial motility [29] and NFE2L2 induction elicits neuroprotection in AD models [97–99, 115].

In AD, excessive ROS generation caused by Aβ exacerbates mitochondrial dysfunction and redox imbalance within neurons, which leads to neuronal damage [116, 117]. As a result, mitochondria suffer membrane depolarization, calcium overload, and cytochrome c release, which collectively induces apoptosis [117, 118]. In a different study examining AD pathology, overexpression of APP induced mitochondrial oxidative stress that triggers mitochondrial membrane...
permeabilization and cytochrome c release [119]. This suggests an important apoptotic role of mitochondria in the pathophysiology of AD.

The accumulation of redox-active iron in senile plaques and neurofibrillary tangles is another facet of AD pathology (Figure 4) [120–122]. Studies of AD models demonstrated increased iron uptake and storage with reduced iron export [123–125]. Indeed, APP mRNA has an atypical, but functional ferritin-like iron responsive element, and thus, an increase in intracellular iron level enhances APP mRNA translation via the iron regulatory element/iron regulatory protein system [126]. Recent studies demonstrated that the knockdown of MFRN1 in a C. elegans model of AD reduced mitochondrial iron content and mitochondrial ROS and resulted in increased lifespan [127]. This is supported by studies demonstrating that overexpression of mitochondrial ferritin (PtMt) attenuates Aβ-induced neuronal apoptosis [128], while Aβ-induced cognitive decline and neuronal apoptosis were exacerbated in PtMt KO mice relative to WT mice [129]. These findings suggest that increased iron uptake in AD neurons leads to increased mitochondrial iron loading that may exacerbate the pathogenesis of the disease.

7.2. Parkinson’s Disease (PD). Parkinson’s disease (PD) is the second most common neurodegenerative disease after AD and affects 1% of the population above 60 years of age [130]. PD is clinically characterized by motor dysfunction, including muscle rigidity, bradykinesia, and resting tremor, as well as nonmotor symptoms, such as dementia [131]. The major pathological feature of PD is the loss of dopaminergic neurons and the accumulation of α-synuclein-containing Lewy bodies in the substantia nigra [131]. In the majority of PD cases, the cause is unknown, although a number of familial PD cases have been identified due to mutations in genes that are involved in mitochondrial homeostasis [131]. A prominent feature of PD pathology is the inhibition of the activity of mitochondrial complexes I and IV in dopaminergic neurons of the substantia nigra [132–135]. This could be associated with a dysregulation of mitochondrial genome maintenance [136] or a number of PD-associated molecules discussed below.

The α-synuclein protein is critical for the recycling of vesicles at the presynaptic membrane [137]. In the dopaminergic neurons, α-synuclein plays a critical role for the synthesis, regulation, storage, and release of dopamine [138]. Mutations in α-synuclein are associated with highly penetrant, autosomal dominant, familial PD [139]. In dopaminergic neurons, overexpression of WT or mutant α-synuclein reduces dopamine release, potentiates the formation of toxic α-synuclein oligomers, and results in dopamine-dependent neurotoxicity [138, 140, 141]. Aggregation of α-synuclein into Lewy bodies is a prominent pathological feature in PD and other neurodegenerative disorders that are collectively known as α-synucleinopathies [142]. The α-synuclein protein can be imported into mitochondria and associates with the inner mitochondrial membrane of dopaminergic neurons [143–145]. Overexpression of α-synuclein exacerbates mitochondrial dysfunction, oxidative stress, and neuropathology caused by complex I inhibition (Figure 5) [146], while α-synuclein deficiency attenuates these effects [147, 148]. Therefore, it is speculated that the interaction between aggregated α-synuclein with mitochondrial respiratory complex I leads to the impairment of this complex [144].

In addition, oligomeric α-synuclein, or the A53T mutant form, has been demonstrated to interact with outer mitochondrial membrane proteins, including translocase of the outer membrane 20 (TOM20) and voltage-dependent anion-selective channel 1 (VDAC1), to block the import of mitochondrial proteins/metabolites [149, 150] or inhibit mitochondria-ER interactions to disrupt Ca²⁺ signaling [151, 152]. Moreover, while monomeric α-synuclein has also been shown to interact with ATP synthase to improve ATP production [153], the aggregated α-synuclein induces the opening of mitochondrial permeability transition pore (PTP), resulting in mitochondrial swelling and cell death [154]. Furthermore, aggregated or mutant α-synuclein also impairs the mitochondrial network fission/fusion processes [155] and subsequent mitophagy (Figure 5) [156], possibly via regulation of the actin cytoskeleton [157–159]. A recent study by Grassi and colleagues identified a novel and highly neurotoxic form of α-synuclein that results from incomplete autophagic degradation that associates with mitochondria and induces mitochondrial toxicity and fragmentation [160].

Mutations within PINK1 cause autosomal recessive juvenile PD [47]. PINK1 selectively accumulates in dysfunctional mitochondria [161]. Overexpression of PINK1 in neurons prevents apoptosis by decreasing cytochrome c release and the activation of caspases [162]. In models of PD, PINK1 overexpression suppresses α-synuclein-induced toxicity, potentially via the induction of autophagic α-synuclein removal [155, 163, 164], whereas PINK1 deficiency exacerbates the neurotoxicity of aggregated α-synuclein (Figure 5) [165, 166]. PINK1 expression is also increased following α-synuclein overexpression, suggesting a protective role of PINK1 in PD [164].

Mutation of the DJ1 (PARK7) gene encoding a protein deglycase is associated with autosomal recessive juvenile PD [167]. DJ1 is suggested to regulate oxidant defenses [168, 169] and participate in the formation of mitochondrial complex I [170]. DJ1 has also been shown to interact with monomeric or oligomeric α-synuclein to inhibit oligomer formation and prevent toxicity [171, 172]. DJ1 may also interact with PINK1/Parkin [173, 174], but this was disputed in a later study [175]. However, the consensus is that DJ1 mutation or deletion results in dysfunctional mitophagy that may act in parallel to the PINK1/Parkin pathway [175–177]. Oxidative stress results in the acidification of a critical cysteine residue (C106) of DJ1, leading to its localization to the mitochondrion where it exerts a neuroprotective effect [178]. In fact, DJ1 was found to stabilize NFE2L2 by preventing its association with KEAP1 and subsequent NFE2L2 degradation [179]. Therefore, DJ1 mutations could lead to the dysregulation of NFE2L2 and the antioxidative response in PD (Figure 5).

Activators of NFE2L2 have been found to be neuroprotective in PD models caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) induced complex I inhibition [180–182]. In a multicenter study, a NFE2L2 haplotype
Mitochondrial dysfunction in Parkinson’s disease

**α-Synuclein mutations**
- (i) Localized in the mitochondria
- (ii) Causes oxidative stress
- (iii) Impairs complex I function
- (iv) Disrupts Ca\(^{2+}\) signaling
- (v) Disrupts mitochondrial dynamic processes

**PINK1 deficiency**
- (i) Decreases complex I activity
- (ii) Leads to oxidative stress
- (iii) Generation of ROS
- (iv) Exacerbates neurotoxicity

**DJ1 mutations**
- (i) Exacerbates oxidative stress
- (ii) Dysregulation of NFE2L2 and antioxidant defense

**LRRK2 mutations**
- (i) Compromised OXPHOS activity
- (ii) mtDNA damage
- (iii) Reduced mitochondrial mobility
- (iv) Mitochondrial fragmentation

**HTRA2 mutations**
- (i) Dysregulation and impairment of mitochondria-induced apoptosis

**Mitochondrial fragmentation**
- (i) Increased mitochondrial fission

**Impaired respiratory chain activity**

**Mitochondrial dysfunction**

**Complex I dysfunction**
- (i) Reduced complex I activity
- (ii) Causes ROS generation

**Oxidative stress**

**Dysregulated apoptosis**

**Damage to mtDNA**

**Figure 5:** The different causes of mitochondrial dysfunction in the pathology of familial Parkinson’s diseases (PD). Some familial cases of PD include mutations in α-synuclein, PINK1-deficiency, and mutations in DJ1 (PARK7), leucine-rich repeat kinase 2 (LRRK2), and high-temperature requirement protein A2 (HTRA2). Mutations in α-synuclein result in the protein becoming localized in the mitochondria, causing mitochondrial dysfunction via oxidative stress, impaired Ca\(^{2+}\) signaling, complex I dysfunction, and mitochondrial fragmentation. PINK1 deficiency and mutations in LRRK2 also lead to impaired respiratory chain activity. Furthermore, LRRK2 mutations can reduce mitochondrial mobility and cause mtDNA damage. Mutations in DJ1 affect its role to regulate NFE2L2 degradation, resulting in the potential exacerbation of oxidative stress. Furthermore, HTRA2 mutations lead to the dysregulation and impairment of mitochondria-induced apoptosis.

Mitochondrial dysfunction

-associated with high transcriptional activity was found to significantly decrease disease risk and delay the onset of idiopathic PD [183]. Moreover, while mitochondrial membrane potential is greatly reduced in dopaminergic neurons from PINK1-KO mice, treatment with NFE2L2 activators is able to completely rescue this defect, as well as being protective against dopamine-induced neuronal death [184]. This finding suggests that NFE2L2 activation may be a viable therapeutic avenue in PINK1-associated PD.

Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common cause of autosomal dominant familial PD as well as some cases of sporadic PD [185, 186]. PD patient-derived cells carrying a LRRK2 mutation resulted in compromised OXPHOS activity, mtDNA damage, and reduced mitochondrial motility with increased mitochondrial fragmentation (Figure 5) [187–189]. These pathologic effects are dependent on LRRK2 kinase activity and can be reversed by LRRK2 kinase inhibitors [190, 191]. The LRRK2 is a serine-threonine kinase that has been demonstrated to associate with the outer mitochondrial membrane [192], potentially through its interaction with a key regulator of mitochondrial fission, DRP1 [193, 194]. Indeed, PD-associated mutations in LRRK2 kinase domain increases its catalytic activity [192, 195] which results in increased DRP1 Ser616 phosphorylation and activation of mitochondrial fission [188, 189]. These results suggest that the pathogenesis of both familial and sporadic PD associated with LRRK2 mutations may involve a direct perturbation of mitochondrial fission.

High-temperature requirement protein A2 (HTRA2) is a serine protease in the mitochondrial intermembrane space [196]. Disruption to HTRA2 has been associated with increased risk of sporadic PD [197, 198]. HTRA2 is important for mitochondrial quality control and is responsible for the degradation of denatured proteins within the mitochondria [199]. Following apoptotic stimuli, HTRA2 is released from the intermembrane space and binds to the inhibitor of apoptosis proteins (IAP) [196]. Subsequently, HTRA2 induces caspase activity and caspase-independent death through its protease activity (Figure 5) [196]. Recent studies have demonstrated that HTRA2 exerts its neuroprotective effect by targeting DJ1 mutations, thereby linking the two genetic factors of PD [200].

Previous studies in models of PD have also demonstrated the involvement of mitochondria in the apoptosis of dopaminergic neurons [201, 202]. In PD, studies have shown that depolarization of mitochondria results in reduced...
mitochondrial membrane potential and is associated with the early stages of apoptosis [59].

7.3. Amyotrophic Lateral Sclerosis (ALS). Amyotrophic lateral sclerosis (ALS) is a lethal neurodegenerative disorder characterized by progressive degeneration of upper and lower motor neurons [203]. The prevalence of ALS is approximately 4-6 in 100,000 individuals [204]. Approximately 10% of ALS are familial cases, of which about 20% are due to autosomal dominant mutations in Cu/Zn-superoxide dismutase (SOD1), which is a major antioxidant enzyme [205]. Indeed, according to the review by Smith et al., there are at least 11 pathogenic variants of proteins and their respective ALS-associated genes that have the potential to affect mitochondrial function, hence demonstrating the significance of mitochondrial dysfunction in the pathophysiology of ALS [204].

An accumulation of swollen and vacuolated mitochondria with abnormal cristae was one of the first pathological features observed in ALS patient motor neurons [206]. This is recapitulated in animal and cellular models of ALS, where a proliferation of swollen and fragmented mitochondria is frequently observed [207–210]. This process may involve reduced mitochondrial fusion proteins (e.g., MFN1/2, OPA1), increased fission proteins (e.g., DRP1, FIS1), or impaired mitophagy (decreased PINK1, PARKIN) [211–214]. The ALS-associated SOD1 mutation results in an accumulation of misfolded SOD1 in axonal mitochondria of motor neurons [215] and an impaired anterograde axonal transport of mitochondria [207, 215] that is mirrored in other models of familial ALS (Figure 6) [207, 216].

The interaction of ALS-associated mutant protein with the mitochondria is a major cause of mitochondrial damage. In fact, aggregation of mutant SOD1 within mitochondria causes mitochondrial vacuolation through expansion of the intermembrane space (Figure 6) [217, 218]. This may be caused by an interference of the SOD1 aggregates with VDAC1 that interrupts the exchange of vital substrates such as ADP across the outer mitochondrial membrane [219, 220]. In addition, ALS mutant SOD1 has been found

![Figure 6: Mutations in superoxide dismutase (SOD1) and coiled-coil-helix-coiled-helix domain 10 (CHCHD10) cause mitochondrial dysfunction in familial cases of amyotrophic lateral sclerosis (ALS). SOD1 mutations cause a number of mitochondrial defects including mitochondrial fragmentation, impaired mitophagy, and impaired mitochondrial anterograde transport of mitochondria, mitochondrial vacuolation, and apoptosis. CHCHD10 is localized in the mitochondrial intermembrane space, and mutation of the gene encoding this protein leads to a defect in the formation of the respiratory complex, mtDNA instability, and fragmentation of the mitochondrial network. Overall, oxidative stress is a common feature in ALS pathology. This is potentially due to the disruption of the respiratory chain caused by mitochondrial dysfunction.](image-url)
to interact with antiapoptotic BCL2 specifically in the spinal cord (Figure 6) [221, 222]. This causes a proapoptotic conformational change in BCL2 that exposes its toxic BH3 domain and compromises mitochondrial membrane integrity and results in cytochrome c release [222]. The mutant SOD1-BCL2 complex prevents the interaction between BCL2 and VDAC1 and thus reduces the permeability of the outer mitochondrial membrane [223].

Moreover, a number of mutations in the genes encoding DNA/RNA-binding proteins have recently been associated with both familial and sporadic ALS [207, 209, 210, 216, 224]. These include TDP43, TARDBP, C9ORF72, and FUS proteins [207, 209, 210, 216, 224]. The interaction of these ALS mutant proteins with mtDNA transcripts disrupts their transcription and impairs the formation of the respiratory complex [210, 224, 225]. On the other hand, a newly identified mutation in the gene encoding the mitochondrial protein, coiled-coil-helix-coiled-coil helix domain 10 (CHCHD10), causes ALS-like symptoms in humans and is characterized by mtDNA instability, respiratory chain deficiency, and mitochondrial network fragmentation (Figure 6) [226]. CHCHD10 is localized in the mitochondrial intermembrane space, and it is enriched at cristae junctions within the mitochondrial contact site and cristae organizing system (MICOS) complex [226, 227]. Mutant CHCHD10 leads to fragmentation of the mitochondrial network, disassembly of the MICOS complex that disrupts the assembly of OXPHOS complexes, and decreased nucleoid number and nucleoid disorganization that potentiates mtDNA instability (Figure 6) [226, 227]. Disruptions to these crucial mitochondrial components ultimately impair mitochondrial function and potentiate the ROS generation reported in ALS patients (Figure 6) [228].

7.4. Huntington’s Disease (HD). HD is an autosomal dominant progressive neurodegenerative disorder clinically characterized by chorea, dystonia, incoordination, and cognitive decline [229]. The prevalence of HD is estimated to be 10.6-13.7 individuals per 100,000 people in Western populations [230]. HD is caused by a CAG trinucleotide repeat expansion in the huntingtin (HTT) gene, resulting in polyglutamine repeats in the HTT protein [229]. The activity of respiratory complexes II and III is decreased in HD (Figure 7) [231]. In a mutant HD mouse model, mitochondrial respiration and ATP synthesis are significantly decreased (Figure 7) [232]. Conversely, the protein, rather than mRNA, expression of two important constituents of mitochondrial complex II, the 30 kDa iron-sulfur (Ip) subunit and the 70 kDa FAD (Fp) subunit, is preferentially decreased in the striatum of HD patients [236]. Overexpression of either complex II subunits restores complex II activity and attenuates mitochondrial dysfunction and death in mutant HTT neuronal cells [236].
HTT has been found to be associated directly with the outer mitochondrial membrane [237, 238]. Mitochondria from HD patient lymphoblasts or from a HD mouse model have a lower membrane potential and become depolarized at lower Ca\(^{2+}\) loads than relevant controls [237, 238]. Mutant HTT may also affect mitochondrial function through its interaction with transcription factors, such as p53, CREB-binding protein and specificity protein 1 [239]. Of note, p53 activates mitochondrial apoptosis through transcriptional induction of p53 upregulated modulator of apoptosis (PUMA) or the posttranscriptional activation of BAX (Figure 7) [240, 241]. In neuronal cultures, mutant HTT binds p53 and enhances nuclear p53 expression and its transcriptional activity [242]. Conversely, p53 inhibition in mutant HTT fly and mouse models attenuates HTT-mediated neurodegeneration [242].

The pathogenesis of HD also involves increased mtDNA lesions and mtDNA depletion [243]. This pathological alteration could be attributed to decreased PGC1α mRNA observed in early-stage HD patients [244, 245]. Mutant HTT directly inhibits transcription of PGC1α by associating with the promoter region and interfering with the activation functions of the transcription factors CREB and TAF4 (Figure 7) [244]. Moreover, overexpression of PGC1α partially attenuated mutant HTT-induced neurotoxicity [244]. In contrast, PGC1α KO mice demonstrate impaired mitochondrial function and possess HD features such as a hyperkinetic movement disorder and striatal neuron degeneration [246].

Mutant HTT protein also potentiates mitochondrial fragmentation [247]. This occurs through the induction and activation of mitochondrial fission regulators DRP1 and FIS1, while reducing the expression of fusion proteins, such as MFN1/2 (Figure 7) [247–252]. A fragmentation of the mitochondrial network may also be potentiated by the inhibition of mitophagy [253]. Indeed, overexpression of PINK1 was neuroprotective in Drosophila and mouse HD models through increased mitophagy [254]. Wild-type HTT protein may also directly participate in autophagy/mitophagy via its interaction with autophagic adaptor, p62 [255], or with the mitoprotein, BCL2-interacting protein 3 (BNIP3) (Figure 7) [256]. Therefore, mutant HTT may directly disrupt autophagic or mitophagic process via these mechanisms.

Furthermore, oxidative stress and neuroinflammation are other common pathogenic factors in HD [257]. A number of ARE-containing genes are found to be induced in human HD brain [258], suggesting that NFE2L2 activation may be involved in the pathogenesis. In animal HD models with mitochondrial complex II inhibition, overexpression of NFE2L2 exerts a neuroprotective effect [259]. While the expression of NFE2L2 protein did not alter in a HD model, the expression of the NFE2L2 modulators, KEAP1 and p62, were found to be reduced, and thus, this could affect NFE2L2 activity [260]. Moreover, cotransfection of NFE2L2 with mutant HTT in primary striatal neurons reduced the half-life of mutant HTT and improved cell viability [261]. In fact, activation of NFE2L2 is protective against mutant HTT-induced toxicity [262, 263], highlighting the potential of NFE2L2 induction for HD patients.

7.5. Friedreich’s Ataxia (FA). Friedreich’s ataxia is the most prevalent autosomal recessive spinocerebellar disorder that affects approximately one in 50,000 Caucasians [264]. It is characterized by progressive neuro- and cardiodegeneration and mitochondrial iron accumulation [264, 265]. The disorder is predominantly caused by a GAA repeat expansion in the first intron of the FRDA gene that results in a marked reduction in the expression of the encoded protein, frataxin [266, 267]. Approximately 2% of the remainder FA cases are due to point mutations in the FRDA gene [264].

The manifestation of FA symptoms is most prominently characterized by progressive neurological disability and fatal dilated cardiomyopathy, as well as a tendency for diabetes mellitus in approximately 10% of FA patients [268, 269]. The pathogenesis of FA is associated with mitochondrial iron accumulation that results in ROS-induced toxicity (Figure 8) [270–272]. As such, iron-chelation therapy has been shown to be beneficial in reducing both neurologic and cardiologic FA pathology, presumably by preventing oxidant-mediated cell death [272–275]. In addition to mitochondrial iron accumulation and oxidative damage, FA patients also exhibit a deficit of ISC enzymes, leading to decreased energy metabolism as evident by complex I dysfunction, as well as perturbed heme synthesis (Figure 8) [270, 276]. This is due to the dysregulation of cellular and mitochondrial iron metabolism upon frataxin deficiency, which disrupts proper utilization of iron and causes mitochondrial dysfunction (Figure 8) [271, 277].

Recent studies utilizing a conditional frataxin knockout mice model of FA have demonstrated that frataxin deficiency leads to pronounced trafficking of iron from the cytosol to the mitochondrion, leading to a cytosolic iron deficiency and mitochondrial iron accumulation in the form of nonprotein-bound, biomineral iron aggregates [270, 272, 278]. Due to the depletion of mitochondrial ferritin in frataxin deficiency [270, 278], these iron aggregates within the redox active mitochondria result in increased protein oxidation and depletion of the cellular antioxidant pool [271]. Paradoxically, despite the apparent oxidative stress, the expression and activity of NFE2L2 is markedly depressed [271], due to a mechanism involving increased KEAP1- and GSK3β-mediated NFE2L2 degradation in the cytosol and nucleus, respectively (Figure 8) [271]. As such, the marked decrease in NFE2L2 levels results in the deficient expression of its downstream target genes for antioxidant defense, hence exacerbating oxidative stress (Figure 8) [271]. The defective induction of NFE2L2 despite clear oxidative stress in FA suggests that NFE2L2 may be a potential target for treatment against FA.

Frataxin deficiency has also been associated with autophagy and apoptosis. Frataxin-silenced neuron-like cells undergo apoptosis through the upregulation of p53 and BAX, as well as caspase activation, which suggests the involvement of mitochondrial dysfunction in the pathogenic initiation of apoptosis [279]. Notably, increased autophagic and apoptotic markers in a cardiac mouse model of FA that exhibit frataxin deficiency implicate their role in the observed cardiomyopathy [280]. Therefore, mitochondrial dysfunction is probably responsible for the activation of autophagy,
and promoting apoptosis, potentially through the intrinsic pathway involving the mitochondrion (Figure 8). Furthermore, considering the extent of mitochondrial dysfunction in FA, it is possible that dynamic mitochondrial processes, such as mitophagy, are also perturbed (Figure 8). Collectively, the resulting accumulation of redox active iron, oxidative stress, defective antioxidant response, dysfunction in energy metabolism, and activation of autophagy and apoptosis due to frataxin deficiency leads to the neurodegeneration, ataxia, and cardiomyopathy observed in FA.

7.6. Potential Therapies for Degenerative Disorders Targeting Mitochondrial Function. There has been a substantial increase in the interest and generation of potential mitochondrial targeted therapeutics over the past 20 years. Several advancements are considered here as interesting examples relevant to the current review. For disease-specific analysis of mitochondrial targeted therapeutics, the reader is encouraged to examine the following comprehensive reviews [281–283].

Mitochondrial dysfunction and damage induced by ROS play a critical role in the pathogenesis of many degenerative diseases [284]. Therefore, NFE2L2 and its signaling pathway have become a major therapeutic target for the treatment of diseases such as AD, PD, ALS, HD, and FA, which focuses on improving mitochondrial bioenergetics and function through the alleviation of oxidative stress and the activation of antioxidant defense [34, 115, 285].

In a study using cellular models of AD, the activation of the NFE2L2 signaling pathway by the potent free radical scavenger, 3H-1,2-dithiole-3-thione, was able to reduce Aβ levels and attenuate ROS generation, which partially rescued mitochondrial membrane potential [115]. In PD models, NFE2L2 inducers are able to restore mitochondrial membrane potential in PINK1-deficient cells and rescue dopamine-induced toxicity [184]. Previous studies on FA have assessed the effectiveness of promoting NFE2L2 levels in the rescue of oxidative stress-induced mitochondrial impairments [286]. One particular study has shown that the NFE2L2-inducer, omaveloxolone, was able to restore...
complex I activity and protect against oxidative stress in neuronal mouse models of FA, as well as in fibroblasts from FA patients [286]. The mitochondrial membrane potential was also maintained upon incubation of cells with the NFE2L2 inducer, which suggests its potential in improving mitochondrial function in addition to its effect on oxidative stress [286]. As a further example of defense against neural oxidative stress, studies have shown that pretreatment with NFE2L2-inducing agents, sulforaphane, or carnosic acid, was able to induce the NFE2L2 pathway and protect cortical mitochondria from the effects of the neurotoxic lipid peroxidation by-product, 4-hydroxynonenal [287]. Moreover, NFE2L2 has been suggested to also influence mitochondrial activity by affecting the availability of substrates such as NADH and FADH2 for mitochondrial respiration [34, 184]. Hence, the pharmacological activation of NFE2L2 could potentially rescue OXPHOS activity and mitochondrial bioenergetics in disease states.

Alternatively, melatonin is an interesting mitochondrial-targeted antioxidant that has been recently explored for the treatment of AD and PD [288–290]. Evidences suggest that the mechanism of neuroprotection of melatonin involved increasing NFE2L2 expression and activation of the NFE2L2/ARE pathway [288–293]. In addition to activating the NFE2L2 pathway, previous studies in mice subjected to irradiation-induced neurodegeneration have also shown that pretreatment of melatonin accumulates in mitochondria and was able to promote PINK1 mitochondrial accumulation that alters mitochondrial dynamics and prevents loss of mitophagic progression [288]. Overall, melatonin pretreatment was able to increase mitochondrial respiratory chain activity and enhance cognitive performance in these animals [288]. In fact, there is evidence to suggest that NFE2L2 can regulate PINK1 expression due to the presence of ARE in the promoter regions of the PINK1 gene [294, 295]. Hence, NFE2L2 may have a role in mediating mitophagy, and the upregulation of NFE2L2 could potentially restore mitochondrial homeostasis in PD [288].

Additionally, triterpenoids are antioxidants that activate the NFE2L2 signaling pathway to inhibit oxidative stress and were found in a number of studies to have neuroprotective effects that could improve behavioral phenotype in mouse models of AD [296]. In relation to mitochondria, the triterpenoid, asiatic acid, reportedly protects neurons from cell death by preventing mitochondria-dependent apoptosis in a cellular model of AD [297]. Another study also demonstrated that asiatic acid blocked the translocation of α-synuclein into mitochondria, thereby protecting it against oxidative stress and apoptosis [298]. Asiatic acid also prevented the α-synuclein-induced decrease in mitochondrial membrane potential in a Drosophila model of PD [298].

Impairment of the NFE2L2 signaling pathway and mitochondrial dysfunction is evident in the pathogenesis of degenerative diseases, yet the development of drugs that exploit the targeting of mitochondria through the activation of NFE2L2 is only in its infancy. Recent studies have already begun to demonstrate the effect of this relationship to rescue mitochondrial function in neurodegenerative diseases. Hence, the combined effect of ameliorating oxidative stress and mitochondrial dysfunction would be a novel approach in future drug design for the treatment of various neurodegenerative diseases.

Another avenue in the development of new therapeutics involves the targeted chelation of cytosolic and/or mitochondrial iron, as it is known to play a significant role in potentiating oxidative stress and ROS generation for many degenerative diseases in addition to a defect in mitochondrial respiration [299–304].

Previous studies on AD have shown that the sequestration of iron by FtMt have neuroprotective effects in cell models, which prevented neuronal cell damage induced by Aβ [128]. Similarly, the regulation of FtMt helps maintain mitochondrial and neuronal iron homeostasis, in which its overexpression was shown in a mouse model of PD to inhibit mitochondrial damage and reduce ROS production, thus having neuronal protection [305]. These studies indicate the importance of regulating mitochondrial iron levels, especially in iron overload conditions. Studies have also examined the use of metal chelation, such as the metal-binding agent, PBT2, that has been in clinical trials for the treatment of AD and HD, which demonstrated the potential for binding iron, copper, and zinc in the brain and reduce amyloid plaque formation with signs of cognitive improvement [306]. The design of chelators with specificity for mitochondrial iron and other metals could increase the effectiveness of iron chelation therapy for neurodegenerative diseases. Other studies have also reported that intracellular oxidative stress enhances HO-1 activity that leads to the accumulation of iron in the mitochondria of astrocytes in AD and PD brains [307]. This deposition of mitochondrial iron in glial cells increases the risk of neighboring neurons to further oxidative damage [307, 308]. These findings give rise to the prospect of iron chelation therapy, especially in the targeting of mitochondrial iron, as a new neuroprotective strategy for AD and PD.

In FA, mitochondrial iron loading is well-characterized in the heart of a mouse cardiac model of FA, which resulted in severe defects in mitochondrial function [272, 280, 309, 310]. In fact, Mössbauer spectroscopic analysis and transmission electron microscopy demonstrate that iron appears as a nonferritin, high spin form of ferric iron that exists without a permeate biological membranes, including the mitochondrial and neuronal iron homeostasis, in which its overexpression was shown in a mouse model of PD to inhibit mitochondrial damage and reduce ROS generation, thus having neuronal protection [305]. These studies indicate the importance of regulating mitochondrial iron levels, especially in iron overload conditions. Studies have also examined the use of metal chelation, such as the metal-binding agent, PBT2, that has been in clinical trials for the treatment of AD and HD, which demonstrated the potential for binding iron, copper, and zinc in the brain and reduce amyloid plaque formation with signs of cognitive improvement [306]. The design of chelators with specificity for mitochondrial iron and other metals could increase the effectiveness of iron chelation therapy for neurodegenerative diseases. Other studies have also reported that intracellular oxidative stress enhances HO-1 activity that leads to the accumulation of iron in the mitochondria of astrocytes in AD and PD brains [307]. This deposition of mitochondrial iron in glial cells increases the risk of neighboring neurons to further oxidative damage [307, 308]. These findings give rise to the prospect of iron chelation therapy, especially in the targeting of mitochondrial iron, as a new neuroprotective strategy for AD and PD.
of PIH and DFO prevented iron loading in the heart and reduced cardiac hypertrophy but did not rescue the defective iron metabolism caused by the loss of frataxin [272]. Considering that the spinal cord and dorsal root ganglia are highly vulnerable to frataxin deficiency [317, 318], cellular and mitochondrial iron dysregulation could contribute to the pathophysiology of these tissues. As such, it is necessary to consider the design of iron chelators that targets these pathogenic regions.

The use of iron chelators in targeting mitochondrial iron as a therapeutic strategy for degenerative diseases deserves further investigation. The combination of antioxidants and iron chelators could potentially be an effect approach to ameliorate oxidative stress and boost mitochondrial function, while also eliminating harmful iron that would otherwise potentiate redox damage.

8. Conclusions

The mitochondrion emerges as a central hub that orchestrates cellular antioxidant defense, energy production, and apoptosis. The regulation of NFE2L2 has been shown to play an essential role in antioxidant defense, and the role of this key protein in mitochondrial homeostasis has only been recently elucidated, linking antioxidant defense to neuronal mitochondrial trafficking. This includes recent evidence of the direct interaction of NFE2L2 with this organelle.

The exquisite dependence of high-energy-demanding cells, such as neurons and cardiomyocytes, on mitochondria for energy production means that mitochondrial dysfunction can lead to their demise. This is exemplified by the number of deleterious neurodegenerative diseases, such as AD, PD, ALS, HD, and FA, where perturbation of mitochondrial function is an essential component of their pathogenesis. Therefore, the maintenance of mitochondrial homeostasis is a crucial factor and a potential therapeutic target to treat these diseases. Our understanding of mitochondrial homeostasis and metabolism is also broadened by the discovery of novel mutations causing these neurodegenerative diseases, with an appropriate example being the identification of the role of frataxin in Friedreich’s ataxia.

Considering the key role of the mitochondrion in this array of degenerative diseases, therapeutic strategies targeting this organelle has been a focus of the increasing body of research. The additional linkage of NFE2L2 with mitochondria may lead to the convergence of previously considered disparate avenues of treatment that could result in exciting and innovative therapeutic advances.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding publication of this article.

Authors’ Contributions

M.L.H.H., S.C., and D.R.R. contributed equally to this work in terms of initial ideas, planning, writing, preparing figures, and proofreading of this review. D.S.K., D.H.B, and S.S. wrote sections and edited the article. Michael L.-H. Huang, Shannon Chiang, and Des R. Richardson contributed equally as senior authors.

Acknowledgments

M.L.H.H. appreciates the award of an NHMRC Peter Doherty Early Career Fellowship (APP1074033), DVCWR Fellowship (University of Sydney), and Development Grant from the Muscular Dystrophy Association (MDA417129). D.R.R. kindly thanks the National Health and Medical Research Council of Australia (NHMRC) for a Senior Principal Research Fellowship (APP1062607) and Project Grant (APP1128152). S.C. thanks the University of Sydney for a Postgraduate Ph.D Scholarship. S.S. appreciates a Young Investigator PdCCRS Grant jointly funded by Cancer Australia and the Cure Cancer Australia Foundation. D.S.K. appreciates the award of an NHMRC Career Development Fellowship (APP1048972).

References

[1] I. Napier, P. Ponka, and D. R. Richardson, “Iron trafficking in the mitochondrion: novel pathways revealed by disease,” Blood, vol. 105, no. 5, pp. 1867–1874, 2005.
[2] M. L. Circiu and T. Y. Aw, “Reactive oxygen species, cellular redox systems, and apoptosis,” Free Radical Biology and Medicine, vol. 48, no. 6, pp. 749–762, 2010.
[3] M. T. Lin and M. F. Beal, “Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases,” Nature, vol. 443, no. 7113, pp. 787–795, 2006.
[4] Y. R. Chen and J. L. Zweier, “Cardiac mitochondria and reactive oxygen species generation,” Circulation Research, vol. 114, no. 3, pp. 524–537, 2014.
[5] T. Finkel and N. J. Holbrook, “Oxidants, oxidative stress and the biology of ageing,” Nature, vol. 408, no. 6809, pp. 239–247, 2000.
[6] M. T. Islam, “Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders,” Neurological Research, vol. 39, no. 1, pp. 73–82, 2017.
[7] M.-Y. Cha, D. K. Kim, and I. Mook-Jung, “The role of mitochondrial DNA mutation on neurodegenerative diseases,” Experimental and Molecular Medicine, vol. 47, no. 3, article e150, 2015.
[8] R. Shakeri, A. Kheirollahi, and J. Davoodi, “Apaf-1: regulation and function in cell death,” Biochimie, vol. 135, pp. 111–125, 2017.
[9] J.-W. Taanman, “The mitochondrial genome: structure, transcription, translation, and replication,” Biochimica et Biophysica Acta - Bioenergetics, vol. 1410, no. 2, pp. 103–123, 1999.
[10] A. Trifunovic, “Mitochondrial DNA and ageing,” Biochimica et Biophysica Acta, vol. 1757, no. 5-6, pp. 611–617, 2006.
[11] M. Corral-Debrinski, T. Horton, M. T. Lott, J. M. Shoffner, M. Flint Beal, and D. C. Wallace, “Mitochondrial DNA deletions in human brain: regional variability and increase with advanced age,” Nature Genetics, vol. 2, no. 4, pp. 324–329, 1992.
[12] J. V. Leonard and A. H. V. Schapira, “Mitochondrial respiratory chain disorders I: mitochondrial DNA defects,” The Lancet, vol. 355, no. 9200, pp. 299–304, 2000.
Oxidative Medicine and Cellular Longevity

[13] N. C. MacGarvey, H. B. Suliman, R. R. Bartz et al., "Activation of mitochondrial biogenesis by heme oxygenase-1-mediated NF-E2-related factor-2 induction rescues mice from lethal Staphylococcus aureus sepsis," American Journal of Respiratory and Critical Care Medicine, vol. 185, no. 8, pp. 851–861, 2012.

[14] C. A. Piantadosi, M. S. Carraway, A. Babiker, and H. B. Suliman, "Heme oxygenase-1 regulates cardiac mitochondrial biogenesis via Nrf2-mediated transcriptional control of nuclear respiratory factor-1," Circulation Research, vol. 103, no. 11, pp. 1232–1240, 2008.

[15] K. Itoh, T. Chiba, S. Takahashi et al., "Alkyl hydroperoxide reductase 1 mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements," Biochemical and Biophysical Research Communications, vol. 236, no. 2, pp. 313–322, 1997.

[16] S. Dhakshinamoorthy and A. K. Jaiswal, "Small maf (MafG and MafK) proteins negatively regulate antioxidant response element-mediated expression and antioxidant induction of the NAD(P)H:Quinone oxidoreductase1 gene," Journal of Biological Chemistry, vol. 275, no. 51, pp. 40134–40141, 2000.

[17] L. E. Tebay, H. Robertson, S. T. Durant et al., "Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status and the pathways through which it attenuates degenerative disease," Free Radical Biology and Medicine, vol. 88, Part B, pp. 108–146, 2015.

[18] P. Rada, A. I. Rojo, N. Evrard-Todeschi et al., "Structural and functional characterization of Nrf2 degradation by the glycosynase kinase 3β-TrCP axis," Molecular and Cellular Biology, vol. 32, no. 17, pp. 3486–3499, 2012.

[19] S. Chowdhry, Y. Zhang, M. McMahon, C. Sutherland, A. Cuadrado, and J. D. Hayes, "Nrf2 is controlled by two distinct β-TrCP recognition motifs in its Neh6 domain, one of which can be modulated by GSK-3 activity," Oncogene, vol. 32, no. 32, pp. 3765–3781, 2013.

[20] J. W. Kaspar and A. K. Jaiswal, "Tyrosine phosphorylation controls nuclear export of Fyn, allowing Nrf2 activation of cytotoxic protein expression," The FASEB Journal, vol. 25, no. 3, pp. 1076–1087, 2011.

[21] A. K. Jain and A. K. Jaiswal, "GSK-3beta acts upstream of Fyn kinase in regulation of nuclear export and degradation of NF-E2 related factor 2," Journal of Biological Chemistry, vol. 282, no. 22, pp. 16502–16510, 2007.

[22] K. Taguchi, N. Fujikawa, M. Komatsu et al., "Keap1 degradation by autophagy for the maintenance of redox homeostasis," Proceedings of the National Academy of Sciences of the United States of America, vol. 109, no. 34, pp. 13561–13566, 2012.

[23] A. Jain, T. Lamark, E. Sjøttem et al., "p62/SQSTM1 is a target gene for transcription factor NRF2 and creates a positive feedback loop by inducing antioxidant response element-driven gene transcription," Journal of Biological Chemistry, vol. 285, no. 29, pp. 22576–22591, 2010.

[24] A. Lau, X.-J. Wang, F. Zhao et al., "A noncanonical mechanism of Nrf2 activation by autophagy deficiency: direct interaction between Keap1 and p62," Molecular and Cellular Biology, vol. 30, no. 13, pp. 3275–3285, 2010.

[25] M. Komatsu, H. Kurokawa, S. Waguri et al., "The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1," Nature Cell Biology, vol. 12, no. 3, pp. 213–223, 2010.

[26] Y. Ichimura, S. Waguri, Y. S. Sou et al., "Phosphorylation of p62 activates the Keap1-Nrf2 pathway during selective autophagy," Molecular Cell, vol. 51, no. 5, pp. 618–631, 2013.

[27] H. B. Suliman, M. S. Carraway, L. G. Tatro, and C. A. Piantadosi, "A new activating role for CO in cardiac mitochondrial biogenesis," Journal of Cell Science, vol. 120, no. 2, pp. 299–308, 2007.

[28] K. M. Holmstrom, L. Baird, Y. Zhang et al., "Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration," Biology Open, vol. 2, no. 8, pp. 761–770, 2013.

[29] G. B. O’Mealey, K. S. Pfafker, W. L. Berry, R. Janknecht, J. Y. Chan, and S. M. Pfafker, "A PGAM5-Keap1-Nrf2 complex is required for stress-induced mitochondrial retrograde trafficking," Journal of Cell Science, vol. 130, no. 20, pp. 3467–3480, 2017.

[30] S. C. Lo and M. Hannink, "PGAM5 tethers a ternary complex containing Keap1 and Nrf2 to mitochondria," Experimental Cell Research, vol. 314, no. 8, pp. 1789–1803, 2008.

[31] S. C. Lo and M. Hannink, "PGAM5, a Bcl-XL-interacting protein, is a novel substrate for the redox-regulated Keap1-dependent ubiquitin ligase complex," Journal of Biological Chemistry, vol. 281, no. 49, pp. 37892–37903, 2006.

[32] C. Yang, X. Liu, F. Yang et al., "Mitochondrial phosphatase PGAM5 regulates Keap1-mediated Bcl-XL degradation and controls cardiomyocyte apoptosis driven by myocardial ischemia/reperfusion injury," In Vitro Cellular & Developmental Biology - Animal, vol. 53, no. 3, pp. 248–257, 2017.

[33] J. Berezik-Hahn, "Chapter four - mitochondrial dynamics in aging and disease," in The Mitochondrion in Aging and Disease, vol. 127 of Progress in Molecular Biology and Translational Science, pp. 93–131, 2014.

[34] N. Esteras, A. T. Dinkova-Kostova, and A. Y. Abramov, "Nrf2 activation in the treatment of neurodegenerative diseases: a focus on its role in mitochondrial bioenergetics and function," Biological Chemistry, vol. 397, no. 5, pp. 383–400, 2016.

[35] N. Kubben, W. Zhang, L. Wang et al., "Repression of the antioxidant Nrf2 pathway in premature aging," Cell, vol. 165, no. 6, pp. 1361–1374, 2016.

[36] S. Frank, "Dysregulation of mitochondrial fusion and fission: an emerging concept in neurodegeneration," Acta Neuropathologica, vol. 111, no. 2, pp. 93–100, 2006.

[37] Y. Ikeda, S. Sciarretta, N. Nagarajan et al., "New insights into the role of mitochondrial dynamics and autophagy during oxidative stress and aging in the heart," Oxidative Medicine and Cellular Longevity, vol. 2014, Article ID 210934, 13 pages, 2014.

[38] Y. Chen, Y. Liu, and G. W. Dorn II, "Mitochondrial fusion is essential for organellar function and cardiac homeostasis," Circulation Research, vol. 109, no. 12, pp. 1327–1331, 2011.

[39] R. J. Youle and A. M. van der Bliek, "Mitochondrial fission, fusion, and stress," Science, vol. 337, no. 6098, pp. 1062–1065, 2012.

[40] S. L. Meeusen and J. Nunnari, "OPA1 requires mitofusin 1 to promote mitochondrial fusion," Proceedings of the National Academy of Sciences of the United States of America, vol. 109, no. 4, pp. 389–394, 2005.

[41] A. Cipolat, O. M. de Brito, B. Dal Zilio, and L. Scorrano, "OPA1 requires mitofusin 1 to promote mitochondrial fusion," Proceedings of the National Academy of Sciences of the United States of America, vol. 101, no. 45, pp. 15927–15932, 2004.
[42] O. M. de Brito and L. Scorrano, “Mitofusin 2: a mitochondria-shaping protein with signaling roles beyond fusion,” *Antioxidants & Redox Signaling*, vol. 10, no. 3, pp. 621–634, 2008.

[43] E. Smirnova, L. Griparic, D. L. Shurland, and A. M. van der Bliek, “Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells,” *Molecular Biology of the Cell*, vol. 12, no. 8, pp. 2245–2256, 2001.

[44] J. J. Lemasters, “Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging,” *Rejuvenation Research*, vol. 8, no. 1, pp. 3–5, 2005.

[45] L. A. Scarffe, D. A. Stevens, V. L. Dawson, and T. M. Dawson, “Parkin and PINK1: much more than mitophagy,” *Trends in Neurosciences*, vol. 37, no. 6, pp. 315–324, 2014.

[46] D. Narendra, A. Tanaka, D. F. Suen, and R. J. Youle, “Parkin is recruited selectively to impaired mitochondria and promotes their autophagy,” *The Journal of Cell Biology*, vol. 183, no. 5, pp. 795–803, 2008.

[47] E. M. Valente, P. M. Abou-Sleiman, V. Caputo et al., “Hereditary early-onset Parkinson’s disease caused by mutations in PINK1,” *Science*, vol. 304, no. 5674, pp. 1158–1160, 2004.

[48] A. Tanaka, M. M. Cleland, S. Xu et al., “Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin,” *The Journal of Cell Biology*, vol. 191, no. 7, pp. 1367–1380, 2010.

[49] M. Lazarou, D. A. Sliter, L. A. Kane et al., “The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy,” *Nature*, vol. 524, no. 7565, pp. 309–314, 2015.

[50] C. Kondapalli, A. Kazlauskaite, N. Zhang et al., “PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating serine 65,” *Open Biology*, vol. 2, no. 5, article 120080, 2012.

[51] T. Wauer, K. N. Swatek, J. L. Wagstaff et al., “Ubiquitin Ser65 phosphorylation affects ubiquitin structure, chain assembly and hydrolysis,” *The EMBO Journal*, vol. 34, no. 3, pp. 307–325, 2015.

[52] E. Ziviani, R. N. Tao, and A. J. Whitworth, “Drosophila parkin requires PINK1 for mitochondrial translocation and ubiquitinitates mitofusin,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 11, pp. 5018–5023, 2010.

[53] T. G. McWilliams, A. R. Prescott, L. Montava-Garriga et al., “Basal mitophagy occurs independently of PINK1 in mouse tissues of high metabolic demand,” *Cell Metabolism*, vol. 27, no. 2, pp. 439–449.e5, 2018.

[54] M. Lazarou, “Keeping the immune system in check: a role for mitophagy,” *Immunology and Cell Biology*, vol. 93, no. 1, pp. 3–10, 2015.

[55] I. Novak, V. Kirkin, D. G. McEwan et al., “Nix is a selective autophagy receptor for mitochondrial clearance,” *EMBO Reports*, vol. 11, no. 1, pp. 45–51, 2010.

[56] L. Liu, D. Feng, G. Chen et al., “Mitochondrial outer membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells,” *Nature Cell Biology*, vol. 14, no. 2, pp. 177–185, 2012.

[57] A. Di Rita, A. Peschiarioli, P. D’Acunzo et al., “HUE1 E3 ligase promotes PINK1/PARKIN-independent mitophagy by regulating AMBRA1 activation via IKKα,” *Nature Communications*, vol. 9, no. 1, article 3755, p. 3755, 2018.

[58] I. Manoli, S. Alesci, M. R. Blackman, Y. A. Su, O. M. Rennert, and G. P. Chrousos, “Mitochondria as key components of the stress response,” *Trends in Endocrinology and Metabolism*, vol. 18, no. 5, pp. 190–198, 2007.

[59] R. Qadri, M. Namdeo, M. Behari, V. Goyal, S. Sharma, and A. K. Mukhopadhyay, “Alterations in mitochondrial membrane potential in peripheral blood mononuclear cells in Parkinson’s disease: potential for a novel biomarker,” *Restorative Neurology and Neuroscience*, vol. 36, no. 6, pp. 719–727, 2018.

[60] V. Borutaite, “Mitochondria as decision-makers in cell death,” *Environmental and Molecular Mutagenesis*, vol. 51, no. 5, pp. 406–416, 2010.

[61] E. Ulukaya, C. Acilan, and Y. Yilmaz, “Apoptosis: why and how does it occur in biology?,” *Cell Biochemistry and Function*, vol. 29, no. 6, pp. 468–480, 2011.

[62] H. A. Kalpage, V. Bazylianska, M. A. Recanati et al., “Tissue-specific regulation of cytochrome c by post-translational modifications: respiration, the mitochondrial membrane potential, ROS, and apoptosis,” *The FASEB Journal*, vol. 33, no. 2, pp. 1540–1553, 2019.

[63] S. Yuan, M. Topf, T. F. Reubold, S. Eschenburg, and C. W. Akey, “Changes in Apaf-1 conformation that drive apoptosis assembly,” *Biochemistry*, vol. 52, no. 13, pp. 2319–2327, 2013.

[64] P. Li, D. Nijhawan, I. Budihardjo et al., “Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade,” *Cell*, vol. 91, no. 4, pp. 479–489, 1997.

[65] M. Enari, H. Sakahira, H. Yokoyama, K. Okawa, A. Iwamatsu, and S. Nagata, “A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor IACD,” *Nature*, vol. 391, no. 6662, pp. 43–50, 1998.

[66] F. Gonzalez and E. Gottlieb, “Cardiolipin: setting the beat of apoptosis,” *Apolisis*, vol. 12, no. 5, pp. 877–885, 2007.

[67] G. O. Fruhwirth and A. Hermetter, “Mediation of apoptosis by oxidized phospholipids,” *Sub-Cellular Biochemistry*, vol. 49, pp. 351–367, 2008.

[68] S. Lucken-Ardjomande, S. Montessuit, and J. C. Martinou, “Contributions to Bax insertion and oligomerization of lipids of the mitochondrial outer membrane,” *Cell Death and Differentiation*, vol. 15, no. 5, pp. 929–937, 2008.

[69] A. P. G. Dingeldein, T. Sparrmann, and G. Grobner, “Oxidatively stressed mitochondria-mimicking membranes: a molecular insight into their organization during apoptosis,” *Biochimica et Biophysica Acta, Biomembranes*, vol. 1860, no. 12, pp. 2644–2654, 2018.

[70] M. Ott, J. D. Robertson, V. Gogvadze, B. Zhivotovsky, and S. Orrenius, “Cytochrome c release from mitochondria proceeds by a two-step process,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 3, pp. 1259–1263, 2002.

[71] P. Santambrogio, G. Biasiotti, F. Sanvito, S. Olivieri, P. Arosio, and S. Levi, “Mitochondrial ferritin expression in adult mouse tissues,” *The Journal of Histochemistry and Cytochemistry*, vol. 55, no. 11, pp. 1129–1137, 2007.

[72] G. Petrosillo, F. M. Ruggiero, M. Pistolese, and G. Paradies, “Reactive oxygen species generated from the mitochondrial electron transport chain induce cytochrome c dissociation from beef-heart submitochondrial particles via cardiolipin peroxidation. Possible role in the apoptosis,” *FEBS Letters*, vol. 509, no. 3, pp. 435–438, 2001.
[73] H. K. Lorenzo and S. A. Susin, “Mitochondrial effectors in caspase-independent cell death,” FEBS Letters, vol. 557, no. 1-3, pp. 14–20, 2004.

[74] H. Ye, C. Cande, N. C. Stephanou et al., “DNA binding is required for the apoptogenic action of apoptosis inducing factor,” Nature Structural Biology, vol. 9, no. 9, pp. 680–684, 2002.

[75] L. Yang, W. Han, Y. Luo et al., “Adaptenpronitrile, a new dipeptidyl peptidase-IV inhibitor, ameliorates diabetic neuronal injury through inhibiting mitochondria-related oxidative stress and apoptosis,” Frontiers in Cellular Neuroscience, vol. 12, p. 214, 2018.

[76] B. Martín-Fernández and R. Gredilla, “Mitochondrial oxidative stress and cardiac ageing,” Clínica e Investigación en Arteriosclerosis (English Edition), vol. 30, no. 2, pp. 74–83, 2018.

[77] J. D. Marshall, I. Bazan, Y. Zhang, W. H. Fares, and P. J. Lee, “Mitochondrial dysfunction and pulmonary hypertension: cause, effect, or both,” American Journal of Physiology - Lung Cellular and Molecular Physiology, vol. 314, no. 5, pp. L782–L796, 2018.

[78] D. R. Richardson and P. Ponka, “The molecular mechanisms of the metabolism and transport of iron in normal and neoplastic cells,” Biochimica et Biophysica Acta, vol. 1331, no. 1, pp. 1–40, 1997.

[79] G. C. Shaw, J. J. Cope, L. Li et al., “Mitoferrin is essential for erythroid iron assimilation,” Nature, vol. 440, no. 7080, pp. 96–100, 2006.

[80] F. Foury and T. Roganti, “Deletion of the mitochondrial carrier genes MRS3 and MRS4 suppresses mitochondrial iron accumulation in a yeast frataxin-deficient strain,” Journal of Biological Chemistry, vol. 277, no. 27, pp. 24475–24483, 2002.

[81] U. Mühlenhoff, J. A. Statler, N. Richrath et al., “A specific role of the yeast mitochondrial carriers Mr3/4p in mitochondrial iron acquisition under iron-limiting conditions,” Journal of Biological Chemistry, vol. 278, no. 42, pp. 40612–40620, 2003.

[82] U. Mühlenhoff, S. Molik, J. R. Godoy et al., “Cytosolic monothi glutaredoxins function in intracellular iron sensing and trafficking via their bound iron-sulfur cluster,” Cell Metabolism, vol. 12, no. 4, pp. 373–385, 2010.

[83] C. C. Philpott, “Coming into view: eukaryotic iron chaperones and intracellular iron delivery,” Journal of Biological Chemistry, vol. 287, no. 17, pp. 15318–15323, 2012.

[84] M. Shvartsman and Z. Ilov Cabantchik, “Intracellular iron trafficking: role of cytosolic ligands,” Biometals, vol. 25, no. 4, pp. 711–723, 2012.

[85] A. D. Shetel, A. S. Zhang, C. Brown, O. S. Shirihai, and P. Ponka, “Direct interorganellar transfer of iron from endosome to mitochondrion,” Blood, vol. 110, no. 1, pp. 125–132, 2007.

[86] W. Chen, P. N. Paradkar, L. Li et al., “Abcb10 physically interacts with mitoferrin-1 (Scl25a37) to enhance its stability and function in the erythroid mitochondria,” Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 38, pp. 16263–16268, 2009.

[87] E. Engl and D. Attwell, “Non-signalling energy use in the brain,” Journal of Physiology, vol. 593, no. 16, pp. 3417–3429, 2015.

[88] M. Okouchi, O. Ekshyyan, M. Maracine, and T. Y. Aw, “Neuronal apoptosis in neurodegeneration,” Antioxidants & Redox Signaling, vol. 9, no. 8, pp. 1059–1096, 2007.

[89] M. Prince, A. Wimo, M. Guerchet, G. Ali, Y. Wu, and M. Prina, World Alzheimer Report 2015: The Global Impact of Dementia: an Analysis of Prevalence, Incidence, Cost and Trends, vol. 2017, 2015Google Scholar.

[90] H. K. Anandatheerthagoda, G. Biswas, M. A. Robin, and N. G. Avadhani, “Mitochondrial targeting and a novel transmembrane arrest of Alzheimer’s amyloid precursor protein impairs mitochondrial function in neuronal cells,” The Journal of Cell Biology, vol. 161, no. 1, pp. 41–54, 2003.

[91] M. Ankarcrona and K. Hultenby, “Presenilin-1 is located in rat mitochondria,” Biochemical and Biophysical Research Communications, vol. 295, no. 3, pp. 766–770, 2002.

[92] C. A. Hansson, S. Frykman, M. R. Farmery et al., “Nicotinol, presenilin, APH-1, and PEN-2 form active γ-secretase complexes in mitochondria,” Journal of Biological Chemistry, vol. 279, no. 49, pp. 51654–51660, 2004.

[93] J. W. Lustbader, M. Cirilli, C. Lin et al., “ABAD directly links Aβ to mitochondrial toxicity in Alzheimer’s disease,” Science, vol. 304, no. 5669, pp. 448–452, 2004.

[94] H. Du, L. Guo, F. Fang et al., “Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer’s disease,” Nature Medicine, vol. 14, no. 10, pp. 1097–1105, 2008.

[95] R. H. Swerdlow, J. K. Parks, D. S. Cassarino et al., “Cybrids in Alzheimer’s disease: a cellular model of the disease?,” Neurology, vol. 49, no. 4, pp. 918–925, 1997.

[96] P. E. Coskun, M. F. Beal, and D. C. Wallace, “Alzheimer’s brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication,” Proceedings of the National Academy of Sciences of the United States of America, vol. 101, no. 29, pp. 10726–10731, 2004.

[97] Y. Zou, B. Hong, L. Fan et al., “Protective effect of puerarin against beta-amyloid-induced oxidative stress in neuronal cultures from rat hippocampus: involvement of the GSK-3β/Nrf2 signaling pathway,” Free Radical Research, vol. 47, no. 1, pp. 55–63, 2013.

[98] C. Jiao, F. Gao, L. Ou et al., “Tetrahydroxy stilbene glycoside (TSG) antagonizes Aβ-induced hippocampal neuron injury by suppressing mitochondrial dysfunction via Nrf2-dependent HÖ-1 pathway,” Biomedicine & Pharmacotherapy, vol. 96, pp. 222–228, 2017.

[99] A. Cuadrado, S. Kugler, and I. Lastres-Becker, “Pharmacological targeting of GSK-3 and NFR2 provides neuroprotection in a preclinical model of tauopathy,” Redox Biology, vol. 14, pp. 522–534, 2018.

[100] C. D. San Martin, T. Adams, C. Hidalgo, and A. C. Paula-Lima, “The antioxidant N-acetylcysteine prevents the mitochondrial fragmentation induced by soluble amyloid-F peptide oligomers,” Neurodegenerative Diseases, vol. 10, no. 1-4, pp. 34–37, 2012.

[101] X. Wang, B. Su, S. L. Siedlak et al., “Amyloid-β overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fission/fusion proteins,” Proceedings of the National Academy of Sciences of the United States of America, vol. 105, no. 49, pp. 19318–19323, 2008.

[102] M. Manczak, M. J. Calkins, and P. H. Reddy, “Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from
patients with Alzheimer’s disease: implications for neuronal damage,” Human Molecular Genetics, vol. 20, no. 13, pp. 2495–2509, 2011.

[103] M. Manczak, R. Kandimalla, D. Fry, H. Sesaki, and P. H. Reddy, "Protective effects of reduced dynamin-related protein 1 against amyloid beta-induced mitochondrial dysfunction and synaptic damage in Alzheimer’s disease," Human Molecular Genetics, vol. 25, no. 23, pp. 5148–5166, 2016.

[104] S. H. Baek, S. J. Park, J. I. Jeong et al., “Inhibition of Drp1 ameliorates synaptic depression, Aβ deposition, and cognitive impairment in an Alzheimer’s disease model,” Journal of Neuroscience, vol. 37, no. 20, pp. 5099–5110, 2017.

[105] P. H. Reddy, M. Manczak, and X. L. Yin, "Mitochondria-division inhibitor 1 protects against amyloid-β induced mitochondrial fragmentation and synaptic damage in Alzheimer’s disease,” Journal of Alzheimer’s Disease, vol. 58, no. 1, pp. 147–162, 2017.

[106] R. D. Terry, E. Masliah, D. P. Salmon et al., “Physical basis of cognitive alterations in Alzheimer’s disease: synapse loss is the major correlate of cognitive impairment,” Annals of Neurology, vol. 30, no. 4, pp. 572–580, 1991.

[107] S. T. DeKosky and S. W. Scheff, "Synapse loss in frontal cortex biopsies in Alzheimer’s disease: correlation with cognitive severity,” Annals of Neurology, vol. 27, no. 5, pp. 457–464, 1990.

[108] E. K. Pickett, J. Rose, C. McCrory et al., "Region-specific depletion of synaptic mitochondria in the brains of patients with Alzheimer’s disease,” Acta Neuropathologica, vol. 136, no. 5, pp. 747–757, 2018.

[109] D. Drubin, S. Kobayashi, and M. Kirschner, "Association of tau protein with microtubules in living cells,” Annals of the New York Academy of Sciences, vol. 466, 1 Dynamic Aspec, pp. 257–268, 1986.

[110] K. J. Kopeikina, G. A. Carlson, R. Pitstick et al., “Tau accumulation causes mitochondrial distribution deficits in neurons in a mouse model of tauopathy and in human Alzheimer’s disease brain,” The American Journal of Pathology, vol. 179, no. 4, pp. 2071–2082, 2011.

[111] W. Stoothoff, P. B. Jones, T. L. Spires-Jones et al., “Differential effect of three-repeat and four-repeat tau on mitochondrial axonal transport,” Journal of Neurochemistry, vol. 111, no. 2, pp. 417–427, 2009.

[112] M. J. Calkins and P. H. Reddy, "Amyloid beta impairs mitochondrial anterograde transport and degenerates synapses in Alzheimer’s disease neurons,” Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, vol. 1812, no. 4, pp. 507–513, 2011.

[113] H. Decker, K. Y. Lo, S. M. Unger, S. T. Ferreira, and M. A. Silverman, "Amyloid-β peptide oligomers disrupt axonal transport through an NMDA receptor-dependent mechanism that is mediated by glycosyn thase kinase 3β in primary cultured hippocampal neurons,” Journal of Neuroscience, vol. 30, no. 27, pp. 9166–9171, 2010.

[114] Y. Rui and J. Q. Zheng, "Amyloid β oligomers elicit mitochondrial transport defects and fragmentation in a time-dependent and pathway-specific manner,” Molecular Brain, vol. 9, no. 1, p. 79, 2016.

[115] L. Wang, M. Wang, J. Hu et al., “Protective effect of 3H-1, 2-dithiole-3-thione on cellular model of Alzheimer’s disease involves Nrf2/ARE signaling pathway,” European Journal of Pharmacology, vol. 795, pp. 115–123, 2017.

[116] J. Busciglio, A. Pelsman, C. Wong et al., “Altered metabolism of the amyloid β precursor protein is associated with mitochondrial dysfunction in Down’s syndrome,” Neuron, vol. 33, no. 5, pp. 677–688, 2002.

[117] E. Alberdi, M. V. Sánchez-Gómez, A. Ruiz et al., “Mangiferin and morin attenuate oxidative stress, mitochondrial dysfunction, and neurocycotoxity, induced by amyloid beta oligomers,” Oxidative Medicine and Cellular Longevity, vol. 2018, Article ID 2856063, 13 pages, 2018.

[118] A. B. Reiss, H. A. Arain, M. M. Stecker, N. M. Siegart, and L. J. Kasselman, “Amyloid toxicity in Alzheimer’s disease,” Reviews in the Neurosciences, vol. 29, no. 6, pp. 613–627, 2018.

[119] M. G. Bartley, K. Marquardt, D. Kirchhof, H. M. Wilkins, D. Patterson, and D. A. Linseman, "Overexpression of amyloid-β protein precursor induces mitochondrial oxidative stress and activates the intrinsic apoptotic cascade,” Journal of Alzheimer’s Disease, vol. 28, no. 4, pp. 855–868, 2012.

[120] B. Ding, K. M. Chen, H. W. Ling et al., "Correlation of iron in the hippocampus with MMSE in patients with Alzheimer’s disease,” Journal of Magnetic Resonance Imaging, vol. 29, no. 4, pp. 793–798, 2009.

[121] M. A. Smith, P. L. R. Harris, L. M. Sayre, and G. Perry, "Iron accumulation in Alzheimer disease is a source of redox-generated free radicals,” Proceedings of the National Academy of Sciences of the United States of America, vol. 94, no. 18, pp. 9866–9868, 1997.

[122] A. A. Belaidi and A. I. Bush, "Iron neurochemistry in Alzheimer’s disease and Parkinson’s disease: targets for therapeutics,” Journal of Neurochemistry, vol. 139, Supplement 1, pp. 179–197, 2016.

[123] W. Zheng, N. Xin, Z. H. Chi et al., "Divalent metal transporter 1 is involved in amyloid precursor protein processing and Aβ generation,” The FASEB Journal, vol. 23, no. 12, pp. 4207–4217, 2009.

[124] J. R. Connor, S. L. Menzies, S. M. St Martin, and E. J. Mufson, "A histochemical study of iron, transferrin, and ferritin in Alzheimer’s diseased brains,” Journal of Neuroscience Research, vol. 31, no. 1, pp. 75–83, 1992.

[125] A. A. Raha, R. A. Vaishnav, R. P. Friedland, A. Bomford, and R. Raha-Chowdhury, "The systemic iron-regulatory proteins hepcidin and ferroportin are reduced in the brain in Alzheimer’s disease,” Acta Neuropathologica Communications, vol. 1, no. 1, p. 55, 2013.

[126] J. T. Rogers, J. D. Randall, C. M. Cahill et al., "An iron-responsive element type II in the 5′-untranslated region of the Alzheimer’s amyloid precursor protein transcript,” Journal of Biological Chemistry, vol. 277, no. 47, pp. 45518–45528, 2002.

[127] J. Huang, S. Chen, L. Hu et al., "Mitoferrin-1 is involved in the progression of Alzheimer’s disease through targeting mitochondrial iron metabolism in a Caenorhabditis elegans model of Alzheimer’s disease,” Neuroscience, vol. 385, pp. 90–101, 2018.

[128] W. S. Wu, Y. S. Zhao, Z. H. Shi et al., "Mitochondrial ferritin attenuates β-amyloid-induced neurotoxicity: reduction in oxidative damage through the Erk/P38 mitogen-activated protein kinase pathways,” Antioxidants & Redox Signaling, vol. 18, no. 2, pp. 158–169, 2013.

[129] P. Wang, Q. Wu, W. Wu et al., "Mitochondrial ferritin deletion exacerbates β-amyloid-induced neurotoxicity in mice.”
Oxidative Medicine and Cellular Longevity, vol. 2017, Article ID 1020357, 10 pages, 2017.

[130] L. M. de Lau and M. M. Breteler, “Epidemiology of Parkinson’s disease,” The Lancet Neurology, vol. 5, no. 6, pp. 525–535, 2006.

[131] O.-B. Tysnes and A. Storstein, “Epidemiology of Parkinson’s disease,” Journal of Neural Transmission, vol. 124, no. 8, pp. 901–905, 2017.

[132] A. H. V. Schapira, A. H. V. Schapira, J. M. Cooper, D. Dexter, P. Jenner, J. B. Clark, and C. D. Marsden, “Mitochondrial complex I deficiency in Parkinson’s disease,” The Lancet, vol. 333, no. 8649, p. 1269, 1989.

[133] A. H. V. Schapira, V. M. Mann, J. M. Cooper et al., “Anatomic and disease specificity of NADH CoQ reductase (complex I) deficiency in Parkinson’s disease,” Journal of Neurochemistry, vol. 55, no. 6, pp. 2142–2145, 1990.

[134] A. Grünewald, K. A. Rygjeid, P. D. Hepplewhite, C. M. Morris, M. Picard, and D. M. Turnbull, “Mitochondrial DNA depletion in respiratory chain-deficient Parkinson disease neurons,” Annals of Neurology, vol. 79, no. 3, pp. 366–378, 2016.

[135] C. Y. Chung, V. Khurana, S. Yi et al., “Localization of α-synuclein to mitochondria within midbrain of mice,” Neuron, vol. 94, no. 4, pp. 683–698, 2017.

[136] A. H. V. Schapira, K. R. Kumar, and C. M. Sue, “New insights into the complex role of mitochondria in Parkinson’s disease,” Progress in Neurobiology, 2018.

[137] A. Iwai, E. Masliah, M. Yoshimoto et al., “The precursor protein of non-Ab component of Alzheimer’s disease amyloid is a presynaptic protein of the central nervous system,” Neuron, vol. 14, no. 2, pp. 467–475, 1995.

[138] J. Burré, “The synaptic function of α-synuclein,” Journal of Parkinson’s Disease, vol. 5, no. 4, pp. 699–713, 2015.

[139] N. Hattori, H. Kobayashi, Y. Sasaki-Hatano, K. Sato, and Y. Mizuno, “Familial Parkinson’s disease: a hint to elucidate the mechanisms of nigral degeneration,” Journal of Neurology, vol. 250, Supplement 3, pp. iii2–iii10, 2003.

[140] J. Xu, S. Y. Kao, F. J. S. Lee, W. Song, L. W. Jin, and B. A. Yankner, “Dopamine-dependent neurotoxicity of α-synuclein: a mechanism for selective neurodegeneration in Parkinson disease,” Nature Medicine, vol. 8, no. 6, pp. 600–606, 2002.

[141] D. E. Mor, E. Tsika, J. R. Mazzulli et al., “Dopamine induces soluble α-synuclein oligomers and nigrostriatal degeneration,” Nature Neuroscience, vol. 20, no. 11, pp. 1560–1568, 2017.

[142] A. E. Budson and P. R. Solomon, “Chapter 5 - dementia with Lewy bodies (including Parkinson’s disease dementia),” in Memory Loss, Alzheimer’s Disease, and Dementia (Second Edition): A Practical Guide for Clinicians, A. E. Budson and P. R. Solomon, Eds., pp. 70–79, Elsevier, London, 2016.

[143] W.-W. Li, R. Yang, J.-C. Guo et al., “Localisation of α-synuclein to mitochondria within midbrain of mice,” Neureport, vol. 18, no. 15, pp. 1543–1546, 2007.

[144] A. K. Reeve, M. H. R. Ludtmann, P. R. Angelova et al., “Aggregated α-synuclein and complex I deficiency: exploration of their relationship in differentiated neurons,” Cell Death & Disease, vol. 6, no. 7, article e1820, 2015.

[145] L. Devi, V. Raghavendran, B. M. Prabhu, N. G. Avadhani, and H. K. Anandatheerthavarada, “Mitochondrial import and accumulation of α-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain,” Journal of Biological Chemistry, vol. 283, no. 14, pp. 9089–9100, 2008.

[146] D. D. Song, C. W. Shults, A. Sisk, E. Rockenstein, and E. Masliah, “Enhanced substantia nigra mitochondrial patholgy in human α-synuclein transgenic mice after treatment with MPTP,” Experimental Neurology, vol. 186, no. 2, pp. 158–172, 2004.

[147] F. Fortun, O. M. Schluter, P. Lenzi et al., “Parkinson-like syndrome induced by continuous MPTP infusion: convergent roles of the ubiquitin-proteasome system and α-synuclein,” Proceedings of the National Academy of Sciences of the United States of America, vol. 102, no. 9, pp. 3413–3418, 2005.

[148] P. Klivenyi, D. Siwek, G. Gardian et al., “Mice lacking alpha-synuclein are resistant to mitochondrial toxins,” Neurobiology of Disease, vol. 21, no. 3, pp. 541–548, 2006.

[149] R. Di Maio, P. J. Barrett, E. K. Hoffman et al., “α-Synuclein binds to TOM20 and inhibits mitochondrial protein import in Parkinson’s disease,” Science Translational Medicine, vol. 8, no. 342, article 342ra78, 2016.

[150] T. K. Rostovtseva, P. A. Gurney, O. Protchenko et al., “α-Synuclein shows high affinity interaction with voltage-dependent anion channel, suggesting mechanisms of mitochondrial regulation and toxicity in Parkinson disease,” Journal of Biological Chemistry, vol. 290, no. 30, pp. 18467–18477, 2015.

[151] S. Paillusson, P. Gomez-Suaga, R. Stoica et al., “α-Synuclein binds to the ER–mitochondria tethering protein VAPB to disrupt Ca^{2+} homeostasis and mitochondrial ATP production,” Acta Neuropathologica, vol. 134, no. 1, pp. 129–149, 2017.

[152] C. Guardia-Laguarta, E. Area-Gomez, C. Rub et al., “α-Synuclein is localized to mitochondria-associated ER membranes,” Journal of Neuroscience, vol. 34, no. 1, pp. 249–259, 2013.

[153] M. H. R. Ludtmann, P. R. Angelova, N. N. Ninkina, S. Gandhi, V. L. Buchman, and A. Y. Abramov, “Monomeric alpha-synuclein exerts a physiological role on brain ATP synthase,” Journal of Neuroscience, vol. 36, no. 41, pp. 10510–10521, 2016.

[154] M. H. R. Ludtmann, P. R. Angelova, M. H. Horrocks et al., “α-Synuclein oligomers interact with ATP synthase and open the permeability transition pore in Parkinson’s disease,” Nature Communications, vol. 9, no. 1, article 2293, 2018.

[155] F. Kamp, N. Exner, A. K. Lutz et al., “Inhibition of mitochondrial fusion by α-synuclein is rescued by PINK1, Parkin and DJ-1,” The EMBO Journal, vol. 29, no. 20, pp. 3571–3589, 2010.

[156] L. Chen, Z. Xie, S. Turkson, and X. Zhuang, “A53T human α-synuclein overexpression in transgenic mice induces pervasive mitochondrial macroautophagy defects preceding dopamine neuron degeneration,” Journal of Neuroscience, vol. 35, no. 3, pp. 890–905, 2015.

[157] C. Y. Chung, V. Khurana, S. Yi et al., “In situ peroxidase labeling and mass-spectrometry connects alpha-synuclein directly to endocytic trafficking and mRNA metabolism in neurons,” Cell Systems, vol. 4, no. 2, pp. 242–250.e4, 2017.

[158] H. J. Lee, K. Lee, and H. Im, “α-Synuclein modulates neurite outgrowth by interacting with SPTBN1,” Biochemical and Biophysical Research Communications, vol. 424, no. 3, pp. 497–502, 2012.
Oxidative Medicine and Cellular Longevity

[159] D. G. Ordonez, M. K. Lee, and M. B. Feany, "α-Synuclein induces mitochondrial dysfunction through Spectrin and the actin cytoskeleton," Neuron, vol. 97, no. 1, pp. 108–124.e6, 2018.

[160] D. Grassi, S. Howard, M. Zhou et al., "Identification of a highly neurotoxic α-synuclein species inducing mitochondrial damage and mitophagy in Parkinson’s disease," Proceedings of the National Academy of Sciences of the United States of America, vol. 115, no. 11, pp. E2634–e2643, 2018.

[161] D. P. Narendra, S. M. Jin, A. Tanaka et al., "PIN1 is selectively stabilized on impaired mitochondria to activate Parkin," PLoS Biology, vol. 8, no. 1, article e1000298, 2010.

[162] A. Petit, T. Kawarai, E. Paitel et al., "Wild-type PIN1 prevents basal and induced neuronal apoptosis, a protective effect abrogated by Parkinson disease-related mutations," Journal of Biological Chemistry, vol. 280, no. 40, pp. 34025–34032, 2005.

[163] A. M. Todd and B. E. Staveley, "Expression of Pin1 with α-synuclein in the dopaminergic neurons of Drosophila leads to increases in both lifespan and healthspan," Genetics and Molecular Research, vol. 11, no. 2, pp. 1497–1502, 2012.

[164] J. Liu, X. Wang, Y. Lu et al., "Pin1 interacts with α-synuclein and abrogates α-synuclein-induced neurotoxicity by activating autophagy," Cell Death & Disease, vol. 8, no. 9, article e3050, 2017.

[165] M. Oliveras-Salvá, F. Macchi, V. Coessens et al., "Alpha-synuclein-induced neurodegeneration is exacerbated in PIN1 knockout mice," Neurobiology of Aging, vol. 35, no. 11, pp. 2625–2636, 2014.

[166] S. Gispert, N. Brehm, J. Weil et al., "Potentiation of neurotoxicity in double-mutant mice with Pin1 ablation and A53T-SNCA overexpression," Human Molecular Genetics, vol. 24, no. 4, pp. 1061–1076, 2015.

[167] V. Bonifatti, P. Rizzu, M. van Baren et al., "Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism," Science, vol. 299, no. 5604, pp. 256–259, 2003.

[168] E. Andres-Mateos, C. Perier, L. Zhang et al., "DJ-1 gene deletion reveals that DJ-1 is an atypical peroxiredoxin-like peroxidase," Proceedings of the National Academy of Sciences of the United States of America, vol. 104, no. 37, pp. 14807–14812, 2007.

[169] J. N. Guzman, J. Sanchez-Padilla, D. Wokosin et al., "Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1," Nature, vol. 468, no. 7324, pp. 696–700, 2010.

[170] J. Y. Heo, J. H. Park, S. J. Kim et al., "DJ-1 null dopaminergic neuronal cells exhibit defects in mitochondrial function and structure: involvement of mitochondrial complex I assembly," PLoS One, vol. 7, no. 3, article e26292, 2012.

[171] M. C. Meulener, C. L. Graves, D. M. Sampathu, C. E. Armstrong-Gold, N. M. Bonini, and B. I. Giasson, "DJ-1 is present in a large molecular complex in human brain tissue and interacts with α-synuclein," Journal of Neurochemistry, vol. 93, no. 6, pp. 1524–1532, 2005.

[172] L. Zondler, L. Miller-Fleming, M. Repici et al., "DJ-1 interactions with α-synuclein attenuate aggregation and cellular toxicity in models of Parkinson’s disease," Cell Death & Disease, vol. 5, no. 7, article e1350, 2014.

[173] D. J. Moore, L. Zhang, J. Troncoso et al., "Association of DJ-1 and parkin mediated by pathogenic DJ-1 mutations and oxidative stress," Human Molecular Genetics, vol. 14, no. 1, pp. 71–84, 2005.

[174] B. Tang, H. Xiong, P. Sun et al., "Association of PINK1 and DJ-1 confers digenic inheritance of early-onset Parkinson’s disease," Human Molecular Genetics, vol. 15, no. 11, pp. 1816–1825, 2006.

[175] K. J. Thomas, M. K. McCoy, J. Blackinton et al., "DJ-1 acts in parallel to the PINK1/parkin pathway to control mitochondrial function and autophagy," Human Molecular Genetics, vol. 20, no. 1, pp. 40–50, 2011.

[176] G. Krebiehl, S. Ruckebauer, L. F. Burbulla et al., "Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson’s disease-associated protein DJ-1," PLoS One, vol. 5, no. 2, article e9337, 2010.

[177] I. Ircher, H. Aleyasin, E. L. Seifert et al., "Loss of the Parkinson’s disease-linked gene DJ-1 perturbs mitochondrial dynamics," Human Molecular Genetics, vol. 19, no. 19, pp. 3734–3746, 2010.

[178] R. M. Canet-Avilés, M. A. Wilson, D. W. Miller et al., "The Parkinson’s disease protein DJ-1 is neuroprotective due to caveolae-sulfonic acid-driven mitochondrial localization," Proceedings of the National Academy of Sciences of the United States of America, vol. 101, no. 24, pp. 9103–9108, 2004.

[179] C. M. Clements, R. S. McNally, B. J. Conti, T. W. Mak, and J. P.-Y. Ting, "DJ-1, a cancer- and Parkinson’s disease-associated protein, stabilizes the antioxidant transcriptional master regulator Nrf2," Proceedings of the National Academy of Sciences of the United States of America, vol. 103, no. 41, pp. 15091–15096, 2006.

[180] N. C. Burton, T. W. Kessler, and T. R. Gu Pearlor, "In vivo modulation of the parkinsonian phenotype by Nrf2," Neurotoxicology, vol. 27, no. 6, pp. 1094–1100, 2006.

[181] P.-C. Chen, M. R. Vargas, A. K. Pani et al., "Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson’s disease: critical role for the astrocyte," Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 8, pp. 2933–2938, 2009.

[182] A. Jazwa, A. I. Rojo, N. G. Innamorato, M. Hesse, J. Fernández-Ruiz, and A. Cuadrado, "Modulation of the parkinsonian phenotype by Nrf2, a master regulator Nrf2, Parkinson’s disease-linked gene DJ-1 perturbs mitochondrial dynamics," Antioxidants & Redox Signaling, vol. 14, no. 12, pp. 2347–2360, 2011.

[183] M. von Otter, S. Landgren, S. Nilsson et al., "Association of Nrf2-encoding NFE2L2 haplotypes with Parkinson’s disease," BMC Medical Genetics, vol. 11, no. 1, p. 36, 2010.

[184] A. T. Dinkova-Kostova, L. Baird, K. M. Holmström, C. J. Meyer, and A. Y. Abramov, "The spatiotemporal regulation of the Keap1–Nrf2 pathway and its importance in cellular bioenergetics," Biochemical Society Transactions, vol. 43, no. 4, pp. 602–610, 2015.

[185] C. Paisán-Ruiz, S. Jain, E. W. Evans et al., "Cloning of the gene containing mutations that cause PARK8-linked Parkinson’s disease," Neuron, vol. 44, no. 4, pp. 595–600, 2004.

[186] A. Zimprich, S. Biskup, P. Leitner et al., "Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology," Neuron, vol. 44, no. 4, pp. 601–607, 2004.

[187] L. H. Sanders, J. Laganière, O. Cooper et al., "LRRK2 mutations cause mitochondrial DNA damage in iPS-deriv derived neural cells from Parkinson’s disease patients: reversal by
gene correction," *Neurobiology of Disease*, vol. 62, pp. 381–386, 2014.

[188] O. Cooper, H. Seo, S. Andrabi et al., "Pharmacological rescue of mitochondrial deficits in iPSC-derived neural cells from patients with familial Parkinson’s disease," *Science Translational Medicine*, vol. 4, no. 141, article 141ra90, 2012.

[189] D. Santos, A. R. Esteves, D. F. Silva, C. Januário, and S. M. Cardoso, "The impact of mitochondrial fusion and fission modulation in sporadic Parkinson’s disease," *Molecular Neurobiology*, vol. 52, no. 1, pp. 573–586, 2015.

[190] E. Greggio, S. Jain, A. Kingsbury et al., "Kinase activity is required for the toxic effects of mutant LRRK2/dardarin," *Neurobiology of Disease*, vol. 23, no. 2, pp. 329–341, 2006.

[191] E. H. Howlett, N. Jensen, F. Belmonte et al., "LRRK2 G2019S-induced mitochondrial DNA damage is LRRK2 kinase dependent and inhibition restores mtDNA integrity in Parkinson’s disease," *Human Molecular Genetics*, vol. 26, no. 22, pp. 4340–4351, 2017.

[192] A. B. West, D. J. Moore, S. Biskup et al., "Parkinson’s disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 46, pp. 16842–16847, 2005.

[193] X. Wang, M. H. Yan, H. Fujioka et al., "LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLPL1," *Human Molecular Genetics*, vol. 21, no. 9, pp. 1931–1944, 2012.

[194] K. Stafa, E. Tsika, R. Moser et al., "Functional interaction of Parkinson’s disease-associated LRRK2 with members of the dynamin GTPase superfamily," *Human Molecular Genetics*, vol. 23, no. 8, pp. 2055–2077, 2014.

[195] C. J. Gloeckner, N. Kinkl, A. Schumacher et al., "The Parkinson disease causing LRRK2 mutation I2020T is associated with increased kinase activity," *Human Molecular Genetics*, vol. 15, no. 2, pp. 223–232, 2006.

[196] L. M. Martins, A. Morrison, K. Klupsch et al., "Neuroprotective role of the reaper-related serine protease HtrA2/Omi revealed by targeted deletion in mice," *Molecular and Cellular Biology*, vol. 24, no. 22, pp. 9848–9862, 2004.

[197] K. M. Strauss, L. M. Martins, H. Plun-Favreau et al., "Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson’s disease," *Human Molecular Genetics*, vol. 14, no. 15, pp. 2099–2111, 2005.

[198] V. Bogaerts, K. Nuytemans, J. Reumers et al., "Genetic variability in the mitochondrial serine protease HTRA2 contributes to risk for Parkinson disease," *Human Mutation*, vol. 29, no. 6, pp. 832–840, 2008.

[199] R. K. Dagda and C. T. Chu, "Mitochondrial quality control: insights on how Parkinson’s disease related genes PARK1,parkin, and Omi/HtrA2 interact to maintain mitochondrial homeostasis," *Journal of Bioenergetics and Biomembranes*, vol. 41, no. 6, pp. 473–479, 2009.

[200] K. Fu, Y. Wang, D. Guo, G. Wang, and H. Ren, "Familial Parkinson’s disease-associated L166P mutant DJ-1 is cleaved by mitochondrial serine protease Omi/HtrA2," *Neuroscience Bulletin*, vol. 33, no. 6, pp. 685–694, 2017.

[201] Y. Yang, L. J. Xue, X. Xue, Z. Ou, T. Jiang, and Y. D. Zhang, "MFN2 ameliorates cell apoptosis in a cellular model of Parkinson’s disease induced by rotenone," *Experimental and Therapeutic Medicine*, vol. 16, no. 4, pp. 3680–3685, 2018.

[202] Z. Ou, T. Jiang, Q. Gao et al., "Mitochondrial-dependent mechanisms are involved in angiotensin II-induced apoptosis in dopaminergic neurons," *Journal of the Renin-Angiotensin-Aldosterone System*, vol. 17, no. 4, 2016.

[203] M. C. Kiernan, S. Yucic, B. C. Cheah et al., "Amyotrophic lateral sclerosis," *The Lancet*, vol. 377, no. 9769, pp. 942–955, 2011.

[204] E. F. Smith, P. J. Shaw, and K. J. De Vos, "The role of mitochondria in amyotrophic lateral sclerosis," *Neuroscience Letters*, 2017.

[205] D. R. Rosen, T. Siddique, D. Patterson et al., "Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis," *Nature*, vol. 362, no. 6415, pp. 59–62, 1993.

[206] S. Sasaki and M. Iwata, "Mitochondrial alterations in the spinal cord of patients with sporadic amyotrophic lateral sclerosis," *Journal of Neuropathology & Experimental Neurology*, vol. 66, no. 1, pp. 10–16, 2007.

[207] J. Magrané, C. Cortez, W.-B. Gan, and G. Manfredi, "Abnormal mitochondrial transport and morphology are common pathophenotypic denominators in SOD1 and TDP43 ALS mouse models," *Human Molecular Genetics*, vol. 23, no. 6, pp. 1413–1424, 2014.

[208] W. Wang, L. Li, W.-L. Lin et al., "The ALS disease-associated mutant TDP-43 impairs mitochondrial dynamics and function in motor neurons," *Human Molecular Genetics*, vol. 22, no. 23, pp. 4706–4719, 2013.

[209] R. Dafinca, J. Scaber, N.A. Abubneh et al., "C9orf72 hexanucleotide expansions are associated with altered endoplasmic reticulum calcium homeostasis and stress granule formation in induced pluripotent stem cell-derived neurons from patients with amyotrophic lateral sclerosis and frontotemporal dementia," *Stem Cells*, vol. 34, no. 8, pp. 2063–2078, 2016.

[210] E. Onesto, C. Colombrita, V. Gumnita et al., "Gene-specific mitochondria dysfunctions in human TARDBP and C9orf72 fibroblasts," *Acta Neuropathologica Communications*, vol. 4, no. 1, p. 47, 2016.

[211] A. Ferri, P. Fiorenzo, M. Nencini et al., "Glutaredoxin 2 prevents aggregation of mutant SOD1 in mitochondria and abolishes its toxicity," *Human Molecular Genetics*, vol. 19, no. 22, pp. 4529–4542, 2010.

[212] W. Liu, T. Yamashita, F. Tian et al., "Mitochondrial fusion and fission proteins expression dynamically change in a murine model of amyotrophic lateral sclerosis," *Current Neurovascular Research*, vol. 10, no. 3, pp. 222–230, 2013.

[213] Y.-F. Xu, T. F. Gendron, Y.-J. Zhang et al., "Wild-type human TDP-43 expression causes TDP-43 phosphorylation, mitochondrial aggregation, motor deficits, and early mortality in transgenic mice," *The Journal of Neuroscience*, vol. 30, no. 32, pp. 10851–10859, 2010.

[214] C. Stribl, A. Samara, D. Trümbach et al., "Mitochondrial dysfunction and decrease in body weight of a transgenic knock-in mouse model for TDP-43," *Journal of Biological Chemistry*, vol. 289, no. 15, pp. 10769–10784, 2014.

[215] C. Vande Velde, K. K. McDonald, Y. Boukhedimi et al., "Misfolded SOD1 associated with motor neuron mitochondria alters mitochondrial shape and distribution prior to clinical onset," *PLoS One*, vol. 6, no. 7, article e22031, 2011.

[216] K. J. De Vos, A. L. Chapman, M. E. Tennant et al., "Familial amyotrophic lateral sclerosis-linked SOD1 mutants perturb
fast axonal transport to reduce axonal mitochondria content,” *Human Molecular Genetics*, vol. 16, no. 22, pp. 2720–2728, 2007.

[217] C. M. Higgins, C. Jung, and Z. Xu, “ALS-associated mutant SOD1<sup>105X</sup> causes mitochondrial vacuolation by expansion of the intermembrane space and by involvement of SOD1 aggregation and peroxisomes,” *BMC Neuroscience*, vol. 4, no. 1, p. 16, 2003.

[218] D. Jaarsma, F. Rognoni, W. van Duijn, H. W. Verspaget, E. D. Haasdijk, and J. C. Holstege, “Cu/Zn superoxide dismutase (SOD1) accumulates in vacuolated mitochondria in transgenic mice expressing amyotrophic lateral sclerosis-linked SOD1 mutations,” *Acta Neuropathologica*, vol. 102, no. 4, pp. 293–305, 2001.

[219] J. Liu, C. Lillo, P. A. Jonsson et al., “Toxicity of familial ALS-linked SOD1 mutants from selective recruitment to spinal mitochondria,” *Neuron*, vol. 43, no. 1, pp. 5–17, 2004.

[220] A. Israelson, N. Arbel, S. da Cruz et al., “Misfolded mutant SOD1 directly inhibits VDAC1 conductance in a mouse model of inherited ALS,” *Neuron*, vol. 67, no. 4, pp. 575–587, 2010.

[221] P. Pasinelli, M. E. Belford, N. Lennon et al., “Amyotrophic lateral sclerosis-associated SOD1 mutant proteins bind and aggregate with Bcl-2 in spinal cord mitochondria,” *Neuron*, vol. 43, no. 1, pp. 19–30, 2004.

[222] S. Pedrini, D. Sau, S. Guareschi et al., “ALS-linked mutant SOD1 damages mitochondria by promoting conformational changes in Bcl-2,” *Human Molecular Genetics*, vol. 19, no. 15, pp. 2974–2986, 2010.

[223] W. Tan, N. Naniche, A. Bogush, S. Pedrini, D. Trotti, and P. Pasinelli, “Small peptides against the mutant SOD1/Bcl-2 toxic mitochondrial complex restore mitochondrial function and cell viability in mutant SOD1-mediated ALS,” *Journal of Neuroscience*, vol. 33, no. 28, pp. 11588–11598, 2013.

[224] T. Nakaya and M. Maragkakis, “Amyotrophic lateral sclerosis associated FUS mutation shortens mitochondria and induces neurotoxicity,” *Scientific Reports*, vol. 8, no. 1, article 15575, 2018.

[225] W. Wang, L. Wang, J. Lu et al., “The inhibition of TDP-43 mitochondrial localization blocks its neuronal toxicity,” *Nature Medicine*, vol. 22, no. 8, pp. 869–878, 2016.

[226] S. Bannwarth, S. Ait-el-Mkadem, A. Chaussenot et al., “A mitochondrial origin for frontotemporal dementia and amyotrophic lateral sclerosis through CHCHD10 involvement,” *Brain*, vol. 137, no. 8, pp. 2329–2345, 2014.

[227] E. C. Genin, M. Plutino, S. Bannwarth et al., “CHCHD10 mutations promote loss of mitochondrial cristae junctions with impaired mitochondrial genome maintenance and inhibition of apoptosis,” *EMBO Molecular Medicine*, vol. 8, no. 1, pp. 58–72, 2016.

[228] S. C. Barber and P. J. Shaw, “Oxidative stress in ALS: key role in motor neuron injury and therapeutic target,” *Free Radical Biology and Medicine*, vol. 48, no. 5, pp. 629–641, 2010.

[229] F. O. Walker, “Huntington’s disease,” *The Lancet*, vol. 369, no. 9557, pp. 218–228, 2007.

[230] G. P. Bates, R. Dorsey, J. F. Gusella et al., “Huntington disease,” *Nature Reviews Disease Primers*, vol. 1, article 15005, 2015.

[231] M. Gu, M. T. Gash, V. M. Mann, F. Javoy-Agid, J. M. Cooper, and A. H. V. Schapira, “Mitochondrial defect in Huntington’s disease caudate nucleus,” *Annals of Neurology*, vol. 39, no. 3, pp. 385–389, 1996.

[232] T. Milakov and G. V. W. Johnson, “Mitochondrial respiration and ATP production are significantly impaired in striatal cells expressing mutant huntingtin,” *Journal of Biological Chemistry*, vol. 280, no. 35, pp. 30773–30782, 2005.

[233] E. Brouillet, P. Hantraye, R. J. Ferrante et al., “Chronic mitochondrial energy impairment produces selective striatal degeneration and abnormal choreiform movements in primates,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 92, no. 15, pp. 7105–7109, 1995.

[234] J. G. Greene, R. H. P. Porter, R. V. Eller, and J. T. Greenamyre, “Inhibition of succinate dehydrogenase by malonic acid produces an “excitotoxic” lesion in rat striatum,” *Journal of Neurochemistry*, vol. 61, no. 3, pp. 1151–1154, 1993.

[235] M. F. Beal, B. T. Hyman, and W. Koroshetz, “Do defecs in mitochondrial energy metabolism underlie the pathology of neurodegenerative diseases?” *Trends in Neurosciences*, vol. 16, no. 4, pp. 125–131, 1993.

[236] A. Benchoua, Y. Trioulier, D. Zala et al., “Involvement of mitochondrial complex II defects in neuronal death produced by N-terminus fragment of mutated huntingtin,” *Molecular Biology of the Cell*, vol. 17, no. 4, pp. 1652–1663, 2006.

[237] A. V. Panov, C. A. Gutekunst, B. R. Leavitt et al., “Early mitochondrial calcium defects in Huntington’s disease are a direct effect of polyglutamines,” *Nature Neuroscience*, vol. 5, no. 8, pp. 731–736, 2002.

[238] Y. S. Choo, G. V. Johnson, M. MacDonald, P. J. Delloff, and M. Lesort, “Mutant huntingtin directly increases susceptibility of mitochondria to the calcium-induced permeability transition and cytochrome c release,” *Human Molecular Genetics*, vol. 13, no. 14, pp. 1407–1420, 2004.

[239] R. Luthi-Carter and J.-H. J. Cha, “Mechanisms of transcriptional dysregulation in Huntington’s disease,” *Clinical Neuroscience Research*, vol. 3, no. 3, pp. 165–177, 2003.

[240] J. Yu, L. Zhang, P. M. Hwang, K. W. Kinzler, and B. Vogelstein, “PUMA induces the rapid apoptosis of colorectal cancer cells,” *Molecular Cell*, vol. 7, no. 3, pp. 673–682, 2001.

[241] J. E. Chipuk, T. Kuwana, L. Bouchier-Hayes et al., “Direct activation of Bax by p53 mediates mitochondrial membrane permeabilization and apoptosis,” *Science*, vol. 303, no. 5660, pp. 1010–1014, 2004.

[242] B. I. Bae, H. Xu, S. Igarashi et al., “p53 mediates cellular dysfunction and behavioral abnormalities in Huntington’s disease,” *Neuron*, vol. 47, no. 1, pp. 29–41, 2005.

[243] A. Siddiqui, S. Rivera-Sánchez, M. . R. Castro et al., “Mitochondrial DNA damage is associated with reduced mitochondrial bioenergetics in Huntington’s disease,” *Free Radical Biology and Medicine*, vol. 53, no. 7, pp. 1478–1488, 2012.

[244] L. Cui, H. Jeong, F. Borovecki, C. N. Parkhurst, N. Tanese, and D. Kainic, “Transcriptional repression of PGC-1α by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration,” *Cell*, vol. 127, no. 1, pp. 59–69, 2006.

[245] P. Weydt, V. V. Pineda, A. E. Torrence et al., “Thermoregulatory and metabolic defects in Huntington’s disease transgenic mice implicate PGC-1α in Huntington’s disease neurodegeneration,” *Cell Metabolism*, vol. 4, no. 5, pp. 349–362, 2006.
[246] J. Lin, P. H. Wu, P. T. Tarr et al., “Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1α null mice,” Cell, vol. 119, no. 1, pp. 121–135, 2004.

[247] V. Costa, M. Giacomello, R. Hudec et al., “Mitochondrial fission and cristae disruption increase the response of cell models of Huntington’s disease to apoptotic stimuli,” EMBO Molecular Medicine, vol. 2, no. 12, pp. 490–503, 2010.

[248] W. Song, J. Chen, A. Pettrilli et al., “Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity,” Nature Medicine, vol. 17, no. 3, pp. 377–382, 2011.

[249] C.-R. Chang and C. Blackstone, “Dynamic regulation of mitochondrial fission through modification of the dynamin-related protein Drp1,” Annals of the New York Academy of Sciences, vol. 1201, no. 1, pp. 34–39, 2010.

[250] J. Kim, J. P. Moody, C. K. Edgerly et al., “Mitochondrial loss, dysfunction and altered dynamics in Huntington’s disease,” Human Molecular Genetics, vol. 19, no. 20, pp. 3919–3935, 2010.

[251] U. Shirendeb, A. P. Reddy, M. Manczak et al., “Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington’s disease: implications for selective neuronal damage,” Human Molecular Genetics, vol. 20, no. 7, pp. 1438–1455, 2011.

[252] U. P. Shirendeb, M. J. Calkins, M. Manczak et al., “Mutant huntingtin’s interaction with mitochondrial protein Drp1 impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in Huntington’s disease,” Human Molecular Genetics, vol. 21, no. 2, pp. 406–420, 2012.

[253] Y. C. Wong and E. L. F. Holzbaur, “The regulation of autophagosomal dynamics by huntingtin and HAP1 is disrupted by expression of mutant huntingtin, leading to defective cargo degradation,” Journal of Neuroscience, vol. 34, no. 4, pp. 1293–1305, 2014.

[254] B. Khalil, N. El Fissi, A. Aouane, M. J. Cabirol-Pol, T. Rival, and J. C. Liévens, “PINK1-induced mitophagy promotes neuroprotection in Huntington’s disease,” Cell Death & Disease, vol. 6, no. 1, article e1617, 2015.

[255] Y.-N. Rui, Z. Xu, B. Patel et al., “Huntingtin functions as a scaffold for selective macroautophagy,” Nature Cell Biology, vol. 17, no. 3, pp. 262–275, 2015.

[256] J. Ochaba, T. Lukacsovich, G. Csikos et al., “Potential function for the huntingtin protein as a scaffold for selective autophagy,” Proceedings of the National Academy of Sciences of the United States of America, vol. 111, no. 47, pp. 16889–16894, 2014.

[257] S. E. Browne and M. F. Beal, “Oxidative damage in Huntington’s disease pathogenesis,” Antioxidants & Redox Signaling, vol. 8, no. 11–12, pp. 2061–2073, 2006.

[258] M. A. Sorolla, G. Reverter-Branchat, J. Tamarit, I. Ferrer, J. Ros, and E. Cabisco, “Proteomic and oxidative stress analysis in human brain samples of Huntington disease,” Free Radical Biology and Medicine, vol. 45, no. 5, pp. 667–678, 2008.

[259] M. J. Calkins, R. J. Jakel, D. A. Johnson, K. Chan, Y. W. Kan, and J. A. Johnson, “Protection from mitochondrial complex II inhibition in vitro and in vivo by Nrf2-mediated transcription,” Proceedings of the National Academy of Sciences of the United States of America, vol. 102, no. 1, pp. 244–249, 2005.

[260] Y. N. Jin, Y. V. Yu, S. Gundemir et al., “Impaired mitochondrial dynamics and Nrf2 signaling contribute to compromised responses to oxidative stress in striatal cells expressing full-length mutant huntingtin,” PLoS One, vol. 8, no. 3, article e57932, 2013.

[261] A. S. Tsvetkov, M. Arrasate, S. Barnmada et al., “Proteostasis of polyglutamine varies among neurons and predicts neurodegeneration,” Nature Chemical Biology, vol. 9, no. 9, pp. 586–592, 2013.

[262] L. Quinti, S. Dayalan Naidu, U. Träger et al., “KEAP1-modifying small molecule reveals muted NRF2 signaling responses in neural stem cells from Huntington’s disease patients,” Proceedings of the National Academy of Sciences of the United States of America, vol. 114, no. 23, pp. E4676–E4685, 2017.

[263] C. Stack, D. Ho, E. Wille et al., “Triterpenoids CDDO-ethyl amide and CDDO-trifluoroethyl amide improve the behavioral phenotype and brain pathology in a transgenic mouse model of Huntington’s disease,” Free Radical Biology and Medicine, vol. 49, no. 2, pp. 147–158, 2010.

[264] V. Campuzano, L. Montermini, M. D. Molto et al., “Friedreich’s ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion,” Science, vol. 271, no. 5254, pp. 1423–1427, 1996.

[265] G. Alper and V. Narayanan, “Friedreich’s ataxia,” Pediatric Neurology, vol. 28, no. 5, pp. 335–341, 2003.

[266] N. Sakamoto, K. Ohshima, L. Montermini, M. Pandolfo, and R. D. Wells, “Sticky DNA, a self-associated complex formed at long GAA-TTC repeats in intron 1 of the frataxin gene, inhibits transcription,” Journal of Biological Chemistry, vol. 276, no. 29, pp. 27171–27177, 2001.

[267] V. Campuzano, L. Montermini, Y. Lutz et al., “Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes,” Human Molecular Genetics, vol. 6, no. 11, pp. 1771–1780, 1997.

[268] A. Dürr, M. Cossee, Y. Agid et al., “Clinical and genetic abnormalities in patients with Friedreich’s ataxia,” New England Journal of Medicine, vol. 335, no. 16, pp. 1169–1175, 1996.

[269] A. H. Koeppen, “Friedreich’s ataxia: pathology, pathogenesis, and molecular genetics,” Journal of the Neurological Sciences, vol. 303, no. 1–2, pp. 1–12, 2011.

[270] M. L.-H. Huang, E. M. Becker, M. Whitnall, Y. S. Rahmanto, P. Ponka, and D. R. Richardson, “Elucidation of the mechanism of mitochondrial iron loading in Friedreich’s ataxia by analysis of a mouse mutant,” Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 38, pp. 16381–16386, 2009.

[271] A. Anzovino, S. Chiang, B. E. Brown, C. L. Hawkins, D. R. Richardson, and M. L. H. Huang, “Molecular alterations in a mouse cardiac model of Friedreich ataxia: an impaired Nrf2 response mediated via upregulation of Keap1 and activation of the Gsk3β axis,” The American Journal of Pathology, vol. 187, no. 12, pp. 2858–2875, 2017.

[272] M. Whitnall, Y. S. Rahmanto, R. Sutak et al., “The MCK mouse heart model of Friedreich’s ataxia: alterations in iron-regulated proteins and cardiac hypertrophy are limited by iron chelation,” Proceedings of the National Academy of Sciences of the United States of America, vol. 105, no. 28, pp. 9757–9762, 2008.

[273] E. Becker and D. R. Richardson, “Frataxin: its role in iron metabolism and the pathogenesis of Friedreich’s ataxia,” Oxidative Medicine and Cellular Longevity
Oxidative Medicine and Cellular Longevity

The International Journal of Biochemistry & Cell Biology, vol. 33, no. 1, pp. 1–10, 2001.

[274] J. M. Cooper and A. H. V. Schapira, “Friedreich’s ataxia: disease mechanisms, antioxidant and coenzyme Q\textsubscript{10} therapy,” BioFactors, vol. 18, no. 1-4, pp. 163–171, 2003.

[275] N. Bodaert, K. H. le Quan Sang, A. Rotig et al., “Selective iron chelation in Friedreich ataxia: biologic and clinical implications,” Blood, vol. 110, no. 1, pp. 401–408, 2007.

[276] M. M. Heidari, M. Houshmand, S. Hosseinikhan, S. Nafissi, and M. Khatami, “Complex I and ATP content deficiency in lymphocytes from Friedreich’s ataxia,” Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques, vol. 36, no. 01, pp. 26–31, 2009.

[277] S. Chiang, Z. Kovacevic, S. Sahni et al., “Frataxin and the molecular mechanism of mitochondrial iron-loading in Friedreich’s ataxia,” Clinical Science, vol. 130, no. 11, pp. 853–870, 2016.

[278] M. Whitnall, Y. S. Rahmanto, M. L.-H. Huang et al., “Identification of nonferritin mitochondrial iron deposits in a mouse model of Friedreich ataxia,” Proceedings of the National Academy of Sciences of the United States of America, vol. 109, no. 50, pp. 20590–20595, 2012.

[279] G. M. Palomo, T. Cerrato, R. Gargini, and J. Díaz-Nido, “Silencing of frataxin gene expression triggers p53-dependent apoptosis in human neuron-like cells,” Human Molecular Genetics, vol. 20, no. 14, pp. 2807–2822, 2011.

[280] M.-L.-H. Huang, S. Sivagurunathan, S. Ting et al., “Molecular and functional alterations in a mouse cardiac model of Friedreich ataxia: activation of the integrated stress response, eIF2\alpha phosphorylation, and the induction of downstream targets,” The American Journal of Pathology, vol. 183, no. 3, pp. 745–757, 2013.

[281] J. Skoda, K. Borankova, P. J. Jansson, M. L. H. Huang, R. Veselska, and D. R. Richardson, “Pharmacological targeting of mitochondria in cancer stem cells: an ancient organelle at the crossroad of novel anti-cancer therapies,” Pharmacological Research, vol. 139, pp. 298–313, 2019.

[282] Y. Luo, A. Hoffer, B. Hoffer, and X. Qi, “Mitochondria: a therapeutic target for Parkinson’s disease!,” International Journal of Molecular Sciences, vol. 16, no. 9, pp. 20704–20730, 2015.

[283] S. Cardoso, R. M. Seiça, and P. I. Moreira, “Mitochondria as a target for neuroprotection: implications for Alzheimer’s disease,” Expert Review of Neurotherapeutics, vol. 17, no. 1, pp. 77–91, 2017.

[284] J. Ruszkiewicz and J. Albrecht, “Changes in the mitochondrial antioxidant systems in neurodegenerative diseases and acute brain disorders,” Neurochemistry International, vol. 88, pp. 66–72, 2015.

[285] Q. Ma, “Role of nr2f2 in oxidative stress and toxicity,” Annual Review of Pharmacology and Toxicology, vol. 53, no. 1, pp. 401–426, 2013.

[286] R. Abeti, A. Baccaro, N. Esteras, and P. Giunti, “Novel Nr2f2-inducer prevents mitochondrial defects and oxidative stress in Friedreich’s ataxia models,” Frontiers in Cellular Neuroscience, vol. 12, p. 188, 2018.

[287] D. M. Miller, I. N. Singh, J. A. Wang, and E. D. Hall, “Administration of the Nr2f2-ARE activators sulforaphane and carnosic acid attenuates 4-hydroxy-2-nonenal-induced mitochondrial dysfunction ex vivo,” Free Radical Biology and Medicine, vol. 57, pp. 1–9, 2013.

[288] Y. Liu, J. Yan, C. Sun et al., “Ameliorating mitochondrial dysfunction restores carbon ion-induced cognitive deficits via co-activation of NRF2 and PINK1 signaling pathway,” Redox Biology, vol. 17, pp. 143–157, 2018.

[289] A. Naskar, V. Prabhakar, R. Singh, D. Dutta, and K. P. Mohanakumar, “Melatonin enhances L-DOPA therapeutic effects, helps to reduce its dose, and protects dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrindine-induced parkinsonism in mice,” Journal of Pineal Research, vol. 58, no. 3, pp. 262–274, 2015.

[290] S. A. Rosales-Corral, D. Acuña-Castroviejo, A. Coto-Montes et al., “Alzheimer’s disease: pathological mechanisms and the beneficial role of melatonin,” Journal of Pineal Research, vol. 52, no. 2, pp. 167–202, 2012.

[291] Z. Wang, C. Ma, C. J. Meng et al., “Melatonin activates the Nrf2-ARE pathway when it protects against early brain injury in a subarachnoid hemorrhage model,” Journal of Pineal Research, vol. 53, no. 2, pp. 129–137, 2012.

[292] E. Parada, I. Buendia, R. Leon et al., “Neuroprotective effect of melatonin against ischemia is partially mediated by alpha-7 nicotinic receptor modulation and HO-1 overexpression,” Journal of Pineal Research, vol. 56, no. 2, pp. 204–212, 2014.

[293] S. A. Shah, M. Khan, M. H. Jo, M. G. Jo, F. U. Amin, and M. O. Kim, “Melatonin stimulates the SIRT1/Nrf2 signaling pathway counteracting lipopolysaccharide (LPS)-induced oxidative stress to rescue postnatal rat brain,” CNS Neuroscience & Therapeutics, vol. 23, no. 1, pp. 33–44, 2017.

[294] H. Murata, H. Takamatsu, S. Liu, K. Kataoka, N. H. Huh, and M. Sakaguchi, “Nrf2 regulates PINK1 expression under oxidative stress conditions,” PLoS One, vol. 10, no. 11, article e0142438, 2015.

[295] A. P. Gureev and V. N. Popov, “Nrf2/ARE pathway as a therapeutic target for the treatment of Parkinson diseases,” Neurochemical Research, pp. 1–7, 2019.

[296] R. K. Chaturvedi and M. Flint Beal, “Mitochondrial diseases of the brain,” Free Radical Biology and Medicine, vol. 63, pp. 1–29, 2013.

[297] X. Zhang, J. Wu, Y. Dou et al., “Asiatic acid protects primary neurons against C\textsubscript{6}-ceramide-induced apoptosis,” European Journal of Pharmacology, vol. 679, no. 1-3, pp. 51–59, 2012.

[298] H. Ding, Y. Xiong, J. Sun, C. Chen, J. Gao, and H. Xu, “Asiatic acid prevents oxidative stress and apoptosis by inhibiting the translocation of \(\alpha\)-synuclein into mitochondria,” Frontiers in Neuroendocrinology, vol. 12, p. 431, 2018.

[299] H. Jiang, J. Wang, J. Rogers, and J. Xie, “Brain iron metabolism dysfunction in Parkinson’s disease,” Molecular Neurobiology, vol. 54, no. 4, pp. 3078–3101, 2017.

[300] D. Devos, C. Moreau, J. C. Devedjian et al., “Targeting chelatable iron as a therapeutic modality in Parkinson’s disease,” Antioxidants & Redox Signaling, vol. 21, no. 2, pp. 195–210, 2014.

[301] R. J. Ward, D. T. Dexter, and R. R. Crichton, “Neurodegenerative diseases and therapeutic strategies using iron chelators,” Journal of Trace Elements in Medicine and Biology, vol. 31, pp. 267–273, 2015.

[302] P. Dusek, S. A. Schneider, and J. Aaseth, “Iron chelation in the treatment of neurodegenerative diseases,” Journal of Trace Elements in Medicine and Biology, vol. 38, pp. 81–92, 2016.
J. L. Liu, Y. G. Fan, Z. S. Yang, Z. Y. Wang, and C. Guo, “Iron and Alzheimer’s disease: from pathogenesis to therapeutic implications,” Frontiers in Neuroscience, vol. 12, p. 632, 2018.

N. P. Mena, O. García-Beltrán, F. Lourido et al., “The novel mitochondrial iron chelator 5-((methylamino)methyl)-8-hydroxyquinoline protects against mitochondrial-induced oxidative damage and neuronal death,” Biochemical and Biophysical Research Communications, vol. 463, no. 4, pp. 787–792, 2015.

Z. H. Shi, G. Nie, X. L. Duan et al., “Neuroprotective mechanism of mitochondrial ferritin on 6-hydroxydopamine-induced dopaminergic cell damage: implication for neuroprotection in Parkinson’s disease,” Antioxidants & Redox Signaling, vol. 13, no. 6, pp. 783–796, 2010.

L. Lannfelt, K. Blennow, H. Zetterberg et al., “Safety, efficacy, and biomarker findings of PBT2 in targeting Aβ as a modifying therapy for Alzheimer’s disease: a phase IIa, double-blind, randomised, placebo-controlled trial,” The Lancet Neurology, vol. 7, no. 9, pp. 779–786, 2008.

H. M. Schipper, “Heme oxygenase expression in human central nervous system disorders,” Free Radical Biology and Medicine, vol. 37, no. 12, pp. 1995–2011, 2004.

L. Song, W. Song, and H. M. Schipper, “Astroglia overexpressing heme oxygenase-1 predispose co-cultured PC12 cells to oxidative injury,” Journal of Neuroscience Research, vol. 85, no. 10, pp. 2186–2195, 2007.

D. R. Richardson, D. J. R. Lane, E. M. Becker et al., “Mitochondrial iron trafficking and the integration of iron metabolism between the mitochondrion and cytosol,” Proceedings of the National Academy of Sciences of the United States of America, vol. 107, no. 24, pp. 10775–10782, 2010.

M. L. H. Huang, D. J. R. Lane, and D. R. Richardson, “Mitochondrial mayhem: the mitochondrion as a modulator of iron metabolism and its role in disease,” Antioxidants & Redox Signaling, vol. 15, no. 12, pp. 3003–3019, 2011.

D. R. Richardson and P. Ponka, “Pyridoxal isonicotinoyl hydrazone and its analogs: potential orally effective iron-chelating agents for the treatment of iron overload disease,” Journal of Laboratory and Clinical Medicine, vol. 131, no. 4, pp. 306–315, 1998.

D. R. Richardson, C. Mouralian, P. Ponka, and E. Becker, “Development of potential iron chelators for the treatment of Friedreich’s ataxia: ligands that mobilize mitochondrial iron,” Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, vol. 1536, no. 2-3, pp. 133–140, 2001.

P. Ponka, A. Wilczynska, and H. M. Schulman, “Iron utilization in rabbit reticulocytes: a study using succinylacetone as an inhibitor of heme synthesis,” Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, vol. 720, no. 1, pp. 96–105, 1982.

E. Becker and D. R. Richardson, “Development of novel aroylhydrazone ligands for iron chelation therapy: 2-pyridylcarboxaldehyde isonicotinoyl hydrazone analogs,” The Journal of Laboratory and Clinical Medicine, vol. 134, no. 5, pp. 510–521, 1999.

C. K. Lim, D. S. Kalinowski, and D. R. Richardson, “Protection against hydrogen peroxide-mediated cytotoxicity in Friedreich’s ataxia fibroblasts using novel iron chelators of the 2-pyridylcarboxaldehyde isonicotinoyl hydrazone class,” Molecular Pharmacology, vol. 74, no. 1, pp. 225–235, 2008.