Progress in Neurobiology 106–107 (2013) 17–32

Contents lists available at SciVerse ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Mitochondrial dysfunction and oxidative stress in Parkinson's disease

Sudhakar Raja Subramaniam, Marie-Francoise Chesselet *

Department of Neurology, David Geffen School of Medicine, UCLA, 710 Westwood Plaza, Los Angeles, CA 90095-1769, USA

ARTICLE INFO

Article history:
Received 17 January 2013
Received in revised form 13 April 2013
Accepted 22 April 2013
Available online 30 April 2013

Keywords:
Parkinson's disease
Mitochondrial dysfunction

ABSTRACT

Parkinson's disease (PD) is a movement disorder that is characterized by the progressive degeneration of dopaminergic neurons in substantia nigra pars compacta resulting in dopamine deficiency in the striatum. Although majority of the PD cases are sporadic several genetic mutations have also been linked to the disease thus providing new opportunities to study the pathology of the illness. Studies in humans and various animal models of PD reveal that mitochondrial dysfunction might be a defect that occurs early in PD pathogenesis and appears to be a widespread feature in both sporadic and monogenic forms of PD. The general mitochondrial abnormalities linked with the disease include mitochondrial electron transport chain impairment, alterations in mitochondrial morphology and dynamics, mitochondrial DNA mutations and anomaly in calcium homeostasis. Mitochondria are vital organelles with multiple functions and their dysfunction can lead to a decline in energy production, generation of reactive oxygen species and induction of stress-induced apoptosis. In this review, we give an outline of mitochondrial functions that are affected in the pathogenesis of sporadic and familial PD, and hence provide insights that might be valuable for focused future research to exploit possible mitochondrial targets for neuroprotective interventions in PD.

Contents

* Corresponding author. Tel.: +1 310 267 1781.
E-mail addresses: mchesselet@mednet.ucla.edu, mfcb114@mednet.ucla.edu (M.-F. Chesselet).

0301-0082/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pneurobio.2013.04.004

1. Introduction

Parkinson's disease (PD) is the most common movement disorder and the second most prevalent neurodegenerative disorder worldwide, affecting ~2% of population over the age of 65. PD is pathologically characterized by: (i) the loss of dopaminergic neurons in substantia nigra pars compacta leading to decreased dopamine levels in the basal ganglia and (ii) the formation of Lewy bodies – intracytoplasmic inclusions containing fibrillar α-synuclein (Spillantini et al., 1997). It is believed that dopamine loss causes dysregulation of the basal ganglia circuitries resulting in prominent clinical motor symptoms including bradykinesia, resting tremor, rigidity and postural instability. In addition to the motor symptoms, non-motor symptoms such as sleep disturbances, depression, cognitive deficits, and autonomic and sensory dysfunction are also well documented in PD (Perez and Palmiter, 2005; Choi et al., 2008; McDowell and Chesselet, 2012).

The etiology of PD has been the focus of research for several decades and considerable advances have been made in understanding the genetic and environmental factors, and the underlying molecular mechanisms of the disease. PD was considered to have no genetic links for nearly a century until a few decades ago, when large-scale linkage analysis studies on PD patients exposed mutations in several different genes. The mutations in the following genes are associated to familial PD: α-synuclein (*PARK1/4*), parkin (*PARK2*), PINK1 (*PARK6*), DJ-1 (*PARK7*), LRRK2 (*PARK8*) and ATP13A2 (*PARK9*) whereas more rarely associated genes include *PARK3*, UCHL1 (*PARK5*), GIGYF2 (*PARK11*), HTRA2 (*PARK13*) and PLA2G6 (*PARK14*), which may represent risk factors rather than causative mutations (Schapira, 2011). Despite the recent advancements in PD genetics, the etiology of PD remains not completely understood. In fact a majority (~95%) of the PD cases is sporadic and are believed to result from complex interactions between genetic susceptibility and environmental factors. In spite of their differing etiology, sporadic and monogenic PD cases share common biochemical, pathological and clinical features. Mitochondrial dysfunction is one such feature observed in both forms of PD. Since mitochondrial complex I deficiency was first identified in PD brains by Schapira and co-workers in 1989 (Schapira et al., 1989), numerous studies have implicated mitochondrial dysfunction in PD pathogenesis. In this review, we summarize current knowledge on the role of mitochondrial dysfunction in the pathology of sporadic and monogenic PD.

2. Mitochondrial complex I deficiency and oxidative stress in sporadic PD

Mitochondria produce ATP (adenosine triphosphate) through the process of respiration and oxidative phosphorylation thereby acting as the primary source of energy in the cell. The process of oxidative phosphorylation involves coupling of both redox and phosphorylation reactions in the inner membrane of mitochondria resulting in effective ATP synthesis. During this process, electrons from NADH (nicotinamide adenine dinucleotide) or $FADH_2$ (flavin adenine dinucleotide) are transported through the electron transport chain (ETC), comprising of complexes I–IV, to create a proton gradient across the inner mitochondrial membrane. The consequent movement of the protons from the mitochondrial matrix to the intermembrane space creates an electrochemical gradient. This electrochemical gradient consists of a pH gradient (ΔpH) and an electrical gradient ($\Delta\psi$) that drives the synthesis of ATP from ADP (adenosine diphosphate) through the enzyme ATP synthase (complex V).

Mounting evidence suggests that mitochondria are the primary source of reactive oxygen species that may contribute to intracellular oxidative stress (Starkov, 2008; Murphy, 2009). In the process of oxidative phosphorylation, complex I (NADH-quinone oxidoreductase) acts as the entry point for electrons from the mitochondrial matrix into the ETC by catalyzing the electron transfer from NADH into the ETC subunits. Complex I and to a smaller extent complex III in the ETC are considered to be the main sites of ROS production in mitochondria. Superoxide radical is the primary ROS produced in mitochondria as a result of single electron transfer to oxygen in the respiratory chain. Superoxide dismutase 2 or MnSOD converts superoxide radical to hydrogen peroxide which is further detoxified by the enzyme catalase. However, in the presence of metal ions such as Fe^{2+}, hydrogen peroxide may be converted into a highly reactive hydroxyl radical as a result of Fenton reaction which causes severe oxidative damage to the cellular components. The production of superoxide is believed to be dependent on factors such as the concentration of electron donors, localized oxygen concentration and the second order rate kinetics between them (Starkov, 2008; Murphy, 2009). In mitochondrial complex I, the following conditions lead to the production of superoxide radicals: (i) low ATP production, consequent high proton-motive force (ΔpH and $\Delta\psi$) and a reduced coenzyme Q pool; and (ii) high NADH/NAD^+ ratio in the mitochondrial matrix. On the other hand, mitochondria with normal ATP production, subsequent low proton-motive force and low NADH/NAD^+ ratio in the mitochondrial matrix produce much lesser superoxide radical (Murphy, 2009). In addition to the above conditions, ROS formation in complex I is also significantly increased during the reverse electron transport process. Reverse electron transport takes place when there is a reduction of ubiquinone pool that forces electrons uphill from ubiquinol into complex I under high proton-motive force conditions (Winklhofer and Haass, 2010).

Increased stress resulting from ROS production is one of the proposed mechanisms for the death of dopaminergic neurons in PD and mitochondrial complex I is considered to be one of the primary sources of ROS. Disease-specific reduction in mitochondrial complex I activity or protein level in the postmortem substantia nigra of patients with idiopathic PD has been known for a long time (Schapira et al., 1990; Hattori et al., 1991). A study using purified mitochondria also showed a mitochondrial complex I deficiency in the frontal cortex of PD patients (Parker et al., 2008). Mild deficits in complex I activity were also detected in the striatum (Mizuno et al., 1989), cortical brain tissue (Parker et al., 2008), fibroblasts (Mytilineou et al., 1994), blood platelets (Krige et al., 1992; Haas et al., 1995) and rather variably, in skeletal muscle (Blin et al., 1994) and lymphocytes (Yoshino et al., 1992; Haas et al., 1995) of PD patients. Catalytic subunits of complex I were found to contain oxidized proteins and a correlation between increased protein oxidation and reduction in electron transfer capacity was observed in PD patients indicating that oxidative damage to these subunits may result in complex I impairment (Keeney et al., 2006). Interestingly, a recent study shows that the levels of oxidized coenzyme Q-10 and 8-hydroxy-2′-deoxyguanosine in cerebrospinal fluid of PD patients were significantly increased suggesting a role for mitochondrial oxidative damage and oxidative DNA damage in PD pathology (Isobe et al., 2010). In addition, a reduction in complex I activity was observed in cytoplasmic hybrid (cybrid) cell lines that contain mitochondrial DNA from sporadic PD patients (Swerdlow et al., 2001).

Interestingly, a mouse model with complex I deficiency that lacked the Ndufs4 gene, one of the 49 subunits of complex I, appeared healthy until 5 weeks but developed progressive encephalomyopathy at 7 weeks of age leading to death. Ndufs4 knockout mouse showed a reduction in complex I driven oxygen consumption and intact complex I protein levels suggesting that Ndufs4 may facilitate the assembly or stabilization of complex I.

On the contrary, total oxygen consumption and ATP levels were at normal levels in these mice (Kruse et al., 2008). The lack of nigrostriatal degeneration in these mice could be due to the fact that the Ndufs4 knockout mouse does not reflect the aging pathology of PD where there is a gradual loss of complex I activity over a long period of time. However, midbrain mesencephalic neuron cultures from Ndufs4 knockout mice did not show loss of dopaminergic neurons despite the lack of complex I activity. Although dopaminergic neuron were more susceptible to rotenone, MPP± or paraquat, their lack of complex I activity did not protect from these toxin suggesting that dopaminergic cell death induced by these toxins may not solely be due to their effect on of complex I but also include other effects, for example on the microtubules (Choi et al., 2008). A recent study also reported that tissue-specific knockout of Ndufs4 gene in mid-brain dopaminergic neurons showed no obvious neurodegeneration or loss of striatal innervations or symptoms of parkinsonism, although impairment in dopamine homeostasis and increase in dopamine metabolites were observed in these mice. Ndufs4 dopaminergic neuron knockouts did not develop a loss of nigrostriatal neuron but not surprisingly, were more vulnerable to neurotoxicity induced by the mitochondrial complex 1 toxin MPTP (Sterky et al., 2012). These data suggest that complex 1 deficiency could contribute to the demise of dopaminergic neurons in the presence of other toxic factors.

Rotenone, a mitochondrial toxin, can induce the loss of dopaminergic neurons, and this toxicity was significantly attenuated by methylene blue, a compound that functions as an alternative electron carrier that bypasses complex I/III blockade emphasizing the role of complex 1 deficiency in rotenone-induced toxicity (Wen et al., 2011). It has been known that loss of dopamine homeostasis can affect mitochondrial function, and in line with this, another study shows that the redox modifications of dopamine can inhibit mitochondrial respiratory chain complexes. Oxidized dopamine and 3,4-dihydrophenylacetic acid (DOPAC) inhibited complex I and complex II activities in a dose-dependent manner whereas reduced dopamine but not DOPAC inhibited complex II activity. These findings reveal the possible downstream targets of dopamine metabolites that could potentially contribute to the susceptibility of dopaminergic neurons in PD (Gautam and Zeevalk, 2011). It is believed that substantia nigra is more vulnerable to complex I dysfunction compared to other brain regions due to the generation of ROS by the nigral dopaminergic neurons during dopamine metabolism (Chinta and Andersen, 2008). In addition, mouse substantia nigra dopaminergic neurons also showed decreased mitochondrial mass compared to the non-dopaminergic neurons and the neurons of the ventral tegmental area indicating that this deficit might contribute to the selective vulnerability of these neurons in PD mouse models (Liang et al., 2007). Altogether, these findings suggest that mitochondrial respiratory chain impairment, in particular complex I deficiency and the subsequent increase in ROS production may indirectly or directly contribute to the pathology of sporadic PD.

3. Mitochondrial DNA mutations

Mitochondrial DNA (mtDNA) is a double-stranded circular genome, 16.6 kb in size, and replicates separately from the cell cycle and nuclear DNA replication. MtDNA encodes for 13 proteins all of which are subunits of the mitochondrial respiratory chain complexes. It also codes for 22 tRNAs and 2 rRNAs that are vital for mitochondrial protein synthesis (Reeve et al., 2008). It appears that the close proximity of mtDNA to ROS generated by the respiratory chain dysfunction, and the lack of proficient DNA repair mechanisms and protective histones, makes the mtDNA vulnerable to mutations (Richter et al., 1988; Ozawa, 1997). As discussed in the previous section, reduction in complex I activity increases ROS generation which may affect mtDNA which codes for 7 of the 45 subunits of complex I enzyme. Alteration of mitochondrial metabolism in cells with mtDNA from PD patients showed changes in the microtubular net and autophagic-lysosomal pathway (Cardoso et al., 2012). Although sequencing of the mitochondrial DNA from control and PD patients did not show any characteristic pathogenic mutation responsible for PD (Vives-Bauza et al., 2002), an age-dependent increase in mtDNA deletions associated with respiratory chain dysfunction has been observed in the dopaminergic neurons of substantia nigra (Bender et al., 2006b; Kraytsberg et al., 2006). In addition, neurons lacking complex IV (cytochrome c oxidase) showed high mtDNA deletions. These findings reveal that any significant changes to mtDNA composition might directly affect the mitochondrial respiratory chain activity and function. Moreover, somatic mtDNA deletions were slightly higher in substantia nigra of PD patients compared to age-matched controls. However, mtDNA deletions in aged-brains were not seen in other types of neurons such as pyramidal neurons of the cortex, hippocampal neurons or cerebellar Purkinje cells (Bender et al., 2006b; Kraytsberg et al., 2006).

These observations demonstrate that mtDNA deletions are specific to nigral neurons (Bender et al., 2006b) which may increase their susceptibility to oxidative stress and hence contribute to their selective loss in PD. This is supported by studies in MitoPark mice with a conditional knockout in dopaminergic neurons for mitochondrial transcription factor A (Tfam) gene, which regulates the transcription of mtDNA, showed reduced mtDNA expression and respiratory chain deficiency in midbrain dopaminergic neurons, which led to a progressive impairment of motor function accompanied by intraneural inclusions and loss of dopaminergic neurons (Ekstrand et al., 2007). In addition, MitoPark mice at the age of 6–7 weeks showed impaired dopamine uptake in striatum and lack of pacemaker activity in the nigral dopaminergic neurons suggesting that nigrostriatal dysfunction precedes parkinsonism-like behavioral deficits in these mice (Good et al., 2011).

MtDNA replication is also controlled by mtDNA polymerase gamma 1 (POLG1), an enzyme encoded by nuclear DNA. POLG1 is imported into the inner mitochondrial membrane of mitochondria and it is involved in mtDNA synthesis, replication and repair (Filosto et al., 2003). Mitochondrial dysfunction induced by downregulation of the catalytic subunit of mtDNA polymerase in *Drosophila* resulted in lower respiratory chain activity, premature aging, age-related motor deficits, progressive and cell type-specific neurodegeneration and was alleviated by bypassing respiratory chain deficiencies using alternative oxidase (Humphrey et al., 2012). Mutations in POLG1 lead to severe progressive multisystem disorder including parkinsonism (Luoma et al., 2004). Recently, POLG1 mutations were shown to have strong association with parkinsonism in a Swedish population, further supporting the involvement of mitochondrial dysfunction in PD pathology (Anvret et al., 2010). Taken together, these results indicate that mitochondrial impairment caused by mtDNA mutations and mutations of nuclear encoded mitochondrial proteins might be involved in PD pathogenesis.

4. Mitochondria and calcium homeostasis

Calcium is the principal modulator of mitochondria and endoplasmic reticulum (ER). Calcium readily enters the neurons through open pores like L-type Cav 1.3 calcium channels or by activation of *N*-methyl-D-aspartate (NMDA) receptors. Intracellular calcium levels are mainly regulated by calcium-binding proteins and by metabotropic glutamate receptors (mGluRs) *via* ER calcium stores. Calcium once inside the cell is transported

across the plasma membrane or sequestered in intracellular organelles such as mitochondria and ER. Calcium enters the matrix of mitochondria through (1) a calcium uniporter or (2) mitochondrial-associated membrane (MAM) pores that allow communication with ER and mitochondria directly. Calcium efflux from mitochondria takes place by several mechanisms including mitochondrial sodium/calcium exchanger (NCX) and high conductance ion channels like mitochondrial permeability transition pore (mPTP). mPTP has two conductance states (1) a low conductance state that is reversible and involved in calcium handling and (2) a high conductance state that is irreversible and leads to mitochondrial swelling and leakage of molecules like cytochrome c that triggers apoptosis.

Interestingly, recent work shows that substantia nigra pars compacta dopaminergic neurons are autonomously active and generate broad, slow action potentials regularly in the absence of synaptic input (Grace and Bunney, 1983). L-type Cav 1.3 calcium channels are used for this pacemaking property (Surmeier, 2007) which is believed to be essential for the maintenance of ambient dopamine concentrations in regions innervated by these neurons, in particular striatum (Romo and Schultz, 1990). While most other neurons depend exclusively on monovalent cation channels for pacemaking, substantia nigra pars compacta dopaminergic neurons also involve ion channels that allow extracellular calcium into the cytoplasm (Ping and Shepard, 1996; Bonci et al., 1998; Puopolo et al., 2007), causing increased intracellular calcium levels (Wilson and Callaway, 2000; Chan et al., 2007). It is reported that calcium entry through L-type channels increases dopamine metabolism in substantia nigra pars compacta dopaminergic neurons thereby shifting cytosolic dopamine concentration to a toxic range with L-DOPA loading (Mosharov et al., 2009). Recent work shows that maintained opening of L-type calcium channels in substantia nigra pars compacta dopaminergic neurons produces a basal mitochondrial oxidant stress accelerated aging and ultimate cell death (Surmeier et al., 2011). Altogether these studies suggest that calcium signaling might contribute to mitochondria oxidant stress in the pathogenesis of PD.

5. Environmental toxins, mitochondrial dysfunction and oxidative stress (summarized in Table 1)

5.1. MPTP

In the late 1970s, a group of heroin users in the USA developed acute and irreversible parkinsonism after using illicit drugs intravenously. It was later discovered that this was due the neurotoxic effects of the compound MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a by-product in the synthesis of a meperidine analog (Davis et al., 1979; Langston et al., 1983). One of these patients who died 2 years after the onset of parkinsonian symptoms showed degeneration of dopaminergic neurons in the substantia nigra pars compacta without Lewy bodies (Davis et al., 1979). Similar observations were noticed in patients who died 3–16 years after MPTP toxicity (Langston et al., 1999) confirming that MPTP exposure led to the development of parkinsonism. The remarkable resemblance of parkinsonian symptoms after MPTP intoxication to those observed in sporadic PD led to investigating the effects of this neurotoxin in various animal species. MPTP administration to non-human primates reproduced most but not all of the clinical and pathological symptoms (Moratalla et al., 1992; Forno et al., 1993; Hantraye et al., 1993; Varastet et al., 1994), and in mice at least degeneration of dopaminergic neurons was observed (Heikkila et al., 1984). However, rats were resistant and none of the symptoms could be reproduced (Chiueh et al., 1984). Concurrent to the neuropathological studies, the molecular mechanism of MPTP was also studied intensively. It was shown that MPTP actively crosses the blood–brain barrier due to its lipophilicity and is oxidized to a toxic molecule, MPP+ (1-methyl-4-phenylpyridinium) by monoamine oxidase in the glial cells (Langston et al., 1984; Markey et al., 1984). MPP+ is taken into the dopaminergic neurons by the dopamine transporter (DAT) and accumulates in the mitochondria. MPP+ inhibits the mitochondrial complex I (Nicklas et al., 1985; Ramsay et al., 1986) in the ETC and thereby disrupts the flow of electrons resulting in decreased ATP production and increased generation of ROS (Hasegawa et al., 1990; Chan et al., 1991; Hantraye et al., 1996; Przedborski et al., 1996; Fabre et al., 1999; Pennathur et al., 1999). The events downstream of complex I inhibition leading to neuronal cell death are still incompletely understood. Nevertheless, various studies showed the involvement of pro-apoptotic pathways which include caspases, p53, Bcl-2 family members and JNK (Przedborski et al., 1992; Hartmann et al., 2000; Hartmann et al., 2001a; Hartmann et al., 2001b; Beal, 2003; Dauer and Przedborski, 2003; Hald and Lotharius, 2005; Perier et al., 2005; Perier et al., 2007). In addition to complex I inhibition, MPTP has also been reported to inhibit mitochondrial complexes III and IV *in vitro*, adding to the cellular oxidative stress (Desai et al., 1996). Moreover, MPP+ treatment decreased mitochondrial activity and mitochondrial gene expressions *in vitro* and a similar reduction in expression of mitochondrial genes and tyrosine hydroxylase was observed after MPTP

Table 1
Summary of mitochondrial dysfunction caused by environmental toxins used to model PD.

Toxin	Mitochondrial dysfunction	Reference
MPP+/MPTP	1. Inhibits the mitochondrial complex i	1. (Nicklas et al., 1985; Ramsay et al., 1986)
	2. Decreases ATP production and increases generation of ROS	2. (Hasegawa et al., 1990; Chan et al., 1991; Hantraye et al., 1996; Przedborski et al., 1996; Fabre et al., 1999; Pennathur et al., 1999)
	3. Inhibits mitochondrial complexes III and IV	3. (Desai et al., 1996)
	4. Decreases mitochondrial activity and mitochondrial gene expression	4. (Piao et al., 2012)
	5. Alters mitochondrial proteins such as chaperones, metabolic enzymes, oxidative phosphorylation-related proteins, inner mitochondrial protein (mitofilin) and outer mitochondrial protein (VDAC1)	5. (Burte et al., 2011)
	6. Alters proteins associated with mitochondrial dysfunction, dopamine signaling, ubiquitin system, calcium signaling, oxidative stress response and apoptosis	6. (Zhang et al., 2010)
	7. Causes DNA damage	7. (Hoang et al., 2009)
Rotenone	Reduces complex I activity	(Betarbet et al., 2000)
Paraquat	1. Accumulates in mitochondria	1. (Cocheme and Murphy, 2008)
	2. Acts as a potent redox cycler which converts free radicals that interact with molecular oxygen to superoxide and other ROS	2. (Jones and Vale, 2000; Yumino et al., 2002) (Thiruchelvam et al., 2005) (Mollace et al., 2003)
Maneb	Inhibits mitochondrial complex III	(Zhang et al., 2003)

administration *in vivo* (Piao et al., 2012). In cells exposed to subtoxic concentrations of MPTP, alterations in mitochondrial proteins such as chaperones, metabolic enzymes, oxidative phosphorylation-related proteins, inner mitochondrial protein (mitofilin) and outer mitochondrial protein (VDAC1) were identified (Burte et al., 2011). Furthermore, another study looked at the overall proteome changes in different regions of mouse brain after MPTP administration and reported a total of 518 proteins showing alterations across all brain regions. Among them, 270 proteins exhibited specific changes only in the striatum and/or the brain region containing substantia nigra indicating that these proteins are associated with the nigrostriatal pathway. A majority of these altered proteins are associated with mitochondrial dysfunction, dopamine signaling, ubiquitin system, calcium signaling, oxidative stress response and apoptosis (Zhang et al., 2010). Evidence that MPTP causes DNA damage *in vivo* is compatible with these findings (Hoang et al., 2009). Collectively, these findings suggest mechanisms by which MPTP can cause mitochondrial impairment leading to neurotoxicity and loss of nigrostriatal dopaminergic neurons. Whether or not these mechanisms also contribute to the pathogenic process of PD remains a matter of debate. Indeed, a number of compounds have been shown to effectively protect dopaminergic neurons from MPTP toxicity *in vivo* and *in vitro*, yet none has yet been shown to be neuroprotective in PD patients in clinical studies (Muller et al., 2003; Anonymous, 2007).

5.2. Rotenone

Rotenone is a naturally occurring organic compound that has been used as a pesticide for several decades to control unwanted fish populations, in nurseries, and in organic farming. Rotenone is a specific mitochondrial complex I inhibitor which can act systemically due to its high lipophilicity enabling it to readily cross the blood–brain barrier and biological membranes independent of any receptor or transporter. Rotenone inhibits mitochondrial complex I by binding to the acceptor end of the enzyme causing an increase in the reduction state of the complex and thus leading to the leakage of electrons that combine with oxygen to form superoxide (Nicholls, 2008). Complex I inhibition by rotenone leads to initiation of several deleterious effects which include generation of ROS resulting in oxidative stress which is attenuated by antioxidants (Sherer et al., 2003), NMDA receptor-mediated bioenergetic crisis due to reduction in ATP levels and apoptotic or necrotic cell death due to depolarization caused by aberrant opening of the mPTP. Interestingly, recent reports have implicated rotenone in an increased risk of developing PD in humans (Tanner et al., 2011). In rats, chronic intravenous administration of rotenone caused selective nigral dopaminergic neuron loss and a significant reduction in complex I activity (Betarbet et al., 2000). In this study, the rotenone pathology closely resembled sporadic PD in that the neurodegeneration began in the nerve terminals of striatum and progressed to the cell bodies in the substantia nigra. Rotenone toxicity involved oxidative damage to proteins, showed PD-related motor deficits (Fleming et al., 2004) and Lewy body-like inclusions that immunostained for α-synuclein and ubiquitin were observed in the substantia nigra and striatum (Betarbet et al., 2000; Sherer et al., 2003). However, the observations of these studies were limited due to the inconsistency in development of these deficits in rats after rotenone administration, and others confirmed a high rate of variability in rotenone toxicity in rats (Zhu et al., 2004). Altogether, these findings show that generation of ROS and related oxidative stress are one of the key mechanisms involved in rotenone-mediated toxicity and further implicate their role in nigrostriatal dopamine vulnerability.

5.3. Paraquat and Maneb

Paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride) is a commonly used herbicide that is structurally very similar to MPTP and has long been linked to human PD (Shults et al., 1998; Couzin, 2007; Tanner et al., 2011; Wu et al., 2012). Paraquat has a long half-life following systemic administration and causes lipid peroxidation in mouse brain (Prasad et al., 2007). Administration of paraquat caused selective and dose-dependant loss of dopaminergic neurons in the substantia nigra, associated with mild reduction in dopaminergic nerve terminals in the striatum and modest decrease in motor behavior (Brooks et al., 1999; McCormack et al., 2002). Chronic administration of paraquat showed progressive increase in dopaminergic neuron loss and reduction in dopamine levels (Ossowska et al., 2005). Though paraquat is a weak inhibitor of mitochondrial complex I and causes production of ROS, its toxicity on dopaminergic neurons is exerted by a mechanism that is independent of complex I inhibition and DAT (Richardson et al., 2005). Rather, paraquat accumulates in mitochondria (Cocheme and Murphy, 2008) and acts as a potent redox cycler which converts free radicals that interact with molecular oxygen to superoxide and other ROS (Jones and Vale, 2000; Yumino et al., 2002). The redox cycling of paraquat is further confirmed by studies showing that overexpression of SOD (Thiruchelvam et al., 2005) or compounds that mimic SOD (Mollace et al., 2003) show protection against the adverse effects of paraquat. Paraquat increases the generation of ROS and also reduces antioxidant enzyme expression *in vitro* (Yang and Tiffany-Castiglioni, 2005). On the other hand, a reduction in antioxidant enzyme levels leads to increased sensitivity to paraquat (Van Remmen et al., 2004). Another mechanism by which paraquat increases ROS generation in the mitochondria is through its interactions with glutamate which causes excitotoxicity through Ca^{2+} efflux by depolarization of NMDA receptor channels and activation of non-NMDA receptor channels. This process generates NOS (nitric oxide synthase) and the resulting nitric oxide enters the dopaminergic neurons leading to further mitochondrial dysfunction (Shimizu et al., 2003). Collectively, these studies suggest that paraquat can induce oxidative stress *in vitro* and *in vivo* by multiple mechanisms such as ROS generation by inhibition of mitochondrial complex I and redox cycling, and NOS production by interactions with glutamate in mitochondria.

Maneb is a manganese-containing ethylene-bis-dithiocarbamate compound that is used as a fungicide to treat numerous plant diseases. Maneb has been related to development of parkinsonism in humans (Meco et al., 1994) and to an increased risk of developing PD in individuals also exposed to paraquat (Costello et al., 2009; Ritz et al., 2009). Administration of maneb to mouse models induced deficits in motor behavior (Morato et al., 1989) but most studies used a combination of paraquat and maneb to induce nigrostriatal cell death (Thiruchelvam et al., 2002; Saint-Pierre et al., 2006; Kachroo et al., 2010). Literature on the mechanisms of Maneb toxicity is very limited however it is known that maneb increases the toxic effects of paraquat in mice (Barlow et al., 2005; Roede et al., 2011). Studies show that maneb inhibits proteosome activity *in vitro* (Zhou et al., 2004; Wang et al., 2006). In addition, maneb has also been shown to inhibit mitochondrial complex III of the ETC resulting in ROS production in isolated mitochondria of rat brain (Zhang et al., 2003) and impaired mitochondrial function in primary mesencephalic neuronal culture (Domico et al., 2006). These observations indicate that maneb could potentiate mitochondrial ROS production by causing mitochondrial dysfunction and inhibiting mitochondrial complex III. These effects may contribute to its ability to increase PD risk in humans (Ritz et al., 2009).

Table 2
Summary of mitochondrial dysfunction in familial PD.

Gene	Mitochondrial dysfunction	Reference
α-Synuclein (*PARK1*, *SNCA*)	1. Causes accumulation of α-synuclein in mitochondria in specific regions	1. (Li et al., 2007; Nakamura et al., 2008; Shavali et al., 2008; Zhang et al., 2008)
(A53T or overexpression)	2. Mutant A53T human α-synuclein gene in mice causes mtDNA damage and respiratory complex IV impairment	2. (Martin et al., 2006)
	3. Overexpression of wild-type human α-synuclein increases mitochondrial pathology in nigrostriatal dopaminergic neurons when exposed to low doses of MPTP	3. (Song et al., 2004)
	4. Mutant A53T human α-synuclein gene in cell lines reduces mitochondrial complex I activity	4. (Butler et al., 2012)
	5. Mutant A53T human α-synuclein gene in mice increases sensitivity to mitochondrial toxins such as MPTP and paraquat	5. (Norris et al., 2007; Thomas and Beal, 2007)
	6. Overexpression of mutant A53T or wild-type human α-synuclein in cell lines causes mitochondrial association and leads to cytochrome c release, enhanced mitochondrial calcium and nitric oxide, and oxidative modification of mitochondrial components	6. (Parihar et al., 2008)
	7. Mitochondria of PD patients show accumulation of α-synuclein in substantia nigra and striatum, and decreased complex I activity	7. (Devi et al., 2008)
Parkin (*PARK2*)	1. Localizes in mitochondria where it binds to mitochondrial transcription factor (TFAM) to regulate mitochondrial transcription and replication	1. (Kuroda et al., 2006)
	2. Overexpression prevents ceramide-induced mitochondrial swelling and cytochrome c release	2. (Darios et al., 2003)
	3. Knockout mice have reduced mitochondrial complex I and IV activity	3. (Palacino et al., 2004)
	4. Homozygous parkin mutations in humans impair mitochondrial complex I and complex IV activities in leukocytes	4. (Muftuoglu et al., 2004)
	5. Mice lacking parkin gene increases sensitivity to mitochondrial toxin, rotenone	5. (Rosen et al., 2006)
	6. Critical for mitochondrial dynamics and autophagy	6. (Narendra et al., 2008; Sun et al., 2012)
	7. PINK1-parkin pathway promotes mitochondrial fission/fusion and controls mitochondrial dynamics	7. (Clark et al., 2006; Deng et al., 2008; Poole et al., 2008; Yang et al., 2008; Park et al., 2009; Yu et al., 2011)
PINK1 (*PARK6*)	1. Sub-localized in different regions including inner mitochondrial membrane, intermembrane space and outer mitochondrial membrane	1. (Silvestri et al., 2005; Gandhi et al., 2006; Pridgeon et al., 2007)
	2. PINK1 knockout mice and human dopaminergic neurons have abnormalities in mitochondrial morphology, reduced membrane potential, increased ROS generation and high sensitivity to apoptosis	2. (Wood-Kaczmar et al., 2008)
	3. PINK1 KO mice fibroblasts show low mitochondrial membrane potential, reduced cellular ATP levels and decline in mitochondrial respiratory activity	3. (Amo et al., 2011; Exner et al., 2007)
	4. PINK1-deficient mice showed reduction in complex I-IV activity	4. (Gautier et al., 2008)
	5. PINK1 knockout mice show region-dependent alterations in mitochondrial proteins related to energy metabolism and membrane potential	5. (Diedrich et al., 2011)
	6. Lack of PINK1 in *Drosophila* results in abnormal mitochondrial morphology, loss of nigrostriatal dopaminergic neurons, apoptotic muscle degeneration and enhances vulnerability to oxidative stress	6. (Clark et al., 2006; Park et al., 2006; Yang et al., 2006)
	7. Loss causes mitochondrial defects, respiratory chain abnormalities and ATP synthesis defects in human peripheral tissues	7. (Hoepken et al., 2007; Piccoli et al., 2008)
	8. Overexpression of PINK1 in restores normal mitochondrial morphology and inhibits ROS production	8. (Wang et al., 2011)
	9. Overexpression of wild-type PINK1 inhibits mitochondrial cytochrome c release and prevents neuronal apoptosis	9. (Petit et al., 2005; Wang et al., 2007)
	10. PINK1-parkin pathway promotes mitochondrial fission/fusion and controls mitochondrial dynamics	10. (Clark et al., 2006; Deng et al., 2008; Poole et al., 2008; Yang et al., 2008; Park et al., 2009; Yu et al., 2011)
DJ-1 (*PARK7*)	1. DJ-1 knockout mice display a reduction in mitochondrial transmembrane potential and an increase in mitochondrial permeability transition pore opening	1. (Giaime et al., 2012)
	2. DJ-1 null dopaminergic neurons show deficiency in mitochondrial complex I activity	2. (Heo et al., 2012; Kwon et al., 2011)
	3. DJ-1 mutation cause impaired mitochondrial respiration, enhanced intra-mitochondrial ROS, reduced mitochondrial membrane potential, altered mitochondrial morphology and importantly, accumulation of defective mitochondria	3. (Krebiehl et al., 2010)
	4. DJ-1 may support mitochondrial function during oxidative stress by interacting with several targets such as PINK1 and parkin	4. (Tang et al., 2006) (Moore et al., 2005)
	5. DJ-1 activates transcription of Mn-SOD gene, which encodes for the mitochondrial antioxidant enzyme	5. (Zhong and Xu, 2008)
LRRK2 (*PARK8*)	1. LRRK2 binds to outer mitochondrial membrane	1. (West et al., 2005; Biskup et al., 2006; Gloeckner et al., 2006)
	2. LRRK2 G2019S mutation causes defects in mitochondrial morphology and dynamics	2. (Niu et al., 2012)
	3. PD patients carrying LRRK2 G2019S mutation show a decrease in mitochondrial membrane potential and low total intracellular ATP levels in addition to mitochondrial elongation and interconnectivity	3. (Mortiboys et al., 2010)

6. Mitochondrial dysfunction and oxidative stress in monogenic PD (summarized in Table 2)

6.1. α-Synuclein

Three different missense mutations (A530T, A30P and E46K) and duplication or triplication of the α-synuclein gene (*PARK1*, *SNCA*) are associated with autosomal dominant PD (Polymeropoulos et al., 1997; Kruger et al., 1998; Singleton et al., 2003; Zarranz et al., 2004). α-Synuclein is a 140-amino acid presynaptic protein expressed in the central nervous system, which is prone to fibrillar aggregation due to its hydrophobic non-amyloid beta component domain. Fibrillar forms of α-synuclein are a major component of the Lewy bodies, hence providing a link between sporadic and familial PD and implicating α-synuclein in both forms of the disease. Indeed, this link is further supported by genome-wide association and epidemiological studies (Spillantini and Goedert, 2000; Edwards et al., 2010; Gatto et al., 2010; Huang et al., 2011; Ritz et al., 2012; Silva et al., 2013; Wang et al., 2012). α-Synuclein fibrils are believed to play a pivotal role in PD pathogenesis due to their toxicity, which may be caused by the intermediate oligomeric forms of α-synuclein rather than by their final aggregates (Lansbury and Lashuel, 2006; Uversky, 2007; Cookson and van der Brug, 2008; Winklhofer et al., 2008). Familial mutations and overexpression of α-synuclein *in vitro* increase the formation of α-synuclein protofibrils (Conway et al., 1998; Conway et al., 2000; Fredenburg et al., 2007). Administration of mitochondrial toxins to rodents and cell cultures leads to the formation of α-synuclein aggregates and inclusions (Betarbet et al., 2000; Fornai et al., 2005). Similarly, inhibition of ubiquitin proteosomal pathway *in vitro* causes accumulation of unfolded proteins leading to mitochondrial dysfunction and neuronal cell death (Tanaka et al., 2001). The role of protein aggregation and mitochondrial dysfunction in PD pathogenesis has been well documented and recent studies show that these two processes are interlinked and complementary to each other in the pathogenesis. Interestingly, a study investigating mitochondrial α-synuclein in human brain found significant accumulation of α-synuclein in the substantia nigra and striatum of PD patients (Devi et al., 2008). A fraction of cytosolic α-synuclein has been found within the mitochondria in specific regions (Li et al., 2007; Nakamura et al., 2008; Shavali et al., 2008; Zhang et al., 2008). In mice carrying a mutant A53T human α-synuclein gene, mitochondrial accumulation of α-synuclein was observed in tandem with mitochondrial degeneration associated with mtDNA damage and respiratory complex IV impairment leading to neurodegeneration (Martin et al., 2006). Our recent unpublished studies in Thy1-aSyn mice overexpressing wild-type α-synuclein (Chesselet et al., 2012) showed accumulation of α-synuclein in mitochondria enriched fractions of brain tissue from ventral mesencephalon consisting of substantia nigra, striatum and mid-cortex. In addition, reduced mitochondrial complex I activity and enhanced lipid peroxidation was observed specifically in substantia nigra tissue compared to striatum and mid-cortex. The same mice exhibit an increase in mitochondrial pathology in nigrostriatal dopaminergic neurons when exposed to low doses of MPTP (Song et al., 2004).

In another recent study decreased expression of mitochondrial chaperone protein tumor necrosis factor receptor associated protein-1 (TRAP1) in *Drosophila* with mutant A53T human α-synuclein expression caused an increase in age-dependent loss of dopaminergic neurons and decrease in dopamine levels, loss of climbing ability and sensitivity to oxidative stress. Overexpression of human TRAP1 rescued this phenotype. Knockdown of TRAP1 in human neuronal cell lines enhanced A53T α-synuclein-induced sensitivity to oxidative stress and, in HEK293 cells, A53T α-synuclein expression reduced mitochondrial complex I activity suggesting a link between α-synuclein and mitochondrial dysfunction (Butler et al., 2012). In transgenic mice overexpressing A30P α-synuclein more than two-fold, selective increase in carbonyl levels of the metabolic proteins carbonic anhydrase 2, alpha-enolase and lactate dehydrogenase 2 were observed (Poon et al., 2005). In addition, expression of A53T α-synuclein in SH-SY5Y cell lines caused increased sensitivity to MPP+ and 6-hydroxydopamine which was protected by antioxidants edaravone and ( )-epigallocatechin-3-O-gallate respectively (Ma et al., 2010). Similarly, in mouse models overexpressing human α-synuclein the sensitivity of the mice to mitochondrial toxins such as MPTP and paraquat was enhanced (Norris et al., 2007; Thomas and Beal, 2007). On the other hand, mice lacking α-synuclein were resistant to neurotoxicity induced by the toxins MPTP, malonate and 3-nitropropionic acid (Nicklas et al., 1985; Klivenyi et al., 2006; Elm, 2012).

Interaction of α-synuclein with mitochondria *in vitro* and in isolated mitochondria leads to cytochrome c release, enhanced mitochondrial calcium and nitric oxide, and oxidative modification of mitochondrial components (Parihar et al., 2008). Another study shows that the N-terminal 32 amino acids of human α-synuclein contain cryptic targeting signal that is essential for mitochondrial targeting of α-synuclein. Mitochondria imported α-synuclein is primarily associated with the inner membrane and the accumulation of wild-type α-synuclein in dopaminergic neurons leads to a reduction in mitochondrial complex I activity and elevated ROS production. Moreover, overexpression of A53T α-synuclein accelerated this effect (Devi et al., 2008). In addition, translocation of α-synuclein to the surface of mitochondria was increased by cytosolic acidification. This translocation takes place rapidly under artificially induced low pH conditions and as a result of pH changes during the process of oxidative or metabolic stress, thus indicating a direct role for α-synuclein in mitochondrial physiology, especially under pathological conditions (Cole et al., 2008). These findings suggest that protein aggregation and mitochondrial dysfunction act jointly with complementary mechanisms with α-synuclein acting as a modulator of oxidative stress leading to neurodegeneration. Additionally, these results also highlight that both the genetic and biochemical alterations of α-synuclein lead to its increased association with mitochondria and consecutively affect mitochondrial function in the dopaminergic neurons.

6.2. Parkin

Mutations in parkin (*PARK2*) gene were reported to cause autosomal-recessive juvenile parkinsonism (Kitada et al., 1998; Abbas et al., 1999). The parkin gene encodes a 465 amino acid protein which possesses E3 ubiquitin ligase activity and is involved in the proteasome-mediated degradation of numerous proteins *in vitro* (Shimura et al., 2000). Studies show that some of these proteins are deposited in the brains of patients with parkin mutations (Murakami et al., 2004; Periquet et al., 2005). Parkin mediates the polyubiquitination reaction that clears proteins susceptible to aggregation by the process of proteasomal degradation. The loss of E3 ligase activity causes accumulation of toxic protein aggregates leading to autosomal-recessive juvenile parkinsonism (Dawson, 2006). Additionally, mounting evidences show that parkin can also induce proteasome-independent ubiquitylation (Doss-Pepe et al., 2005; Lim et al., 2005; Fallon et al., 2006; Hampe et al., 2006; Henn et al., 2007) and such modifications are reported to mediate transcriptional regulation, protein trafficking and neuroprotective signaling (Fallon et al., 2006; Mukhopadhyay and Riezman, 2007). Several recent studies show that parkin is localized in the mitochondria and its functions are associated with mitochondria as well. In proliferating SH-SY5Y cells, parkin was found exclusively inside mitochondria where it

binds to mitochondrial transcription factor (TFAM) to regulate mitochondrial transcription and replication (Kuroda et al., 2006). Moreover, parkin overexpression in differentiated PC12 cell cultures prevented ceramide-induced mitochondrial swelling and cytochrome c release (Darios et al., 2003). Overexpression of parkin in mice attenuated dopaminergic cell loss induced by MPTP through protection of mitochondria and reduction of α-synuclein (Bian et al., 2012). In contrast, knockdown of parkin gene in *Drosophila* and animal models exhibit drastic mitochondrial deficits. *Drosophila* lacking parkin gene exhibit mitochondria associated apoptotic muscle degeneration and high vulnerability to oxidative stress (Greene et al., 2003; Pesah et al., 2004). *Drosophila* deficient in parkin also showed reduced lifespan that was reversed by chelation of redox active metals, antioxidants and overexpression of superoxide dismutase 1 (Saini et al., 2010). Parkin knockout mice displayed decreased amounts of several proteins involved in mitochondrial function or oxidative stress in addition to an increase in protein oxidation and lipid peroxidation. These mice also exhibited reduction in respiratory complex I and IV subunits consistent with impairment of mitochondrial respiratory capacity in striatum suggesting mitochondrial dysfunction and oxidative damage (Palacino et al., 2004). In parallel, in humans with homozygous parkin mutations, mitochondrial complex I and complex IV activities in leukocytes are impaired (Muftuoglu et al., 2004). Moreover, mice lacking parkin gene show increased sensitivity to mitochondrial toxins such as rotenone (Rosen et al., 2006). Chronic exposure of rats to rotenone induced behavioral impairments that co-related with histopathological changes and tyrosine hydroxylase signaling, decrease in cytoprotective proteins including parkin, DJ-1 and Hsp70, and increase in caspase 9, caspase 3 and ubiquitin (Sonia Angeline et al., 2012). In addition, numerous studies have also established that parkin protects cells against several mitochondrial toxins in various cellular and animal models (Darios et al., 2003; Hyun et al., 2005; Casarejos et al., 2006; Rosen et al., 2006; Vercammen et al., 2006; Henn et al., 2007; Manfredsson et al., 2007; Paterna et al., 2007). A major finding was the demonstration that parkin is recruited to defective mitochondria and is critical for mitochondrial dynamics and autophagy (also see Section 5.3) (Narendra et al., 2008; Sun et al., 2012). Altogether these results indicate that parkin in addition to other functions such as proteasome-dependent and independent ubiquitylation is also vital for mitochondrial respiration and function. On the other hand, it is also reported that a parkin-deficient mice model on a B6;129S4 genetic background did not show robust signs of parkinsonism including nigrostriatal, cognitive or noradrenergic dysfunction questioning the credibility of the parkin null mice as a model for PD (Perez and Palmiter, 2005).

6.3. PINK1

PINK1 (PTEN-induced putative kinase; *PARK6*) gene mutations are the second most common cause of autosomal recessive, early onset PD after parkin mutations (Valente et al., 2004). PINK1 is a 581 amino acid protein with a highly conserved serine/threonine kinase domain and an N-terminal mitochondrial targeting sequence (Valente et al., 2004, Silvestri et al., 2005). In mitochondria, it has been reported that PINK1 is sub-localized in different regions including inner mitochondrial membrane (Silvestri et al., 2005; Gandhi et al., 2006; Pridgeon et al., 2007), intermembrane space (Silvestri et al., 2005; Pridgeon et al., 2007) and outer mitochondrial membrane (Gandhi et al., 2006). PINK1 knockdown in human dopaminergic neurons and loss of Pink 1 in primary neurons derived from PINK1 knockout mice result in widespread mitochondrial dysfunction including abnormalities in mitochondrial morphology, reduced membrane potential, increased ROS generation and high sensitivity to apoptosis (Wood-Kaczmar et al., 2008). In substantia nigra dopaminergic neurons prepared from PINK1 KO mice brains, fragmented mitochondria were observed in addition to increased basal mitochondria superoxide and hydrogen peroxide-induced ROS generation. Overexpression of PINK1 restored normal mitochondrial morphology and inhibited ROS production indicating the importance of PINK1 in maintaining mitochondrial morphology and protecting neurons from ROS (Wang et al., 2011). In addition, embryonic fibroblasts derived from PINK1 KO mice showed low mitochondrial membrane potential, decreased cellular ATP levels and decline in mitochondrial respiratory activity (Amo et al., 2011). Primary fibroblast cell lines established from PD patients with PINK1 mutation showed a reduced capacity to effectively remove ROS due to decreased expression of antioxidant enzymes including glutathione peroxidase-1, MnSOD, peroxiredoxin-3 and thioredoxin-2 (Maj et al., 2010). PINK1 knockdown in human cell lines displayed defects in mitochondrial morphology and low mitochondrial membrane potential, and these deficits were reversed by wild-type PINK1 but not PD-linked PINK1 mutants (Exner et al., 2007). An increased sensitivity to MPP+ toxicity in cortical neurons was observed in the lack of PINK1 function and this effect was attenuated by overexpression of wild-type PINK1 (Haque et al., 2008). In *Drosophila*, studies show that lack of PINK1 resulted in abnormal mitochondrial morphology, loss of nigrostriatal dopaminergic neurons, apoptotic muscle degeneration and enhanced vulnerability to oxidative stress (Clark et al., 2006; Park et al., 2006; Yang et al., 2006). Studies on mice with PINK1 deficiency showed similar mitochondrial deficits including reduction in complex I-IV activity in the striatum and impairment in mitochondrial respiration. PINK1 loss of function also displayed increased exacerbation to mitochondrial respiration when exposed to oxidant hydrogen peroxide and mild heat shock (Gautier et al., 2008). In addition, these mice showed a decline in dopamine release and synaptic plasticity in striatum which is critical for normal physiological function (Kitada et al., 2007). In contrast, *in vitro* studies on different cell lines show that overexpression of wild-type PINK1 inhibited mitochondrial cytochrome c release and prevented neuronal apoptosis (Petit et al., 2005; Wang et al., 2007). In mouse midbrain dopaminergic neurons, overexpression of PINK1 using adenoviral vectors prevented against MPTP-induced neuronal toxicity (Haque et al., 2008). Moreover, it has been shown that dopamine-induced toxicity in PINK1 knockout mice is mediated by mPTP opening which is dependent on ROS production and calcium signaling. Dopamine-induced cell death could be prevented by blocking ROS production, supply of respiratory chain substrates and modification of calcium signaling (Gandhi et al., 2012). PINK1 knockout mice showed region-dependent alterations in mitochondrial proteins related to energy metabolism and membrane potential in midbrain, striatum and cerebral cortex. In particular midbrain region, containing the substantia nigra, showed high turnover of defective mitochondria, whereas striatum and cortex compensated for mitophagy non-function by alternative mechanisms. Cerebral cortex tissue also showed low levels of protein oxidation in both wild-type and PINK1 KO mice indicating low ROS production or better protective mechanism in this brain region (Diedrich et al., 2011). Interestingly, in humans with PINK1 mutation mitochondrial defects and respiratory chain abnormalities were observed in the peripheral tissues (Hoepken et al., 2007). In another study, a PD patient with a mutant PINK1 gene showed mitochondrial respiratory abnormalities and ATP synthesis defects in fibroblasts (Piccoli et al., 2008). Overall the observations show that PINK1 mutation affects mitochondrial function, integrity and associated increase in oxidative stress.

Mitochondria are dynamic organelles that are regulated by fusion and fission. These dynamic events are essential for cellular

functions such as energy metabolism, quality control mechanisms and regulation of cell death (Benard and Karbowski, 2009; Soubannier and McBride, 2009). Both mitochondrial fusion and fission contribute to mitochondrial quality control, and any dysfunction in mitochondrial repair will affect normal functions such as mtDNA maintenance (Hoppins and Nunnari, 2009), mitochondrial transport (Ishihara et al., 2009) and mitophagy (Twig et al., 2008). The mitochondrial fusion in outer mitochondrial membrane is regulated by mitofusins (MFN1 and MFN2) whereas optic atrophy protein 1 (OPA1) is required for inner mitochondrial membrane fusion (Zorzano et al., 2010). Mitochondrial fission is controlled by dynamin-related protein 1 (DRP1) (Reddy et al., 2011). Studies show that neurons are particularly vulnerable to mitochondrial fusion and fission (Knott and Bossy-Wetzel, 2008; Mattson et al., 2008; Chen and Chan, 2009; Schon and Przedborski, 2011). PINK1 promotes the recruitment of parkin into mitochondria which triggers mitophagy. This process depolarizes the inner mitochondrial membrane and alerts the cell of a damaged organelle, which will eventually be removed (Narendra et al., 2010). In *Drosophila*, parkin and PINK1 promote mitochondrial fission and/or inhibit fusion by negatively regulating MFN and OPA1 functions, and/or positively regulating DRP1 function (Clark et al., 2006; Deng et al., 2008). In rat hippocampal neurons, overexpression of parkin or PINK1 showed increased mitochondrial number, smaller size and reduced mitochondrial occupancy of neuronal processes indicating the mitochondrial fission/fusion dynamics is tipped toward fission. In converse, PINK1 inactivation resulted in elongated mitochondria suggesting the balance of the mitochondrial dynamics is tipped towards fusion. Moreover, overexpression of the fission protein (DRP1) or knockdown of the fusion protein OPA1 suppressed PINK1-RNAi induced mitochondrial morphological defect, and overexpression of Parkin or PINK1 suppressed elongation of mitochondria caused by DRP1 RNAi. Similarly, PINK1/Parkin influenced mitochondrial dynamics in rat midbrain dopaminergic neurons (Yu et al., 2011). More studies in *Drosophila* and mammalian cells also underline the role of PINK1-Parkin pathway in controlling mitochondrial dynamics (Poole et al., 2008; Yang et al., 2008; Park et al., 2009). Interestingly, some studies also indicate that mitochondrial fusion proteins play an important neuroprotective role in oxidative stress and mitochondrial stress models (Meuer et al., 2007; Gomez-Lazaro et al., 2008).

6.4. DJ-1

Mutations in DJ-1 (*PARK7*) gene cause rare cases of autosomal recessive, early onset parkinsonism (Bonifati et al., 2003). DJ-1 is a multifunctional 189 amino acid protein with antioxidant and transcription modulation properties. It is believed that under basal conditions DJ-1 is localized in the cytosol and to a lesser extent in nucleus and mitochondria (Zhang et al., 2005). However, in oxidative stress conditions DJ-1 translocates to mitochondria, where it is found in the matrix and intermembrane space, and later to the nucleus. This translocation of DJ-1 into the mitochondria and nucleus is associated with its ability to provide neuroprotection (Canet-Aviles et al., 2004; Ashley et al., 2009; Junn et al., 2009). The translocation of DJ-1 is facilitated by the oxidation of cysteine 106 to cysteine-sulfinic acid which is vital for DJ-1 function in the mitochondria (Canet-Aviles et al., 2004; Blackinton et al., 2009). *In vitro* silencing of DJ-1 using siRNA in neuronal cells showed increased cell death induced by oxidative stress, ER stress and inhibition of proteasome (Yokota et al., 2003; Taira et al., 2004). Primary mouse embryonic fibroblasts from DJ-1 KO mice displayed a reduction in mitochondrial transmembrane potential and an increase in mPTP opening both of which were restored by antioxidant treatment. In addition, an increase in production of ROS was observed in these cell lines but the antioxidant enzyme levels remained constant (Giaime et al., 2012). DJ-1 null dopaminergic neurons showed deficiency in mitochondrial complex I activity as a result of defect in the assembly of complex I leading to defective supercomplex formation. These defects were reversed by DJ-1 overexpression indicating the specific role of DJ-1 in mitochondrial dysfunction (Heo et al., 2012). Another study also showed that DJ-1 null cells from mouse embryos exhibit reduced mitochondrial complex I activity that was rescued partially by overexpression of DJ-1 (Kwon et al., 2011). *In vitro* cell models from DJ-1 KO mice and human carriers of E64D mutation of the DJ-1 gene displayed impaired mitochondrial respiration, enhanced intra-mitochondrial ROS, reduced mitochondrial membrane potential, altered mitochondrial morphology and importantly, accumulation of defective mitochondria (Krebiehl et al., 2010). Additionally, cell lines, cultured neurons, mouse brain and lymphoblast cells derived from DJ-1-deficient patients display abnormal mitochondrial morphology. Mitochondria from DJ-1-deficient mice produce more ROS and scavengers of ROS rescued the phenotype indicating the critical role played by ROS in this model (Irrcher et al., 2010). Mice lacking DJ-1 gene showed nigrostriatal dopaminergic neuronal loss, elevated striatal dopamine levels, enhanced dopamine re-uptake and hypokinesia (Chen et al., 2005; Goldberg et al., 2005). In addition, mice deficient for DJ-1 showed further increased in dopaminergic neuron loss after MPTP administration (Kim et al., 2005). Similarly, administration of paraquat to DJ-1 knockout mice caused dopaminergic system defects and proteasome impairment (Yang et al., 2007). Conversely, overexpression of DJ-1 using viral vectors into the mice nigrostriatal system prevented MPTP-induced dopaminergic neuron loss. In addition, DJ-1 may support mitochondrial function during oxidative stress by interacting with several targets such as PINK1 (Tang et al., 2006) and parkin (Moore et al., 2005). Furthermore, under increased oxidative stress DJ-1 may also be involved in the activation of transcription of Mn-SOD gene, which encodes for the mitochondrial antioxidant enzyme (Zhong and Xu, 2008). Altogether, these findings suggest that DJ-1 may prevent protein misfolding and aggregation under oxidative stress conditions.

6.5. LRRK2

LRRK2 (Leucine-rich repeat kinase 2; *PARK8*) mutations are known to cause autosomal-dominant PD. These mutations are associated with a majority of familial PD cases and are also linked to sporadic late-onset PD (Paisan-Ruiz et al., 2004; Zimprich et al., 2004; Klein and Schlossmacher, 2006). The LRRK2 gene encodes a 2527 amino acid protein which is a serine/threonine kinase containing a conserved mitogen-activated protein kinase kinase kinase (MAPKKK), a Roc domain with Ras/GTPase, a WD40-repeat domain and leucine-rich repeats (Mata et al., 2006; Biskup and West, 2009; Gandhi et al., 2009). Several LRRK2 mutations lead to an increase in LRRK2 kinase activity that was responsible for the neurotoxicity *in vitro*, suggesting a toxic gain of function mechanism (Gloeckner et al., 2006; Greggio et al., 2006; Smith et al., 2006). Overexpression of LRRK2 mutated proteins *in vitro* leads to apoptotic neuronal cell death that was blocked by caspase inhibitors and required Apaf1 indicating that LRRK2 mutations cause mitochondrial dysfunction (Iaccarino et al., 2007). In cortical neurons the LRRK2 G2019S mutation can cause defects in mitochondrial morphology and dynamics. Expression of LRRK2 also increases production of ROS in cells. In addition, endogenous LRRK2 interacts with Dynamin like protein 1 (DLP1) in neurons and expression of LRRK2 leads to translocation of DLP1 from the cytosol into the mitochondria suggesting a functional role for LRRK2 (Niu et al., 2012). Skin biopsies from PD patients carrying LRRK2 G2019S

mutation showed a decrease in mitochondrial membrane potential and low total intracellular ATP levels as a result of mitochondrial dysfunction. Additionally, mitochondrial elongation and interconnectivity were also elevated in LRRK2 G2019S mutant patients indicating that LRRK2 mutations affect mitochondrial function and morphology (Mortiboys et al., 2010). LRRK2 was shown to bind to outer mitochondrial membrane, localized in rat mitochondria by immunohistochemistry and 10% of overexpressed LRRK2 was found to be associated with the mitochondrial fraction (West et al., 2005; Biskup et al., 2006; Gloeckner et al., 2006). Although knowledge about the physiological function of LRRK2 protein is limited, these studies indicate that the mechanism of LRRK2 mutation toxicity could be associated with mitochondria.

7. Perspective

Numerous studies conducted using various genetic and toxin models of PD have contributed to a better understanding of the disease pathogenesis. As detailed in this review, many of these studies point to mitochondrial dysfunction as a common occurrence in both sporadic and monogenic PD, and suggest that it may play a major role in the pathophysiology of the disease. The findings suggest that complex I deficiency and related oxidative stress in addition to mitochondrial DNA mutations are associated with PD pathogenesis. The factors that potentially cause mitochondrial damage in sporadic PD are still unknown. Exposure to environmental factors such as pesticides may cause mitochondrial dysfunction that result in PD in both humans and animal models of PD. In addition, familial mutations in genes can also lead to mitochondrial dysfunction that leads to PD. In PD patients and animal models, the general biochemical abnormalities that are observed in mitochondria include complex I impairment, reduced ATP synthesis, increased ROS production, mitochondrial DNA mutations and defective mitochondrial repair pathways. However, the sequence of events leading to the mitochondrial impairment and degeneration of neurons remains elusive. The studies also indicate that dopaminergic neurons in the substantia nigra are highly vulnerable under stress conditions compared to other neuronal types. High oxidative burden during dopamine metabolism, excitotoxicity, high iron content (Chinta and Andersen, 2008) and low mitochondrial mass (Liang et al., 2007) in substantia nigra dopaminergic neurons compared to other neurons might contribute to its selective vulnerability in stress conditions. In addition, high concentrations of intracellular Ca^{2+} are also observed in substantia nigra dopaminergic neurons (Wilson and Callaway, 2000; Chan et al., 2007) that contribute to a basal mitochondrial oxidant stress which was specific in substantia nigra dopaminergic neurons and not in neighboring ventral tegmental area nigra dopaminergic neurons (Guzman et al., 2010). These observations in substantia nigra dopaminergic neurons underline the importance of mitochondrial functions, which are vital for the survival of these neurons, particularly during aging. In view of the vital functions of mitochondria including energy metabolism, calcium homeostasis, cellular quality control and death regulation, it is important to consider mitochondrial dysfunction as one of the major factors that can contribute to dopaminergic neuronal cell death in PD. Given that mitochondrial dysfunction is widespread in both sporadic and monogenic PD, and the current knowledge on the mechanistic aspects of mitochondrial impairment, mitochondria remain attractive targets for the development of neuroprotective strategies for PD. However, clinical trials using compounds targeting mitochondria such as coenzyme Q10 (CoQ10) (Shults et al., 1998; Muller et al., 2003; Anonymous, 2007; Storch et al., 2007), an essential cofactor in mitochondrial ETC, and creatine (Bender et al., 2006a), a naturally occurring compound that boosts ATP levels and protects mitochondria have so far showed mild symptomatic or no significant beneficial effect in PD patients. However, reaching sufficient brain concentrations of Co-Q is notoriously difficult. Rather than arguing against the potential of mitochondria-targeted therapies, these results point to the need for developing more effective and specific agents that achieve high brain levels, reduce oxidative stress at its source rather than by quenching reactive oxidative species, and/or improve the removal of defective mitochondria. Nevertheless, it is important to remember that PD is a multifaceted disease and mitochondrial dysfunction might be a part of the complex pathology of the disease. Future neuroprotective therapies will likely need to target multiple pathological pathways including mitochondrial dysfunction.

Acknowledgments

This work was supported by Public Health Service grant P50 NS38367 (UCLA, Morris K. Udall Parkinson Disease Research Center of Excellence) and P01ES016732 (the UCLA Center for Gene Environment in Parkinson's Disease).

References

Abbas, N., Lucking, C.B., Ricard, S., Durr, A., Bonifati, V., De Michele, G., Bouley, S., Vaughan, J.R., Gasser, T., Marconi, R., Broussolle, E., Brefel-Courbon, C., Harhangi, B.S., Oostra, B.A., Fabrizio, E., Bohme, G.A., Pradier, L., Wood, N.W., Filla, A., Meco, G., Denefle, P., Agid, Y., Brice, A., 1999. A wide variety of mutations in the parkin gene are responsible for autosomal recessive parkinsonism in Europe. French Parkinson's Disease Genetics Study Group and the European Consortium on Genetic Susceptibility in Parkinson's Disease. Human Molecular Genetics 8, 567–574.

Amo, T., Sato, S., Saiki, S., Wolf, A.M., Toyomizu, M., Gautier, C.A., Shen, J., Ohta, S., Hattori, N., 2011. Mitochondrial membrane potential decrease caused by loss of PINK1 is not due to proton leak, but to respiratory chain defects. Neurobiology of Disease 41, 111–118.

Anonymous, 2007. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. Neurology 68, 20–28.

Anvret, A., Westerlund, M., Sydow, O., Willows, T., Lind, C., Galter, D., Belin, A.C., 2010. Variations of the CAG trinucleotide repeat in DNA polymerase gamma (POLG1) is associated with Parkinson's disease in Sweden. Neuroscience Letters 485, 117–120.

Ashley, A.K., Hanneman, W.H., Katoh, T., Moreno, J.A., Pollack, A., Tjalkens, R.B., Legare, M.E., 2009. Analysis of targeted mutation in DJ-1 on cellular function in primary astrocytes. Toxicology Letters 184, 186–191.

Barlow, B.K., Lee, D.W., Cory-Slechta, D.A., Opanashuk, L.A., 2005. Modulation of antioxidant defense systems by the environmental pesticide maneb in dopaminergic cells. Neurotoxicology 26, 63–75.

Beal, M.F., 2003. Mitochondria, oxidative damage, and inflammation in Parkinson's disease. Annals of the New York Academy of Sciences 991, 120–131.

Benard, G., Karbowski, M., 2009. Mitochondrial fusion and division: regulation and role in cell viability. Seminars in Cell & Developmental Biology 20, 365–374.

Bender, A., Koch, W., Elstner, M., Schombacher, Y., Bender, J., Moeschl, M., Gekeler, F., Muller-Myhsok, B., Gasser, T., Tatsch, K., Klopstock, T., 2006a. Creatine supplementation in Parkinson disease: a placebo-controlled randomized pilot trial. Neurology 67, 1262–1264.

Bender, A., Krishnan, K.J., Morris, C.M., Taylor, G.A., Reeve, A.K., Perry, R.H., Jaros, E., Hersheson, J.S., Betts, J., Klopstock, T., Taylor, R.W., Turnbull, D.M., 2006b. High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. Nature Genetics 38, 515–517.

Betarbet, R., Sherer, T.B., MacKenzie, G., Garcia-Osuna, M., Panov, A.V., Greenamyre, J.T., 2000. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nature Neuroscience 3, 1301–1306.

Bian, M., Liu, J., Hong, X., Yu, M., Huang, Y., Sheng, Z., Fei, J., Huang, F., 2012. Overexpression of parkin ameliorates dopaminergic neurodegeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. PloS One 7, e39953.

Biskup, S., West, A.B., 2009. Zeroing in on LRRK2-linked pathogenic mechanisms in Parkinson's disease. Biochimica et Biophysica Acta 1792, 625–633.

Biskup, S., Moore, D.J., Celsi, F., Higashi, S., West, A.B., Andrabi, S.A., Kurkinen, K., Yu, S.W., Savitt, J.M., Waldvogel, H.J., Faull, R.L., Emson, P.C., Torp, R., Ottersen, O.P., Dawson, T.M., Dawson, V.L., 2006. Localization of LRRK2 to membranous and vesicular structures in mammalian brain. Annals of Neurology 60, 557–569.

Blackinton, J., Lakshminarasimhan, M., Thomas, K.J., Ahmad, R., Greggio, E., Raza, A.S., Cookson, M.R., Wilson, M.A., 2009. Formation of a stabilized cysteine sulfinic acid is critical for the mitochondrial function of the parkinsonism protein DJ-1. The Journal of Biological Chemistry 284, 6476–6485.

Blin, O., Desnuelle, C., Rascol, O., Borg, M., Peyro Saint Paul, H., Azulay, J.P., Bille, F., Figarella, D., Coulom, F., Pellissier, J.F., et al., 1994. Mitochondrial respiratory

failure in skeletal muscle from patients with Parkinson's disease and multiple system atrophy. Journal of the Neurological Sciences 125, 95–101.
Bonci, A., Grillner, P., Mercuri, N.B., Bernardi, G., 1998. L-type calcium channels mediate a slow excitatory synaptic transmission in rat midbrain dopaminergic neurons. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience 18, 6693–6703.
Bonifati, V., Rizzu, P., van Baren, M.J., Schaap, O., Breedveld, G.J., Krieger, E., Dekker, M.C., Squitieri, F., Ibanez, P., Joosse, M., van Dongen, J.W., Vanacore, N., van Swieten, J.C., Brice, A., Meco, G., van Duijn, C.M., Oostra, B.A., Heutink, P., 2003. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 299, 256–259.
Brooks, A.I., Chadwick, C.A., Gelbard, H.A., Cory-Slechta, D.A., Federoff, H.J., 1999. Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. Brain Research 823, 1–10.
Burte, F., De Girolamo, L.A., Hargreaves, A.J., Billett, E.E., 2011. Alterations in the mitochondrial proteome of neuroblastoma cells in response to complex 1 inhibition. Journal of Proteome Research 10, 1974–1986.
Butler, E.K., Voigt, A., Lutz, A.K., Toegel, J.P., Gerhardt, E., Karsten, P., Falkenburger, B., Reinartz, A., Winklhofer, K.F., Schulz, J.B., 2012. The mitochondrial chaperone protein TRAP1 mitigates alpha-Synuclein toxicity. PLoS Genetics 8, e1002488.
Canet-Aviles, R.M., Wilson, M.A., Miller, D.W., Ahmad, R., McLendon, C., Bandyopadhyay, S., Baptista, M.J., Ringe, D., Petsko, G.A., Cookson, M.R., 2004. The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfinic acid-driven mitochondrial localization. Proceedings of the National Academy of Sciences of the United States of America 101, 9103–9108.
Cardoso, S.M., Esteves, A.R., Arduino, D.M., 2012. Mitochondrial metabolic control of microtubule dynamics impairs the autophagic pathway in Parkinson's disease. Neuro-Degenerative Diseases 10, 38–40.
Casarejos, M.J., Menendez, J., Solano, R.M., Rodriguez-Navarro, J.A., Garcia de Yebenes, J., Mena, M.A., 2006. Susceptibility to rotenone is increased in neurons from parkin null mice and is reduced by minocycline. Journal of Neurochemistry 97, 934–946.
Chan, P., DeLanney, L.E., Irwin, I., Langston, J.W., Di Monte, D., 1991. Rapid ATP loss caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mouse brain. Journal of Neurochemistry 57, 348–351.
Chan, C.S., Guzman, J.N., Ilijic, E., Mercer, J.N., Rick, C., Tkatch, T., Meredith, G.E., Surmeier, D.J., 2007. 'Rejuvenation' protects neurons in mouse models of Parkinson's disease. Nature 447, 1081–1086.
Chen, H., Chan, D.C., 2009. Mitochondrial dynamics – fusion, fission, movement, and mitophagy – in neurodegenerative diseases. Human Molecular Genetics 18, R169–R176.
Chen, L., Cagniard, B., Mathews, T., Jones, S., Koh, H.C., Ding, Y., Carvey, P.M., Ling, Z., Kang, U.J., Zhuang, X., 2005. Age-dependent motor deficits and dopaminergic dysfunction in DJ-1 null mice. The Journal of Biological Chemistry 280, 21418–21426.
Chesselet, M.F., Richter, F., Zhu, C., Magen, I., Watson, M.B., Subramaniam, S.R., 2012. A progressive mouse model of Parkinson's disease: the Thy1-aSyn ("Line 61") mice. Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics 9, 297–314.
Chinta, S.J., Andersen, J.K., 2008. Redox imbalance in Parkinson's disease. Biochimica et Biophysica Acta 1780, 1362–1367.
Chiueh, C.C., Markey, S.P., Burns, R.S., Johannessen, J.N., Jacobowitz, D.M., Kopin, I.J., 1984. Neurochemical and behavioral effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in rat, guinea pig, and monkey. Psychopharmacology Bulletin 20, 548–553.
Choi, W.S., Kruse, S.E., Palmiter, R.D., Xia, Z., 2008. Mitochondrial complex I inhibition is not required for dopaminergic neuron death induced by rotenone, MPP+, or paraquat. Proceedings of the National Academy of Sciences of the United States of America 105, 15136–15141.
Clark, I.E., Dodson, M.W., Jiang, C., Cao, J.H., Huh, J.R., Seol, J.H., Yoo, S.J., Hay, B.A., Guo, M., 2006. *Drosophila* pink1 is required for mitochondrial function and interacts genetically with parkin. Nature 441, 1162–1166.
Cocheme, H.M., Murphy, M.P., 2008. Complex I is the major site of mitochondrial superoxide production by paraquat. The Journal of Biological Chemistry 283, 1786–1798.
Cole, N.B., Dieuliis, D., Leo, P., Mitchell, D.C., Nussbaum, R.L., 2008. Mitochondrial translocation of alpha-synuclein is promoted by intracellular acidification. Experimental Cell Research 314, 2076–2089.
Conway, K.A., Harper, J.D., Lansbury, P.T., 1998. Accelerated in vitro fibril formation by a mutant alpha-synuclein linked to early-onset Parkinson disease. Nature Medicine 4, 1318–1320.
Conway, K.A., Lee, S.J., Rochet, J.C., Ding, T.T., Williamson, R.E., Lansbury Jr., P.T., 2000. Acceleration of oligomerization, not fibrillization, is a shared property of both alpha-synuclein mutations linked to early-onset Parkinson's disease: implications for pathogenesis and therapy. Proceedings of the National Academy of Sciences of the United States of America 97, 571–576.
Cookson, M.R., van der Brug, M., 2008. Cell systems and the toxic mechanism(s) of alpha-synuclein. Experimental Neurology 209, 5–11.
Costello, S., Cockburn, M., Bronstein, J., Zhang, X., Ritz, B., 2009. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. American Journal of Epidemiology 169, 919–926.
Couzin, J., 2007. Clinical research: testing a novel strategy against Parkinson's disease. Science 315, 1778.
Darios, F., Corti, O., Lucking, C.B., Hampe, C., Muriel, M.P., Abbas, N., Gu, W.J., Hirsch, E.C., Rooney, T., Ruberg, M., Brice, A., 2003. Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. Human Molecular Genetics 12, 517–526.
Dauer, W., Przedborski, S., 2003. Parkinson's disease: mechanisms and models. Neuron 39, 889–909.
Davis, G.C., Williams, A.C., Markey, S.P., Ebert, M.H., Caine, E.D., Reichert, C.M., Kopin, I.J., 1979. Chronic Parkinsonism secondary to intravenous injection of meperidine analogues. Psychiatry Research 1, 249–254.
Dawson, T.M., 2006. Parkin and defective ubiquitination in Parkinson's disease. Journal of Neural Transmission 70 (Suppl.) 209–213.
Deng, H., Dodson, M.W., Huang, H., Guo, M., 2008. The Parkinson's disease genes pink1 and parkin promote mitochondrial fission and/or inhibit fusion in *Drosophila*. Proceedings of the National Academy of Sciences of the United States of America 105, 14503–14508.
Desai, V.G., Feuers, R.J., Hart, R.W., Ali, S.F., 1996. MPP(+)-induced neurotoxicity in mouse is age-dependent: evidenced by the selective inhibition of complexes of electron transport. Brain Research 715, 1–8.
Devi, L., Raghavendran, V., Prabhu, B.M., Avadhani, N.G., Anandatheerthavarada, H.K., 2008. Mitochondrial import and accumulation of alpha-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain. The Journal of Biological Chemistry 283, 9089–9100.
Diedrich, M., Kitada, T., Nebrich, G., Koppelstaetter, A., Shen, J., Zabel, C., Klose, J., Mao, L., 2011. Brain region specific mitophagy capacity could contribute to selective neuronal vulnerability in Parkinson's disease. Proteome Science 9, 59.
Domico, L.M., Zeevalk, G.D., Bernard, L.P., Cooper, K.R., 2006. Acute neurotoxic effects of mancozeb and maneb in mesencephalic neuronal cultures are associated with mitochondrial dysfunction. Neurotoxicology 27, 816–825.
Doss-Pepe, E.W., Chen, L., Madura, K., 2005. Alpha-synuclein and parkin contribute to the assembly of ubiquitin lysine 63-linked multiubiquitin chains. The Journal of Biological Chemistry 280, 16619–16624.
Edwards, T.L., Scott, W.K., Almonte, C., Burt, A., Powell, E.H., Beecham, G.W., Wang, L., Zuchner, S., Konidari, I., Wang, G., Singer, C., Nahab, F., Scott, B., Stajich, J.M., Pericak-Vance, M., Haines, J., Vance, J.M., Martin, E.R., 2010. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. Annals of Human Genetics 74, 97–109.
Ekstrand, M.I., Terzioglu, M., Galter, D., Zhu, S., Hofstetter, C., Lindqvist, E., Thams, S., Bergstrand, A., Hansson, F.S., Trifunovic, A., Hoffer, B., Cullheim, S., Mohammed, A.H., Olson, L., Larsson, N.G., 2007. Progressive parkinsonism in mice with respiratory-chain-deficient dopamine neurons. Proceedings of the National Academy of Sciences of the United States of America 104, 1325–1330.
Elm, J.J., 2012. Design innovations and baseline findings in a long-term Parkinson's trial: the National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson's Disease Long-Term Study-1. Movement Disorders:Official Journal of the Movement Disorder Society 27, 1513–1521.
Exner, N., Treske, B., Paquet, D., Holmstrom, K., Schiesling, C., Gispert, S., Carballo-Carbajal, I., Berg, D., Hoepken, H.H., Gasser, T., Kruger, R., Winklhofer, K.F., Vogel, F., Reichert, A.S., Auburger, G., Kahle, P.J., Schmid, B., Haass, C., 2007. Loss-of-function of human PINK1 results in mitochondrial pathology and can be rescued by parkin. The Journal of Neuroscience:the Official Journal of the Society for Neuroscience 27, 12413–12418.
Fabre, E., Monserrat, J., Herrero, A., Barja, G., Leret, M.L., 1999. Effect of MPTP on brain mitochondrial H_2O_2 and ATP production and on dopamine and DOPAC in the striatum. Journal of Physiology and Biochemistry 55, 325–331.
Fallon, L., Belanger, C.M., Corera, A.T., Kontogiannea, M., Regan-Klapisz, E., Moreau, F., Voortman, J., Haber, M., Rouleau, G., Thorarinsdottir, T., Brice, A., van Bergen En Henegouwen, P.M., Fon, E.A., 2006. A regulated interaction with the UIM protein Eps15 implicates parkin in EGF receptor trafficking and PI(3)K-Akt signalling. Nature Cell Biology 8, 834–842.
Filosto, M., Mancuso, M., Nishigaki, Y., Pancrudo, J., Harati, Y., Gooch, C., Mankodi, A., Bayne, L., Bonilla, E., Shanske, S., Hirano, M., DiMauro, S., 2003. Clinical and genetic heterogeneity in progressive external ophthalmoplegia due to mutations in polymerase gamma. Archives of Neurology 60, 1279–1284.
Fleming, S.M., Salcedo, J., Fernagut, P.O., Rockenstein, E., Masliah, E., Levine, M.S., Chesselet, M.F., 2004. Early and progressive sensorimotor anomalies in mice overexpressing wild-type human alpha-synuclein. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience 24, 9434–9440.
Fornai, F., Schluter, O.M., Lenzi, P., Gesi, M., Ruffoli, R., Ferrucci, M., Lazzeri, G., Busceti, C.L., Pontarelli, F., Battaglia, G., Pellegrini, A., Nicoletti, F., Ruggieri, S., Paparelli, A., Sudhof, T.C., 2005. Parkinson-like syndrome induced by continuous MPTP infusion: convergent roles of the ubiquitin-proteasome system and alpha-synuclein. Proceedings of the National Academy of Sciences of the United States of America 102, 3413–3418.
Forno, L.S., DeLanney, L.E., Irwin, I., Langston, J.W., 1993. Similarities and differences between MPTP-induced parkinsonsim and Parkinson's disease. Neuropathologic considerations. Advances in Neurology 60, 600–608.
Fredenburg, R.A., Rospigliosi, C., Meray, R.K., Kessler, J.C., Lashuel, H.A., Eliezer, D., Lansbury Jr., P.T., 2007. The impact of the E46K mutation on the properties of alpha-synuclein in its monomeric and oligomeric states. Biochemistry 46, 7107–7118.
Gandhi, S., Muqit, M.M., Stanyer, L., Healy, D.G., Abou-Sleiman, P.M., Hargreaves, I., Heales, S., Ganguly, M., Parsons, L., Lees, A.J., Latchman, D.S., Holton, J.L., Wood, N.W., Revesz, T., 2006. PINK1 protein in normal human brain and Parkinson's disease. Brain: a Journal of Neurology 129, 1720–1731.
Gandhi, P.N., Chen, S.G., Wilson-Delfosse, A.L., 2009. Leucine-rich repeat kinase 2 (LRRK2): a key player in the pathogenesis of Parkinson's disease. Journal of Neuroscience Research 87, 1283–1295.

Gandhi, S., Vaarmann, A., Yao, Z., Duchen, M.R., Wood, N.W., Abramov, A.Y., 2012. Dopamine induced neurodegeneration in a PINK1 model of Parkinson's disease. PloS One 7, e37564.

Gatto, N.M., Rhodes, S.L., Manthripragada, A.D., Bronstein, J., Cockburn, M., Farrer, M., Ritz, B., 2010. Alpha-Synuclein gene may interact with environmental factors in increasing risk of Parkinson's disease. Neuroepidemiology 35, 191–195.

Gautam, A.H., Zeevalk, G.D., 2011. Characterization of reduced and oxidized dopamine and 3,4-dihydrophenylacetic acid, on brain mitochondrial electron transport chain activities. Biochimica et Biophysica Acta 1807, 819–828.

Gautier, C.A., Kitada, T., Shen, J., 2008. Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proceedings of the National Academy of Sciences of the United States of America 105, 11364–11369.

Giaime, E., Yamaguchi, H., Gautier, C.A., Kitada, T., Shen, J., 2012. Loss of DJ-1 does not affect mitochondrial respiration but increases ROS production and mitochondrial permeability transition pore opening. PloS One 7, e40501.

Gloeckner, C.J., Kinkl, N., Schumacher, A., Braun, R.J., O'Neill, E., Meitinger, T., Kolch, W., Prokisch, H., Ueffing, M., 2006. The Parkinson disease causing LRRK2 mutation I2020T is associated with increased kinase activity. Human Molecular Genetics 15, 223–232.

Goldberg, M.S., Pisani, A., Haburcak, M., Vortherms, T.A., Kitada, T., Costa, C., Tong, Y., Martella, G., Tscherter, A., Martins, A., Bernardi, G., Roth, B.L., Pothos, E.N., Calabresi, P., Shen, J., 2005. Nigrostriatal dopaminergic deficits and hypokinesia caused by inactivation of the familial Parkinsonism-linked gene DJ-1. Neuron 45, 489–496.

Gomez-Lazaro, M., Bonekamp, N.A., Galindo, M.F., Jordan, J., Schrader, M., 2008. 6-Hydroxydopamine (6-OHDA) induces Drp1-dependent mitochondrial fragmentation in SH-SY5Y cells. Free Radical Biology & Medicine 44, 1960–1969.

Good, C.H., Hoffman, A.F., Hoffer, B.J., Chefer, V.I., Shippenberg, T.S., Backman, C.M., Larsson, N.G., Olson, L., Gellhaar, S., Galter, D., Lupica, C.R., 2011. Impaired nigrostriatal function precedes behavioral deficits in a genetic mitochondrial model of Parkinson's disease. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology 25, 1333–1344.

Grace, A.A., Bunney, B.S., 1983. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons – 2 Action potential generating mechanisms and morphological correlates. Neuroscience 10, 317–331.

Greene, J.C., Whitworth, A.J., Kuo, I., Andrews, L.A., Feany, M.B., Pallanck, L.J., 2003. Mitochondrial pathology and apoptotic muscle degeneration in *Drosophila* parkin mutants. Proceedings of the National Academy of Sciences of the United States of America 100, 4078–4083.

Greggio, E., Jain, S., Kingsbury, A., Bandopadhyay, R., Lewis, P., Kaganovich, A., van der Brug, M.P., Beilina, A., Blackinton, J., Thomas, K.J., Ahmad, R., Miller, D.W., Kesavapany, S., Singleton, A., Lees, A., Harvey, R.J., Harvey, K., Cookson, M.R., 2006. Kinase activity is required for the toxic effects of mutant LRRK2/dardarin. Neurobiology of Disease 23, 329–341.

Guzman, J.N., Sanchez-Padilla, J., Wokosin, D., Kondapalli, J., Ilijic, E., Schumacker, P.T., Surmeier, D.J., 2010. Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. Nature 468, 696–700.

Haas, R.H., Nasirian, F., Nakano, K., Ward, D., Pay, M., Hill, R., Shults, C.W., 1995. Low platelet mitochondrial complex I and complex II/III activity in early untreated Parkinson's disease. Annals of Neurology 37, 714–722.

Hald, A., Lotharius, J., 2005. Oxidative stress and inflammation in Parkinson's disease: is there a causal link? Experimental Neurology 193, 279–290.

Hampe, C., Ardila-Osorio, H., Fournier, M., Brice, A., Corti, O., 2006. Biochemical analysis of Parkinson's disease-causing variants of Parkin, an E3 ubiquitin-protein ligase with monoubiquitylation capacity. Human Molecular Genetics 15, 2059–2075.

Hantraye, P., Varastet, M., Peschanski, M., Riche, D., Cesaro, P., Willer, J.C., Maziere, M., 1993. Stable parkinsonian syndrome and uneven loss of striatal dopamine fibres following chronic MPTP administration in baboons. Neuroscience 53, 169–178.

Hantraye, P., Brouillet, E., Ferrante, R., Palfi, S., Dolan, R., Matthews, R.T., Beal, M.F., 1996. Inhibition of neuronal nitric oxide synthase prevents MPTP-induced parkinsonism in baboons. Nature Medicine 2, 1017–1021.

Haque, M.E., Thomas, K.J., D'Souza, C., Callaghan, S., Kitada, T., Slack, R.S., Fraser, P., Cookson, M.R., Tandon, A., Park, D.S., 2008. Cytoplasmic Pink1 activity protects neurons from dopaminergic neurotoxin MPTP. Proceedings of the National Academy of Sciences of the United States of America 105, 1716–1721.

Hartmann, A., Hunot, S., Michel, P.P., Muriel, M.P., Vyas, S., Faucheux, B.A., Mouatt-Prigent, A., Turmel, H., Srinivasan, A., Ruberg, M., Evan, G.I., Agid, Y., Hirsch, E.C., 2000. Caspase-3: a vulnerability factor and final effector in apoptotic death of dopaminergic neurons in Parkinson's disease. Proceedings of the National Academy of Sciences of the United States of America 97, 2875–2880.

Hartmann, A., Michel, P.P., Troadec, J.D., Mouatt-Prigent, A., Faucheux, B.A., Ruberg, M., Agid, Y., Hirsch, E.C., 2001a. Is Bax a mitochondrial mediator in apoptotic death of dopaminergic neurons in Parkinson's disease? Journal of Neurochemistry 76, 1785–1793.

Hartmann, A., Troadec, J.D., Hunot, S., Kikly, K., Faucheux, B.A., Mouatt-Prigent, A., Ruberg, M., Agid, Y., Hirsch, E.C., 2001b. Caspase-8 is an effector in apoptotic death of dopaminergic neurons in Parkinson's disease, but pathway inhibition results in neuronal necrosis. The Journal of neuroscience: the official journal of the Society for Neuroscience 21, 2247–2255.

Hasegawa, E., Takeshige, K., Oishi, T., Murai, Y., Minakami, S., 1990. 1-Methyl-4-phenylpyridinium (MPP+) induces NADH-dependent superoxide formation and enhances NADH-dependent lipid peroxidation in bovine heart submitochondrial particles. Biochemical and Biophysical Research Communications 170, 1049–1055.

Hattori, N., Tanaka, M., Ozawa, T., Mizuno, Y., 1991. Immunohistochemical studies on complexes I, II, III, and IV of mitochondria in Parkinson's disease. Annals of Neurology 30, 563–571.

Heikkila, R.E., Hess, A., Duvoisin, R.C., 1984. Dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine in mice. Science 224, 1451–1453.

Henn, I.H., Bouman, L., Schlehe, J.S., Schlierf, A., Schramm, J.E., Wegener, E., Nakaso, K., Culmsee, C., Berninger, B., Krappmann, D., Tatzelt, J., Winklhofer, K.F., 2007. Parkin mediates neuroprotection through activation of IkappaB kinase/nuclear factor-kappaB signaling. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience 27, 1868–1878.

Heo, J.Y., Park, J.H., Kim, S.J., Seo, K.S., Han, J.S., Lee, S.H., Kim, J.M., Park, J.I., Park, S.K., Lim, K., Hwang, B.D., Shong, M., Kweon, G.R., 2012. DJ-1 null dopaminergic neuronal cells exhibit defects in mitochondrial function and structure: involvement of mitochondrial complex I assembly. PloS One 7, e32629.

Hoang, T., Choi, D.K., Nagai, M., Wu, D.C., Nagata, T., Prou, D., Wilson, G.L., Vila, M., Jackson-Lewis, V., Dawson, V.L., Dawson, T.M., Chesselet, M.F., Przedborski, S., 2009. Neuronal NOS and cyclooxygenase-2 contribute to DNA damage in a mouse model of Parkinson disease. Free Radical Biology & Medicine 47, 1049–1056.

Hoepken, H.H., Gispert, S., Morales, B., Wingerter, O., Del Turco, D., Mulsch, A., Nussbaum, R.L., Muller, K., Drose, S., Brandt, U., Deller, T., Wirth, B., Kudin, A.P., Kunz, W.S., Auburger, G., 2007. Mitochondrial dysfunction, peroxidation damage and changes in glutathione metabolism in PARK6. Neurobiology of Disease 25, 401–411.

Hoppins, S., Nunnari, J., 2009. The molecular mechanism of mitochondrial fusion. Biochimica et Biophysica Acta 1793, 20–26.

Huang, Y., Rowe, D.B., Halliday, G.M., 2011. Interaction between α-Synuclein and tau genotypes and the progression of parkinson's disease. Journal of Parkinson's Disease 1, 271–276.

Humphrey, D.M., Parsons, R.B., Ludlow, Z.N., Riemensperger, T., Esposito, G., Verstreken, P., Jacobs, H.T., Birman, S., Hirth, F., 2012. Alternative oxidase rescues mitochondria-mediated dopaminergic cell loss in *Drosophila*. Human Molecular Genetics 21, 2698–2712.

Hyun, D.H., Lee, M., Halliwell, B., Jenner, P., 2005. Effect of overexpression of wild-type or mutant parkin on the cellular response induced by toxic insults. Journal of Neuroscience Research 82, 232–244.

Iaccarino, C., Crosio, C., Vitale, C., Sanna, G., Carri, M.T., Barone, P., 2007. Apoptotic mechanisms in mutant LRRK2-mediated cell death. Human Molecular Genetics 16, 1319–1326.

Irrcher, I., Aleyasin, H., Seifert, E.L., Hewitt, S.J., Chhabra, S., Phillips, M., Lutz, A.K., Rousseaux, M.W., Bevilacqua, L., Jahani-Asl, A., Callaghan, S., MacLaurin, J.G., Winklhofer, K.F., Rizzu, P., Rippstein, P., Kim, R.H., Chen, C.X., Fon, E.A., Slack, R.S., Harper, M.E., McBride, H.M., Mak, T.W., Park, D.S., 2010. Loss of the Parkinson's disease-linked gene DJ-1 perturbs mitochondrial dynamics. Human Molecular Genetics 19, 3734–3746.

Ishihara, N., Nomura, M., Jofuku, A., Kato, H., Suzuki, S.O., Masuda, K., Otera, H., Nakanishi, Y., Nonaka, I., Goto, Y., Taguchi, N., Morinaga, H., Maeda, M., Takayanagi, R., Yokota, S., Mihara, K., 2009. Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. Nature Cell Biology 11, 958–966.

Isobe, C., Abe, T., Terayama, Y., 2010. Levels of reduced and oxidized coenzyme Q-10 and 8-hydroxy-2′-deoxyguanosine in the cerebrospinal fluid of patients with living Parkinson's disease demonstrate that mitochondrial oxidative damage and/or oxidative DNA damage contributes to the neurodegenerative process. Neuroscience Letters 469, 159–163.

Jones, G.M., Vale, J.A., 2000. Mechanisms of toxicity, clinical features, and management of diquat poisoning: a review. Journal of Toxicology Clinical Toxicology 38, 123–128.

Junn, E., Jang, W.H., Zhao, X., Jeong, B.S., Mouradian, M.M., 2009. Mitochondrial localization of DJ-1 leads to enhanced neuroprotection. Journal of Neuroscience Research 87, 123–129.

Kachroo, A., Irizarry, M.C., Schwarzschild, M.A., 2010. Caffeine protects against combined paraquat and maneb-induced dopaminergic neuron degeneration. Experimental Neurology 223, 657–661.

Keeney, P.M., Xie, J., Capaldi, R.A., Bennett Jr., J.P., 2006. Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience 26, 5256–5264.

Kim, R.H., Smith, P.D., Aleyasin, H., Hayley, S., Mount, M.P., Pownall, S., Wakeham, A., You-Ten, A.J., Kalia, S.K., Horne, P., Westaway, D., Lozano, A.M., Anisman, H., Park, D.S., Mak, T.W., 2005. Hypersensitivity of DJ-1-deficient mice to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrindine (MPTP) and oxidative stress. Proceedings of the National Academy of Sciences of the United States of America 102, 5215–5220.

Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y., Shimizu, N., 1998. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392, 605–608.

Kitada, T., Pisani, A., Porter, D.R., Yamaguchi, H., Tscherter, A., Martella, G., Bonsi, P., Zhang, C., Pothos, E.N., Shen, J., 2007. Impaired dopamine release and synaptic plasticity in the striatum of PINK1-deficient mice. Proceedings of the National Academy of Sciences of the United States of America 104, 11441–11446.

Klein, C., Schlossmacher, M.G., 2006. The genetics of Parkinson disease: implications for neurological care. Nature Clinical Practice Neurology 2, 136–146.

Klivenyi, P., Siwek, D., Gardian, G., Yang, L., Starkov, A., Cleren, C., Ferrante, R.J., Kowall, N.W., Abeliovich, A., Beal, M.F., 2006. Mice lacking alpha-synuclein are resistant to mitochondrial toxins. Neurobiology of Disease 21, 541–548.

Knott, A.B., Bossy-Wetzel, E., 2008. Impairing the mitochondrial fission and fusion balance: a new mechanism of neurodegeneration. Annals of the New York Academy of Sciences 1147, 283–292.

Kraytsberg, Y., Kudryavtseva, E., McKee, A.C., Geula, C., Kowall, N.W., Khrapko, K., 2006. Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. Nature Genetics 38, 518–520.

Krebiehl, G., Ruckerbauer, S., Burbulla, L.F., Kieper, N., Maurer, B., Waak, J., Wolburg, H., Gizatullina, Z., Gellerich, F.N., Woitalla, D., Riess, O., Kahle, P.J., Proikas-Cezanne, T., Kruger, R., 2010. Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson's disease-associated protein DJ-1. PloS One 5, e9367.

Krige, D., Carroll, M.T., Cooper, J.M., Marsden, C.D., Schapira, A.H., 1992. Platelet mitochondrial function in Parkinson's disease. The Royal Kings and Queens Parkinson Disease Research Group. Annals of Neurology 32, 782–788.

Kruger, R., Kuhn, W., Muller, T., Woitalla, D., Graeber, M., Kosel, S., Przuntek, H., Epplen, J.T., Schols, L., Riess, O., 1998. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nature Genetics 18, 106–108.

Kruse, S.E., Watt, W.C., Marcinek, D.J., Kapur, R.P., Schenkman, K.A., Palmiter, R.D., 2008. Mice with mitochondrial complex I deficiency develop a fatal encephalomyopathy. Cell Metabolism 7, 312–320.

Kuroda, Y., Mitsui, T., Kunishige, M., Shono, M., Akaike, M., Azuma, H., Matsumoto, T., 2006. Parkin enhances mitochondrial biogenesis in proliferating cells. Human Molecular Genetics 15, 883–895.

Kwon, H.J., Heo, J.Y., Shim, J.H., Park, J.H., Seo, K.S., Ryu, M.J., Han, J.S., Shong, M., Son, J.H., Kweon, G.R., 2011. DJ-1 mediates paraquat-induced dopaminergic neuronal cell death. Toxicology Letters 202, 85–92.

Langston, J.W., Ballard, P., Tetrud, J.W., Irwin, I., 1983. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science 219, 979–980.

Langston, J.W., Irwin, I., Langston, E.B., Forno, L.S., 1984. 1-Methyl-4-phenylpyridinium ion (MPP+): identification of a metabolite of MPTP, a toxin selective to the substantia nigra. Neuroscience Letters 48, 87–92.

Langston, J.W., Forno, L.S., Tetrud, J., Reeves, A.G., Kaplan, J.A., Karluk, D., 1999. Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure. Annals of Neurology 46, 598–605.

Lansbury, P.T., Lashuel, H.A., 2006. A century-old debate on protein aggregation and neurodegeneration enters the clinic. Nature 443, 774–779.

Li, W.W., Yang, R., Guo, J.C., Ren, H.M., Zha, X.L., Cheng, J.S., Cai, D.F., 2007. Localization of alpha-synuclein to mitochondria within midbrain of mice. Neuroreport 18, 1543–1546.

Liang, C.L., Wang, T.T., Luby-Phelps, K., German, D.C., 2007. Mitochondria mass is low in mouse substantia nigra dopamine neurons: implications for Parkinson's disease. Experimental Neurology 203, 370–380.

Lim, K.L., Chew, K.C., Tan, J.M., Wang, C., Chung, K.K., Zhang, Y., Tanaka, Y., Smith, W., Engelender, S., Ross, C.A., Dawson, V.L., Dawson, T.M., 2005. Parkin mediates nonclassical, proteasomal-independent ubiquitination of synphilin-1: implications for Lewy body formation. The Journal of Neuroscience:the Official Journal of the Society for Neuroscience 25, 2002–2009.

Luoma, P., Melberg, A., Rinne, J.O., Kaukonen, J.A., Nupponen, N.N., Chalmers, R.M., Oldfors, A., Rautakorpi, I., Peltonen, L., Majamaa, K., Somer, H., Suomalainen, A., 2004. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study. Lancet 364, 875–882.

Ma, L., Cao, T.T., Kandpal, G., Warren, L., Fred Hess, J., Seabrook, G.R., Ray, W.J., 2010. Genome-wide microarray analysis of the differential neuroprotective effects of antioxidants in neuroblastoma cells overexpressing the familial Parkinson's disease alpha-synuclein A53T mutation. Neurochemical Research 35, 130–142.

Maj, M.C., Tkachyova, I., Patel, P., Addis, J.B., Mackay, N., Levandovskiy, V., Lee, J., Lang, A.E., Cameron, J.M., Robinson, B.H., 2010. Oxidative stress alters the regulatory control of p66Shc and Akt in PINK1 deficient cells. Biochemical and Biophysical Research Communications 399, 331–335.

Manfredsson, F.P., Burger, C., Sullivan, L.F., Muzyczka, N., Lewin, A.S., Mandel, R.J., 2007. rAAV-mediated nigral human parkin over-expression partially ameliorates motor deficits via enhanced dopamine neurotransmission in a rat model of Parkinson's disease. Experimental Neurology 207, 289–301.

Markey, S.P., Johannessen, J.N., Chiueh, C.C., Burns, R.S., Herkenham, M.A., 1984. Intraneuronal generation of a pyridinium metabolite may cause drug-induced parkinsonism. Nature 311, 464–467.

Martin, L.J., Pan, Y., Price, A.C., Sterling, W., Copeland, N.G., Jenkins, N.A., Price, D.L., Lee, M.K., 2006. Parkinson's disease alpha-synuclein transgenic mice develop neuronal mitochondrial degeneration and cell death. The Journal of Neuroscience:the Official Journal of the Society for Neuroscience 26, 41–50.

Mata, I.F., Wedemeyer, W.J., Farrer, M.J., Taylor, J.P., Gallo, K.A., 2006. LRRK2 in Parkinson's disease: protein domains and functional insights. Trends in Neurosciences 29, 286–293.

Mattson, M.P., Gleichmann, M., Cheng, A., 2008. Mitochondria in neuroplasticity and neurological disorders. Neuron 60, 748–766.

McCormack, A.L., Thiruchelvam, M., Manning-Bog, A.B., Thiffault, C., Langston, J.W., Cory-Slechta, D.A., Di Monte, D.A., 2002. Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiology of Disease 10, 119–127.

McDowell, K., Chesselet, M.F., 2012. Animal models of the non-motor features of Parkinson's disease. Neurobiology of Disease 46, 597–606.

Meco, G., Bonifati, V., Vanacore, N., Fabrizio, E., 1994. Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). Scandinavian Journal of Work, Environment & Health 20, 301–305.

Meuer, K., Suppanz, I.E., Lingor, P., Planchamp, V., Goricke, B., Fichtner, L., Braus, G.H., Dietz, G.P., Jakobs, S., Bahr, M., Weishaupt, J.H., 2007. Cyclin-dependent kinase 5 is an upstream regulator of mitochondrial fission during neuronal apoptosis. Cell Death and Differentiation 14, 651–661.

Mizuno, Y., Ohta, S., Tanaka, M., Takamiya, S., Suzuki, K., Sato, T., Oya, H., Ozawa, T., Kagawa, Y., 1989. Deficiencies in complex I subunits of the respiratory chain in Parkinson's disease. Biochemical and Biophysical Research Communications 163, 1450–1455.

Mollace, V., Iannone, M., Muscoli, C., Palma, E., Granato, T., Rispoli, V., Nistico, R., Rotiroti, D., Salvemini, D., 2003. The role of oxidative stress in paraquat-induced neurotoxicity in rats: protection by non peptidyl superoxide dismutase mimetic. Neuroscience Letters 335, 163–166.

Moore, D.J., Zhang, L., Troncoso, J., Lee, M.K., Hattori, N., Mizuno, Y., Dawson, T.M., Dawson, V.L., 2005. Association of DJ-1 and parkin mediated by pathogenic DJ-1 mutations and oxidative stress. Human Molecular Genetics 14, 71–84.

Moratalla, R., Quinn, B., DeLanney, L.E., Irwin, I., Langston, J.W., Graybiel, A.M., 1992. Differential vulnerability of primate caudate-putamen and striosome-matrix dopamine systems to the neurotoxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proceedings of the National Academy of Sciences of the United States of America 89, 3859–3863.

Morato, G.S., Lemos, T., Takahashi, R.N., 1989. Acute exposure to maneb alters some behavioral functions in the mouse. Neurotoxicology and Teratology 11, 421–425.

Mortiboys, H., Johansen, K.K., Aasly, J.O., Bandmann, O., 2010. Mitochondrial impairment in patients with Parkinson disease with the G2019S mutation in LRRK2. Neurology 75, 2017–2020.

Mosharov, E.V., Larsen, K.E., Kanter, E., Phillips, K.A., Wilson, K., Schmitz, Y., Krantz, D.E., Kobayashi, K., Edwards, R.H., Sulzer, D., 2009. Interplay between cytosolic dopamine, calcium, and alpha-synuclein causes selective death of substantia nigra neurons. Neuron 62, 218–229.

Muftuoglu, M., Elibol, B., Dalmizrak, O., Ercan, A., Kulaksiz, G., Ogus, H., Dalkara, T., Ozer, N., 2004. Mitochondrial complex I and IV activities in leukocytes from patients with parkin mutations. Movement Disorders:Official Journal of the Movement Disorder Society 19, 544–548.

Mukhopadhyay, D., Riezman, H., 2007. Proteasome-independent functions of ubiquitin in endocytosis and signaling. Science 315, 201–205.

Muller, T., Buttner, T., Gholipour, A.F., Kuhn, W., 2003. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. Neuroscience Letters 341, 201–204.

Murakami, T., Shoji, M., Imai, Y., Inoue, H., Kawarabayashi, T., Matsubara, E., Harigaya, Y., Sasaki, A., Takahashi, R., Abe, K., 2004. Pael-R is accumulated in Lewy bodies of Parkinson's disease. Annals of Neurology 55, 439–442.

Murphy, M.P., 2009. How mitochondria produce reactive oxygen species. The Biochemical Journal 417, 1–13.

Mytilineou, C., Werner, P., Molinari, S., Di Rocco, A., Cohen, G., Yahr, M.D., 1994. Impaired oxidative decarboxylation of pyruvate in fibroblasts from patients with Parkinson's disease. Journal of Neural Transmission Parkinson's Disease and Dementia Section 8, 223–228.

Nakamura, K., Nemani, V.M., Wallender, E.K., Kaehlcke, K., Ott, M., Edwards, R.H., 2008. Optical reporters for the conformation of alpha-synuclein reveal a specific interaction with mitochondria. The Journal of Neuroscience:the Official Journal of the Society for Neuroscience 28, 12305–12317.

Narendra, D., Tanaka, A., Suen, D.F., Youle, R.J., 2008. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. The Journal of Cell Biology 183, 795–803.

Narendra, D.P., Jin, S.M., Tanaka, A., Suen, D.F., Gautier, C.A., Shen, J., Cookson, M.R., Youle, R.J., 2010. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biology 8, e1000298.

Nicholls, D.G., 2008. Oxidative stress and energy crises in neuronal dysfunction. Annals of the New York Academy of Sciences 1147, 53–60.

Nicklas, W.J., Vyas, I., Heikkila, R.E., 1985. Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. Life Sciences 36, 2503–2508.

Niu, J., Yu, M., Wang, C., Xu, Z., 2012. Leucine-rich repeat kinase 2 disturbs mitochondrial dynamics via dynamin-like protein. Journal of Neurochemistry 122, 650–658.

Norris, E.H., Uryu, K., Leight, S., Giasson, B.I., Trojanowski, J.Q., Lee, V.M., 2007. Pesticide exposure exacerbates alpha-synucleinopathy in an A53T transgenic mouse model. The American Journal of Pathology 170, 658–666.

Ossowska, K., Wardas, J., Smialowska, M., Kuter, K., Lenda, T., Wieronska, J.M., Zieba, B., Nowak, P., Dabrowska, J., Bortel, A., Kwiecinski, A., Wolfarth, S., 2005. A slowly developing dysfunction of dopaminergic nigrostriatal neurons induced by long-term paraquat administration in rats: an animal model of preclinical stages of Parkinson's disease? The European Journal of Neuroscience 22, 1294–1304.

Ozawa, T., 1997. Oxidative damage and fragmentation of mitochondrial DNA in cellular apoptosis. Bioscience Reports 17, 237–250.

Paisan-Ruiz, C., Jain, S., Evans, E.W., Gilks, W.P., Simon, J., van der Brug, M., Lopez de Munain, A., Aparicio, S., Gil, A.M., Khan, N., Johnson, J., Martinez, J.R., Nicholl, D., Carrera, I.M., Pena, A.S., de Silva, R., Lees, A., Marti-Masso, J.F., Perez-Tur, J.,

Wood, N.W., Singleton, A.B., 2004. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 44, 595–600.
Palacino, J.J., Sagi, D., Goldberg, M.S., Krauss, S., Motz, C., Wacker, M., Klose, J., Shen, J., 2004. Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. The Journal of Biological Chemistry 279, 18614–18622.
Parihar, M.S., Parihar, A., Fujita, M., Hashimoto, M., Ghafourifar, P., 2008. Mitochondrial association of alpha-synuclein causes oxidative stress. Cellular and Molecular Life Sciences:CMLS 65, 1272–1284.
Park, J., Lee, S.B., Lee, S., Kim, Y., Song, S., Kim, S., Bae, E., Kim, J., Shong, M., Kim, J.M., Chung, J., 2006. Mitochondrial dysfunction in *Drosophila* PINK1 mutants is complemented by parkin. Nature 441, 1157–1161.
Park, J., Lee, G., Chung, J., 2009. The PINK1-Parkin pathway is involved in the regulation of mitochondrial remodeling process. Biochemical and Biophysical Research Communications 378, 518–523.
Parker Jr., W.D., Parks, J.K., Swerdlow, R.H., 2008. Complex I deficiency in Parkinson's disease frontal cortex. Brain Research 1189, 215–218.
Paterna, J.C., Leng, A., Weber, E., Feldon, J., Bueler, H., 2007. DJ-1 and Parkin modulate dopamine-dependent behavior and inhibit MPTP-induced nigral dopamine neuron loss in mice. Molecular Therapy:the Journal of the American Society of Gene Therapy 15, 698–704.
Pennathur, S., Jackson-Lewis, V., Przedborski, S., Heinecke, J.W., 1999. Mass spectrometric quantification of 3-nitrotyrosine, ortho-tyrosine, and o,o′-dityrosine in brain tissue of 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine-treated mice, a model of oxidative stress in Parkinson's disease. The Journal of Biological Chemistry 274, 34621–34628.
Perez, F.A., Palmiter, R.D., 2005. Parkin-deficient mice are not a robust model of parkinsonism. Proceedings of the National Academy of Sciences of the United States of America 102, 2174–2179.
Perier, C., Tieu, K., Guegan, C., Caspersen, C., Jackson-Lewis, V., Carelli, V., Martinuzzi, A., Hirano, M., Przedborski, S., Vila, M., 2005. Complex I deficiency primes Bax-dependent neuronal apoptosis through mitochondrial oxidative damage. Proceedings of the National Academy of Sciences of the United States of America 102, 19126–19131.
Perier, C., Bove, J., Wu, D.C., Dehay, B., Choi, D.K., Jackson-Lewis, V., Rathke-Hartlieb, S., Bouillet, P., Strasser, A., Schulz, J.B., Przedborski, S., Vila, M., 2007. Two molecular pathways initiate mitochondria-dependent dopaminergic neurodegeneration in experimental Parkinson's disease. Proceedings of the National Academy of Sciences of the United States of America 104, 8161–8166.
Periquet, M., Corti, O., Jacquier, S., Brice, A., 2005. Proteomic analysis of parkin knockout mice: alterations in energy metabolism protein handling and synaptic function. Journal of Neurochemistry 95, 1259–1276.
Pesah, Y., Pham, T., Burgess, H., Middlebrooks, B., Verstreken, P., Zhou, Y., Harding, M., Bellen, H., Mardon, G., 2004. *Drosophila* parkin mutants have decreased mass and cell size and increased sensitivity to oxygen radical stress. Development 131, 2183–2194.
Petit, A., Kawarai, T., Paitel, E., Sanjo, N., Maj, M., Scheid, M., Chen, F., Gu, Y., Hasegawa, H., Salehi-Rad, S., Wang, L., Rogaeva, E., Fraser, P., Robinson, B., St George-Hyslop, P., Tandon, A., 2005. Wild-type PINK1 prevents basal and induced neuronal apoptosis, a protective effect abrogated by Parkinson disease-related mutations. The Journal of Biological Chemistry 280, 34025–34032.
Piao, Y., Kim, H.G., Oh, M.S., Pak, Y.K., 2012. Overexpression of TFAM, NRF-1 and myr-AKT protects the MPP(+)-induced mitochondrial dysfunctions in neuronal cells. Biochimica et Biophysica Acta 1820, 577–585.
Piccoli, C., Sardanelli, A., Scrima, R., Ripoli, M., Quarato, G., D'Aprile, A., Bellomo, F., Scacco, S., De Michele, G., Filla, A., Iuso, A., Boffoli, D., Capitanio, N., Papa, S., 2008. Mitochondrial respiratory dysfunction in familiar parkinsonism associated with PINK1 mutation. Neurochemical Research 33, 2565–2574.
Ping, H.X., Shepard, P.D., 1996. Apamin-sensitive Ca(2+)-activated K+ channels regulate pacemaker activity in nigral dopamine neurons. Neuroreport 7, 809–814.
Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E.S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Di Iorio, G., Golbe, L.I., Nussbaum, R.L., 1997. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276, 2045–2047.
Poole, A.C., Thomas, R.E., Andrews, L.A., McBride, H.M., Whitworth, A.J., Pallanck, L.J., 2008. The PINK1/Parkin pathway regulates mitochondrial morphology. Proceedings of the National Academy of Sciences of the United States of America 105, 1638–1643.
Poon, H.F., Frasier, M., Shreve, N., Calabrese, V., Wolozin, B., Butterfield, D.A., 2005. Mitochondrial associated metabolic proteins are selectively oxidized in A30P alpha-synuclein transgenic mice – a model of familial Parkinson's disease. Neurobiology of Disease 18, 492–498.
Prasad, K., Winnik, B., Thiruchelvam, M.J., Buckley, B., Mirochnitchenko, O., Richfield, E.K., 2007. Prolonged toxicokinetics and toxicodynamics of paraquat in mouse brain. Environmental Health Perspectives 115, 1448–1453.
Pridgeon, J.W., Olzmann, J.A., Chin, L.S., Li, L., 2007. PINK1 protects against oxidative stress by phosphorylating mitochondrial chaperone TRAP1. PLoS Biology 5, e172.
Przedborski, S., Kostic, V., Jackson-Lewis, V., Naini, A.B., Simonetti, S., Fahn, S., Carlson, E., Epstein, C.J., Cadet, J.L., 1992. Transgenic mice with increased Cu/Zn-superoxide dismutase activity are resistant to N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity. The Journal of neuroscience:the official journal of the Society for Neuroscience 12, 1658–1667.
Przedborski, S., Jackson-Lewis, V., Yokoyama, R., Shibata, T., Dawson, V.L., Dawson, T.M., 1996. Role of neuronal nitric oxide in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neurotoxicity. Proceedings of the National Academy of Sciences of the United States of America 93, 4565–4571.
Puopolo, M., Raviola, E., Bean, B.P., 2007. Roles of subthreshold calcium current and sodium current in spontaneous firing of mouse midbrain dopamine neurons. The Journal of Neuroscience:the Official Journal of the Society for Neuroscience 27, 645–656.
Ramsay, R.R., Salach, J.I., Dadgar, J., Singer, T.P., 1986. Inhibition of mitochondrial NADH dehydrogenase by pyridine derivatives and its possible relation to experimental and idiopathic parkinsonism. Biochemical and Biophysical Research Communications 135, 269–275.
Reddy, P.H., Reddy, T.P., Manczak, M., Calkins, M.J., Shirendeb, U., Mao, P., 2011. Dynamin-related protein 1 and mitochondrial fragmentation in neurodegenerative diseases. Brain Research Reviews 67, 103–118.
Reeve, A.K., Krishnan, K.J., Turnbull, D., 2008. Mitochondrial DNA mutations in disease, aging, and neurodegeneration. Annals of the New York Academy of Sciences 1147, 21–29.
Richardson, J.R., Quan, Y., Sherer, T.B., Greenamyre, J.T., Miller, G.W., 2005. Paraquat neurotoxicity is distinct from that of MPTP and rotenone. Toxicological Sciences: an Official Journal of the Society of Toxicology 88, 193–201.
Richter, C., Park, J.W., Ames, B.N., 1988. Normal oxidative damage to mitochondrial and nuclear DNA is extensive. Proceedings of the National Academy of Sciences of the United States of America 85, 6465–6467.
Ritz, B.R., Manthripragada, A.D., Costello, S., Lincoln, S.J., Farrer, M.J., Cockburn, M., Bronstein, J., 2009. Dopamine transporter genetic variants and pesticides in Parkinson's disease. Environmental Health Perspectives 117, 964–969.
Ritz, B., Rhodes, S.L., Bordelon, Y., Bronstein, J., 2012. Alpha-Synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease. PloS One 7, e36199.
Roede, J.R., Hansen, J.M., Go, Y.M., Jones, D.P., 2011. Maneb and paraquat-mediated neurotoxicity: involvement of peroxiredoxin/thioredoxin system. Toxicological Sciences: an Official Journal of the Society of Toxicology 121, 368–375.
Romo, R., Schultz, W., 1990. Dopamine neurons of the monkey midbrain: contingencies of responses to active touch during self-initiated arm movements. Journal of Neurophysiology 63, 592–606.
Rosen, K.M., Veereshwarayya, V., Moussa, C.E., Fu, Q., Goldberg, M.S., Schlossmacher, M.G., Shen, J., Querfurth, H.W., 2006. Parkin protects against mitochondrial toxins and beta-amyloid accumulation in skeletal muscle cells. The Journal of Biological Chemistry 281, 12809–12816.
Saini, N., Oelhafen, S., Hua, H., Georgiev, O., Schaffner, W., Bueler, H., 2010. Extended lifespan of *Drosophila* parkin mutants through sequestration of redox-active metals and enhancement of anti-oxidative pathways. Neurobiology of Disease 40, 82–92.
Saint-Pierre, M., Tremblay, M.E., Sik, A., Gross, R.E., Cicchetti, F., 2006. Temporal effects of paraquat/maneb on microglial activation and dopamine neuronal loss in older rats. Journal of Neurochemistry 98, 760–772.
Schapira, A.H., 2011. Mitochondrial pathology in Parkinson's disease. The Mount Sinai Journal of Medicine, New York 78, 872–881.
Schapira, A.H., Cooper, J.M., Dexter, D., Jenner, P., Clark, J.B., Marsden, C.D., 1989. Mitochondrial complex I deficiency in Parkinson's disease. Lancet 1, 1269.
Schapira, A.H., Cooper, J.M., Dexter, D., Clark, J.B., Jenner, P., Marsden, C.D., 1990. Mitochondrial complex I deficiency in Parkinson's disease. Journal of Neurochemistry 54, 823–827.
Schon, E.A., Przedborski, S., 2011. Mitochondria: the next (neurode)generation. Neuron 70, 1033–1053.
Shavali, S., Brown-Borg, H.M., Ebadi, M., Porter, J., 2008. Mitochondrial localization of alpha-synuclein protein in alpha-synuclein overexpressing cells. Neuroscience Letters 439, 125–128.
Sherer, T.B., Betarbet, R., Testa, C.M., Seo, B.B., Richardson, J.R., Kim, J.H., Miller, G.W., Yagi, T., Matsuno-Yagi, A., Greenamyre, J.T., 2003. Mechanism of toxicity in rotenone models of Parkinson's disease. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience 23, 10756–10764.
Shimizu, K., Matsubara, K., Ohtaki, K., Fujimaru, S., Saito, O., Shiono, H., 2003. Paraquat induces long-lasting dopamine overflow through the excitotoxic pathway in the striatum of freely moving rats. Brain Research 976, 243–252.
Shimura, H., Hattori, N., Kubo, S., Mizuno, Y., Asakawa, S., Minoshima, S., Shimizu, N., Iwai, K., Chiba, T., Tanaka, K., Suzuki, T., 2000. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nature Genetics 25, 302–305.
Shults, C.W., Beal, M.F., Fontaine, D., Nakano, K., Haas, R.H., 1998. Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients. Neurology 50, 793–795.
Silva, B.A., Breydo, L., Fink, A.L., Uversky, V.N., 2013. Agrochemicals, alpha-Synuclein, and Parkinson's Disease. Molecular Neurobiology 47 (2) 598–612.
Silvestri, L., Caputo, V., Bellacchio, E., Atorino, L., Dallapiccola, B., Valente, E.M., Casari, G., 2005. Mitochondrial import and enzymatic activity of PINK1 mutants associated to recessive parkinsonism. Human Molecular Genetics 14, 3477–3492.
Singleton, A.B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., Hulihan, M., Peuralinna, T., Dutra, A., Nussbaum, R., Lincoln, S., Crawley, A., Hanson, M., Maraganore, D., Adler, C., Cookson, M.R., Muenter, M., Baptista, M., Miller, D., Blancato, J., Hardy, J., Gwinn-Hardy, K., 2003. alpha-Synuclein locus triplication causes Parkinson's disease. Science 302, 841.
Smith, W.W., Pei, Z., Jiang, H., Dawson, V.L., Dawson, T.M., Ross, C.A., 2006. Kinase activity of mutant LRRK2 mediates neuronal toxicity. Nature Neuroscience 9, 1231–1233.
Song, D.D., Shults, C.W., Sisk, A., Rockenstein, E., Masliah E, 2004. Enhanced substantia nigra mitochondrial pathology in human alpha-synuclein transgenic mice after treatment with MPTP. Experimental Neurology 186, 158–172.

Sonia Angeline, M., Chaterjee, P., Anand, K., Ambasta, R.K., Kumar, P., 2012. Rotenone-induced parkinsonism elicits behavioral impairments and differential expression of parkin, heat shock proteins and caspases in the rat. Neuroscience 220, 291–301.

Soubannier, V., McBride, H.M., 2009. Positioning mitochondrial plasticity within cellular signaling cascades. Biochimica et Biophysica Acta 1793, 154–170.

Spillantini, M.G., Goedert, M., 2000. The alpha-synucleinopathies: Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Annals of the New York Academy of Sciences 920, 16–27.

Spillantini, M.G., Schmidt, M.L., Lee, V.M., Trojanowski, J.Q., Jakes, R., Goedert, M., 1997. Alpha-synuclein in Lewy bodies. Nature 388, 839–840.

Starkov, A.A., 2008. The role of mitochondria in reactive oxygen species metabolism and signaling. Annals of the New York Academy of Sciences 1147, 37–52.

Sterky, F.H., Hoffman, A.F., Milenkovic, D., Bao, B., Paganelli, A., Edgar, D., Wibom, R., Lupica, C.R., Olson, L., Larsson, N.G., 2012. Altered dopamine metabolism and increased vulnerability to MPTP in mice with partial deficiency of mitochondrial complex I in dopamine neurons. Human Molecular Genetics 21, 1078–1089.

Storch, A., Jost, W.H., Vieregge, P., Spiegel, J., Greulich, W., Durner, J., Muller, T., Kupsch, A., Henningsen, H., Oertel, W.H., Fuchs, G., Kuhn, W., Niklowitz, P., Koch, R., Herting, B., Reichmann, H., 2007. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson disease. Archives of Neurology 64, 938–944.

Sun, Y., Vashisht, A.A., Tchieu, J., Wohlschlegel, J.A., Dreier, L., 2012. Voltage-dependent anion channels (VDACs) recruit Parkin to defective mitochondria to promote mitochondrial autophagy. The Journal of Biological Chemistry 287, 40652–40660.

Surmeier, D.J., 2007. Calcium, ageing, and neuronal vulnerability in Parkinson's disease. Lancet Neurology 6, 933–938.

Surmeier, D.J., Guzman, J.N., Sanchez-Padilla, J., Schumacker PT, 2011. The role of calcium and mitochondrial oxidant stress in the loss of substantia nigra pars compacta dopaminergic neurons in Parkinson's disease. Neuroscience 198, 221–231.

Swerdlow, R.H., Parks, J.K., Cassarino, D.S., Binder, D.R., Bennett Jr., J.P., Di Iorio, G., Golbe, L.I., Parker Jr., W.D., 2001. Biochemical analysis of cybrids expressing mitochondrial DNA from Contursi kindred Parkinson's subjects. Experimental Neurology 169, 479–485.

Taira, T., Saito, Y., Niki, T., Iguchi-Ariga, S.M., Takahashi, K., Ariga, H., 2004. DJ-1 has a role in antioxidative stress to prevent cell death. EMBO Reports 5, 213–218.

Tanaka, Y., Engelender, S., Igarashi, S., Rao, R.K., Wanner, T., Tanzi, R.E., Sawa, A.V., Dawson, L.D., Ross CA, T.M., 2001. Inducible expression of mutant alpha-synuclein decreases proteasome activity and increases sensitivity to mitochondria-dependent apoptosis. Human Molecular Genetics 10, 919–926.

Tang, B., Xiong, H., Sun, P., Zhang, Y., Wang, D., Hu, Z., Zhu, Z., Ma, H., Pan, Q., Xia, J.H., Xia, K., Zhang Z, 2006. Association of PINK1 and DJ-1 confers digenic inheritance of early-onset Parkinson's disease. Human Molecular Genetics 15, 1816–1825.

Tanner, C.M., Kamel, F., Ross, G.W., Hoppin, J.A., Goldman, S.M., Korell, M., Marras, C., Bhudhikanok, G.S., Kasten, M., Chade, A.R., Comyns, K., Richards, M.B., Meng, C., Priestley, B., Fernandez, H.H., Cambi, F., Umbach, D.M., Blair, A., Sandler, D.P., Langston, J.W., 2011. Rotenone, paraquat, and Parkinson's disease. Environmental Health Perspectives 119, 866–872.

Thiruchelvam, M., Richfield, E.K., Goodman, B.M., Baggs, R.B., Cory-Slechta, D.A., 2002. Developmental exposure to the pesticides paraquat and maneb and the Parkinson's disease phenotype. Neurotoxicology 23, 621–633.

Thiruchelvam, M., Prokopenko, O., Cory-Slechta, D.A., Buckley, B., Mirochnitchenko, O., 2005. Overexpression of superoxide dismutase or glutathione peroxidase protects against the paraquat + maneb-induced Parkinson disease phenotype. The Journal of Biological Chemistry 280, 22530–22539.

Thomas, B., Beal MF, 2007. Parkinson's disease. Human Molecular Genetics 16 Spec No. 2, R183–R194.

Twig, G., Elorza, A., Molina, A.J., Mohamed, H., Wikstrom, J.D., Walzer, G., Stiles, L., Haigh, S.E., Katz, S., Las, G., Alroy, J., Wu, M., Py, B.F., Yuan, J., Deeney, J.T., Corkey, B.E., Shirihai, O.S., 2008. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. The EMBO Journal 27, 433–446.

Uversky, V.N., 2007. Neuropathology, biochemistry, and biophysics of alpha-synuclein aggregation. Journal of Neurochemistry 103, 17–37.

Valente, E.M., Abou-Sleiman, P.M., Caputo, V., Muqit, M.M., Harvey, K., Gispert, S., Ali, Z., Del Turco, D., Bentivoglio, A.R., Healy, D.G., Albanese, A., Nussbaum, R., Gonzalez-Maldonado, R., Deller, T., Salvi, S., Cortelli, P., Gilks, W.P., Latchman, D.S., Harvey, R.J., Dallapiccola, B., Auburger, G., Wood, N.W., 2004. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 304, 1158–1160.

Van Remmen, H., Qi, W., Sabia, M., Freeman, G., Estlack, L., Yang, H., Mao Guo, Z., Huang, T.T., Strong, R., Lee, S., Epstein, C.J., Richardson, A., 2004. Multiple deficiencies in antioxidant enzymes in mice result in a compound increase in sensitivity to oxidative stress. Free Radical Biology & Medicine 36, 1625–1634.

Varastet, M., Riche, D., Maziere, M., Hantraye P, 1994. Chronic MPTP treatment reproduces in baboons the differential vulnerability of mesencephalic dopaminergic neurons observed in Parkinson's disease. Neuroscience 63, 47–56.

Vercammen, L., Van der Perren, A., Vaudano, E., Gijsbers, R., Debyser, Z., Van den Haute, C., Baekelandt, V., 2006. Parkin protects against neurotoxicity in the 6-hydroxydopamine rat model for Parkinson's disease. Molecular therapy. The Journal of the American Society of Gene Therapy 14, 716–723.

Vives-Bauza, C., Andreu, A.L., Manfredi, G., Beal, M.F., Janetzky, B., Gruenewald, T.H., Lin, M.T., 2002. Sequence analysis of the entire mitochondrial genome in Parkinson's disease. Biochemical and Biophysical Research Communications 290, 1593–1601.

Wang, X.F., Li, S., Chou, A.P., Bronstein JM, 2006. Inhibitory effects of pesticides on proteasome activity: implication in Parkinson's disease. Neurobiology of Disease 23, 198–205.

Wang, H.L., Chou, A.H., Yeh, T.H., Li, A.H., Chen, Y.L., Kuo, Y.L., Tsai, S.R., Yu, S.T., 2007. PINK1 mutants associated with recessive Parkinson's disease are defective in inhibiting mitochondrial release of cytochrome c. Neurobiology of Disease 28, 216–226.

Wang, H.L., Chou, A.H., Wu, A.S., Chen, S.Y., Weng, Y.H., Kao, Y.C., Yeh, T.H., Chu, P.J., Lu, C.S., 2011. PARK6 PINK1 mutants are defective in maintaining mitochondrial membrane potential and inhibiting ROS formation of substantia nigra dopaminergic neurons. Biochimica et Biophysica Acta 1812, 674–684.

Wang, Y., Shi, M., Chung, K.A., Zabetian, C.P., Leverenz, J.B., Berg, D., Srulijes, K., Trojanowski, J.Q., Lee, V.M., Siderowf, A.D., Hurtig, H., Litvan, I., Schiess, M.C., Peskind, E.R., Masuda, M., Hasegawa, M., Lin, X., Pan, C., Galasko, D., Goldstein, D.S., Jensen, P.H., Yang, H., Cain, K.C., Zhang, J., 2012. Phosphorylated alpha-synuclein in Parkinson's disease. Science Translational Medicine 121 (4) ra120.

Wen, Y., Li, W., Poteet, E.C., Xie, L., Tan, C., Yan, L.J., Ju, X., Liu, R., Qian, H., Marvin, M.A., Goldberg, M.S., She, H., Mao, Z., Simpkins, J.W., Yang, S.H., 2011. Alternative mitochondrial electron transfer as a novel strategy for neuroprotection. The Journal of Biological Chemistry 286, 16504–16515.

West, A.B., Moore, D.J., Biskup, S., Bugayenko, A., Smith, W.W., Ross, C.A., Dawson, V.L., Dawson, T.M., 2005. 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 102, 16842–16847.

Wilson, C.J., Callaway, J.C., 2000. Coupled oscillator model of the dopaminergic neuron of the substantia nigra. Journal of Neurophysiology 83, 3084–3100.

Winklhofer, K.F., Haass, C., 2010. Mitochondrial dysfunction in Parkinson's disease. Biochimica et Biophysica Acta 1802, 29–44.

Winklhofer, K.F., Tatzelt, J., Haass, C., 2008. The two faces of protein misfolding: gain- and loss-of-function in neurodegenerative diseases. The EMBO Journal 27, 336–349.

Wood-Kaczmar, A., Gandhi, S., Yao, Z., Abramov, A.Y., Miljan, E.A., Keen, G., Stanyer, L., Hargreaves, I., Klupsch, K., Deas, E., Downward, J., Mansfield, L., Jat, P., Taylor, J., Heales, S., Duchen, M.R., Latchman, D., Tabrizi, S.J., Wood, N.W., 2008. PINK1 is necessary for long term survival and mitochondrial function in human dopaminergic neurons. PloS One 3, e2455.

Wu, B.L., Song, B., Tian, S.Z., Huo, S.H., Cui, C.X., Guo, Y.S., Liu, H.J., 2012. Central nervous system damage due to acute paraquat poisoning: a neuroimaging study with 3.0T MRI. Neurotoxicology 33 (5) 1330–1337.

Yang, W., Tiffany-Castiglioni, E., 2005. The bipyridyl herbicide paraquat produces oxidative stress-mediated toxicity in human neuroblastoma SH-SY5Y cells: relevance to the dopaminergic pathogenesis. Journal of Toxicology and Environmental Health Part A 68, 1939–1961.

Yang, Y., Gehrke, S., Imai, Y., Huang, Z., Ouyang, Y., Wang, J.W., Yang, L., Beal, M.F., Vogel, H., Lu, B., 2006. Mitochondrial pathology and muscle and dopaminergic neuron degeneration caused by inactivation of *Drosophila* Pink1 is rescued by Parkin. Proceedings of the National Academy of Sciences of the United States of America 103, 10793–10798.

Yang, W., Chen, L., Ding, Y., Zhuang, X., Kang, U.J., 2007. Paraquat induces dopaminergic dysfunction and proteasome impairment in DJ-1-deficient mice. Human Molecular Genetics 16, 2900–2910.

Yang, Y., Ouyang, Y., Yang, L., Beal, M.F., McQuibban, A., Vogel, H., Lu, B., 2008. Pink1 regulates mitochondrial dynamics through interaction with the fission/fusion machinery. Proceedings of the National Academy of Sciences of the United States of America 105, 7070–7075.

Yokota, T., Sugawara, K., Ito, K., Takahashi, R., Ariga, H., Mizusawa, H., 2003. Down regulation of DJ-1 enhances cell death by oxidative stress, ER stress, and proteasome inhibition. Biochemical and Biophysical Research Communications 312, 1342–1348.

Yoshino, H., Nakagawa-Hattori, Y., Kondo, T., Mizuno, Y., 1992. Mitochondrial complex I and II activities of lymphocytes and platelets in Parkinson's disease. Journal of Neural Transmission Parkinson's Disease and Dementia Section 4, 27–34.

Yu, W., Sun, Y., Guo, S., Lu, B., 2011. The PINK1/Parkin pathway regulates mitochondrial dynamics and function in mammalian hippocampal and dopaminergic neurons. Human Molecular Genetics 20, 3227–3240.

Yumino, K., Kawakami, I., Tamura, M., Hayashi, T., Nakamura, M., 2002. Paraquat- and diquat-induced oxygen radical generation and lipid peroxidation in rat brain microsomes. Journal of Biochemistry 131, 565–570.

Zarranz, J.J., Alegre, J., Gomez-Esteban, J.C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atares, B., Llorens, V., Gomez Tortosa, E., del Ser, T., Munoz, D.G., de Yebenes, J.G., 2004. The new mutation E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Annals of Neurology 55, 164–173.

Zhang, J., Fitsanakis, V.A., Gu, G., Jing, D., Ao, M., Amarnath, V., Montine, T.J., 2003. Manganese ethylene-bis-dithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. Journal of Neurochemistry 84, 336–346.

Zhang, L., Shimoji, M., Thomas, B., Moore, D.J., Yu, S.W., Marupudi, N.I., Torp, R., Torgner, I.A., Ottersen, O.P., Dawson, T.M., Dawson, V.L., 2005. Mitochondrial localization of the Parkinson's disease related protein DJ-1: implications for pathogenesis. Human Molecular Genetics 14, 2063–2073.

Zhang, L., Zhang, C., Zhu, Y., Cai, Q., Chan, P., Ueda, K., Yu, S., Yang, H., 2008. Semi-quantitative analysis of alpha-synuclein in subcellular pools of rat brain

neurons: an immunogold electron microscopic study using a C-terminal specific monoclonal antibody. Brain Research 1244, 40–52.

Zhang, X., Zhou, J.Y., Chin, M.H., Schepmoes, A.A., Petyuk, V.A., Weitz, K.K., Petritis, B.O., Monroe, M.E., Camp, D.G., Wood, S.A., Melega, W.P., Bigelow, D.J., Smith, D.J., Qian, W.J., Smith, R.D., 2010. Region-specific protein abundance changes in the brain of MPTP-induced Parkinson's disease mouse model. Journal of Proteome Research 9, 1496–1509.

Zhong, N., Xu, J., 2008. Synergistic activation of the human MnSOD promoter by DJ-1 and PGC-1alpha: regulation by SUMOylation and oxidation. Human Molecular Genetics 17, 3357–3367.

Zhou, Y., Shie, F.S., Piccardo, P., Montine, T.J., Zhang, J., 2004. Proteasomal inhibition induced by manganese ethylene-bis-dithiocarbamate: relevance to Parkinson's disease. Neuroscience 128, 281–291.

Zhu, C., Vourc'h, P., Fernagut, P.O., Fleming, S.M., Lacan, S., Dicarlo, C.D., Seaman, R.L., Chesselet, M.F., 2004. Variable effects of chronic subcutaneous administration of rotenone on striatal histology. The Journal of Comparative Neurology 478, 418–426.

Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., Kachergus, J., Hulihan, M., Uitti, R.J., Calne, D.B., Stoessl, A.J., Pfeiffer, R.F., Patenge, N., Carbajal, I.C., Vieregge, P., Asmus, F., Muller-Myhsok, B., Dickson, D.W., Meitinger, T., Strom, T.M., Wszolek, Z.K., Gasser, T., 2004. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 44, 601–607.

Zorzano, A., Liesa, M., Sebastian, D., Segales, J., Palacin, M., 2010. Mitochondrial fusion proteins: dual regulators of morphology and metabolism. Seminars in Cell & DevelopmentalB 21, 566–574.