Front. Biol. 2014, 9(6): 489–503
DOI 10.1007/s11515-014-1337-8

REVIEW

Mitochondrial dysfunction in Parkinson's disease: a possible target for neuroprotection

Jacqueline A. GLEAVE, Peter D. PERRI, Joanne E. NASH (✉)

Centre for Neurobiology of Stress, Department of Biological Sciences, University of Toronto Scarborough, Toronto, Ontario, M1C1A4, Canada

Abstract **Mitochondria are dynamic organelles which are required for maintaining cellular homeostasis. Thus, it is not surprising that irregularities in mitochondrial function result in cellular damage and are linked with neurodegenerative diseases, such as Parkinson's disease. Evidence that mitochondrial dysfunction is key to the pathogenesis of Parkinson's disease is founded in studies in post-mortem tissue from patients with Parkinson's disease, and also from genetic studies stemming from patients with familial Parkinson's disease. Whether triggered by environmental or genetic factors, mitochondrial dysfunction occurs early in the pathogenic process, and is central to Parkinson's disease pathology. As such, targeting the mitochondria to slow or halt disease progression is an attractive strategy for disease-modifying agents in Parkinson's disease. Indeed, several therapies which target the mitochondria have been investigated as neuroprotective treatments for Parkinson's disease. This review will discuss the evidence supporting mitochondrial dysfunction in Parkinson's disease pathology as well as treatment strategies that target the mitochondria.**

Keywords Parkinson's disease, mitochondria, oxidative stress, lysosome, UPS

Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, which affects 1%–2% of the population above the age of 65. This percentage will increase as the population ages (Dorsey et al., 2007). PD presents with characteristic motor abnormalities, which include resting tremor, bradykinesia, and rigidity (Bernheimer et al., 1973). The principle lesion underlying these symptoms is the loss of dopaminergic neurons that project from the substantia nigra *pars compacta* (SNc) to the striatum as the nigrostriatal pathway (Bernheimer et al., 1973). At the time of diagnosis, approximately 50% of the neurons in the nigrostriatal pathway have degenerated (Bernheimer et al., 1973), and many of the remaining neurons are undergoing cell stress (Murray et al., 1995). Presently, the most commonly used, and most effective treatment is the dopamine precursor, levodopa (L-DOPA), which initially restores motor abnormalities extremely effectively (Katzenschlager and Lees, 2002). However, within 5 to 10 years, most patients begin to experience uncontrollable writhing movements, known as dyskinesias, which can be as disabling as the symptoms of PD (Katzenschlager and Lees, 2002). Thus, the need to find disease modifying agents able to halt or slow the progression of PD pathology would be extremely beneficial to patients, and would also decrease the economic load of PD on society, as the need for palliative care would be reduced. Currently, there are no neuroprotective treatments available for PD. If, upon diagnosis, patients could be given such a neuroprotective treatment that could halt or slow the disease process, patient's symptoms would not advance to the more debilitating stages, increasing patient quality of life. To develop neuroprotective treatments for PD, we must first understand how the neurons degenerate. The aim of this review is to first describe what we know about the pathological processes linked with PD, then to discuss possible avenues for neuroprotective treatments, with a specific focus on the mitochondria as this is thought to be central to all cell death processes in PD. With regards to the pathological processes linked with cell death in PD, we will focus mostly on post mortem and genetic studies.

Received August 14, 2014; accepted September 25, 2014
Correspondence: Joanne E. NASH
E-mail: jnash@utsc.utoronto.ca

Pathological processes involved in PD pathology

Although the mechanism by which neurons degenerate in PD is poorly understood, two key pathways have been implicated in PD: (1) aberrant protein homeostasis (via dysfunction of the ubiquitin-proteasome system (UPS) and lysosomes), and (2) mitochondrial dysfunction. Increased oxidative stress likely plays a contributory role in all of these processes. Aberrant protein homeostasis and mitochondria dysfunction are discussed below.

Evidence for aberrant protein homeostasis in Parkinson's disease

The presence of protein inclusions called Lewy bodies (LB) in affected brain regions provides evidence that the handling of misfolded proteins is impaired in PD. Lewy bodies are spherical proteinacous inclusions, which are localized in affected brain regions that are usually identified post-mortem. LBs contain a high concentration of ubiquinated proteins, predominantly mis-folded α-synuclein and ubiquitin (Spillantini et al., 1997, 1998). Protein ubiquination is one of the main ways that cells remove dysfunctional or misfolded proteins. It is also used, along with lysosomal degradation, to regulate physiologic processes in order to remove proteins that are no longer required. In PD, either due to a mutation in α-synuclein, or due to mutations in the UPS and lysosome system, protein degradation mechanisms within the cell are sub-functional, resulting in accumulation of mis-folded protein, initially in the form of aggregates or protofibrils, which are toxic to the cell. These deleterious protofibrils are eventually rounded up by the cell into the inert LB formations where they are no longer thought to have a toxic impact on the cell (Tanaka et al., 2004).

The discovery of mutations in the parkin gene, an E3 ubiquitin-protein ligase, in familial PD supports the idea that dysfunction of the UPS plays a role in PD pathology. Parkin contributes to protein homeostasis by tagging misfolded proteins for degradation by the proteasome (Cookson , 2003; Sakata et al., 2003). Furthermore, ubiquitin C-terminal hydrolase (UCHL1) mutations have been identified in familial PD (Leroy et al., 1998). UCHL1 is part of a family of deubiquitinating enzymes responsible for cleaving polymeric ubiquitin into monomers (Leroy et al., 1998). Disruption of this process could lead to inhibition of proper UPS function. However, a meta-analysis did not find a link between UCHL1 mutations and PD in Caucasian patients (Healy et al., 2006). In support of protein mishandling being a key contributor to the pathogenic process in PD, several groups have shown evidence of SNc neurodegeneration, associated with neuronal inclusions, when proteasome inhibitors were delivered to rodents (McNaught et al., 2004; Lim, 2007). These studies have been questioned, as other groups were not able to reproduce the data (Bové et al., 2006; Kordower et al., 2006), although genetic approaches have yielded similar results (Bedford et al., 2008). In addition to the disruption of the proteasome, lysosomal dysfunction has been implicated in PD pathology. Mutations in lysosomal P-type ATPase, *ATP13A2*, cause a juvenile, early-onset parkinsonism; however, it is also characterized by dementia and pyramidal degeneration (Ramirez et al., 2006). Taken together, there is compelling evidence that protein homeostasis is disrupted and a key event in PD pathology.

Mitochondrial dysfunction in Parkinson's disease

Both toxin-based and genetic evidence highlight the important role of mitochondria in the pathology of PD. Mitochondrial dysfunction has been implicated in PD pathology since the early 1980s when young addicts drugs accidently ingested 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), causing degeneration of the SNc and parkinsonian symptoms (Langston et al., 1983). MPTP inhibits complex I of the electron transport chain (ETC) in mitochondria. L-DOPA and carbidopa have been successfully used to treat MPTP-induced PD suggesting similar mechanisms underlying sporadic PD and MPTP-induced parkinsonism (Langston et al., 1983). Mitochondrial dysfunction as a key event in PD pathology was further supported by the use of MPTP and rotenone, a mitochondrial toxin, to create PD models by impairing the ETC in the mitochondria. This allowed study of the impact of inhibition of complex I function in the SNc (Dauer and Przedborski, 2003). These initial studies, as well as later ones showed that nigral neurons are less capable of dealing with oxidative stress than other neuronal cells, and their inherent properties make them more susceptible to injury than most cells. Nigral neurons are extremely reliant on healthy mitochondria to maintain their viability because of their reduced calcium buffering capacity (Surmeier , 2007; Chan et al., 2010; Surmeier et al., 2010), increased ATP demands (Chan et al., 2010), elevated oxidative stress (Sulzer and Zecca, 2000; Greene et al., 2003; Chinta et al., 2010), and intrinsic calcium channel pacemaker activity (Ping and Shepard, 1999; Chan et al., 2007; Guzman et al., 2010).

Post-mortem studies provide evidence that mitochondrial dysfunction is part of the disease process. Post-mortem studies in PD patients show decreased complex I function (Schapira et al., 1989). Furthermore, complex I becomes increasingly impaired as the disease progresses (Parker et al., 1989; Haas et al., 1995). As well, other complexes in the ETC have reduced activity in PD patients (Haas et al., 1995). PD patients also have a high number of mitochondrial DNA (mtDNA) mutations in the SNc, many of which are associated with the ETC, which implicates a role in mitochondrial dysfunction resulting in cell death (Bender et al., 2006; Kraytsberg et al., 2006). Further supporting this is the mouse model where mitochondrial transcription factor A (TFAM), a mitochondrial transcription factor that plays a role in maintaining mtDNA, is disrupted resulting in decreased

ETC activity and progressive loss of DA neurons (Ekstrand et al., 2007). With the discovery of genetic factors that lead to familial PD, the importance of proper mitochondrial function has been highlighted. Several gene mutations found in familial PD are associated with the mitochondria and their toxic gain of function mutations, or loss of function leads to mitochondrial dysfunction. These proteins also play a vital role in mitochondrial health by controlling mitochondrial dynamics to remove damaged mitochondria through fusion/fission events.

Using a cell model of PD, recent work from our group showed that mitochondrial dysfunction is an early event in cell death processes linked with PD, regardless of whether the initial insult is focused on mitochondria (Yong-Kee et al., 2012). For these studies, we utilized a catecholaminergic cell line (SH-SY5Y) and exposed these cells to LD50 concentrations of toxins that mimic three cell death mechanisms associated with PD: (1) UPS dysfunction, lysosomal dysfunction, and mitochondria abnormalities (Yong-Kee et al., 2011). Other studies have also shown that no matter what the initiating cause of cell death, mitochondrial dysfunction represents a convergence between all PD-linked cell death mechanisms (Greenamyre et al., 2003; Höglinger et al., 2003).

Understanding PD pathology through the origins of familial PD

Most cases of PD (90%–95%) are believed to be sporadic, while the remaining 5%–10% of the cases have been linked to genetic mutations. Such genetic mutations include α-synuclein, LRRK2, PINK1, parkin, DJ-1, UCHL1 and ATP13A2, and have provided tremendous insight into the molecular pathology underlying PD. The clinical manifestation of sporadic and familial PD is similar, which supports the idea that some of the pathogenic mechanisms are common to both forms of PD.

Genetic evidence for the role of mitochondrial dysfunction in Parkinson's disease

Both autosomal dominant and recessive genetic mutations associated with PD have been linked to the mitochondria, implicating mitochondrial dysfunction as central to PD pathology. These mutant proteins may primarily impact other sub-cellular processes, such as UPS or lysosome function, but the majority of these mutant proteins have also been shown to impact the mitochondria.

Alpha-synuclein (α-synuclein)

α-synuclein is a 140 amino acid protein that is associated with synaptic terminal membranes at the presynapse (Goedert , 2001; Cole and Murphy, 2002). LB, which are commonly associated with PD, are largely composed of α-synuclein (Spillantini et al., 1997). Several mutations in α-synuclein have been identified in both sporadic and familial forms of PD, these are A53T (Polymeropoulos et al., 1997), A30P (Krüger et al., 1998), E46K (Zarranz et al., 2004), and duplication and triplication of the α-synuclein gene (Chartier-Harlin et al., 2004; Fuchs et al., 2007).

Misfolded α-synuclein is broken down by both the UPS and chaperone-mediated autophagy (CMA) (Cuervo et al., 2004). Misfolded forms of mutant α-synuclein that are linked with PD have a direct dysfunctional effect on the UPS, autophagy, and CMA function (Snyder et al., 2003; Xilouri et al., 2009; Winslow et al., 2010; Zhang et al., 2008). Several lines of evidence also suggest a role for wild-type and mutant α-synuclein in mitochondrial dysfunction. Initial studies showed that animals overexpressing wild-type and mutant α-synuclein had increased sensitivity to MPTP (Richfield et al., 2002). In addition MPTP mice overexpressing wild-type α-synuclein had an increased number of mitochondrial abnormalities that are specific to the substantia nigra (Song et al., 2004). This was further corroborated in studies that demonstrated α-synuclein deficient mice were resistant to MPTP, malonate, and 2-nitropropionic acid, which are mitochondrial toxins (Klivenyi et al., 2006). Finally, rotenone toxicity in cells was increased when wild-type α-synuclein was overexpressed (Shavali et al., 2008). Taken together, these studies indicate that both mutant α-synuclein and the overexpression of wild-type α-synuclein may play an important role in mitochondrial function.

Several studies have demonstrated that wild-type and/or A53T mutant α-synuclein localizes to the mitochondria in cells (Parihar et al., 2008; Shavali et al., 2008) and dopaminergic neurons (Devi et al., 2008; Chinta et al., 2010), rodents (Liu et al., 2009; Sarafian et al., 2013), and in patients with PD (Devi et al., 2008). In PD patients, the amount of α-synuclein bound to the mitochondria was elevated in brain regions that undergo degeneration during the disease process (Devi et al., 2008). The first 32 amino acids target α-synuclein to the mitochondria, which involves an outer mitochondrial membrane import channel (Devi et al., 2008). It has been suggested that α-synuclein associates with the inner mitochondrial membrane (Devi et al., 2008; Shavali et al., 2008) and once localized to the mitochondria, it caused an increase in intra-mitochondrial calcium and nitric oxide and the release of cytochrome c (Parihar et al., 2008). Once localized in the mitochondria, α-synuclein interacted with complex I, inhibiting it and causing oxidative stress (Devi et al., 2008; Liu et al., 2009). More recent work has suggested that α-synuclein was localized to mitochondrial-associated ER membranes (MAMs) (Guardia-Laguarta et al., 2014). Mutations in α-synuclein, such as the ones identified in PD, caused the redistribution of α-synuclein from MAMs to the pure mitochondrial fraction resulting in reduced ER-mitochondrial connectivity and increased mitochondrial fragmen-

tation (Guardia-Laguarta et al., 2014). In this study, the overexpression of wild-type α-synuclein did not result in mitochondrial localization as suggested in previous studies (Devi et al., 2008; Parihar et al., 2008; Shavali et al., 2008). This could be due to a threshold level of overexpression needed to redistribute wild-type α-synuclein from MAMs to the mitochondria and that this threshold may not have been reached in the study.

Early studies demonstrated that it was aggregated α-synuclein and not monomeric α-synuclein that associated with the mitochondria (Parihar et al., 2008). This was corroborated in recent studies performed in cell culture demonstrating that preformed fibrils increase mitochondrial oxidative stress (Dryanovski et al., 2013). Likewise, in PD, preformed fibrils of α-synuclein were proposed to be the main toxic α-synuclein species (Marques and Outeiro, 2012). These studies lend evidence that α-synuclein disrupts mitochondrial function, contributing to the pathogenesis of PD.

Leucine Rich Repeat Kinase 2 (LRRK2)

Leucine Rich Repeat Kinase 2 (LRRK2) is a 2527 amino acid protein with several conserved domains including a leucine-rich repeat, a c-terminal of Roc domain (roc-COR), a kinase domain, and a WD40 domain (Li and Beal, 2005). There are at least 20 LRRK2 mutations linked with PD, such as G2019S, R1441C, I2020T, I1122V, and Y1699C (Li and Beal, 2005; Greggio et al., 2006) with the G2019S substitution being the most prevalent. This mutation increases autophosphorylation of LRRK2 and also kinase activity, resulting in neuronal death, suggesting that toxic gain of function underlies neurotoxicity (Greggio et al., 2006; West et al., 2005). Mutations in LRRK2 are seen in both autosomal-dominant familial PD and sporadic PD. LRRK2 is degraded by CMA and mutations in LRRK2 cause inhibition of CMA function indicating that LRRK2 disrupts lysosomal function (Orenstein et al., 2013). In addition to the effect of LRRK2 on protein degradation, several studies have suggested a link between LRRK2 and mitochondrial dysfunction in PD (Ng et al., 2009; Saha et al., 2009). Furthermore, LRRK2 mutations caused increased sensitivity to mitochondrial toxins in cells, model organisms, and rodents (Ramonet et al., 2011; Wang et al., 2012).

LRRK2 is present in the mitochondria and specifically associated with the mitochondrial membrane (Papkovskaia et al., 2012) where it may play a role in mitochondrial dynamics. Several studies have shown that overexpression of LRRK2 or expression of the G2019S or R1441C mutation resulted in increased mitochondrial fragmentation (Niu et al., 2012; Wang et al., 2012; Su and Qi, 2013). In contrast, another study demonstrated increased mitochondrial connectivity in fibroblasts from PD patients with the G2019S mutation (Mortiboys et al., 2010). However, this discrepancy could be due to the different cell types used in the studies, as disparities in the effect of mutations on mitochondrial function have been demonstrated between neuronal cells and fibroblasts (Mortiboys et al., 2008; Lutz et al., 2009). Studies by Wang et al. showed that mitochondrial fusion was slowed with the overexpression of wild-type LRRK2 and this was further enhanced with expression of the G2019S or R1441C mutations. The changes in mitochondrial dynamics observed in this study were dependent on LRRK2 kinase activity. DLP1, a protein involved in mitochondrial fission, was responsible for the increased fragmentation seen with over-expression of LRRK2 (Niu et al., 2012; Wang et al., 2012). A direct interaction of DLP1 and LRRK2 was demonstrated using co-immunoprecipitation (Wang et al., 2012). Further studies demonstrated that DLP1 translocates from the cytosol to the mitochondria with wild-type LRRK2 or mutant (G2019S) overexpression, and that the roc-COR domain of LRRK2 interacts with DLP1 (Niu et al., 2012). However, other studies were unable to demonstrate that LRRK2 interacted with DLP1 or influenced the expression levels of this protein (Papkovskaia et al., 2012). The G2019S-LRRK2 mutation has also been demonstrated to cause excessive mitochondria-associated autophagy, lysosomal hyperactivity, and an increased number of autophagosomes indicative of increased mitophagy (Cherra et al., 2013; Su and Qi, 2013). This is thought to be caused by the G2019S-mediated hyperactivation of DLP1 (Su and Qi, 2013). In addition, mitochondrial calcium homeostasis is disrupted (Cherra et al., 2013), which would further increase mitochondrial stress.

Mitochondrial homeostasis is essential for proper mitochondrial function. Several studies have demonstrated that wild type LRRK2 or mutant (G2019S) overexpression caused an increase in reactive oxygen species (ROS) and a decrease in mitochondrial membrane potential and ATP levels (Mortiboys et al., 2010; Niu et al., 2012; Wang et al., 2012; Papkovskaia et al., 2012; Cherra et al., 2013; Su and Qi, 2013). A decrease in the function of ETC complexes has been suggested as a reason for the decrease in mitochondrial membrane potential and ATP production (Mortiboys et al., 2010; Su and Qi, 2013). It has also been suggested that an upregulation of the uncoupled proteins by the G2019S-LRRK2 mutant caused proton leaking, which is responsible for decreased mitochondrial membrane potential and a reduction in ATP levels without the generation of free radicals (Papkovskaia et al., 2012). Taken together, studies to date suggest that LRRK2 mutations in sporadic and familial PD, combined with its association with mitochondrial function, lend evidence to mitochondrial dysfunction being central to PD pathogenesis.

PTEN induced kinase 1 (PINK1)

PTEN induced kinase 1 (PINK1) is a 581 amino acid protein with a predicted mitochondrial targeting domain, protein kinase domain, and homology to serine/threonine kinases of the calcium/calmodulin family (Valente et al., 2004).

Mutations in PINK1 are associated with juvenile, autosomal recessive, early-onset PD. Large deletions or frame-shift truncations indicate a loss-of-function pathogenic mechanism (Valente et al., 2004; Clark et al., 2006; Park et al., 2006). The mitochondrial targeting sequence of PINK1 suggests that it directly interacts with, and functions, at the level of the mitochondria.

PINK1 localizes to the mitochondria (Valente et al., 2004; Park et al., 2006) and mutations in PINK1 cause an increased sensitivity to cell stress (Valente et al., 2004; Gautier et al., 2008), which does not occur under basal conditions (Valente et al., 2004). The loss of mitochondrial membrane potential with PINK1 mutations results in a loss of ATP in cells and mice (Valente et al., 2004; Wood-Kaczmar et al., 2008; Gispert et al., 2009; Gómez-Sánchez et al., 2014; Morais et al., 2014). Loss of PINK1 also affects the normal function of the mitochondria in mice (Gautier et al., 2008; Gispert et al., 2009). In these mice, there is reduced respiration in the ETC complexes (Gautier et al., 2008; Gispert et al., 2009). More recently, it has been demonstrated that PINK1 is required to maintain complex I function in the ETC (Wood-Kaczmar et al., 2008; Morais et al., 2014). The mitochondrial deficits caused by PINK1 deficiency were rescued by a phosphomimetic mutant of NdufA2, a component of complex I of the ETC. Taken together, these studies demonstrate the PINK1 is necessary for proper function of the mitochondria.

In addition, studies have shown that PINK1 has an important role in mitochondrial dynamics in cell (Wood-Kaczmar et al., 2008), drosophila (Clark et al., 2006; Park et al., 2006), and rodent models (Kitada et al., 2007; Gautier et al., 2008; Gispert et al., 2009) of PD. PINK1 functions with parkin to ensure appropriate mitochondrial dynamics (Park et al., 2006; Gispert et al., 2009; Wang et al., 2011; Scarffe et al., 2014). Loss of PINK1 function results in impaired fission in both drosophila and mice (Park et al., 2006; Gautier et al., 2008; Gispert et al., 2009). Impairments in mitochondrial dynamics involve parkin, a protein associated with autosomal recessive, early-onset PD and will be discussed in the next section.

Although loss of dopamine neurons has not been seen in PINK1 deficient mice (Kitada et al., 2007; Gautier et al., 2008; Gispert et al., 2009), behavioral phenotypes and changes in striatal dopamine levels have been identified. PINK1 knockout mice have decreased weight and locomotor function in comparison to wild-type mice (Gispert et al., 2009). In the striatum, there is decreased dopamine content in aged mice and defects in pre-synaptic dopaminergic function (Kitada et al., 2007; Gispert et al., 2009). It has been proposed that PINK1 deficiency alone is not enough to cause neuronal loss, but rather sensitizes cells to a second insult, which leads to dopaminergic cell loss. Indeed, it was demonstrated in mice that loss of PINK1 combined with mitochondrial stress recapitulates many of the cardinal features in PD, interestingly, these deficits were not rescued by L-DOPA treatment (Moisoi et al., 2014).

Parkin

Parkin is a large gene encoding a 465 amino acid protein that has a ubiquitin-like domain at the N terminus, two C-terminal ring finger motifs, and an in-between ring-finger domain (Kitada et al., 1998; Greene et al., 2003). Parkin can act as an E3 ligase, and binds to, then ubiquinates many specific substrates (Imai et al., 2000; Shimura et al., 2000; Itier et al., 2003)

Many parkin studies have demonstrated its involvement in regulating mitochondrial function. In drosophila, loss of parkin reduced longevity and resulted in swollen mitochondria with disintegration of cristae, ultimately leading to cell death (Greene et al., 2003; Pesah et al., 2004). Mitochondrial pathology is the primary defect in parkin knockout drosophila, along with motor deficits (Greene et al., 2003). Further supporting a role for parkin in mitochondrial function was the increased sensitivity of drosophila to oxidative stress following loss of parkin (Pesah et al., 2004). Parkin-deficient mice, like drosophila, have reduced bodyweight (Itier et al., 2003; Pesah et al., 2004). However, unlike drosophila, parkin knockout mice are viable, fertile, and have the same mortality rate in comparison to wild-type mice (Itier et al., 2003). This suggests that in mice, another gene is able to compensate for lost parkin, which is not the case in drosophila.

Studies in parkin knockout mice showed that parkin plays a role in the dopaminergic system, as these mice have reduced levels of dopamine transporter and vesicular monoamine transporter in the striatum (Itier et al., 2003). In the limbic system, it was found that parkin dysfunction impaired dopamine release and increased the intra-neuronal metabolism of dopamine via monoamine oxidase (Itier et al., 2003). Using primary midbrain cultures from parkin-deficient mice, a decrease in newly synthesized dopamine release and a decrease in dopamine reuptake was demonstrated (Itier et al., 2003). In other studies, it was found that the levels of dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were similar in the striatum of parkin-deficient mice and wild-type mice (Goldberg et al., 2003). This study also showed elevated dopamine release as well as extracellular dopamine in the striatum (Goldberg et al., 2003). The medium spiny neurons were also less excitable due to post-synaptic alterations (Goldberg et al., 2003). Taken together, these data demonstrate that parkin plays a role in mitochondrial function and loss of parkin function causes changes in dopamine release and neuronal function in the nigrostriatal pathway.

Parkin is also involved in the degradation of mitochondria through the autophagosome-lysosome pathway. Parkin is recruited to mitochondria upon loss of mitochondrial membrane potential by PINK1 (Narendra et al., 2008; Poole et al., 2008; Wang et al., 2011). Once recruited to dysfunctional mitochondria, parkin works downstream of PINK1, causing mitochondrial engulfment by autophagosomes (Narendra et al., 2008). It has been demonstrated that

overexpression of parkin can rescue the PINK1 knockout phenotype in drosophila and in human cells (Park et al., 2006; Exner et al., 2012). Further studies have demonstrated that parkin and PINK1 function to target dysfunctional mitochondria for mitophagy. Parkin is required for PINK1-mediated loss of Miro, a protein involved in tethering the mitochondria to kinesin, which is responsible for the mobility of mitochondria (Wang et al., 2011). When parkin is recruited to the mitochondria, PINK1 phosphorylates Miro, causing the release of kinesin, which inhibits mitochondrial movement. Parkin then targets Miro for degradation (Wang et al., 2011). The dysfunctional mitochondria are also degraded by mitophagy. More recently it has been proposed that parkin and PINK1 function to remove damaged proteins from the mitochondria in mitochondrial derived vesicles (MDV), which are directed to the lysosome, prior to complete loss of mitochondrial membrane potential (McLelland et al., 2014). MDVs bud off the mitochondria using a mechanism that is independent of the mitochondrial fission machinery (Neuspiel et al., 2008; Soubannier et al., 2012). This process is kinetically faster than mitophagy, and may provide a mechanism to preserve the integrity of mitochondria (McLelland et al., 2014). Therefore, parkin and PINK1 can function together in two distinct mitochondrial quality control mechanisms: the first to shuttle selective cargo to lysosomes to preserve the mitochondria, and the second to deliver whole mitochondria to autophagosomes to enable mitophagy. The former mechanism functions in a fission-independent manner and is initiated by ROS, whereas the latter is initiated by loss of mitochondrial membrane potential.

DJ-1

DJ-1 mutations are found in autosomal recessive, early-onset PD. DJ-1 belongs to the DJ-1/Thi/PfpI superfamily of proteins and is localized to the mitochondria (Canet-Avilés et al., 2004; Zhang et al., 2005). Loss of function of DJ-1 contributes to the development of PD, although how DJ-1 contributes to PD pathogenesis is largely unknown. DJ-1 is involved in mediating oxidative stress and loss of DJ-1 function results in increased oxidative stress, which is thought to play a role in the onset of PD pathology (Zhang et al., 2005). The subcellular location of DJ-1, and its role as an antioxidant indicates that physiologically, DJ-1 is involved in maintaining the quality of the mitochondria. DJ-1 is specifically localized to the mitochondria under basal conditions and its association with mitochondria increases under conditions of oxidative stress (Canet-Avilés et al., 2004; Blackinton et al., 2009). However, some studies contradict these findings (Zhang et al., 2005). Despite these disparities, all studies to date (both *in vivo* and *in vitro*) agree that loss of DJ-1 results in increased oxidative stress and reduced mitochondrial membrane potential (Kim et al., 2005; Andres-Mateos et al., 2007; González-Polo et al., 2009; Krebiehl et al., 2010; Minakawa et al., 2013). Studies *in vitro* showed that DJ-1 scavenges H_2O_2, thus, H_2O_2-induced cell death is exacerbated when DJ-1 was knocked down (Taira et al., 2004). *In vivo*, DJ-1 mutations resulted in decreased locomotor activity in drosophila, which was exacerbated under conditions of oxidative stress (Park et al., 2005). DJ-1 also provided some protection against 6-hydroxydopamine (6-OHDA) toxicity in rats (Inden et al., 2006). Following administration of 6-OHDA, DJ-1 was delivered to the rat brains, which protected against ROS, reduced dopaminergic cell loss, and corrected behavioral deficits (Inden et al., 2006). This demonstrates that DJ-1 plays an important role in preserving dopaminergic cells when exposed to toxic insult.

DJ-1 may also play a role in regulating mitochondrial dynamics (Minakawa et al., 2013), as loss of DJ-1 lead to fragmented mitochondria (Blackinton et al., 2009; Irrcher et al., 2010; Krebiehl et al., 2010). The role of DJ-1 in mitochondrial dynamics was further supported in DJ-1 deficient cells, where levels of the mitochondrial fusion protein MFN1 were decreased (Irrcher et al., 2010). This could be because DJ-1 plays a direct a role in fusion/fission of the mitochondria, or indirect, by increasing mitochondrial ROS, which would also affect mitochondrial function (Irrcher et al., 2010; Krebiehl et al., 2010).

In addition to the role of DJ-1 in mitochondrial function, studies have demonstrated that it can influence autophagy (Irrcher et al., 2010; Krebiehl et al., 2010). The effect of DJ-1 on autophagy is currently unclear however. For example, loss of DJ-1 has been shown to increase autophagy with no effect on mitochondria function or number (Irrcher et al., 2010;). In contrast, other studies showed that loss of DJ-1 resulted in a decrease in basal autophagy (González-Polo et al., 2009; Krebiehl et al., 2010). However, both studies showed reduced clearance of mitochondria by lysosomes (Irrcher et al., 2010; Krebiehl et al., 2010), which could be due to impaired lysosomal activity (Krebiehl et al., 2010). In summary, although the exact role of DJ-1 in PD pathogenesis is unknown, it is likely that increased oxidative stress caused by loss of function mutations results in the disruption of mitochondrial homeostasis and potentially affects the removal of damaged mitochondria.

Summary so far

Although the precise mechanisms underlying PD pathology have not been fully elucidated, and are likely to vary between patients with PD, based on the current evidence available, it is likely that mitochondrial dysfunction and aberrant protein homeostasis caused by disruption of UPS and lysosomal function are involved. Furthermore, studies from our laboratory and others suggest that mitochondrial dysfunction is an early and convergent event in the cell stress pathway, no matter what the initiating trigger (Yong-Kee et al., 2012). Post-mortem studies, as well as genetic evidence, supports mitochondrial dysfunction in PD. Inhibition of complex I of

the ETC is often seen in both sporadic and familial PD (Parker et al., 1989; Haas et al., 1995; Devi et al., 2008; Liu et al., 2009; Mortiboys et al., 2008; Wood-Kaczmar et al., 2008; Morais et al., 2014). Based on this evidence, therapies focused on improving mitochondrial function may be extremely useful as neuroprotective treatments for PD. Such potential treatment strategies will be discussed in the following section.

Treatment strategies that target the mitochondria

Creatine

Creatine is a nitrogenous organic acid that can be produced endogenously and acquired through dietary intake (Juhn and Tarnopolsky, 1998). Creatine is phosphorylated by creatine kinase (CK) to produce phosphocreatine (Kones, 2010). Creatine and phosphocreatine comprise an effective energy buffering system that is able to maintain ATP levels. When creatine is present, it is phosphorylated by CK, reducing the ATP:ADP ratio, which prevents the inhibition of the ATPase and increases ATP synthesis (Kones, 2010). Conversely, when energy supplies are low, phosphocreatine can be used as a source of high-energy phosphate to convert ADP to ATP (Kones, 2010). The ability to maintain ATP levels in the mitochondria is especially important during metabolic and oxidative stress. For this reason, creatine has been investigated as a potential neuroprotective treatment in several neurodegenerative diseases, including PD.

Creatine protected against toxic insult in both *in vivo* and *in vitro* models of PD. A supplement of creatine protected dopaminergic neurons in primary ventral mesencephalic cultures exposed to either MPP^+ or 6-OHDA (Andres et al., 2005). Furthermore, creatine prevented loss of dopaminergic neurons in a MPTP-mouse model of PD in a dose dependent manner (Andres et al., 1999; Klivenyi et al., 2003). The exact mechanism of how creatine was able to protect neurons from cell death is still unknown. It was proposed that creatine prevents activation of the mitochondrial permeability transition pore (mPTP), which is linked to apoptotic pathways, and is initiated after mitochondrial homeostasis is lost. However, a study by Klivenyi et al. showed that the neuroprotective effects of creatine occured even in the absence of mitochondrial creatine kinase (Klivenyi et al., 2004). Therefore, creatine most likely asserts its neuroprotective effects through its well-established ability to maintain ATP levels, or its supposed antioxidant capabilities. Creatine could enhance mitochondrial function via either of these mechanisms.

A randomized, double-blind futility phase II clinical study has proven that creatine supplementation (10 g/d) for one year delayed the progression of PD by 50% based on the Unified Parkinson's Disease Rating Scale (UPDRS). This study determined that supplementation of creatine was effective, and resulted in the initiation of a larger clinical trial (NINDS NET-PD Investigators, 2006). A double-blind, placebo-controlled, phase III clinical trial is being performed and will included 1720 patients in the early stages of PD (Couzin, 2007). However, this study was halted because interim analysis showed that completion of the study was futile. Although creatine was a promising treatment because of its ability increase the ATP yield from the mitochondria, the treatment group appeared unlikely to show statistical significance to controls.

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α)

PGC1α is a transcription factor that is the major regulator of mitochondrial biogenesis, metabolism, and anti-oxidant genes (St-Pierre et al., 2006; Esteves et al., 2010). In post mortem studies of patients with PD, there were decreased levels of PGC1α (Zheng et al., 2010; Shin et al., 2011). This, combined with its role in mitochondrial health, makes it an interesting target in PD. PGC1α is required to protect cells against ROS by activating detoxifying enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) (St-Pierre et al., 2006), thus maintaining proper mitochondrial function. Interestingly, in parkin-deficient mice, PGC1α levels were reduced (Shin et al., 2011). Parkin is responsible for the ubiquination of its substrate PARIS, which suppresses PGC1α expression. Parkin mutations resulted in an increase in PARIS, which in turn represses PGC1α, leading to decreased mitochondrial function (Shin et al., 2011). In PGC1α null fibroblasts, or cells where PGC1α had been knocked down, there were reduced antioxidant mechanisms, as shown by reductions in the uncoupled proteins, SOD2, and GPx1 (St-Pierre et al., 2006). Overexpression of PGC1α in these cells dramatically protected against cell death by upregulating the antioxidant defense system (St-Pierre et al., 2006). Along with upregulation of antioxidant defense mechanisms in cells, overexpression of PGC1α increased mitochondrial density in both axons and the cell body (Wareski et al., 2009). In this way, PGC1α may compensate for mitochondrial loss in damaged neuronal cells. PGC1α overexpression has also been shown to correct for mitochondrial dysfunction caused by the expression of human α-synuclein in zebrafish, protecting against loss of dopaminergic neurons (O'Donnell et al., 2014), and protecting against MPTP-induced cell loss in mice (Mudò et al., 2012). Although these studies demonstrate the promise of PGC1α as a therapeutic target for patients with PD, it is important that levels of PGC1α are tightly regulated if it were to be targeted as a disease-modifying agent. A recent study overexpressing PGC1α in the striatum and SNc of rats demonstrated a decrease in dopaminergic cell markers and degeneration of dopaminergic neurons in the SNc, that corresponded with a decrease in striatal dopamine levels, as well as an increase in dopamine turnover in this brain region

(Ciron et al., 2012). Therefore, although promising, the therapeutic dose of PGC1α remains to be determined.

Sirtuin 1 and resveratrol

Sirtuins are a family of conserved NAD-dependent class III deacetylases and/or ADP-ribosyltransferases, which are homologs of yeast Sir2. There are seven mammalian sirtuins (SIRT1-7), each containing an NAD binding domain and a catalytic domain (Frye, 2000). SIRT family members differ with respect to the composition of their N- and C-terminal domains resulting in varied tissue and subcellular location, as well as specific enzymatic substrates (Li and Kazgan, 2011). The dependence on NAD for function suggests that sirtuins are involved in regulating metabolic activity and mitochondrial function. This review will focus mainly on SIRT1, as it has been studied in animal models of PD, and also positively impacts mitochondrial function. We will also discuss resveratrol, as its disease modifying effects may be mediated through SIRT1.

SIRT1

SIRT1 is primarily localized to the nucleus, where it deacetylates histones affecting gene expression (Vaquero et al., 2004). SIRT1 can also deacetylate and upregulate the activity of specific methyltransferases (Vaquero et al., 2007). Cells deficient in SIRT1 had decreased transcription due to the hyperacetylation and hypomethylation of histones (Vaquero et al., 2004, 2007). SIRT1 affects gene expression by regulating specific transcription factors, which play an important role in energy metabolism. These transcription factors include PGC1α (Gerhart-Hines et al., 2007), FOXO (Brunet et al., 2004), heat shock factor 1 (HSF1) (Westerheide et al., 2009), and NF-κB (Yeung et al., 2004; Yang et al., 2007). During fasting or caloric restriction, SIRT1 deacetylates PGC1α (Gerhart-Hines et al., 2007), which is a master regulator of mitochondrial biogenesis and oxidative phosphorylation (St-Pierre et al., 2006; Esteves et al., 2010). SIRT1 also deacetylates FOXO transcription factors that work in concert with PGC1α to activate various downstream targets, such as manganese superoxide dismutase 2 (MnSOD), and other antioxidant enzymes, which function to reduce ROS (van der Horst et al., 2004; Pardo et al., 2011).

Resveratrol is a natural polyphenolic compound, which is thought to be an activator of SIRT1 (Howitz et al., 2003). Although some studies indicate that resveratrol may not have an effect on SIRT1 expression and/or activity at all (Beher et al., 2009; Pacholec et al., 2010). Some of these findings may be partially explained by the study performed by Lakshminarasimhan et al., which demonstrates that the ability of resveratrol to downregulate or upregulate SIRT1 activity is substrate sequence dependent (Lakshminarasimhan et al., 2013).

Studies overexpressing SIRT1 or administering resveratrol demonstrate the therapeutic potential of SIRT1 as a neuroprotective agent in PD. In cell studies, resveratrol or oxyresveratrol protected against 6-OHDA, α-synuclein, and rotenone toxicity as well as parkin deficiency (Chao et al., 2008; Albani et al., 2009; Ferretta et al., 2014; Lin et al., 2014). This protection was mediated through activation of SIRT1 and decreasing ROS production (Chao et al., 2008; Albani et al., 2009), which caused enhancement of mitochondrial function (Ferretta et al., 2014). However, one study demonstrated protection by inducing autophagy and did not investigate SIRT1 activation. In rodent models of PD, resveratrol reversed behavioral deficits caused by 6-OHDA and MPTP toxicity (Jin et al., 2008; Lu et al., 2008). Furthermore, overexpression of SIRT1 in a transgenic mouse expressing the human A53T α-syunclein gene increased life span and decreased the formation of LB (Donmez et al., 2012), whereas knock- down of SIRT1 had the opposite effect. However, dopamine-cell specific overexpression of SIRT1 was not protective against neuronal loss in a MPTP mouse model of PD (Kakefuda et al., 2009). This could be due to the increase in SIRT1 consuming the NAD^+ necessary for neuronal survival as has previously been suggested (Liu et al., 2009), which highlights the importance of understanding the mechanism underlying SIRT1-mediated protection, and establishing the correct therapeutic dose in order for SIRT1 and SIRT1 activators to move forward as disease-modifying agents.

Mitochondrial Transcription Factor A (TFAM)

TFAM, a protein found in the mitochondria, is responsible for the initiation of mtDNA transcription and is a packing factor that stabilizes the mtDNA pool, thus it is involved in mtDNA maintenance (Noack et al., 2006; Hayashi et al., 2008). TFAM plays an important role in maintaining mtDNA homeostasis. Several studies have demonstrated that mutations in mtDNA play a role in PD pathogenesis (Ikebe et al., 1995; Gu et al., 2002; Simon et al., 2004). Generation of the "MitoPark" mice, which have a disrupted TFAM gene, demonstrated that loss of TFAM leads to an age-dependent development of parkinsonian-like symptoms including the formation of inclusions and loss of DA neurons (Ekstrand et al., 2007), further implicating mtDNA integrity to be important in PD. Furthermore, loss of TFAM resulted in changes to ion channels and impairment in the release of DA that preceded behavioral abnormalities (Good et al., 2011). Therefore, TFAM may be an interesting target as a disease modifying agent in PD. To support this hypothesis, cybrid cell models of sporadic PD have restored mtDNA, mtRNA levels, and respiratory capacity when TFAM was expressed and targeted to the mitochondria (Keeney et al., 2009). The need for a stable copy number of mtDNA was confirmed in mice where overexpression of TFAM improved the symptoms of mice with severe mitochondrial disease and prolonged lifespan (Nishiyama et al., 2010). When TFAM was over-

expressed in HeLa cells, it inhibited rotenone-induced ROS generation (Hayashi et al., 2008). Furthermore, in aged animals, TFAM decreased the amount of lipid peroxidation products and the decline in complex I and IV function in the mitochondria, therefore protecting the brain from age-related decline (Hayashi et al., 2008). These initial studies have implicated a therapeutic role for TFAM in PD.

Conclusion

There is increasing evidence implicating mitochondrial dysfunction as a key event in the pathogenesis of PD. In familial PD, both α-synuclein and LRRK2 are associated with the mitochondria and there is evidence to suggest they are important for proper mitochondrial function. Strong evidence for mitochondrial involvement in PD pathogenesis comes from the autosomal recessive mutations in PD. PINK1 is directly associated with the mitochondria and functions with parkin to maintain mitochondrial quality. Likewise, DJ-1 plays an important role in mitigating oxidative stress, which is important for proper mitochondrial function.

Several mitochondrial-targeted therapies are now being explored as disease-modifying agents in PD. Although still in early stages, these therapies have tremendous promise. Restoring proper mitochondrial function is likely essential in mitigating the progression of this disease. PGC1α improves overall mitochondrial health regulating mitochondrial biogenesis, metabolism, and antioxidant genes. SIRT1 can globally enhance mitochondrial health and thus, protect the neurons. TFAM is a transcription factor that maintains mtDNA. All of these proteins have been shown to be effective in cell and animal models of disease. Although still in the early stages of development, they show great promise in patients who suffer from PD, where there is currently no effective neuroprotective treatment.

Compliance with ethics guidelines

Dr. Joanne Nash, Dr. Jacqueline Gleave and Mr. Peter Perri declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

Albani D, Polito L, Batelli S, De Mauro S, Fracasso C, Martelli G, Colombo L, Manzoni C, Salmona M, Caccia S, Negro A, Forloni G (2009). The SIRT1 activator resveratrol protects SK-N-BE cells from oxidative stress and against toxicity caused by alpha-synuclein or amyloid-beta (1-42) peptide. J Neurochem, 110(5): 1445–1456

Andres R H, Huber A W, Schlattner U, Pérez-Bouza A, Krebs S H, Seiler R W, Wallimann T, Widmer H R (2005). Effects of creatine treatment on the survival of dopaminergic neurons in cultured fetal ventral mesencephalic tissue. Neuroscience, 133(3): 701–713

Andres-Mateos E, Perier C, Zhang L, Blanchard-Fillion B, Greco T M, Thomas B, Ko H S, Sasaki M, Ischiropoulos H, Przedborski S, Dawson T M, Dawson V L (2007). DJ-1 gene deletion reveals that DJ-1 is an atypical peroxiredoxin-like peroxidase. Proc Natl Acad Sci USA, 104(37): 14807–14812

Bedford L, Hay D, Devoy A, Paine S, Powe D G, Seth R, Gray T, Topham I, Fone K, Rezvani N, Mee M, Soane T, Layfield R, Sheppard P W, Ebendal T, Usoskin D, Lowe J, Mayer R J(2008). Depletion of 26S proteasomes in mouse brain neurons causes neurodegeneration and Lewy-like inclusions resembling human pale bodies. J Neurosci, 28: 8189–8198

Beher D, Wu J, Cumine S, Kim K W, Lu S C, Atangan L, Wang M (2009). Resveratrol is not a direct activator of SIRT1 enzyme activity. Chem Biol Drug Des, 74(6): 619–624

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 (2006). High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. Nat Genet, 38(5): 515–517

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F (1973). Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neurol Sci, 20(4): 415–455

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. J Biol Chem, 284(10): 6476–6485

Bové J, Zhou C, Jackson-Lewis V, Taylor J, Chu Y, Rideout H J, Wu D C, Kordower J H, Petrucelli L, Przedborski S (2006). Proteasome inhibition and Parkinson's disease modeling. Ann Neurol, 60(2): 260–264

Brunet A, Sweeney L B, Sturgill J F, Chua K F, Greer P L, Lin Y, Tran H, Ross S E, Mostoslavsky R, Cohen H Y, Hu L S, Cheng H L, Jedrychowski M P, Gygi S P, Sinclair D A, Alt F W, Greenberg M E (2004). Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science, 303(5666): 2011–2015

Canet-Avilés 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. Proc Natl Acad Sci USA, 101(24): 9103–9108

Chan C S, Gertler T S, Surmeier D J(2010). A molecular basis for the increased vulnerability of substantia nigra dopamine neurons in aging and Parkinson's disease. Mov Disord, 25 (Suppl 1): S63–70

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(7148): 1081–1086

Chao J, Yu M S, Ho Y S, Wang M, Chang R C (2008). Dietary oxyresveratrol prevents parkinsonian mimetic 6-hydroxydopamine neurotoxicity. Free Radic Biol Med, 45(7): 1019–1026

Chartier-Harlin M C, Kachergus J, Roumier C, Mouroux V, Douay X, Lincoln S, Levecque C, Larvor L, Andrieux J, Hulihan M, Waucquier N, Defebvre L, Amouyel P, Farrer M, Destée A (2004). Alpha-synuclein locus duplication as a cause of familial Parkinson's disease.

Lancet, 364(9440): 1167–1169

Cherra S J 3rd, Steer E, Gusdon A M, Kiselyov K, Chu C T (2013). Mutant LRRK2 elicits calcium imbalance and depletion of dendritic mitochondria in neurons. Am J Pathol, 182(2): 474–484

Chinta S J, Mallajosyula J K, Rane A, Andersen J K (2010). Mitochondrial α-synuclein accumulation impairs complex I function in dopaminergic neurons and results in increased mitophagy in vivo. Neurosci Lett, 486(3): 235–239

Ciron C, Lengacher S, Dusonchet J, Aebischer P, Schneider B L (2012). Sustained expression of PGC-1α in the rat nigrostriatal system selectively impairs dopaminergic function. Hum Mol Genet, 21(8): 1861–1876

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(7097): 1162–1166

Cole N B, Murphy D D (2002). The cell biology of alpha-synuclein: a sticky problem? Neuromolecular Med, 1(2): 95–109

Cookson M R (2003). Parkin's substrates and the pathways leading to neuronal damage. Neuromolecular Med, 3(1): 1–13

Couzin J (2007). Clinical research. Testing a novel strategy against Parkinson's disease. Science, 315(5820): 1778

Cuervo A M, Stefanis L, Fredenburg R, Lansbury P T, Sulzer D (2004). Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. Science, 305(5688): 1292–1295

Dauer W, Przedborski S (2003). Parkinson's disease: mechanisms and models. Neuron, 39(6): 889–909

Devi L, Raghavendran V, Prabhu B M, Avadhani N G, Anandatheertha-varada H K (2008). Mitochondrial import and accumulation of alpha-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain. J Biol Chem, 283(14): 9089–9100

Donmez G, Arun A, Chung C Y, McLean P J, Lindquist S, Guarente L (2012). SIRT1 protects against alpha-synuclein aggregation by activating molecular chaperones. J Neurosci, 32: 124–132

Dorsey E R, Constantinescu R, Thompson J P, Biglan K M, Holloway R G, Kieburtz K, Marshall F J, Ravina B M, Schifitto G, Siderowf A, Tanner C M (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology, 68(5): 384–386

Dryanovski D I, Guzman J N, Xie Z, Galteri D J, Volpicelli-Daley L A, Lee V M, Miller R J, Schumacker P T, Surmeier D J (2013). Calcium entry and alpha-synuclein inclusions elevate dendritic mitochondrial oxidant stress in dopaminergic neurons. J Neurosci, 33(24): 10154–10164

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. Proc Natl Acad Sci USA, 104(4): 1325–1330

Esteves A R, Lu J, Rodova M, Onyango I, Lezi E, Dubinsky R, Lyons K E, Pahwa R, Burns J M, Cardoso S M, Swerdlow R H (2010). Mitochondrial respiration and respiration-associated proteins in cell lines created through Parkinson's subject mitochondrial transfer. J Neurochem, 113(3): 674–682

Exner N, Lutz A K, Haass C, Winklhofer K F (2012). Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO J, 31(14): 3038–3062

Ferretta A, Gaballo A, Tanzarella P, Piccoli C, Capitanio N, Nico B, Annese T, Di Paola M, Dell'aquila C, De Mari M, Ferranini E, Bonifati V, Pacelli C, Cocco T (2014). Effect of resveratrol on mitochondrial function: implications in parkin-associated familiar Parkinson's disease. Biochim Biophys Acta, 1842(7): 902–915

Frye R A (2000). Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. Biochem Biophys Res Commun, 273 (2): 793–798

Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson E M, Schüle B, Langston J W, Middleton F A, Ross O A, Hulihan M, Gasser T, Farrer M J (2007). Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. Neurology, 68(12): 916–922

Gautier C A, Kitada T, Shen J (2008). Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc Natl Acad Sci USA, 105(32): 11364–11369

Gerhart-Hines Z, Rodgers J T, Bare O, Lerin C, Kim S H, Mostoslavsky R, Alt F W, Wu Z, Puigserver P (2007). Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha. EMBO J, 26(7): 1913–1923

Gispert S, Ricciardi F, Kurz A, Azizov M, Hoepken H H, Becker D, Voos W, Leuner K, Müller W E, Kudin A P, Kunz W S, Zimmermann A, Roeper J, Wenzel D, Jendrach M, García-Arencíbia M, Fernández-Ruiz J, Huber L, Rohrer H, Barrera M, Reichert A S, Rüb U, Chen A, Nussbaum R L, Auburger G (2009). Parkinson phenotype in aged PINK1-deficient mice is accompanied by progressive mitochondrial dysfunction in absence of neurodegeneration. PLoS ONE, 4(6): e5777

Goedert M (2001). Alpha-synuclein and neurodegenerative diseases. Nat Rev Neurosci, 2(7): 492–501

Goldberg M S, Fleming S M, Palacino J J, Cepeda C, Lam H A, Bhatnagar A, Meloni E G, Wu N, Ackerson L C, Klapstein G J, Gajendiran M, Roth B L, Chesselet M F, Maidment N T, Levine M S, Shen J (2003). Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons. J Biol Chem, 278(44): 43628–43635

Gómez-Sánchez R, Gegg M E, Bravo-San Pedro J M, Niso-Santano M, Alvarez-Erviti L, Pizarro-Estrella E, Gutiérrez-Martín Y, Alvarez-Barrientos A, Fuentes J M, González-Polo R A, Schapira A H (2014). Mitochondrial impairment increases FL-PINK1 levels by calcium-dependent gene expression. Neurobiol Dis, 62: 426–440

González-Polo R, Niso-Santano M, Morán J M, Ortiz-Ortiz M A, Bravo-San Pedro J M, Soler G, Fuentes J M (2009). Silencing DJ-1 reveals its contribution in paraquat-induced autophagy. J Neurochem, 109 (3): 889–898

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 J, 25:1333–1344

Greenamyre J T, Betarbet R, Sherer T B (2003). The rotenone model of Parkinson's disease: genes, environment and mitochondria. Parkinsonism Relat Disord, 9(Suppl 2): S59–S64

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. Proc Natl Acad Sci USA, 100(7): 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. Neurobiol Dis, 23(2): 329–341

Gu G, Reyes P E, Golden G T, Woltjer R L, Hulette C, Montine T J, Zhang J (2002). Mitochondrial DNA deletions/rearrangements in parkinson disease and related neurodegenerative disorders. J Neuropathol Exp Neurol, 61(7): 634–639

Guardia-Laguarta C, Area-Gomez E, Rub C, Liu Y, Magrane J, Becker D, Voos W, Schon E A, Przedborski S(2014). alpha-Synuclein is localized to mitochondria-associated ER membranes. J Neurosc, 34: 249–259

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(7324): 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. Ann Neurol, 37(6): 714–722

Hayashi Y, Yoshida M, Yamato M, Ide T, Wu Z, Ochi-Shindou M, Kanki T, Kang D, Sunagawa K, Tsutsui H, Nakanishi H(2008). Reverse of age-dependent memory impairment and mitochondrial DNA damage in microglia by an overexpression of human mitochondrial transcription factor a in mice. J Neurosci, 28: 8624–8634

Healy D G, Abou-Sleiman P M, Casas J P, Ahmadi K R, Lynch T, Gandhi S, Muqit M M, Foltynie T, Barker R, Bhatia K P, Quinn N P, Lees A J, Gibson J M, Holton J L, Revesz T, Goldstein D B, Wood N W (2006). UCHL-1 is not a Parkinson's disease susceptibility gene. Ann Neurol, 59(4): 627–633

Höglinger G U, Carrard G, Michel P P, Medja F, Lombès A, Ruberg M, Friguet B, Hirsch E C (2003). Dysfunction of mitochondrial complex I and the proteasome: interactions between two biochemical deficits in a cellular model of Parkinson's disease. J Neurochem, 86(5): 1297–1307

Howitz K T, Bitterman K J, Cohen H Y, Lamming D W, Lavu S, Wood J G, Zipkin R E, Chung P, Kisielewski A, Zhang L L, Scherer B, Sinclair D A (2003). Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature, 425(6954): 191–196

Ikebe S, Tanaka M, Ozawa T (1995). Point mutations of mitochondrial genome in Parkinson's disease. Brain Res Mol Brain Res, 28(2): 281–295

Imai Y, Soda M, Takahashi R (2000). Parkin suppresses unfolded protein stress-induced cell death through its E3 ubiquitin-protein ligase activity. J Biol Chem, 275(46): 35661–35664

Inden M, Taira T, Kitamura Y, Yanagida T, Tsuchiya D, Takata K, Yanagisawa D, Nishimura K, Taniguchi T, Kiso Y, Yoshimoto K, Agatsuma T, Koide-Yoshida S, Iguchi-Ariga S M, Shimohama S, Ariga H (2006). PARK7 DJ-1 protects against degeneration of nigral dopaminergic neurons in Parkinson's disease rat model. Neurobiol Dis, 24(1): 144–158

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. Hum Mol Genet, 19(19): 3734–3746

Itier J M, Ibanez P, Mena M A, Abbas N, Cohen-Salmon C, Bohme G A, Laville M, Pratt J, Corti O, Pradier L, Ret G, Joubert C, Periquet M, Araujo F, Negroni J, Casarejos M J, Canals S, Solano R, Serrano A, Gallego E, Sanchez M, Denefle P, Benavides J, Tremp G, Rooney T A, Brice A, Garcia de Yebenes J (2003). Parkin gene inactivation alters behaviour and dopamine neurotransmission in the mouse. Hum Mol Genet, 12(18): 2277–2291

Jin F, Wu Q, Lu Y F, Gong Q H, Shi J S (2008). Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats. Eur J Pharmacol, 600(1-3): 78–82

Juhn M S, Tarnopolsky M(1998). Oral creatine supplementation and athletic performance: a critical review. Clin J Sport Med, 8: 286–297

Kakefuda K, Fujita Y, Oyagi A, Hyakkoku K, Kojima T, Umemura K, Tsuruma K, Shimazawa M, Ito M, Nozawa Y, Hara H (2009). Sirtuin 1 overexpression mice show a reference memory deficit, but not neuroprotection. Biochem Biophys Res Commun, 387(4): 784–788

Katzenschlager R, Lees A J (2002). Treatment of Parkinson's disease: levodopa as the first choice. J Neurol, 249(Suppl 2): II19–II24

Keeney P M, Quigley C K, Dunham L D, Papageorge C M, Iyer S, Thomas R R, Schwarz K M, Trimmer P A, Khan S M, Portell F R, Bergquist K E, Bennett J P Jr (2009). Mitochondrial gene therapy augments mitochondrial physiology in a Parkinson's disease cell model. Hum Gene Ther, 20(8): 897–907

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. Proc Natl Acad Sci USA, 102(14): 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(6676): 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. Proc Natl Acad Sci USA, 104(27): 11441–11446

Klivenyi P, Gardian G, Calingasan N Y, Yang L, Beal M F(2003). Additive neuroprotective effects of creatine and a cyclooxygenase 2 inhibitor against dopamine depletion in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. J Mol Neurosci, MN 21: 191–198

Klivenyi P, Calingasan N Y, Starkov A, Stavrovskaya I G, Kristal B S, Yang L, Wieringa B, Beal M F (2004). Neuroprotective mechanisms of creatine occur in the absence of mitochondrial creatine kinase. Neurobiol Dis, 15(3): 610–617

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. Neurobiol Dis, 21(3): 541–548

Kones R(2010). Mitochondrial therapy for Parkinson's disease: neuroprotective pharmaconutrition may be disease-modifying. Clin pharmacol, 2: 185–198

Kordower J H, Kanaan N M, Chu Y, Suresh Babu R, Stansell J 3rd, Terpstra B T, Sortwell C E, Steece-Collier K, Collier T J (2006). Failure of proteasome inhibitor administration to provide a model of Parkinson's disease in rats and monkeys. Ann Neurol, 60(2): 264–268

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. Nat Genet, 38(5): 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, Krüger R (2010). Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson's disease-associated protein DJ-1. PLoS ONE, 5(2): e9367

Krüger R, Kuhn W, Müller T, Woitalla D, Graeber M, Kösel S, Przuntek H, Epplen J T, Schöls L, Riess O (1998). Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nat Genet, 18 (2): 106–108

Lakshminarasimhan M, Rauh D, Schutkowski M, Steegborn C (2013). Sirt1 activation by resveratrol is substrate sequence-selective. Aging (Albany NY), 5(3): 151–154

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(4587): 979–980

Leroy E, Boyer R, Auburger G, Leube B, Ulm G, Mezey E, Harta G, Brownstein M J, Jonnalagada S, Chernova T, Dehejia A, Lavedan C, Gasser T, Steinbach P J, Wilkinson K D, Polymeropoulos M H (1998). The ubiquitin pathway in Parkinson's disease. Nature, 395 (6701): 451–452

Li C, Beal M F (2005). Leucine-rich repeat kinase 2: a new player with a familiar theme for Parkinson's disease pathogenesis. Proc Natl Acad Sci USA, 102(46): 16535–16536

Li X, Kazgan N (2011). Mammalian sirtuins and energy metabolism. Int J Biol Sci, 7(5): 575–587

Lim K L (2007). Ubiquitin-proteasome system dysfunction in Parkinson's disease: current evidence and controversies. Expert Rev Proteomics, 4(6): 769–781

Lin T K, Chen S D, Chuang Y C, Lin H Y, Huang C R, Chuang J H, Wang P W, Huang S T, Tiao M M, Chen J B, Liou C W (2014). Resveratrol partially prevents rotenone-induced neurotoxicity in dopaminergic SH-SY5Y cells through induction of heme oxygenase-1 dependent autophagy. Int J Mol Sci, 15(1): 1625–1646

Liu D, Gharavi R, Pitta M, Gleichmann M, Mattson M P (2009). Nicotinamide prevents NAD^+ depletion and protects neurons against excitotoxicity and cerebral ischemia: NAD^+ consumption by SIRT1 may endanger energetically compromised neurons. Neuromolecular Med, 11(1): 28–42

Liu G, Zhang C, Yin J, Li X, Cheng F, Li Y, Yang H, Uéda K, Chan P, Yu S (2009). alpha-Synuclein is differentially expressed in mitochondria from different rat brain regions and dose-dependently down-regulates complex I activity. Neurosci Lett, 454(3): 187–192

Lu K T, Ko M C, Chen B Y, Huang J C, Hsieh C W, Lee M C, Chiou R Y, Wung B S, Peng C H, Yang Y L (2008). Neuroprotective effects of resveratrol on MPTP-induced neuron loss mediated by free radical scavenging. J Agric Food Chem, 56(16): 6910–6913

Lutz A K, Exner N, Fett M E, Schlehe J S, Kloos K, Lämmermann K, Brunner B, Kurz-Drexler A, Vogel F, Reichert A S, Bouman L, Vogt-Weisenhorn D, Wurst W, Tatzelt J, Haass C, Winklhofer K F (2009). Loss of parkin or PINK1 function increases Drp1-dependent mitochondrial fragmentation. J Biol Chem, 284(34): 22938–22951

Marques O, Outeiro T F (2012). Alpha-synuclein: from secretion to dysfunction and death. Cell Death Dis, 3(7): e350

Matthews R T, Ferrante R J, Klivenyi P, Yang L, Klein A M, Mueller G, Kaddurah-Daouk R, Beal M F (1999). Creatine and cyclocreatine attenuate MPTP neurotoxicity. Exp Neurol, 157(1): 142–149

McLelland G L, Soubannier V, Chen C X, McBride H M, Fon E A (2014). Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. EMBO J, 33(4): 282–295

McNaught K S, Perl D P, Brownell A L, Olanow C W (2004). Systemic exposure to proteasome inhibitors causes a progressive model of Parkinson's disease. Ann Neurol, 56(1): 149–162

Minakawa E N, Yamakado H, Tanaka A, Uemura K, Takeda S, Takahashi R (2013). Chicken DT40 cell line lacking DJ-1, the gene responsible for familial Parkinson's disease, displays mitochondrial dysfunction. Neurosci Res, 77(4): 228–233

Moisoi N, Fedele V, Edwards J, Martins L M (2014). Loss of PINK1 enhances neurodegeneration in a mouse model of Parkinson's disease triggered by mitochondrial stress. Neuropharmacology, 77: 350–357

Morais V A, Haddad D, Craessaerts K, De Bock P J, Swerts J, Vilain S, Aerts L, Overbergh L, Grünewald A, Seibler P, Klein C, Gevaert K, Verstreken P, De Strooper B (2014). PINK1 loss-of-function mutations affect mitochondrial complex I activity via NdufA10 ubiquinone uncoupling. Science, 344(6180): 203–207

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(22): 2017–2020

Mortiboys H, Thomas K J, Koopman W J, Klaffke S, Abou-Sleiman P, Olpin S, Wood N W, Willems P H, Smeitink J A, Cookson M R, Bandmann O (2008). Mitochondrial function and morphology are impaired in parkin-mutant fibroblasts. Ann Neurol, 64(5): 555–565

Mudò G, Mäkelä J, Di Liberto V, Tselykh T V, Olivieri M, Piepponen P, Eriksson O, Mälkiä A, Bonomo A, Kairisalo M, Aguirre J A, Korhonen L, Belluardo N, Lindholm D (2012). Transgenic expression and activation of PGC-1α protect dopaminergic neurons in the MPTP mouse model of Parkinson's disease. Cell Mol Life Sci, 69(7): 1153–1165

Murray A M, Weihmueller F B, Marshall J F, Hurtig H I, Gottleib G L, Joyce J N (1995). Damage to dopamine systems differs between Parkinson's disease and Alzheimer's disease with parkinsonism. Ann Neurol, 37(3): 300–312

Narendra D, Tanaka A, Suen D F, Youle R J (2008). Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol, 183(5): 795–803

Neuspiel M, Schauss A C, Braschi E, Zunino R, Rippstein P, Rachubinski R A, Andrade-Navarro M A, McBride H M(2008). Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. Curr Biol, CB 18: 102–108

Ng C H, Mok S Z, Koh C, Ouyang X, Fivaz M L, Tan E K, Dawson V L, Dawson T M, Yu F, Lim K L(2009). Parkin protects against LRRK2 G2019S mutant-induced dopaminergic neurodegeneration in Drosophila. J Neurosci, 29: 11257–11262

NINDS NET-PD Investigators (2006). A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology, 66(5): 664–671

Nishiyama S, Shitara H, Nakada K, Ono T, Sato A, Suzuki H, Ogawa T, Masaki H, Hayashi J, Yonekawa H (2010). Over-expression of Tfam improves the mitochondrial disease phenotypes in a mouse model system. Biochem Biophys Res Commun, 401(1): 26–31

Niu J, Yu M, Wang C, Xu Z (2012). Leucine-rich repeat kinase 2 disturbs mitochondrial dynamics via Dynamin-like protein. J Neurochem, 122 (3): 650–658

Noack H, Bednarek T, Heidler J, Ladig R, Holtz J, Szibor M (2006). TFAM-dependent and independent dynamics of mtDNA levels in C2C12 myoblasts caused by redox stress. Biochim Biophys Acta, 1760(2): 141–150

O'Donnell K C, Lulla A, Stahl M C, Wheat N D, Bronstein J M, Sagasti A (2014). Axon degeneration and PGC-1α-mediated protection in a zebrafish model of α-synuclein toxicity. Dis Model Mech, 7(5): 571–582

Orenstein S J, Kuo S H, Tasset I, Arias E, Koga H, Fernandez-Carasa I, Cortes E, Honig L S, Dauer W, Consiglio A, Raya A, Sulzer D, Cuervo A M (2013). Interplay of LRRK2 with chaperone-mediated autophagy. Nat Neurosci, 16(4): 394–406

Pacholec M, Bleasdale J E, Chrunyk B, Cunningham D, Flynn D, Garofalo R S, Griffith D, Griffor M, Loulakis P, Pabst B, Qiu X, Stockman B, Thanabal V, Varghese A, Ward J, Withka J, Ahn K (2010). SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. J Biol Chem, 285(11): 8340–8351

Papkovskaia T D, Chau K Y, Inesta-Vaquera F, Papkovsky D B, Healy D G, Nishio K, Staddon J, Duchen M R, Hardy J, Schapira A H, Cooper J M (2012). G2019S leucine-rich repeat kinase 2 causes uncoupling protein-mediated mitochondrial depolarization. Hum Mol Genet, 21 (19): 4201–4213

Pardo P S, Mohamed J S, Lopez M A, Boriek A M (2011). Induction of Sirt1 by mechanical stretch of skeletal muscle through the early response factor EGR1 triggers an antioxidative response. J Biol Chem, 286(4): 2559–2566

Parihar M S, Parihar A, Fujita M, Hashimoto M, Ghafourifar P (2008). Mitochondrial association of alpha-synuclein causes oxidative stress. Cell Mol Life Sci, 65(7-8): 1272–1284

Park J, Kim S Y, Cha G H, Lee S B, Kim S, Chung J (2005). Drosophila DJ-1 mutants show oxidative stress-sensitive locomotive dysfunction. Gene, 361: 133–139

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(7097): 1157–1161

Parker W D Jr, Boyson S J, Parks J K (1989). Abnormalities of the electron transport chain in idiopathic Parkinson's disease. Ann Neurol, 26(6): 719–723

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(9): 2183–2194

Ping H X, Shepard P D (1999). Blockade of SK-type Ca^{2+}-activated K^{+} channels uncovers a Ca^{2+}-dependent slow afterdepolarization in nigral dopamine neurons. J Neurophysiol, 81(3): 977–984

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(5321): 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. Proc Natl Acad Sci USA, 105(5): 1638–1643

Ramirez A, Heimbach A, Gründemann J, Stiller B, Hampshire D, Cid L P, Goebel I, Mubaidin A F, Wriekat A L, Roeper J, Al-Din A, Hillmer A M, Karsak M, Liss B, Woods C G, Behrens M I, Kubisch C (2006). Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet, 38(10): 1184–1191

Ramonet D, Daher J P, Lin B M, Stafa K, Kim J, Banerjee R, Westerlund M, Pletnikova O, Glauser L, Yang L, Liu Y, Swing D A, Beal M F, Troncoso J C, McCaffery J M, Jenkins N A, Copeland N G, Galter D, Thomas B, Lee M K, Dawson T M, Dawson V L, Moore D J (2011). Dopaminergic neuronal loss, reduced neurite complexity and autophagic abnormalities in transgenic mice expressing G2019S mutant LRRK2. PLoS ONE, 6(4): e18568

Richfield E K, Thiruchelvam M J, Cory-Slechta D A, Wuertzer C, Gainetdinov R R, Caron M G, Di Monte D A, Federoff H J (2002). Behavioral and neurochemical effects of wild-type and mutated human alpha-synuclein in transgenic mice. Exp Neurol, 175(1): 35–48

Saha S, Guillily M D, Ferree A, Lanceta J, Chan D, Ghosh J, Hsu C H, Segal L, Raghavan K, Matsumoto K, Hisamoto N, Kuwahara T, Iwatsubo T, Moore L, Goldstein L, Cookson M, Wolozin B(2009). LRRK2 modulates vulnerability to mitochondrial dysfunction in *Caenorhabditis elegans*. J Neurosci, 29: 9210–9218

Sakata E, Yamaguchi Y, Kurimoto E, Kikuchi J, Yokoyama S, Yamada S, Kawahara H, Yokosawa H, Hattori N, Mizuno Y, Tanaka K, Kato K (2003). Parkin binds the Rpn10 subunit of 26S proteasomes through its ubiquitin-like domain. EMBO Rep, 4(3): 301–306

Sarafian T A, Ryan C M, Souda P, Masliah E, Kar U K, Vinters H V, Mathern G W, Faull K F, Whitelegge J P, Watson J B (2013). Impairment of mitochondria in adult mouse brain overexpressing predominantly full-length, N-terminally acetylated human α-synuclein. PLoS ONE, 8(5): e63557 PMID:23667637

Scarffe L A, Stevens D A, Dawson V L, Dawson T M (2014). Parkin and PINK1: much more than mitophagy. Trends Neurosci, 37(6): 315–324

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(8649): 1269

Shavali S, Brown-Borg H M, Ebadi M, Porter J (2008). Mitochondrial localization of alpha-synuclein protein in alpha-synuclein overexpressing cells. Neurosci Lett, 439(2): 125–128

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. Nat Genet, 25(3): 302–305

Shin J H, Ko H S, Kang H, Lee Y, Lee Y I, Pletinkova O, Troconso J C, Dawson V L, Dawson T M (2011). PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. Cell, 144(5): 689–702

Simon D K, Lin M T, Zheng L, Liu G J, Ahn C H, Kim L M, Mauck W M, Twu F, Beal M F, Johns D R (2004). Somatic mitochondrial DNA

mutations in cortex and substantia nigra in aging and Parkinson's disease. Neurobiol Aging, 25(1): 71–81

Snyder H, Mensah K, Theisler C, Lee J, Matouschek A, Wolozin B (2003). Aggregated and monomeric alpha-synuclein bind to the S6′ proteasomal protein and inhibit proteasomal function. J Biol Chem, 278(14): 11753–11759

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. Exp Neurol, 186(2): 158–172

Soubannier V, McLelland G L, Zunino R, Braschi E, Rippstein P, Fon E A, McBride H M(2012). A vesicular transport pathway shuttles cargo from mitochondria to lysosomes. Curr Biol, CB 22: 135–141

Spillantini M G, Crowther R A, Jakes R, Hasegawa M, Goedert M (1998). alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci USA, 95(11): 6469–6473

Spillantini M G, Schmidt M L, Lee V M, Trojanowski J Q, Jakes R, Goedert M (1997). Alpha-synuclein in Lewy bodies. Nature, 388 (6645): 839–840

St-Pierre J, Drori S, Uldry M, Silvaggi J M, Rhee J, Jäger S, Handschin C, Zheng K, Lin J, Yang W, Simon D K, Bachoo R, Spiegelman B M (2006). Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. Cell, 127(2): 397–408

Su Y C, Qi X (2013). Inhibition of excessive mitochondrial fission reduced aberrant autophagy and neuronal damage caused by LRRK2 G2019S mutation. Hum Mol Genet, 22(22): 4545–4561

Sulzer D, Zecca L (2000). Intraneuronal dopamine-quinone synthesis: a review. Neurotox Res, 1(3): 181–195

Surmeier D J (2007). Calcium, ageing, and neuronal vulnerability in Parkinson's disease. Lancet Neurol, 6(10): 933–938

Surmeier D J, Guzman J N, Sanchez-Padilla J (2010). Calcium, cellular aging, and selective neuronal vulnerability in Parkinson's disease. Cell Calcium, 47(2): 175–182

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 Rep, 5(2): 213–218

Tanaka M, Kim Y M, Lee G, Junn E, Iwatsubo T, Mouradian M M (2004). Aggresomes formed by alpha-synuclein and synphilin-1 are cytoprotective. J Biol Chem, 279(6): 4625–4631

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, González-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(5674): 1158–1160

Valente E M, Salvi S, Ialongo T, Marongiu R, Elia A E, Caputo V, Romito L, Albanese A, Dallapiccola B, Bentivoglio A R (2004). PINK1 mutations are associated with sporadic early-onset parkinsonism. Ann Neurol, 56(3): 336–341

van der Horst A, Tertoolen L G, de Vries-Smits L M, Frye R A, Medema R H, Burgering B M (2004). FOXO4 is acetylated upon peroxide stress and deacetylated by the longevity protein hSir2(SIRT1). J Biol Chem, 279(28): 28873–28879

Vaquero A, Scher M, Erdjument-Bromage H, Tempst P, Serrano L, Reinberg D (2007). SIRT1 regulates the histone methyl-transferase SUV39H1 during heterochromatin formation. Nature, 450(7168): 440–444

Vaquero A, Scher M, Lee D, Erdjument-Bromage H, Tempst P, Reinberg D (2004). Human SirT1 interacts with histone H1 and promotes formation of facultative heterochromatin. Mol Cell, 16(1): 93–105

Wang X, Winter D, Ashrafi G, Schlehe J, Wong Y L, Selkoe D, Rice S, Steen J, LaVoie M J, Schwarz T L (2011). PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. Cell, 147(4): 893–906

Wang X, Yan M H, Fujioka H, Liu J, Wilson-Delfosse A, Chen S G, Perry G, Casadesus G, Zhu X (2012). LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLP1. Hum Mol Genet, 21(9): 1931–1944

Wareski P, Vaarmann A, Choubey V, Safiulina D, Liiv J, Kuum M, Kaasik A (2009). PGC-1alpha and PGC-1beta regulate mitochondrial density in neurons. J Biol Chem, 284(32): 21379–21385

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. Proc Natl Acad Sci USA, 102(46): 16842–16847

Westerheide S D, Anckar J, Stevens S M Jr, Sistonen L, Morimoto R I (2009). Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. Science, 323(5917): 1063–1066

Winslow A R, Chen C W, Corrochano S, Acevedo-Arozena A, Gordon D E, Peden A A, Lichtenberg M, Menzies F M, Ravikumar B, Imarisio S, Brown S, O'Kane C J, Rubinsztein D C (2010). α-Synuclein impairs macroautophagy: implications for Parkinson's disease. J Cell Biol, 190(6): 1023–1037

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(6): e2455

Xilouri M, Vogiatzi T, Vekrellis K, Park D, Stefanis L (2009). Abberant alpha-synuclein confers toxicity to neurons in part through inhibition of chaperone-mediated autophagy. PLoS ONE, 4(5): e5515

Yang S R, Wright J, Bauter M, Seweryniak K, Kode A, Rahman I (2007). Sirtuin regulates cigarette smoke-induced proinflammatory mediator release via RelA/p65 NF-kappaB in macrophages in vitro and in rat lungs *in vivo*: implications for chronic inflammation and aging. Am J Physiol Lung Cel l Mol Physiol, 292(2): L567–L576

Yeung F, Hoberg J E, Ramsey C S, Keller M D, Jones D R, Frye R A, Mayo M W (2004). Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J, 23(12): 2369–2380

Yong-Kee C J, Salomonczyk D, Nash J E (2011). Development and validation of a screening assay for the evaluation of putative neuroprotective agents in the treatment of Parkinson's disease. Neurotox Res, 19(4): 519–526

Yong-Kee C J, Sidorova E, Hanif A, Perera G, Nash J E (2012). Mitochondrial dysfunction precedes other sub-cellular abnormalities in an *in vitro* model linked with cell death in Parkinson's disease. Neurotox Res, 21(2): 185–194

Zarranz J J, Alegre J, Gómez-Esteban J C, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J, Rodriguez O, Atarés B, Llorens V, Gomez Tortosa E, del Ser T, Muñoz D G, de Yebenes J G (2004). The new

mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol, 55(2): 164–173

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. Hum Mol Genet, 14(14): 2063–2073

Zhang N Y, Tang Z, Liu C W (2008). alpha-Synuclein protofibrils inhibit 26 S proteasome-mediated protein degradation: understanding the cytotoxicity of protein protofibrils in neurodegenerative disease pathogenesis. J Biol Chem, 283(29): 20288–20298

Zheng B, Liao Z, Locascio J J, Lesniak K A, Roderick S S, Watt M L, Eklund A C, Zhang-James Y, Kim P D, Hauser M A, Grünblatt E, Moran L B, Mandel S A, Riederer P, Miller R M, Federoff H J, Wüllner U, Papapetropoulos S, Youdim M B, Cantuti-Castelvetri I, Young A B, Vance J M, Davis R L, Hedreen J C, Adler C H, Beach T G, Graeber M B, Middleton F A, Rochet J C, Scherzer C R, Global P D G E C, and the Global PD Gene Expression (GPEX) Consortium (2010). PGC-1α, a potential therapeutic target for early intervention in Parkinson's disease. Sci Transl Med, 2(52): 52ra73