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Current Perspective of Mitochondrial Biology in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is one of the most common neurodegenerative movement disorder characterized by preferential loss of dopaminergic neurons of the substantia nigra pars compacta and the presence of Lewy bodies containing α-synuclein. Although the cause of PD remains elusive, remarkable advances have been made in understanding the possible causative mechanisms of PD pathogenesis. An explosion of discoveries during the past two decades has led to the identification of several autosomal dominant and recessive genes that cause familial forms of PD. The investigations of these familial PD gene products have shed considerable insights into the molecular pathogenesis of the more common sporadic PD. A growing body of evidence suggests that the etiology of PD is multifactorial and involves a complex interplay between genetic and environmental factors. Substantial evidence from human tissues, genetic and toxin-induced animal and cellular models indicates that mitochondrial dysfunction plays a central role in the pathophysiology of PD. Deficits in mitochondrial functions due to bioenergetics defects, alterations in the mitochondrial DNA, generation of reactive oxygen species, aberrant calcium homeostasis, and anomalies in mitochondrial dynamics and quality control are implicated in the underlying mechanisms of neuronal cell death in PD. In this review, we discuss how familial PD-linked genes and environmental factors interface the pathways regulating mitochondrial functions and thereby potentially converge both familial and sporadic PD at the level of mitochondrial integrity. We also provide an overview of the status of therapeutic strategies targeting mitochondrial dysfunction in PD. Unraveling potential pathways that influence mitochondrial homeostasis in PD may hold the key to therapeutic intervention for this debilitating neurodegenerative movement disorder.

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Keywords

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1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer's disease affecting more than 4 million people worldwide (Dorsey et al., 2007). Clinically, PD is diagnosed by the presence of motor symptoms that includes rest tremor, rigidity, bradykinesia, and postural instability. The pathological hallmark of PD includes the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc), and the presence of cytoplasmic and neuritic inclusions named as Lewy bodies (LBs) and Lewy neurites (LNs) that are composed of α-synuclein (Lang and Lozano, 1998a, Lang and Lozano, 1998b). Though the clinical hallmarks and pathological features of PD have been extensively studied, the exact molecular basis underlying DA neuron degeneration remains incompletely understood. Clinically PD cases are mostly sporadic and not classified traditionally as a genetic disease. However, rare familial forms have been identified that account for about 15% of all the PD cases. Despite these differences, both sporadic and familial forms of PD share common clinical, pathological and biochemical features and thus, potential insights into the function and dysfunction of PD-associated gene products have helped elucidate common pathways in PD pathogenesis. Accumulating evidence indicates that both sporadic and familial PD directly or indirectly coalesce on mitochondrial homeostasis thereby providing a link between mitochondrial dysfunction and PD pathogenesis (Banerjee et al., 2009). In the following sections, we discuss current perspectives of mitochondria in sporadic and familial PD and review therapeutic strategies targeting mitochondrial dysfunction in PD and the status of their clinical development.

2. Mitochondrial dysfunction in sporadic Parkinson's disease and the role of environmental toxins

Mitochondria are membrane-bound organelles found in every eukaryotic cell and are especially abundant in tissues with high-energy demands, such as brain and muscle. The major function of mitochondria is energy metabolism, predominantly oxidative phosphorylation (OXPHOS). The OXPHOS system comprises of 5 major multi-subunit complexes: complex I (NADH dehydrogenase-ubiquinone oxidoreductase), complex II (succinate dehydrogenase-ubiquinone oxidoreductase), complex III (ubiquinone-cytochrome c oxidoreductase), complex IV (cytochrome c oxidase), and complex V (ATP synthase). Although the mitochondrial OXPHOS system generates adenosine triphosphate (ATP), crucial for many essential cellular processes, mitochondria are the main cellular source of reactive oxygen species (ROS) and involved in calcium homeostasis and in the regulation and initiation of cell destructive pathways, which could underlie selective DA neurodegeneration in PD (Banerjee et al., 2009). Complex I is a major entry point of the respiratory chain and its deficiencies can be translated into a dramatic loss of bioenergetics functions leading to mitochondrial instability. Complex I also produce most of the ROS

generated in intact mitochondria. There are numerous complex cellular mechanisms in place to help minimize the harmful effects of ROS, and yet intracellular ROS production is implicated in aging and many neurodegenerative pathologies (Grimm and Eckert, 2017). A link between complex I dysfunction and PD was established when several groups reported reduced complex I activity in the SN of the human brain, the major site of neuronal loss in PD (Schapira et al., 1990a, Schapira et al., 1990b, Janetzky et al., 1994). Since then complex I defects has been reported in a variety of other tissues including frontal cortex, platelets, and skeletal muscle of patients with sporadic PD (Parker et al., 2008, Keeney et al., 2006, Parker et al., 1989, Krige et al., 1992, Benecke et al., 1993, Benecke et al., 1993, Bindoff et al., 1991, Blin et al., 1994, Cardellach et al., 1993). However, it is important to note that many laboratories could not confirm complex I defect in PD (Banerjee et al., 2009). Such inconsistency in the experimental data may likely be explained by significant methodological differences and individual variability of PD patients. The most compelling evidence of mitochondrial dysfunction as a causal source of PD was obtained in the 1980s following accidental exposure of drug abusers to an illicit drug contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an inhibitor of mitochondrial complex I, that resulted in irreversible parkinsonian syndromes almost indistinguishable from PD (Langston et al., 1983). The revelation of MPTP mechanisms has resulted in a gold mine of information regarding the involvement of mitochondria in PD. MPTP is metabolized to its toxic form MPP+ (1-methyl-4-phenylpyridinium ion) by mitochondrial monoamine oxidase B and undergoes selective uptake to DA neurons through the dopamine transporter (DAT) and is rapidly concentrated in the mitochondria by an energy-dependent process (Heikkila et al., 1984, Gainetdinov et al., 1997, Ramsay et al., 1987). Mitochondrial accumulation of MPP+ specifically inhibits the oxidation of NAD (nicotinamide adenine dinucleotide) - linked substrates (Nicklas et al., 1985) by blocking the electron transfer through the complex I of the electron transport chain. Several studies reproduced the parkinsonian features induced by MPTP in both primate and murine models (Blesa et al., 2012). A considerable body of evidence epidemiologically links exposure to environmental toxicants like rotenone and paraquat (also known to inhibit mitochondrial respiration) to PD (Blesa et al., 2012, Tanner et al., 2011). The herbicide paraquat is a free radical generator that inhibits mitochondrial respiratory chain activity and causes DA neuron loss, accompanied by α-synuclein aggregation (Day et al., 1999, Manning-Bog et al., 2002). Similarly, chronic administration of the classic complex I inhibitor rotenone in rodents has been reported to produce multisystem degeneration including loss of nigrostriatal DA neurons and LB-like inclusions (Betarbet et al., 2000, Hoglinger et al., 2003, Lapointe et al., 2004).

The general perception is that complex I inhibition causes bioenergetics failure leading to ATP depletion and subsequent cell death. Supporting this view, MPP+ treatment causes a significant depletion of ATP in whole brain and synaptosomal preparations (Scotcher et al., 1990, Cosi and Marien, 1998) (Figure 1). It appears that complex I activity should be reduced more than 50% to cause a significant ATP depletion in non-synaptic brain mitochondria (Davey and Clark, 1996). However ATP is only mildly reduced (~20%) in MPTP treated mouse midbrain and striata (Cosi and Marien, 1998). Given that complex I activity is only reduced by 25–30% in PD patients a direct role of ATP depletion in PD-related DA neurodegeneration is ruled out (Parker et al., 1989, Schapira et al., 1990a).

Despite the discrepancies in complex I activity and ATP levels there is substantial evidence indicating that augmenting the function of complex I with pesticide resistant single subunit complex I from yeast is sufficient to counteract the effects of complex I inhibitors such as MPP^+, rotenone, pyridaben, and annonacin (Marella et al., 2008, Richardson et al., 2007, Seo et al., 2002, Escobar-Khondiker et al., 2007, Sherer et al., 2007). Further support for a role of complex I dysfunction in PD-related DA neurodegeneration was established by the feeding of the mitochondrial electron transport chain directly at complex II by means of the ketone body D-β-hydroxybutyrate. Administration of D-β-hydroxybutyrate was shown to bypass complex I blockade, enhance oxidative phosphorylation, and attenuate DA neurodegeneration in MPTP treated mice (Tieu et al., 2003). Alternatively, administration of inorganic nitrite in phylogenetically distinct animal models of PD improved bioenergetics and rendered protective effects via mitochondrial complex I reversible S-nitrosation and activation of the antioxidant Nrf2 pathway (Milanese et al., 2018).

The OXPHOS components complex I, III, and IV form higher organized structures in the mitochondrial inner membrane called the super complexes. According to the current opinion assembly into super complexes improves enzymatic activities of individual complexes, and facilitates electron transfer through the OXPHOS chain, reducing ROS generation which in turn increases stability of individual complexes and results in efficient ATP synthesis (Enriquez, 2016, Maranzana et al., 2013). In a rodent PD model of 6-OHDA toxicity, neuronal degeneration was accompanied by decreased levels and activities of complex I in almost all forms of super complexes which was accompanied by decrease of complex IV activity in super complexes from striatum (Kuter et al., 2016). These observations were consistent with disassembly and loss of complex I and IV from the super complexes in mitochondria purified from fibroblasts derived from PD patients. The free complex III was only modestly affected, whereas its free versus super complex assembled forms decreased in PD compared to controls (Lopez-Fabuel et al., 2017). These findings suggest that besides complex I dysfunction and damage, the mitochondrial respiratory chain undergoes profound structural remodeling which is likely responsible for the energetic inefficiency and mitochondrial ROS over production observed in PD. Analysis of brain neurons and astrocytes in rodents revealed that the mitochondrial complex I in the neurons are predominantly assembled into super complexes, whereas in astrocytes the abundance of free complex I is higher. The presence of free complex I in astrocytes correlates with the several fold higher ROS production by astrocytes compared to neurons. Incidentally, complex I subunit NADH ubiquinone oxidoreductase core subunit S1 (NDUFS1) was more abundant in neurons than the astrocytes, whereas NDUFS1 knockdown in neurons decreased the association of complex I into super complexes, leading to impaired oxygen consumption and increased mitochondrial ROS. Conversely, overexpression of NDUFS1 in astrocytes promoted complex I incorporation into super complexes, decreasing ROS (Lopez-Fabuel et al., 2016). These findings suggest that complex I assembly into super complexes regulates ROS production and may contribute to bioenergetic differences between neurons and astrocytes. Collectively, these studies strongly support the view that complex I impairments may be central to the pathogenesis of DA neuronal death in sporadic PD. In the current scenario, it is unclear whether deficits in complex I is the triggering factor of all sporadic

cases of PD, but systemic complex I deficiency might be a predominant feature of PD pathogenesis.

3. Genetic perspective of mitochondrial dysfunction in Parkinson's disease

PD was long believed to be a prototypical, non-genetic disorder. However, in the last twenty years, the identification of distinct genetic loci responsible for rare monogenic Mendelian forms and the discovery of numerous genetic risk factors have refined and revolutionized this viewpoint. About 15% of patients with PD have a family history and in about 5–10% of subject's PD is caused by monogenic mutations. To date, at least 23 loci and 19 disease-causing genes for parkinsonism have been found, but many more genetic risk loci and variants for sporadic PD phenotype have been identified in various genome-wide association studies (Deng et al., 2017, Domingo and Klein, 2018). The emerging view from the existing knowledge is that the etiology of PD is multifactorial and presumably involves a complex interplay between a myriad of gene networks, and the environment. Many of the causative or risk factor genes for PD directly or indirectly associate with mitochondrial biology and function (Bose and Beal, 2016) and have provided novel insights into the molecular pathogenesis of PD, which are discussed in this section (Table 1).

3.1 α-synuclein (Park1, Park4)

Point mutations in the α-synuclein gene and multiplications of the wild-type gene are known to be associated with autosomal dominant PD (Schneider and Alcalay, 2017). α-synuclein protein is predominantly cytosolic, but a fraction has been identified in the mitochondria (Li et al., 2007), where it appears to interact directly with mitochondrial membranes (Nakamura et al., 2008). Given the affinity of α-synuclein for high-curvature detergent-resistant lipid-enriched membranes (Jensen et al., 2011, Middleton and Rhoades, 2010), perhaps it is not surprising that α-synuclein was found to have a role in the mitochondrial membrane. Upon binding to lipid membranes and vesicles, α-synuclein adopts an amphipathic α-helical structure, which can favor fibril formation, an important step in the initial process of oligomerization (Lee et al., 2002, Tsigelny et al., 2012). Mitochondrial localization of α-synuclein is also attributed to the presence of a cryptic mitochondrial targeting sequence (MTS) at its N-terminus of the α-synuclein gene (Devi et al., 2008). MTS is a short N-terminal peptide sequence that directs the transport of nuclear-encoded mitochondrial proteins into the mitochondria. Recent studies demonstrate that α-synuclein can disrupt mitochondrial protein import mechanisms in PD. The MTS is recognized by the translocase of the outer membrane (TOM) receptors, which is located on the outer membrane of the mitochondria. These matrix-targeted proteins are then translocated through the TOM complex to the translocase inner membrane (TIM) and finally into the matrix. In models of PD and postmortem PD brain tissues oligomeric, DA-modified, and Ser129E phosphomimetic α-synuclein can interact with members of the TOM complex (such as TOM40 and TOM20), and inhibit mitochondrial protein import resulting in excessive ROS production and mitochondrial impairment (Bender et al., 2013, Di Maio et al., 2016). Whether blockade of mitochondrial protein import is sufficient to drive nigrostriatal DA neurodegeneration remains to be determined, but it appears that accumulation of α-synuclein certainly impacts pathways involved in mitochondrial homeostasis. α-synuclein is

known to inhibit mitochondrial complex I in a dose-dependent manner that reflects the regional brain expression of α-synuclein (Liu et al., 2009, Devi et al., 2008). Interestingly, Thy1-α-synuclein transgenic mice overexpressing the human wild-type α-synuclein showed defects in mitochondrial respiration in the nigrostriatal pathway but not in the cortex, suggest region-specific mitochondrial impairment due to α-synuclein overexpression (Subramaniam et al., 2014). In isolated mitochondria, the prefibrillar oligomeric form of α-synuclein cause complex I dysfunction (Luth et al., 2014). It is postulated that this inhibition of complex I is through direct association of α-synuclein with complex I (Devi et al., 2008). Transgenic mice overexpressing mutant human A53T α-synuclein in DA neurons display α-synuclein-induced inhibition of complex I function (Chinta et al., 2010). Interestingly, in mice overexpressing either human wild-type or mutant human A53T α-synuclein, it was concluded that α-synuclein has a regulatory role in the function of complex I (Loeb et al., 2010). However, contrary to the studies showing detrimental effects of α-synuclein on complex I, in isolated rat brain mitochondria, exposure to wild-type and mutant forms of α-synuclein leads to loss of mitochondrial transmembrane potential without affecting the activity of respiratory complexes (Banerjee et al., 2010). It is difficult to explain such confounding results between different transgenic mouse lines. Functional studies have shown that α-synuclein binding to mitochondria independent of complex I can lead to cytochrome c release, increased calcium, and generation of ROS levels culminating in cell death (Banerjee et al., 2015).

α-synuclein is also known to play an indirect role in modulating complex I activity through interaction with the anionic phospholipid cardiolipin, a protein necessary for complex I function (Fry and Green, 1981, Zhang et al., 2002). Cardiolipin appears to be required for the formation of the mitochondrial supercomplex that involves complex I, III, and IV. Therefore, physical interaction of cardiolipin with α-synuclein can disrupt electron transfer (Mileykovskaya and Dowhan, 2014). Monomeric and oligomeric forms of α-synuclein display a preference for cardiolipin-enriched inner mitochondrial membrane over the outer mitochondrial membrane (Camilleri et al., 2013, Zigoneanu et al., 2012). In response to mitochondrial damage, cardiolipin is externalized on mitochondria where it acts as a “self-destructive” signal and will interact with the autophagy protein LC3-II to mediate mitochondrial degradation machinery called mitophagy in neuronal cells (Chu et al., 2013). Interestingly, α-synuclein oligomers that bind to cardiolipin can form a complex and act as a substrate for cytochrome c peroxidase, which induce mitochondrial damage through permeabilization (Bayir et al., 2009). Collectively, these studies support a role for α-synuclein in regulating mitochondrial complex I activity, though there is some controversy regarding specific mechanisms resulting in complex I dysfunction. It is not yet clear as to which forms of α-synuclein, namely the oligomeric, monomeric, or the post-translationally modified α-synuclein versions are important in causing most significant damage to the mitochondria.

During conditions of oxidative stress, α-synuclein is known to localize in the nucleus where it binds to the promoter of peroxisome proliferator-activated receptor gamma-coactivator-1 alpha (PGC-1α) gene, a transcriptional coactivator known to play a major role in energy metabolism, mitochondrial physiology, and oxidative stress. Binding of α-synuclein to the PGC-1α promoter results in downregulation of PGC1-α target genes that are involved in the

regulation of mitochondrial biogenesis and oxidative stress (Siddiqui et al., 2012). This is consistent with the presence of abnormal mitochondria, impaired mitochondrial respiration, fragmented endoplasmic reticulum, and increased susceptibility of nigral DA neurons to degeneration in the PGC1-α null mice following overexpression of human α-synuclein (Ciron et al., 2015). Moreover, α-synuclein-induced oxidative stress and neurodegeneration in PGC1-α null mice were rescued by expression of PGC1-α (Ciron et al., 2015). Other exogenous factors that link oxidative stress and mitochondrial dysfunction via α-synuclein are also suggested. For instance, *in vivo* studies using rats demonstrate the formation of α-synuclein aggregates following systemic exposure to mitochondrial toxins such as rotenone (Sherer et al., 2007) or dichlorvos (Binukumar et al., 2010). Similarly, α-synuclein transgenic mice exhibit increased proteinase-K-resistant α-synuclein inclusions following paraquat intoxication (Fernagut et al., 2007) and demonstrate increased sensitivity to neurodegeneration to MPTP (Nieto et al., 2006, Song et al., 2004, Lee et al., 2017a). Conversely, mice lacking α-synuclein are resistant to MPTP and other mitochondrial toxins such as malonate and 3-nitropropionic acid (Thomas et al., 2011, Drolet et al., 2004, Klivenyi et al., 2006, Dauer et al., 2002). Paradoxically, while acute MPTP administration to mice does not cause α-synuclein positive aggregates (Meredith and Rademacher, 2011), chronic infusion of MPTP via osmotic minipumps has been shown to produce ubiquitin and α-synuclein positive inclusions in the SN (Fornai et al., 2005, Thomas et al., 2007, Thomas et al., 2012).

There is growing body of evidence that mitochondrial dynamics which includes mitochondrial fission, fusion, transport and autophagic clearance of damaged mitochondria is essential for cellular health. These mechanisms are vital to neurons, as their alteration causes neurodegeneration. The dynamics of the mitochondrial network is intimately linked to the maintenance of mitochondrial activities. It is associated with cycles of fusion and fission events, regulated by fusion factors such as optic atrophy 1 (OPA1), mitofusin (Mfn1 and Mfn2), and by the fission GTPase Drp1. Mitochondrial membrane fusion allows redistribution of mitochondrial content and thus protect against the accumulation of damaged components, such as mitochondrial DNA (mtDNA). It constitutes a pro-survival response under stress conditions, ensuring optimal ATP production and regulating the autophagic removal of mitochondria (Tondera et al., 2009, Gomes et al., 2011, Shutt and McBride, 2013). Severe mitochondrial dysfunction inhibits mitochondrial fusion, resulting in mitochondrial fragmentation due to unopposed fission and subsequent mitophagy.

α-synuclein is known to affect mitochondrial dynamics by disrupting mitochondrial fission/fusion process. In *Caenorhabditis elegans* overexpression of α-synuclein leads to disruption in mitochondrial fusion resulting in mitochondrial fragmentation (Kamp et al., 2010), which is rescued by overexpression of PD proteins such as PINK1, Parkin and DJ-1. Interestingly, reintroduction of known mitochondrial fusion proteins such as Mfn1, Mfn2, and Opa1 failed to rescue these defects (Kamp et al., 2010). Studies from *in vitro and in vivo* model systems show that both wild-type and mutant α-synuclein overexpression induce mitochondrial fragmentation independent of Mfn2 or the fission protein Drp1 (Guardia-Laguarta et al., 2014, Kamp et al., 2010 Nakamura et al., 2011). In addition, mutant A53T α-synuclein is also reported to cause age-dependent abnormalities in mitochondrial morphology *in vivo* and impairments in mitochondrial transport *in vitro* (Xie and Chung, 2012). Indeed α-synuclein

oligomers has been shown to interfere with axonal transport by disrupting the association of kinesin-1 motors with microtubules (Prots et al., 2013). It has been proposed that mechanisms that regulate axonal transport velocity and directionality are regulated by the number of active motors that interact with microtubules (Leidel et al., 2012, Fu and Holzbaur, 2014, Fu and Holzbaur, 2014). α-synuclein oligomers are known to decrease the velocity of microtubule gliding across kinesin-coated surfaces (Prots et al., 2013). These data link the intrinsic aggregation properties of α-synuclein to a mechanism for mitochondrial transport defects due to impairments in kinesin function. Incidentally, the considerable accumulation of proteins, vesicles and mitochondria within axonal swellings that are positive for α-synuclein staining in PD suggest that motility defects contribute to disease pathogenesis (Spillantini et al., 1998, Galvin et al., 1999). Thus, one of the plausible mechanisms by which α-synuclein might regulate mitochondrial homeostasis is by modifying mitochondrial mobility. In this regard, several studies have indicated that fusion-fission dynamics are linked to mitochondrial axonal transport (reviewed by Abeliovich and Gitler, 2016). It is therefore possible that defects in mitochondrial function in PD occur because of abnormal mitochondrial distribution and transport, which in turn could be induced by excessive levels of α-synuclein or due to its abnormal aggregation. Moreover, mitophagy is intricately linked to transport processes owing to the need for recovery of mitochondria for clearance. Thus, even if α-synuclein does not directly regulate mitochondrial clearance via autophagy, the role of α-synuclein fusion-fission and transport processes could indirectly regulate the rate of mitophagy (Pozo Devoto and Falzone, 2017). It will be of great interest to determine the role of α-synuclein in mitochondrial turnover. The existing viewpoint suggests that increase in α-synuclein levels or its aggregation does affect mitochondrial dynamics. Taken together, these studies suggest a direct reciprocal relationship between α-synuclein aggregation and mitochondrial dysfunction that can create a vicious cycle leading to neurodegeneration.

3.2 LRRK2 (Park8)

Autosomal dominant mutations in Leucine-rich repeat kinase-2 (LRRK2) are associated with both familial and late-onset PD. LRRK2 patients have clinical symptoms and pathology typical of sporadic PD (Healy et al., 2008, Martin et al., 2014a). LRRK2 is a complex and large protein constituted by multiple domains executing several functions, including GTP hydrolysis, kinase activity, and protein binding. Although the cellular function of LRRK2 is largely unknown there is increasing evidence that LRRK2 posits a role in autophagic regulation, microtubule dynamics, and mitochondrial function. LRRK2 resides mainly in the cytoplasm and is partially localized to the mitochondria. It is associated with membranes, such as those present in mitochondria, ER and synaptic vesicles (Vitte et al., 2010, West et al., 2005). Expression of mutant LRRK2 and overexpression of wild-type LRRK2 induce a variety of negative effects on mitochondria including increased fragmentation of mitochondria that produce more ROS and less ATP, resulting in increased vulnerability of cells to stressors. Skin biopsies from patients with the G2019S mutation in LRRK2 have reduced mitochondrial membrane potential, abnormal mitochondrial morphology, and decreased total intracellular ATP levels (Mortiboys et al., 2010).

It is likely that these mitochondrial deficits are due to dysregulated fission and fusion events as LRRK2 interacts with several key regulators of mitochondrial fission/fusion, thus indicating it has multiple regulatory roles (Ryan et al., 2015) (Figure 1). In neurons, it was shown that LRRK2 associates with the Dynamin-related protein 1 (Drp1 also referred as DLP1), a known mitochondrial fission factor (Wang et al., 2012b, Niu et al., 2012). Expression of LRRK2 G2019S and R1441C mutants in neurons induced mitochondrial fragmentation and increased their interaction rate with Drp1 which also displayed higher phosphorylation levels, resulting, among others, in an enhanced level of ROS. All these defects could be rescued by silencing of Drp1, suggesting a LRRK2-Drp1 pathway regulating mitochondrial fission events and their clearance (Wang et al., 2012b, Niu et al., 2012). It has been established that in murine primary neurons and human neuroblastoma, endogenous LRRK2 directly interacts with the fission regulator Drp1 at the mitochondrial membrane, by phosphorylating Drp1 leading to Drp1 activity and mitochondrial fission (Wang et al., 2012b, Niu et al., 2012). This LRRK2-Drp1-dependent mitochondrial fragmentation is enhanced by overexpressing wild-type LRRK2 or by expressing the PD-associated G2019S mutant protein and rescued by inhibiting Drp1 or increasing mitochondrial fusion (Wang et al., 2012b, Su and Qi, 2013). Furthermore, kinase-dead or GTP-binding-deficient LRRK2 displays greatly decreased Drp1 interaction (Wang et al. (2012b). Phosphorylation of Ser616 of Drp1 has been shown to promote fission and increased Ser616 Drp1 phosphorylation has been observed in sporadic PD patients (Chang and Blackstone, 2010). However, other data suggest that the G2019S mutant primarily phosphorylates Drp1 at Thr595 resulting in aberrant mitochondrial fragmentation (Su and Qi, 2013). LRRK2 also interacts with the mitochondrial fusion regulators Mfn1, Mfn2 and OPA1 modulating their activities. PD patients carrying the G2019S mutation demonstrate decreased levels of mature OPA1 (Stafa et al., 2014). Furthermore, fibroblasts and neuroblastoma cells expressing LRRK2 G2019S show a very high increase in basal oxygen consumption and a marked decrease in mitochondrial membrane potential, possibly due to mitochondrial proton leak caused by increased mitochondrial uncoupling protein 2 (UCP2) and UCP4 expression, restored to normal level with inhibition of LRRK2 (Papkovskaia et al., 2012). Additionally, UCP2 upregulation has been observed in induced pluripotent stem cell (iPSC) derived neurons from PD patients carrying the G2019S mutation (Grunewald et al., 2014). Together, these data demonstrate that the aberrant LRRK2 activity results in decreased mitochondrial fusion and increased fission and suggest that LRRK2 function may be an important factor in mitochondrial fission/fusion events in PD.

Another aspect of mitochondrial dynamics involves mitochondrial trafficking. Mitochondrial movements are tightly controlled to maintain energy homeostasis. Before initiation of mitophagy by which depolarized mitochondria are degraded through autophagosomes and lysosomes the process of mitochondrial motility ceases (Ashrafi et al., 2014, Liu et al., 2012, Wang et al., 2011). This arrest in mitochondrial motility is required to sequester damaged mitochondria, preventing them from moving and from reintroducing damage to other healthy mitochondria. Miro is an outer mitochondrial membrane protein that anchors the microtubule motors kinesin and dynein to mitochondria (Glater et al., 2006, Koutsopoulos et al., 2010, Wang and Schwarz, 2009). The depolarization-triggered mitochondrial arrest is achieved by removal of Miro from the damaged mitochondrial surface and its subsequent

degradation by the proteasomes (Wang et al., 2011). A recent study discovered that LRRK2 promotes Miro removal from damaged mitochondria by forming a complex with Miro. PD associated LRRK2 G2019S mutant disrupt the LRRK2 Miro complex thus slowing Miro removal and mitochondrial arrest and delaying subsequent mitophagy, whereas partial depletion of Miro levels in LRRK2 G2019S human neurons and *Drosophila* PD models rescued neurodegeneration. Similar to LRRK2, other PD associated proteins PINK1 and Parkin have been shown to act in concert to target Miro for degradation (Ashrafi et al., 2014, Liu et al., 2012, Wang et al., 2011) suggesting that PINK1/Parkin pathways and LRRK2 function in parallel and converge on Miro that may be a common denominator for PD athogenesis.

3.3 PINK1 (Park6) and Parkin (Park2)

Two PD-associated proteins, the mitochondrial kinase PTEN-induced putative Kinase 1 (PINK1) and the E3-ubiquitin ligase Parkin, are central to mitochondrial quality control and provides the strongest evidence of mitochondrial dysfunction in PD pathogenesis (Pickrell and Youle, 2015). Mutations in PINK1 and Parkin are linked to early-onset familial PD (Pickrell and Youle, 2015). PINK1 localizes in the mitochondrial outer membrane and its kinase activity is critical for functions regulating mitochondrial homeostasis. Indeed, most mutations are found in the serine/threonine kinase domain of PINK1 protein, which suggest that loss of kinase activity plays a crucial part in the pathogenesis of PINK1-associated PD. Parkin on the other hand is located mainly in the cytosol and translocated to the mitochondria during stress or upon membrane depolarization in a PINK1-dependent manner to ubiquitinate several mitochondrial substrates mediating mitochondrial fragmentation, degradation and mitophagy (Matsuda et al., 2010). In healthy mitochondria with normal membrane potential, PINK1 is imported into the mitochondria and become degraded by proteolysis through the rhomboid protease presenilin-associated rhomboid-like protein (PARL) (Jin et al., 2010). However, in damaged mitochondria, the depolarization of the membrane potential as when treated with carbonyl cyanide m-chlorophenylhydrazone (CCCP-a mitochondrial uncoupler) allows the stabilization of PINK1 in the outer mitochondrial membrane. Activation and recruitment of Parkin onto damaged mitochondria involves PINK1-mediated phosphorylation of both Parkin and ubiquitin (Iguchi et al., 2013, Koyano et al., 2014). Through a stepwise process, Parkin is converted from an auto-inhibited enzyme into an active phosho-ubiquitin dependent E3 ligase. Upon activation, Parkin ubiquitinates itself in concert with many different substrates including mitochondrial proteins such as Mfn1 and Mfn2 (Gegg et al., 2010, Poole et al., 2010, Tanaka et al., 2010). The ubiquitin conjugates attached to these substrates can in turn be phosphorylated by PINK1, which triggers further cycles of Parkin recruitment and activation. This feed-forward amplification loop regulates both Parkin activity and mitophagy (Figure 1).

Depolarization of mitochondria induces PINK1/Parkin to associate with Miro, a mitochondrial outer membrane protein that recruit’s kinesin to the mitochondrial surface (Wang et al., 2011). PINK1 phosphorylates Miro to induce a Parkin and proteasomal-dependent degradation of Miro, thereby releasing kinesin from mitochondria, stalling the mitochondria, which is considered as an initial step prior to mitophagy (Wang et al., 2011). An additional mechanism for Parkin translocation to mitochondria involves the

phosphorylation of Mfn2 by PINK1 which acts as a receptor for Parkin (Chen and Dorn, 2013). It is suggested that dysregulated PINK1/Parkin signaling leads to impaired mitophagy resulting in the development of PD.

Although PINK1/Parkin dependent mitophagy is highly reproducible *in vitro*, it is difficult to syncretize the contribution of PINK1/Parkin signaling to mitochondrial homeostasis *in vivo* as both PINK1 and Parkin null mice do not recapitulate the overt neuropathology or motor dysfunction that manifests in PD. Majority of the studies used cultured cells which poorly relate to the complex human nigrostriatal DA neurons that selectively degenerate in PD adding to the disconnect. Moreover, high levels of PINK1/Parkin are usually required to detect a robust induction of mitophagy and it is difficult to relate the cytotoxic induction stimuli (for e.g. CCCP/FCCP) to an analogous physiological correlate that evokes a similar level of mitochondrial clearance *in vivo*. It is also suggested that the high concentrations of the uncoupling agents (such as CCCP/FCCP) used to depolarize mitochondria in these studies also depolarize other cellular organelles such as lysosome raising the possibility that the observed effects may be caused by non-specific acidification of the cytosol (Berezhnov et al., 2016). However, two studies from the Dawson group reported that postnatal conditional Parkin null mice results in loss of nigral DA neurons, suggesting a compensatory mechanism that occurs during development in germline knockouts (Shin et al., 2011, Stevens et al., 2015). Although the nature of this compensatory mechanism is currently unclear, Parkin-independent mechanisms of mitophagy have been described and it is possible that one or more of these mechanisms may compensate for Parkin loss of function (Allen et al., 2013, Kageyama et al., 2014). Interestingly and unlike the PINK1 null mice the PINK1 knockout rat model exhibits locomotor deficits and age-dependent loss of nigral DA neurons (Dave et al., 2014, Villeneuve et al., 2016). In contrast, Parkin knockout rats do not exhibit significant PD-related pathology (Dave et al., 2014). However, a recent study failed to confirm the previous reports of loss of nigral DA neurons in the PINK1 knockout rats therefore questioning the validity of this model (Orr et al., 2017). Taken together these findings clearly indicate lack of robustness of nigrostrial pathway in PINK1 and Parkin null rodents in contrast to human, as functional loss of PINK1 or Parkin invariably results in nigral DA neurodegeneration in the latter.

Despite the lack of nigral DA neurodegeneration observed upon germline deletion of Parkin, two recent studies highlighted the importance of endogenous Parkin in mediating mitochondrial homeostasis *in vivo* in rodent models. In the first study Parkin null mice was crossed with a mouse strain that expresses a proofreading-deficient version of the mtDNA polymerase γ, associated with an age-dependent accumulation of mtDNA mutations, known as the “Mutator mouse” (Pickrell et al., 2015). While, individually, Parkin-null mice and Mutator mice did not show a neurodegenerative phenotype, there was a nearly 40 % loss in DA neurons in the SN of aged Parkin-deficient Mutator double mutant mice compared to wild-type mice suggesting the sensitivity to this double hit is selective for nigral DA neurons. Surprisingly, there was no increase in the mtDNA mutation frequency in the double mutants, suggesting that the influence of Parkin deletion in the mutator background was not a consequence of defect in the selective elimination of mutation-bearing mitochondria consistent with the biological role of Parkin in mitochondrial quality control. The second study explored the role of Parkin in mitochondrial quality control by crossing Parkin null

mice with the PD-mito-*Pst*I male mouse, where the mtDNA undergoes double-strand breaks in DA neurons Pinto et al., 2017. The lack of Parkin promoted earlier onset of nigral DA neurodegeneration and motor defects in the PD-mito-*Pst*I mice, but it did not worsen the pathology. The lack of Parkin affected mitochondrial morphology in DA axons and increase in mutant and wild-type mtDNA levels without affecting mitophagy suggests that Parkin affects mtDNA levels in a mitophagy independent manner. These studies support the idea that Parkin protects DA neurons against mitochondrial dysfunction, but it fails to demonstrate that mitophagy as the underlying mechanism. Sterky and colleagues tested the hypothesis that absence of Parkin *in vivo* would prevent the clearance of defective mitochondria and thereby worsen the pathology in the MitoPark mice with conditional knockout of mitochondrial transcription factor A (TFAM) in DA neurons (Sterky et al., 2011). TFAM gene is known to regulate transcription of mtDNA and copy number and its deficiency in MitoPark mice results in progressive loss of DA neurons accompanied by low levels of mtDNA and lower respiratory chain activities (Ekstrand et al., 2007). Sterky and colleagues observed that the dysfunctional mitochondria in the MitoPark mice did not recruit Parkin *in vivo*, and neither affected the clearance of defective mitochondria nor the neurodegeneration phenotypes in the MitoPark Parkin double knockout mice (Sterky et al., 2011). These findings also failed to support a model in which Parkin-induced mitophagy protects against accumulation of mitochondria with severe respiratory chain dysfunction *in vivo*.

PINK1 and Parkin are also known to modulate mitochondrial homeostasis by regulating mitochondrial biogenesis. Parkin was shown to activate PGC-1α, a coregulator of mitochondrial biogenesis by promoting ubiquitin-dependent proteasomal degradation of the zinc finger transcriptional repressor called Parkin interacting substrate (PARIS) (Shin et al., 2011) (Figure 1). Loss of Parkin function results in the accumulation of PARIS, which in turn suppresses PGC-1α-dependent transcription. This was validated by analysis of postmortem SNpc tissue of PD patients, in which DA neurons displayed a reduction in PGC-1α levels. Moreover, viral vector-mediated overexpression of PARIS in the mouse SN led to DA neurodegeneration, which was prevented by Parkin or PGC-1α overexpression. Conversely, defective mitochondrial biogenesis and DA neuron loss following conditional Parkin deletion in adult mice was abrogated by PARIS gene silencing (Stevens et al., 2015). Recent studies indicate that PARIS is phosphorylated by PINK1 to regulate PARIS ubiquitination and clearance by Parkin where it controls PGC-1α levels indicating that PARIS provides a link between Parkin and PINK1 in the regulation of mitochondrial biogenesis (Lee et al., 2017b). Incidentally, some of the mitochondrial protective mechanisms are controlled by PINK1 independently of Parkin. This is highlighted by a specific role of PINK1 in the regulation of complex I activity. PINK1-deficiency in Drosophila and mouse models led to mitochondrial complex I defects (Morais et al., 2009), associated with loss of Ser250 phosphorylation of the complex I subunit NADH ubiquinone oxidoreductase subunit A10 (NDUFA10) (Morais et al., 2014). Incidentally, deficits in complex I activity and mitochondria-related phenotypes in PINK1 mutant flies, and cells derived from PINK1 null mice and patients with PINK1 mutations were rescued by Ser250 phosphorylation of NDUFA10. Another independent study showed that transgenic overexpression of NDUFA10 or its co-chaperone *sicily* rescued phenotypes in in PINK1

mutant flies, however, this study failed to confirm the phosphorylation of NDUFA10 in these phenotypes (Pogson et al., 2014). However, overexpression of NDUFA10 or *sicily* failed to restore phenotypes in Parkin null mutant flies, suggesting that PINK1 acts independently of Parkin in the maintenance of complex I activity. Interestingly, strategies bypassing or restoring complex I activity, through expression of the yeast Ndi1p NADH oxidoreductase or overexpression of NDUFA10 (Vilain et al., 2012, Morais et al., 2014, Pogson et al., 2014), attenuate phenotypes in PINK1 but not in Parkin mutant flies. Collectively, these studies provide strong evidence for the role of PINK1 and Parkin in mitochondrial quality control independent of its role in mitophagy and that future research should determine whether stimulating PINK1/Parkin mediated mitochondrial quality control represents a viable therapeutic target not just for PD but also for other mitochondrial disorders.

3.4 DJ1 (Park7)

Several other familial PD genes also influence either directly or indirectly the integrity of mitochondria in PD pathogenesis. Missense or deletion mutations of DJ-1 are associated with autosomal recessive PD (Bonifati et al., 2003). DJ-1 is a multifunctional protein involved in multiple cellular functions, including oxidative stress chaperone activity, transcription, and protecting mitochondria (Kinumi et al., 2004, Taira et al., 2004, Ren et al., 2011, Clements et al., 2006, Shendelman et al., 2004, Fan et al., 2008, Ishikawa et al., 2010, Ren et al., 2011, Hao et al., 2010). DJ-1 is mainly cytosolic and lacks a MTS but it translocate to mitochondria during oxidative stress-induced cell death (Canet-Aviles et al., 2004). Interestingly, PD causing mutants of DJ-1 such as L166P and M26I are localized on mitochondria and sensitize cells to oxidative stress (Ren et al., 2011). DJ-1 binds to complex I subunits NDUFA4 and ND1. Loss of DJ-1 decreases complex I activity consistent with mitochondrial defects observed in DJ-1 deficient cells (Hayashi et al., 2009). Incidentally, in fly models, DJ-1 mutant flies show compromised mitochondrial function with age whereas upregulation of DJ-1 can ameliorate toxic phenotypes of PINK1 but not Parkin mutant flies suggesting that DJ-1 acts downstream or parallel to the PINK1/Parkin pathway (Hao et al., 2010).

3.5 HTRA2 (Park13)

In humans, point mutations in HTRA2 are a susceptibility factor for PD (Table 1). The HTRA2 gene is a mitochondrial serine protease originally identified as a mammalian homolog to bacterial heat shock endoprotease (Faccio et al., 2000). In response to apoptosis, HTRA2 is released from mitochondria to the cytosol to cleave XIAP inducing apoptosis (Martins et al., 2002). Loss of function mutations in HTRA2 gene resulting in defective protease activity of HTRA2 is associated with autosomal recessive PD (Strauss et al., 2005). Loss of HTRA2 in mice leads to motor abnormalities, lethal neurodegenerative disorder, and accumulation of unfolded proteins in the mitochondria (Martins et al., 2004, Jones et al., 2003, Moisoi et al., 2009. HTRA2 knockout cells show a decrease in mitochondrial membrane potential, reduced mitochondrial density, and cause damage and mitochondrial DNA (mtDNA) mutations. In a fly model of HTRA2 loss of function, PD phenotypes were suppressed by the prosurvival Bcl-2 protein (M'Angale and Staveley, 2017). Additionally, PINK1 interacts with HTRA2 and facilitates HTRA2 phosphorylation, which contributes to increased resistance to mitochondrial stress (Plun-Favreau et al., 2007). Moreover, HTRA2

phosphorylation is decreased in brains from PD patients with PINK1 mutations, suggesting that PINK1 acts upstream of HTRA2 in mitochondrial stress signaling in PD (Plun-Favreau et al., 2007).

3.6 PLA2G6

Mutations in PLA2G6 cause PLA2G6-associated neurodegeneration (PLAN), including infantile neuroaxonal dystrophy (Khateeb et al., 2006) and adult-onset dystonia with parkinsonism (Paisan-Ruiz et al., 2009, Sina et al., 2009). PLA2G6 gene encodes for calcium-independent phospholipase A2b which hydrolyzes the sn-2 acyl chain of glycerophospholipids to release free fatty acids from phospholipids (Ma and Turk, 2001). It is distributed in the cytosol and membrane associated compartments, and considerably in the mitochondria (Seleznev et al., 2006). PLA2G6 null mice develop neuroaxonal dystrophy accompanied by increase phospho-Ser129 α-synuclein immunoreactivity in neuronal granules labeled with mitochondrial outer membrane protein TOM20 with degenerated mitochondria (Sumi-Akamaru et al., 2016). Similarly, loss of PLA2G6 orthologue in flies leads to age-dependent locomotor deficits and neurodegeneration with decreases in mitochondrial membrane potential and ATP production (Kinghorn et al., 2015). Overexpression of PLA2G6 protects cells from staurosporine-induced apoptosis by stabilizing mitochondrial membrane potential and reducing ROS levels (Seleznev et al., 2006). Moreover, PLA2G6 accumulates in LB from idiopathic and PLA2G6 patients (Miki et al., 2017) suggesting a role of PLA2G6 in mitochondrial dysfunction and LB formation (Sumi-Akamaru et al., 2015, Sumi-Akamaru et al., 2016).

3.7 CHCHD2 (Park22)

Missense mutation in CHCHD2 gene is associated with late-onset autosomal dominant PD and is a risk factor for sporadic PD (Funayama et al., 2015, Shi et al., 2016). CHCHD2 encodes coiled-coil-helix-coiled-coil-helix domain-containing protein 2, a protein originally identified as a transcription factor that binds to oxygen responsive element of COX4I2, a gene encoding cytochrome c oxidase (COX) (Aras et al., 2013). CHCHD2 contains an MTS and is localized to mitochondrial intermembrane space bound to COX and regulates its activity (Aras et al., 2015). CHCHD2 protein translocate from mitochondria to the nucleus in response to low oxygen tension and functions as a transcription factor to transactivate COX4I2 gene. Decrease of CHCHD2 protein level results in a decrease of COX activity and mitochondrial membrane potential, increase in ROS production and mitochondrial fragmentation, and disrupt mitochondrial cristae structure and destabilizes cytochrome c (Aras et al., 2015, Meng et al., 2017). Moreover, CHCHD2 protects against apoptosis via interaction with Bcl-xl to inhibit the oligomerization and mitochondrial accumulation of pro-apoptotic protein Bax (Liu et al., 2015). Taken together, CHCHD2 has a prominent role in the regulation of mitochondrial structure, synthesis of respiratory chain components and functions and modulation of apoptosis.

3.8 FBXO7 (Park15)

Mutations in F-box only 7 (FBXO7) results in early onset autosomal recessive PD (Shojaee et al., 2008). FBXO7 is a member of the Skp1-Cullin-F-box-type E3 ubiquitin ligase and plays a role in the ubiquitin proteasome system (Ho et al., 2008). FBXO7 is known to

participate in mitochondrial maintenance through direct interaction with PINK1 and Parkin and modulates Parkin-mediated mitophagy and rescue phenotypes in the fly model of Parkin loss of function, whereas, PD-linked FBXO7 mutants can recruit Parkin to damaged mitochondria and facilitate its aggregation (Burchell et al., 2013, Zhou et al., 2016, Zhou et al., 2015). Incidentally, FBXO7 immunoreactivity has been reported in α-synuclein positive inclusions of PD and multiple system atrophy (MSA) brains (Zhao et al., 2013).

3.9 Vps35 (Park17)

Mutations in the vacuolar protein sorting 35 (Vps35) gene, which encode a core component of the retromer complex, is associated with late-onset autosomal dominant PD (Zimprich et al., 2011). The retromer complex is a critical coordinator of endosomal dynamics with a functional role in multiple cellular processes through sorting cargoes from endosomes to the trans-Golgi network or the plasma membrane. Retromer has been suggested to be associated with mitochondrial function by mediating vesicle transport between mitochondria and peroxisomes. The components of the mammalian retromer Vps35 and Vps26 functionally interact with the small ubiquitin-like modifier E3 ligase known as mitochondria-anchored protein ligase (MAPL) that is enriched in mitochondria-derived vesicles (MDVs) (Braschi et al., 2010). Silencing of Vps35 and Vps26 leads to defects in the formation of MAPL-positive MDVs and thus causes the reduction in the delivery of MAPL to peroxisomes (Braschi et al., 2010). A role of the retromer deficiency/mutation to impairments in mitochondrial dynamics and neurodegeneration is also suggested (Wang et al., 2016). During mitochondrial fission, DLP1 is recruited to mitochondrial outer-membrane to exert fission (Yoon et al., 1998). Retromer has been shown to regulate the removal of DLP1 complexes from mitochondria via a Vps35-DLP1 interaction, and is known to transport these complexes through MDV-dependent mechanisms to lysosomes for degradation (Wang et al., 2016). The Vps35 D620N mutant displays an enhanced interaction with DLP1 and promotes the turnover of mitochondrial DLP1 complexes, resulting in mitochondrial fragmentation and neuronal loss (Wang et al., 2016). A role of the retromer in the regulation of mitochondrial fusion is also suggested (Tang et al., 2015). Retromer promotes the degradation of mitochondrial E3 ubiquitin ligase (MUL1) and known to suppress MUL1-mediated Mfn2 degradation (Tang et al., 2015). In Vps35-deficient DA neurons, MUL1 levels are elevated leading to reduction in Mfn2 subsequently resulting in mitochondrial fragmentation and neurodegeneration. Notably, these phenotypes were restored by the overexpression of Vps35 but not Vps35 D620N mutant (Tang et al., 2015). Consistent with a role in mitochondria-dependent cell death, overexpression of Vps35 also protects DA neurons against MPP+-induced toxicity which is partially compromised by the presence of the PD-linked Vps35 D620N mutation (Bi et al., 2013). Together, these findings suggest a role of retromer in mitochondrial biology beyond its function in endosomal trafficking.

3.10 ATP13A2 (Park9)

Mutations in ATP13A2, which encodes a lysosomal P-type ATPase cause a rare autosomal recessive parkinsonian syndrome (Ramirez et al., 2006, Di Fonzo et al., 2007). Fibroblasts derived from PD patients with ATP13A2 mutation displays fragmented mitochondria with low oxygen consumption rate and ATP synthesis (Grunewald et al., 2012). However, mitochondrial phenotypes in patient-derived cells with the ATP13A2 mutation are

circumstantial and might involve other factors that modify mitochondrial function such as α-synuclein, manganese, H_2O_2 or Zn^{2+} (Gitler et al., 2009, Del Fiacco et al., 1987, Daniel et al., 2015). Incidentally, ATP13A2 is known to regulate mitochondrial bioenergetics indirectly through macroautophagy (Gusdon et al., 2012).

3.11 GBA

The lysosomal hydrolase glucocerebrosidase (GCase) is encoded by the GBA gene. Homozygous GBA mutations cause Gaucher disease (GD), a lysosomal storage disorder. Although not known to cause monogenic form of PD, homozygous and heterozygous GBA mutations are numerically the greatest genetic risk factor for PD (Sidransky et al., 2009, Gegg and Schapira, 2016). The loss of GCase activity results in impairment of the autophagy-lysosomal pathway, which is required for the degradation of macromolecules and damaged organelles. The genetic and pharmacological inhibition of GCase activity via GCase shRNA or conduritol β-epoxide (CβE) respectively, results in significant decrease in mitochondrial membrane potential, inhibition of mitochondrial electron transport chain and mitochondrial fragmentation (Cleeter et al., 2013). Mitochondrial dysfunction is also observed in dermal fibroblasts from GD patients and in mouse models of GD. Fibroblasts from GD patients exhibited impaired oxygen consumption and significantly reduced levels of the respiratory chain electron carrier coenzyme Q10 and subsequent reduction in ATP levels and increased production of ROS (de la Mata et al., 2015). Both astrocytes and neurons derived from the GD null mice showed loss of mitochondrial membrane potential, reduced oxygen consumption and fragmented mitochondria (Osellame et al., 2013). Consistent with mitochondrial dysfunction in GD, GBA mutations or its deficiency in mice increased vulnerability of DA neurons to MPTP (Yun et al., 2018). At this juncture, a direct role of GCase in mitochondrial function is unknown, the loss of mitochondrial function in GD patients and preclinical models could be explained by impairment of the autophagy-lysosomal pathway, combined with changes in cellular lipid/sterol metabolism, neuroinflammation and perturbed calcium homeostasis (Gegg and Schapira, 2016).

To summarize the genetic factors, many familial PD gene products, which reside within the mitochondria or elsewhere in the cell play a crucial role in the maintenance of mitochondrial homeostasis. Deleterious mutations affecting the vital functions of these proteins therefore could dysregulate mitochondrial functions by interaction through innumerable signaling pathways. Based on the evidences a wide range of mitochondrial abnormalities has been reported in familial PD, including lowered ATP production, deficits in mitochondrial respiratory chain complex function, increased ROS production, abnormal morphology, disturbed mitochondrial transport, impaired mitophagy, and deficits in mitochondrial quality control. Future work should focus on resolving the impact of genes, environment, or a complex interaction of both in PD and should clarify which aspects of mitochondria become dysfunctional and when in the context of the entire pathological process leading to neurodegeneration to identify targets for therapeutic interventions.

4. Mitochondrial genome instability in Parkinson's disease

Mitochondria maintain a circular double stranded mtDNA that is 16,569 base pair long in humans. Unlike the nuclear genome, which is present in two copies in each cell, mitochondrion maintains multiple copies of the mitochondrial genome with identical sequence in a normal cell (homoplasmy). This extra-nuclear DNA in the cell gives partial autonomy to mitochondria that codes for 37 genes including two rRNAs, 22 tRNAs and 13 polypeptides that assemble with other nuclear encoded proteins to constitute key enzymes involved in OXPHOS. In the absence of rigorous proof reading mechanism that exists in nuclear DNA, mtDNA accumulate errors resulting in nonidentical copies within the individual mitochondrion or between the mitochondria of the same cell (heteroplasmy). There is a minimal threshold level of mutant mtDNA required to manifest a disease and mitochondrial dysfunction. This threshold for disease is lower in tissues that are highly dependent on oxidative metabolism. Mutations of mtDNA may be inherited or somatic. Somatic mutations of mtDNA are known to develop with aging and are thought to represent cumulative damage due to excess exposure to free radicals (Cooper et al., 1992). The proximity to the respiratory chain is suggested to favor mtDNA damage by ROS production linked to complex I defects (Richter et al., 1988) (Figure 1). Consistent with this view, transgenic mice overexpressing mitochondrial targeted antioxidant enzyme catalase exhibit reduced accumulation of mtDNA mutations during aging (Vermulst et al., 2008).

In general, primary mutations of mtDNA, as opposed to mutations secondary to a nuclear housekeeping gene has rarely shown to manifest PD. Regardless, support for mtDNA encoded defects in PD patients were reported employing the use of cybrid cells. Cybrids are generated by replacing mtDNA of a normal cell with the one derived from a patient or control cell allowing exclusion of nuclear genome effects from that of the mtDNA. PD cybrids have depolarized mitochondria, reduced complex I activity, increased ROS production and lower ATP production (Swerdlow et al., 1996, Esteves et al., 2008). The cybrid studies suggest that complex I defects in PD are inherited either from the mitochondrial genome or from alteration in the somatic mtDNA. In PD, the maternal inheritance pattern of mtDNA mutation is rare (Swerdlow et al., 1998, Wooten et al., 1997, Thyagarajan et al., 2000), although several lines of studies provide genetic evidence that mtDNA abnormality may contribute to PD pathogenesis. A point mutation in mitochondrial 12SrRNA was found in a pedigree with Parkinsonism, with deafness and neuropathy (Thyagarajan et al., 2000), and there is occurrence of Parkinsonism with Leber's optic atrophy with mitochondrial mutation G11778A (Simon et al., 1999). However, these are cases of atypical PD. Moreover, analysis of mtDNA found no homoplasmic mtDNA point mutations in coding regions in PD subjects in either DNA isolated from white blood cells or from the SN (Simon et al., 2000, Vives-Bauza et al., 2002). Whereas low levels of heteroplasmic mutations resulting in non-identical copies of mtDNA in the ND5 subunit of complex I were reported to be associated with PD, (Parker and Parks, 2005) the level of heteroplasmy was much less than seen in diseases caused by mtDNA mutations. Although, mitochondrial heteroplasmy has been highly anticipated, a clinical confirmation largely eluded, perhaps due to the shortcomings of technology to reach high enough resolution to sequence individual DNA molecule of individual mitochondria in large enough numbers. In

contrast, higher burden of mtDNA mutations in SN were reported in individuals with early onset PD and incidental Lewy body disease (Lin et al., 2012).

MtDNA synthesis, replication and repair mechanisms are controlled by mtDNA polymerase gamma 1 (POLG1). POLG1 is a nuclear encoded protein and imported into the mitochondria to localize in the inner mitochondrial membrane. Mutations in POLG1 results in a wide range of complex syndromes including autosomal dominant or recessive progressive ophthalmoplegia and parkinsonism (Luoma et al., 2007, Mancuso et al., 2004, Hudson et al., 2007). PD associated with POLG1 mutations are L-DOPA responsive, characterized by loss of SNpc DA neurons lacking Lewy bodies, and by the presence of multiple mtDNA deletions (Hudson et al., 2007). However, POLG mutant mice (D257A) with reduced ability to proofread accumulate significant amount of mtDNA deletions without neuronal degeneration and mitochondrial dysfunction (Perier et al., 2013). Mutations/polymorphisms in mitochondrial transcription factor gene TFAM, that regulates transcription of mtDNA and copy number has been suspected for its association in PD (Gatt et al., 2013). In contrast to the POLG mutant mice the conditional knockout of TFAM in DA neurons of MitoPark mice showed progressive loss of DA neurons accompanied by low levels of mtDNA and lower respiratory chain activities (Ekstrand et al., 2007). These studies suggest that the presence of increased levels of mtDNA deletions below a certain threshold is not responsible for neurodegeneration in PD.

In European populations, the mtDNA haplotype J and K, associated with mild uncoupling of mitochondria allowing adaptation to colder climates, would lead to reduced mitochondrial ROS production. Haplotype J, determined by a single nucleotide polymorphism (SNP) at 10398G and haplotype K in the control region of mtDNA, reduced the incidence of PD by 50% in these European patients (Ghezzi et al., 2005). However, with increasing age the super-haplogroup HV increases the risk for development of the disease (Hudson et al., 2013). These studies highlight the fact that tiny changes in mitochondrial genome may determine the risk of developing PD. A role of mtDNA deletions in human SN neurons was found by the presence of clonally expanded mtDNA deletions that was associated with a decrease in cytochrome oxidase activity in the SN (Bender et al., 2006, Kraytsberg et al., 2006). The Bender et al., study used long-range PCR to amplify mtDNA from cytochrome oxidase deficient and control neurons, and the Kraytsberg et al., study developed a novel single-molecule PCR technique to quantify the total cellular burden of mtDNA deletions in cytochrome oxidase-deficient neurons harboring mitochondrial respiratory chain defect and control neurons. Both studies found that mtDNA deletions were present at higher levels in aged controls compared to younger individuals and that these deletions were clonally expanded. In addition, Bender et al., study identified that mtDNA deletions were higher still in individuals with PD compared to aged controls (52.3% and 43.3% respectively), although the difference was of borderline significance (P= 0.06). These findings of surprisingly high levels of clonally expanded mtDNA deletions in SN neurons from elderly subjects, and a correlation of mutations with cytochrome oxidase deficiency support the hypothesis that the age-related accumulation of somatic mtDNA mutations may contribute to the aging of human brain and to the pathogenesis of PD. Consistent with these observations Grunewald and colleagues recently showed that mitochondrial complex I and II are most consistently affected in single neurons that also displayed reduced mtDNA copy number (Grunewald et

al., 2016). Also, in idiopathic PD cases increased mtDNA mutations were also reported in iPSC-derived neurons from patients carrying LRRK2 mutations (Sanders et al., 2014). A complete spectrum of mtDNA changes, including deletions, copy number variations, and point mutations in single DA neurons from SN and neurons from other brain regions of individuals with PD and healthy controls was recently studied (Dolle et al., 2016). Dölle and colleagues in this elegant study showed that SN DA neurons from PD patients accumulate higher levels of somatic mtDNA deletions, but not point mutations. Moreover, mtDNA copy number increases with age in healthy individuals, thus maintaining the pool of wild-type mtDNA population in spite of accumulating deletions. Conversely, mtDNA copy number does not increase in individuals with PD, resulting in depletion of the wild-type mtDNA population. Together, these observations suggest that there is a threshold beyond which mtDNA deletions accumulate in DA neurons of SN that results in mitochondrial defects and increase the risk of PD.

In summary, it is unclear if defects in mitochondrial genome are a direct cause of the PD pathogenesis or is a secondary consequence of ongoing mitochondrial dysfunction or neurodegeneration. Based on the studies thus far there is no clear evidence that mtDNA mutations are the primary culprit for PD. It appears that mtDNA mutations occur in the context of increasing cellular stress and decreasing fidelity of cellular defense systems against stress. However, clonal expansions of mtDNA mutations can functionally impair the respiratory capacity and thus lead to degeneration of vulnerable neurons. Despite these issues, the role of mtDNA should not be completely ignored and further investigations with more sophisticated tools are warranted to better understand its role in PD pathogenesis.

5. Mitochondrial permeability transition and the role of calcium homeostasis in Parkinson’s disease

Calcium (Ca^{2+}) plays a significant role in the function of all mammalian cells and is especially important in the nervous system. Extracellular Ca^{2+} affects neuronal excitability and the release of neurotransmitters, whereas intracellular Ca^{2+} is known to function as a second messenger in cell signaling and execute a wide range of functions in the mitochondria and ER (Brini et al., 2014). Ca^{2+} mishandling is associated with pathogenesis of several neurodegenerative diseases, including PD (Surmeier et al., 2010). During normal synaptic activity, intracellular concentration of Ca^{2+} increases transiently with no adverse effects on neurons. Unlike most neurons in the brain, DA neurons in the SNpc are autonomously active through their pacemaking activity, generating action potentials in the absence of synaptic input (Chan et al., 2007). This pacemaking activity is driven by voltage-dependent L-type Ca^{2+} channels, leading to sustained elevations in cytosolic Ca^{2+} levels in the SNpc DA neurons. The large Ca^{2+} buffering burden created by pacemaking activity in these neurons ultimately compromises mitochondrial function, resulting in mitochondrial oxidative stress and oscillations in mitochondrial potential, the latter being associated with compromised ATP production (Guzman et al., 2010) (Figure 1). Supporting a pathogenic role for increased Ca^{2+} load linked to pacemaking activity, the L-type Ca^{2+} channel antagonist-isradipine can attenuate rotenone-induced dendritic loss in brain slices from the adult midbrain and attenuate MPTP-induced DA neurodegeneration in mice (Chan et al.,

2007). These observations suggest that sustained mitochondrial Ca^{2+}overload in adult SNpc DA neurons may render them selectively vulnerable to PD. In agreement with this, neighboring ventral tegmental area (VTA) DA neurons, which do not rely on L-type Ca^{2+} channels for pacemaking, are relatively preserved in PD (Chan et al., 2010, Khaliq and Bean, 2010). In addition to differences in pacemaking another proposed mechanism for differential vulnerability between SN vs VTA DA neurons in PD is because SN DA neurons have a very high basal rate of mitochondrial OXPHOS, a smaller reserve capacity, higher density of axonal mitochondria, elevated levels of oxidative stress, and a considerably more complex axonal arborization compared to VTA neurons (Pacelli et al., 2015). Additionally, in neurons Ca^{2+} plays a significant role in the release of neurotransmitters. A recent study identified that when Ca^{2+} levels in the neurons increase, such as upon neuronal signaling, the α-synuclein binds to synaptic vesicles at multiple points causing the vesicles to come together (Lautenschlager et al., 2018). This may indicate a normal role of α-synuclein to help with chemical transmission across neurons. However, there is a fine balance of Ca^{2+} and α-synuclein maintained in neurons, and in conditions of excessive Ca^{2+} α-synuclein undergoes aggregation resulting in neuronal degeneration (Lautenschlager et al., 2018). To maintain Ca^{2+} homeostasis, Ca^{2+} entering neurons is rapidly sequestered in intracellular organelles, such as the mitochondria and the endoplasmic reticulum (ER), or pumped back across the plasma membrane concentration gradient. Although, the most significant intracellular storage site of Ca^{2+}, is the ER, the ability to accumulate, retain, and release Ca^{2+} is a fundamental property of mitochondria. Accumulation of Ca^{2+} within the mitochondrial matrix depends on both Ca^{2+} uptake into the mitochondria through an electrogenic uniporter, as well as extrusion of Ca^{2+} from the mitochondria through Na^{+}/Ca^{2+} and H^{+}/Ca^{2+} antiporters (Szabadkai et al., 2006, De Stefani et al., 2011). Ca^{2+} handling by mitochondria is involved in energy production for neuronal electrical activity, in buffering and shaping cytosolic Ca^{2+} rises and in determining cell fate by triggering or preventing apoptosis (Contreras et al., 2010).

The mitochondrial permeability transition is a phenomenon characterized by opening of a non-specific channel, known as the permeability transition pore (PTP), located in the inner membranes of the mitochondria (Figure 1). The PTP is opened by Ca^{2+} accumulation in the mitochondria and many other factors, and is traditionally linked to mitochondrial dysfunction because its occurrence leads to mitochondrial depolarization, cessation of ATP synthesis, Ca^{2+} release, pyridine nucleotide depletion, inhibition of respiration, matrix swelling, outer mitochondrial membrane (OMM) rupture and eventually release of pro-apoptotic proteins such as cytochrome c, endonuclease G and apoptosis inducing factor (AIF) (Bernardi et al., 2015). An important point to consider is that these detrimental effects on energy conservation and cell viability are only seen for long-lasting openings of the PTP (Petronilli et al., 2001) while short-term openings, which have been documented both in isolated mitochondria and in situ (Bernardi et al., 2015) may be involved in physiological regulation of Ca^{2+} and ROS homeostasis (Zorov et al., 2014), and provide mitochondria with a fast mechanism for Ca^{2+} release (Barsukova et al., 2011). Despite considerable experimental efforts, the molecular identity of the protein(s) that form the PTP channel remains a mystery. Although, there are multiple proteins implicated in pore formation and its regulation (Bernardi and Di Lisa, 2015, Giorgio et al., 2017), the major proteins proposed to

comprise the PTP are-a) the voltage-dependent anion channel (VDAC) present in the outer membrane, b) the adenine nucleotide translocator (ANT) located in the inner membrane, c) cyclophilin D (CypD) found in the matrix, d) the F1F0 ATP synthase found in the inner mitochondrial membrane (IMM), and other molecules. According to the prevailing point of view, the formation of the pore is initiated by the CypD translocation from the mitochondrial matrix to the IMM to bind with ANT. CypD binding to ANT results in the formation of an ANT channel in IMM. The ANT formed channel together with the channel formed by VDAC in OMM constitutes a tunnel-like structure crossing the mitochondrial membranes, thus connecting mitochondrial matrix with the cytosol (Banerjee et al., 2009). The molecular nature of PTP was further refined with the identification of c-subunit ring of the F1F0 ATP synthase which forms a voltage-sensitive channel of the PTP following the dissociation of the F1 ATP synthase from CypD (Giorgio et al., 2013, Bonora et al., 2013, Alavian et al., 2014).

In the context of PD-related cell death, one of the earliest observations implicating Ca^{2+}-induced mitochondrial dysfunction was that MPP+, 6-hydroxydopamine or dopamine strongly stimulated Ca^{2+} release from mitochondria and hydrolysis of intra-mitochondrial pyridine nucleotides (Frei and Richter, 1986) This was followed by the finding that MPP+ caused mitochondrial swelling and the release of cytochrome c (Cassarino et al., 1999), Ca^{2+} efflux and membrane depolarization (Packer et al., 1996), all of which were inhibited by the CypD inhibitor cyclosporine A, thereby implying a classical PTP. Consistent with these *in vitro* findings we showed that genetic ablation of PTP modulator CypD, which significantly increases the resistance of mitochondria to Ca^{2+}-induced PTP opening, also strongly protects mice against acute MPTP-neurotoxicity (Thomas et al., 2012). Studies using cybrid cells containing mtDNA from PD patients also exhibit lower mitochondrial Ca^{2+} sequestration compared to controls when stimulated for Ca^{2+} entry into the mitochondria (Sheehan et al., 1997). Other studies that support a role for alterations in Ca^{2+} homeostasis in PD are related to dysfunctions in PD related proteins. For eg., both monomeric and oligomeric α-synuclein has been shown to favor entry of Ca^{2+} from extracellular space, whereas increase in intracellular Ca^{2+} is known to enhance α-synuclein aggregation, thus establishing a reciprocal relationship between α-synuclein and Ca^{2+} (Follett et al., 2013, Schmidt et al., 2012, Tsigelny et al., 2012). It is unclear whether this effect is due to increased plasma membrane permeability to Ca^{2+} or due to modulation of the Ca^{2+} channels. The finding that α-synuclein is present in the mitochondria-associated ER membrane fractions also known as (MAM) (Guardia-Laguarta et al., 2015) supports its role in stabilization/formation of the ER-mitochondria interactions and mitochondrial uptake of Ca^{2+}. It is important to note that there is a significant interplay between mitochondria and ER about Ca^{2+}. Both the ER and mitochondria are linked biochemically and physically and facilitate efficient Ca^{2+} transmission from ER to mitochondria (Csordas et al., 2006, de Brito and Scorrano, 2008). Interestingly, α-synuclein has been shown to interact with ANT, one of the components of PTP (Zhu et al., 2011), and genetic ablation of CypD, the PTP modulator, delayed disease onset, and extended lifespan in mutant human A53T α-synuclein transgenic mice (Martin et al., 2014b). These observations are consistent with increased mitochondrial swelling, PTP pore opening and Ca^{2+}-induced cytochrome c release in the presence of soluble pre-fibrillar α-synuclein oligomers (Luth et al., 2014). The PD protein Parkin is

known to exert a protective role by sustaining ATP production via stabilization of ER-mitochondria Ca^{2+} transfer, thus providing a possible mechanism through which Parkin mutations or deficiency might result in neuronal dysfunction (Cali et al., 2013, Gautier et al., 2016). Moreover, Parkin deficiency has been shown to be associated with increased basal Ca^{2+} levels (Sandebring et al., 2009). Similarly, the loss of PD protein PINK1 resulted impaired Ca^{2+} efflux and an overload of Ca^{2+} in the mitochondria (Gandhi et al., 2009). This resulted in lower mitochondrial respiration, an increased ROS production and a lower threshold for the opening of the PTP. In confirmation of this point of view, co-expression of mutant PINK1 and α-synuclein-induced mitochondrial alterations were partially rescued by the PTP inhibitor cyclosporine A (Marongiu et al., 2009). Moreover, loss of PINK1 has been shown to sensitize cells to PTP opening (Gandhi et al., 2009, Gautier et al., 2012) and reduced PKA signaling leading to impaired phosphorylation and activity of the mitochondrial Na^{+}/Ca^{2+} exchanger (NCLX) which is likely responsible for increased mitochondrial Ca^{2+} accumulation (Kostic et al., 2015). An association of PINK1 in Ca^{2+} homeostasis and the development of PD is also established through the mitochondrial calcium uniporter (MCU), located in the inner mitochondrial membrane. Genetic and pharmacologic inactivation of the MCU prevented dopaminergic neuronal loss in $PINK1^{Y431}$ mutant zebra fish (Soman et al., 2017). The PD related protein DJ-1 has been shown to act at the ER-mitochondria contact sites (Ottolini et al., 2013) and is known to mediate direct transfer of Ca^{2+} from ER to mitochondrial matrix. Interestingly, DJ-1 overexpression in a cellular model shows protective response by delaying the opening of the PTP and suggests that DJ-1 plays a crucial role in the control of Ca^{2+} buffering and oxidative stress via uncoupling proteins (UCP4 and UCP5) (Dongworth et al., 2014, Guzman et al., 2010). Another PD-related protein LRRK2 is also linked to PTP function. LRRK2 has been shown to interact with three components of the PTP including ANT, VDAC, and mitochondrial creatine kinase. Expression of both wild-type and mutant LRRK2 retain the mitochondrial creatine kinase at the outer mitochondrial membrane and block its mitochondrial import to promote the interaction between VDAC1 and ANT, thus sensitizing the cell to PTP opening and subsequent cell death (Cui et al., 2011).

In summary, there is convincing evidence for the involvement of derangements in Ca^{2+} signaling and mitochondrial Ca^{2+} mishandling in PD pathogenesis, and that nigral DA neurons act as a major site of neuronal Ca^{2+} impairments in the CNS due to their intrinsic susceptibility (Chan et al., 2009). Given the complexity and insufficient knowledge of the composition of PTP and its regulation, future research should address some important questions, such as the protein composition of the PTP channel, how they regulate PTP opening, and what PD relevant factors/mechanisms influence PTP function? Answering these questions may help establish whether PTP plays a role in the etiology of PD and develop therapeutic agents targeting PTP.

6. Therapeutic approaches targeting mitochondrial dysfunction in Parkinson's disease

Despite intensive research, the etiology of PD remains poorly understood, leaving with no effective neuroprotective therapies. Current therapies are palliative at best by providing

effective control of symptoms, particularly in the early stages of the disease. The current symptomatic therapies cannot completely ameliorate later-stage symptoms, nor can they address the ongoing degeneration that underlies PD pathology. For this reason, a great deal of research has focused on finding the cause of neurodegeneration in PD and on exploring protective, restorative, and replacement therapies. Substantial evidence as detailed in this review suggests a major role of mitochondrial dysfunction in the pathogenesis of both sporadic and familial PD. Given the importance of mitochondrial dysfunction in PD pathogenesis, therapeutics targeting mitochondria have been extensively studied to treat PD. Here, we briefly summarize therapeutic agents that reduced PD pathology in preclinical models of PD and those that eventually made it to human clinical trials (Table 2). Most of the agents tested for neuroprotective effects in clinical trials in PD have used compounds that would slow down neurodegeneration and disease progression by blocking mitochondrial dysfunction, reducing oxidative stress or both.

The Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism (DATATOP) trial was the largest and the first clinical trial to investigate the neuroprotective potential of selegiline, a monoamine oxidase-B inhibitor, along with tocopherol (vitamin E), in patients with early PD with putative rescue mechanisms on mitochondrial function and oxidative stress (Parkinson Study, 1993). The primary outcome was the onset of disability prompting the clinical decision to begin levodopa treatment in PD patients. Although the use of selegiline had a beneficial effect and significantly delayed the time of onset of levodopa treatment during the first 12 months, patients treated with tocopherol showed no benefits nor did the tocopherol added any benefit to selegiline. This study suggests that selegiline may delay disease progression, with mild symptomatic effects known to improve motor symptoms in PD rather than a neuroprotective effect. Rasagiline is a newer monoamine oxidase-B inhibitor that is more potent than selegiline and has metabolites with potential antioxidant properties. It has been studied using a delayed-start clinical trial design intended to reduce the confounding effect of symptomatic efficacy. The outcomes of this study suggest that early treatment confers a long-lasting improvement, but the overall duration of this study was relatively short, and the group sizes were small (Parkinson Study, 2002). However, study in a larger sample and over a longer time course failed to demonstrate disease-modifying effects of the drug at 2 mg dose which was observed with 1 mg. Moreover, small change in Unified Parkinson Disease Rating Scale (UPDRS) scores made the results difficult to interpret (Olanow et al., 2009).

Coenzyme Q10 (CoQ10) is a lipid-soluble endogenous compound that serves as a cofactor for the electron transport chain by accepting electrons from complex I, II and III (Beal, 2003). It serves as a potent free radical scavenger in the inner mitochondrial membranes and microsomal lipid membranes by reducing α-tocopheroxyl radical and by regenerating α-tocopherol (Beal, 2003). CoQ10 is also an obligatory cofactor for mitochondrial uncoupling proteins as they function by regulating ATP production and reducing free radical generation and reduce DA neurodegeneration in mouse PD models (Beal, 2002). A large multicenter QE3 study evaluated the potential neuroprotective effect of two different doses of CoQ10 (1200 and 2400 mg daily) in drug naive participants with PD (Parkinson Study Group et al., 2014a). All participants of this study also received 1200 IU/day of vitamin E. The patients were observed for 16 months or until symptomatic treatments were required. CoQ10 was

safe and well tolerated but did not show any clinical benefits (Parkinson Study Group et al., 2014a). Another mitochondrial targeted antioxidant Mitoquinone (MitoQ-a derivative of mitochondrial quinolone) consists of the lipophilic cation triphenylphosphonium (TPP) covalently attached to the ubiquinone moiety of CoQ10 (Jin et al., 2014). The TPP cation enables MitoQ to cross membranes and to accumulate within the mitochondria (Snow et al., 2010). MitoQ is known to convert hydrogen peroxide to water and oxygen, to reduce toxic insults from free radicals in the mitochondria and enhance mitochondrial bioenergetics. It has been shown to be effective in numerous animal models of mitochondrial dysfunction including PD (Orsucci et al., 2011). A multicenter study in New Zealand and Australia that tested two doses of MitoQ compared to placebo in a double-blind study showed no difference in UPDRS score at 12-month follow-up. Failure of this study was attributed to small sample size and lack of adequate brain penetrance of MitoQ (Snow et al., 2010).

Creatine is a guanidine compound and serves as a crucial energy reservoir for ATP and is a component of the creatine-phosphate system. Most of the creatine is found in the skeletal muscle and is taken up by various organs by specific creatine transporters, and serves as a substrate for mitochondrial and cytosolic creatine kinase (Snow and Murphy, 2001). It is suggested that the creatine enables mitochondrial creatine kinase to remain functionally in the octameric state to inhibit the mitochondrial PTP and block apoptosis (Dolder et al., 2003). Free radicals enable the octameric form of mitochondrial creatine kinase to convert to a dimeric state, which causes opening of the PTP to mediate cell death (O'Gorman et al., 1997). However, the neuroprotective function of creatine/phosphocreatine through creatine kinase-mitochondrial PTP system has been challenged, and instead it enhances cytosolic high energy phosphates that maintain ATP levels (Klivenyi et al., 2004, Brustovetsky et al., 2001). Nevertheless, creatine has been shown in multiple independent studies to block neuronal death and increase lifespan in experimental animal models of neurodegenerative disorders (Beal, 2011). The NIH Exploratory Trials in Parkinson Long-term study-1 (NET-PD LS-1) that tested creatine monohydrate 5 g twice a day and patients followed up for a minimum of 5 years. This study failed to show any difference in UPDRS scores between the placebo and creatine groups and did not improve the outcome in patients with early or treated PD (Writing Group for the et al., 2015).

Pioglitazone is an FDA approved drug for the treatment of type 2 diabetes. It is a peroxisome proliferator-activated receptor γ (PPAR-γ) agonist known to reduce insulin resistance (Smith, 2001). It's cofactor PGC-1α is a transcriptional coactivator and is a master regulator of mitochondrial biogenesis. Activation of PGC-1α is shown to be neuroprotective in many different models of neurodegenerative diseases (Agarwal et al., 2017). There is also strong evidence of impaired PGC-1α regulated transcriptional network in PD (Zheng et al., 2010). A multicenter double-blind, randomized, placebo-controlled, futility trial compared 15 or 45 mg per day pioglitazone or placebo at baseline and 44 weeks. The results were negative and suggested that pioglitazone is unlikely to modify progression in early PD (Investigators, 2015). In addition to PGC-1α, activation of sirtuins and AMPA kinase pathways are also implicated in mitochondrial biogenesis and serve as promising targets for PD therapeutics by preventing mitochondrial dysfunction (Valero, 2014). Another FDA-approved drug licensed for type-2 diabetes is the glucagon-like peptide (GLP-1) agonist Exenatide. The precise mechanism of this drug in PD remains unclear but preclinical

studies in the MPTP mouse model of PD shows protective effects GLP-1 agonists by its stimulating effect on mitochondrial biogenesis (Li et al., 2009, Chen et al., 2015, Fan et al., 2010, Kang et al., 2015). A single-center, randomized, double-blind, placebo-controlled trial in 62 patients with moderate PD received subcutaneous injections of 2 mg or placebo once weekly for 48 weeks, followed by a 12-week washout period. At 60 weeks, the UPDRS improved by 1.0 point in the exenatide arm but worsened by 2.1 points in the placebo group (Athauda et al., 2017). Exenatide had positive effects on practically defined off-medication motor scores in PD, which were sustained beyond the period of exposure. Whether exenatide affects the underlying disease pathophysiology or simply induces long-lasting symptomatic effects is uncertain. Nevertheless, exenatide represents a major new avenue for investigation in PD, and effects on everyday symptoms should be examined in longer-term trials.

Isradipine, a L-type Ca^{2+} channel antagonist, which is FDA-approved for the treatment of high blood pressure. Preclinical studies with isradipine has been shown to protect against DA neuron degeneration in the MPTP mouse model of PD by preventing sustained elevations in cytosolic Ca^{2+} levels resulting in mitochondrial oxidative stress (Guzman et al., 2010, Ilijic et al., 2011, Wang et al., 2017). It has been used in a phase II trial to asses to establish dosage, safety and efficacy. The Safety, Tolerability, and Efficacy Assessment of Dynacirc controlled release for PD controlled release in PD (STEADY-PD) was undertaken (Parkinson Study, 2013, Biglan et al., 2017) and found that isradipine 10 mg daily to be safe and well tolerated in early PD with a dosage that achieves serum concentrations found to be neuroprotective in animal models of PD. The much-anticipated phase III efficacy trial is currently underway and provides a unique opportunity to evaluate the potential impact of this novel therapy to slow progression of PD disability.

Ursodeoxycholic acid (UDCA) is FDA approved for the use in treating primary biliary cirrhosis. Preclinical studies show that UDCA renders protective effect in both toxin and genetic models of PD by blocking mitochondrial perturbations (Abdelkader et al., 2016, Mortiboys et al., 2015). A phase I study is currently underway to determine brain bioenergetics profile and ATPase activity using MR-spectroscopy following repeated oral dosing of UDCA. Additional studies will characterize oral UDCA pharmacokinetics in plasma and develop a pharmacokinetic/pharmacodynamic model to characterize the relationship between peripheral measurements of UDCA and peripheral measures and brain bioenergetic measurements (Table 2). Another compound EPI-589, also known as (R)-troloxamide quinone developed by Edison Pharma for inherited mitochondrial disorders is claimed to have significant effects in modifying cellular glutathione (GSH) levels. Currently a phase II study is underway in idiopathic PD to determine its safety and the ability to alter the biochemical signature of PD as assessed by peripheral blood and brain biomarkers along with clinical measures (Table 2). The GSH precursor N-acetylcysteine currently approved to treat acetaminophen overdose and mucous build-up in cystic fibrosis also showed benefits in preclinical models of PD (Rahimmi et al., 2015, Martinez Banaclocha, 2000, Berman et al., 2011, Clark et al., 2010). Oral administration of N-acetylcysteine is known to boost blood and brain levels of GSH in PD patients (Holmay et al., 2013). A preliminary clinical study significantly increased dopamine transporter binding in the caudate and putamen with mean increase ranging from 4.4% to 7.8% in the PD group treated with N-acetylcysteine, and no measurable changes in the control group. UPDRS scores were also significantly improved in

the N-acetylcysteine group with a mean improvement of 12.9% (Monti et al., 2016). These results demonstrate a positive clinical effects N-acetylcysteine in PD through a direct effect on DA neurons. A large-scale clinical trial to test the therapeutic efficacy of N-acetylcysteine in PD to better elucidate the mechanism of action is warranted.

A promising strategy for the treatment of neurodegenerative diseases involves drug-induced activation of a coordinated antioxidant genetic program to maintain redox equilibrium by the expression of pro-survival proteins and cytoprotective enzymes (Gazaryan and Thomas, 2016). A key transcription factor orchestrating this process is Nrf2. The ability to selectively induce a battery of cytoprotective and antioxidative enzymes that are directly under the genetic control of a single transcription factor such as Nrf2 may have significant advantages over conventional strategies. One can potentially induce multiple antioxidant pathways and associated neuroprotective responses, which would not be dependent on the antioxidant effects of a single molecule or combination of molecules that are frequently consumed while scavenging toxic-free radical species. Others and we have demonstrated that compounds such as synthetic triterpenoids and fumaric acid esters can activate this pathway and offer neuroprotection in animal models of PD (Kaidery et al., 2013, Ahuja et al., 2016, Lastres-Becker et al., 2016). Tecfidera is an oral formulation of dimethylfumarate used to treat multiple sclerosis. We showed that dimethylfumarate and its metabolite monomethylfumarate activate Nrf2 to upregulate genes involved in antioxidant, anti-inflammatory, and mitochondrial biogenesis to protect against MPTP-neurotoxicity via distinct S-alkylating properties and GSH depletion (Ahuja et al., 2016). Our data suggest that activating Nrf2 using MMF rather than DMF is a promising approach to block oxidative stress, neuroinflammation, and mitochondrial dysfunction for therapeutic intervention in PD while minimizing side effects (Ahuja et al., 2016, Gazaryan and Thomas, 2016). Another endogenous chemical Uric acid has been shown to render neuroprotective effects in cell culture and animal models of PD by activating the Nrf2 pathway (Zhang et al., 2014, Jhang et al., 2015). Interestingly, epidemiological studies have shown a decreased incidence of PD in subjects with high serum urate levels (Davis et al., 1996, Weisskopf et al., 2007) and in subjects with gout (Alonso et al., 2007). In patients with early PD, higher plasma urate levels correlate with slower disease progression and subjects on diets that promote high urate levels have a reduced risk of developing PD (Gao et al., 2008). Such a urate-rich diet could serve as a neuroprotective therapy in PD. However, the potential benefits of a urate-rich diet must be weighed against the risk of developing gout and cardiovascular disease. A large-scale clinical trial of the effectiveness of elevating urate in patients with PD is currently underway (Crotty et al., 2017). The Safety of Urate Elevation in Parkinson’s Disease (SURE-PD) study was conducted to test the precursor of urate, inosine and was found to be safe and effective in increasing serum urate levels, and plasma antioxidant capacity of PD patients and thus may prove to be a disease-modifying therapy for PD (Parkinson Study Group et al., 2014b, Bhattacharyya et al., 2016).

In summary, the lack of efficacy observed with many of the drugs described above except for exenatide in human PD may raise concerns regarding the utility of targeting mitochondria for therapeutic approaches. However, failure of a drug in a clinical trial only questions the usefulness of the specific test compound. Moreover, some of the studies appear to be underpowered and for many of the drugs data on blood-brain barrier penetrance in PD

patients are not consistently available. The lack of valid and sensitive biomarkers for the diagnosis and monitoring of the treatment response in PD that would replace clinical endpoints or symptomatic markers to assess disease progression is also a limitation, as these are currently determined by neurological exams. Moreover, much of the disability associated with PD is not considered in the UPDRS scale, such as those related to autonomic dysfunction. Another reason for the failure of potential neuroprotective therapies could also be explained by the limitations of the current preclinical models. Currently, there is no one animal model for PD that mimics the full pathology and clinical symptomology of the illness. Most of the drugs tested thus far in clinical trials showed efficacy in toxin models which show degeneration of nigrostriatal DA neurons, but the time course and pathological features of these are different from human disease (Beal, 2010). The identification of familial PD-linked genes led to the development of genetic-based models as alternatives to toxin models and some of them recapitulate many of the cardinal features of human PD and will undoubtedly support drug development over the coming years (Visanji et al., 2016, Creed and Goldberg, 2018). The predictive power of animal models of PD will be confirmed only if there is success in demonstrating neuroprotection in humans. Lastly, our knowledge about the underlying molecular pathways involved in the pathogenesis of PD is still limited despite intensive research efforts invested in this field. A comprehensive discussion addressing many of these crucial issues combined with treatment modalities that restore mitochondrial function shall provide new ideas and avenues for future development of neuroprotective therapies with a goal to slow or arrest the progression of this disabling disorder.

7. Concluding remarks

Although the etio-pathogenic mechanisms for PD are not fully understood, ample empirical evidence suggests a significant role of mitochondrial dysfunction in disease development. Deficits in mitochondrial functions due to bioenergetics defects, generation of ROS, aberrant calcium homeostasis, and anomalies in mitochondrial dynamics and quality control are implicated as the underlying mechanisms of both sporadic and familial PD. Based on the existing knowledge of mitochondrial alterations in PD it could be speculated that strategies aimed at correcting the above mentioned biochemical abnormalities might be useful to halt or slowdown the progression of PD. In this regard, many of the candidate drugs that showed efficacy in experimental PD models have already made it to clinical trials. However, except for exenatide many other drugs failed to show any beneficial effects in human PD to date. These failures should not cast doubts on targeting mitochondrial rescue as a therapeutic strategy. Instead there should be better integration and meaningful translation from bench to the bedside through better understanding of disease mechanisms, discovery of reliable and sensitive biomarkers, rectifying therapeutic design of clinical trials and by selecting candidate drugs for clinical trials that show efficacy in multiple and mechanistically diverse preclinical models of PD. Such collective efforts should enable the PD community to ultimately find better therapies targeting mitochondrial dysfunction for this debilitating neurodegenerative movement disorder.

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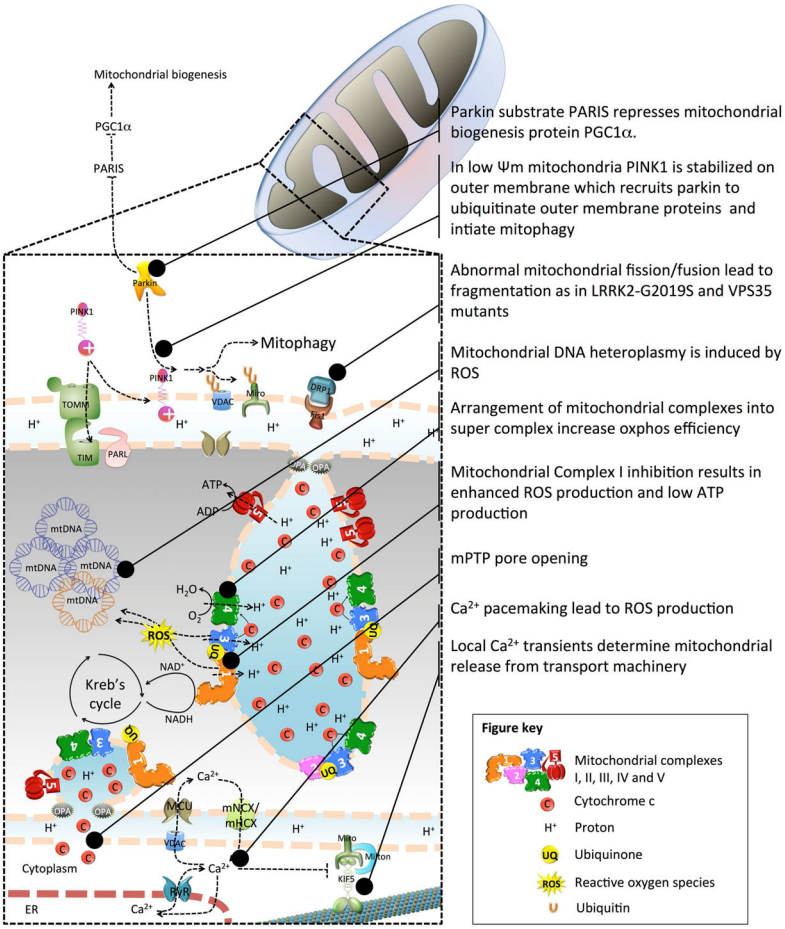

Fig 1.
Mitochondrial pathways to Parkinson's disease.

Table 1

Familial PD genes and genetic risk factors and their potential role in mitochondrial biology

Genes	Mitochondrial phenotype	References
α-synuclein (Park1/4)	Reduced Complex I activity, OCR	Subramaniam et al., 2014
	Abnormal mitochondrial morphology, Ca^{2+} homeostasis	Luth et al., 2014
	Abnormal ER-mitochondria transport	Guardia-Laguarta et al., 2015
Parkin (Park2)	Reduced mitochondrial respiration, oxidative damage	Palacino et al., 2004
	Mitochondrial functional integrity	Chan et al., 2011
	Reduced mitochondrial biogenesis/function	Shin et al., 2011
	Abnormal mitochondria and high mitochondrial ROS	Chung et al., 2016
PINK1 (Park6)	Reduced ETC enzyme function	Papa et al., 2009
	Reduced ATP production, Ca2+ homeostasis	Heeman et al., 2011
	Reduced mitochondrial function, fission	Park et al., 2006
	Abnormal mitochondria and high mitochondrial ROS	Chung et al., 2016
	Abnormal mitochondrial Ca2+ handling	Gandhi et al., 2009
DJ1 (Park7)	Abnormal mitochondrial morphology	Irrcher et al., 2010
	Uncoupled mitochondria, glycolytic shift	Shi et al., 2015
	Mutants induce mitochondrial fragmentation	Wang et al., 2012a
LRRK2 (Park8)	Reduced ATP production and membrane potential	Mortiboys et al., 2010
	Abnormal mitochondrial fission/fusion	Stafa et al., 2014
	Delayed Miro degradation and mitophagy	Hsieh et al., 2016
ATP13A2 (Park9)	Mutant cause low mitochondrial oxygen consumption rate, ATP synthesis	Grunewald et al., 2012
HTRA2 (Park13)	Mitochondrial morphological abnormalities	Martins et al., 2004
	Low respiration, sensitivity to apoptosis	Casadei et al., 2016
FBXO7 (Park15)	Impaired UPS, reduced mitophagy leading to accumulation of dysfunctional mitochondria	Zhou et al., 2016
	Mitochondrial accumulation of aggregates	Zhou et al., 2015
VPS35 Park17	Mitochondrial fragmentation, reduced oxygen consumption	Wang et al., 2016
CHCHD2 (Park22)	Decreased Complex I activity, respiration, increased ROS Transcription factor for Complex IV subunit COX4I2	Aras et al., 2015, Aras et al., 2013
	Regulate apoptosis	Liu et al., 2015
PLA2G6	Decreased mitochondrial membrane potential and function	Kinghorn et al., 2015
GBA	Reduced macro autophagy leading to accumulation of dysfunctional mitochondria	Gegg and Schapira, 2016

Table 2

Current clinical trials targeting mitochondrial dysfunction in PD

Drug	Mechanism of action	Clinical outcome	Reference
Rasagiline	MAO-B inhibitor Antioxidant	Modest UPDRS gain, but inconsistent dose dependency between 1mg and 2mg	NCT00256204 * Smith et al., 2015
Creatine	Antioxidant Mitochondrial biogenesis	No improvement	NCT00449865 * Writing Group for the et al., 2015
Ubiquinone (Coenzyme Q10)	Antioxidant Mitochondrial electron carrier	Trial completed No improvement	NCT00004731 * Parkinson Study Group et al., 2014a
Mitoquinone (MitoQ)	Antioxidant Mitochondrial biogenesis	Trial completed No improvement	NCT00329056 * Liu and Wang, 2014
Isradipine	Calcium channel blocker	Safety study completed Phase III trial underway	NCT00909545 * Swart and Hurley, 2016
Inosine	Antioxidant	Generally safe and tolerated; Slight dose dependent attenuation of clinical decline	NCT00833690 * Parkinson Study Group et al., 2014b
N-acetylcysteine	Antioxidant Glutathione precursor	Moderately improved UPDRS.	Monti et al., 2016
Pioglitazone	Anti-inflammatory PPAR-g agonist	No improvement	NCT01280123 * Investigators, 2015
Exenatide	Anti-apoptotic Anti-inflammatory Mitochondrial activity	Trial completed	NCT01971242 *
Resveratrol	Mitochondrial biogenesis	Safety study	NCT01504854 * Smoliga et al., 2011
EPI-589 (R)-troloxamide quinone	Augments GSH levels	Recruitment stage	NCT02462603 *
Ursodeoxycholic acid	Beneficial effect on mitochondrial dysfunction	Safety study	NCT02967250 * Mortiboys et al., 2013

* ClinicalTrials.gov Identifier