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LRRK2 and mitochondria: Recent advances and current views

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Abstract

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene account for most common causes of familial and sporadic Parkinson's disease (PD) and are one of the strongest genetic risk factors in sporadic PD. Pathways implicated in LRRK2-dependent neurodegeneration include cytoskeletal dynamics, vesicular trafficking, autophagy, mitochondria, and calcium homeostasis. However, the exact molecular mechanisms still need to be elucidated. Both genetic and environmental causes of PD have highlighted the importance of mitochondrial dysfunction in the pathogenesis of PD. Mitochondrial impairment has been observed in fibroblasts and iPSC-derived neural cells from PD patients with LRRK2 mutations, and LRRK2 has been shown to localize to mitochondria and to regulate its function. In this review we discuss recent discoveries relating to LRRK2 mutations and mitochondrial dysfunction.

Keywords

Parkinson's disease; LRRK2; mitochondrial dysfunction; mitochondrial dynamics; mitophagy; trafficking

1. Introduction

Parkinson's disease (PD) is the second most common motor neurodegenerative disorder affecting approximately 1% of the population above 60 years of age. It is characterized by the selective loss of dopaminergic neurons in substantia nigra pars compacta (SNc) innervating the basal ganglia (Lees et al., 2009). Hallmark symptoms of PD include rigidity, bradykinesia, and test tremor. More than 90% of the cases are sporadic; however, 10% of the cases are caused by monogenic mutations and 23 causative genes have so far been identified, including α -synuclein, leucine-rich repeat kinase 2 (LRRK2), PTEN-induced kinase 1 (PINK1), Parkin, DJ-1, etc (Kalia and Lang, 2015). Neurodegeneration in PD is typically accompanied by the presence of protein inclusions termed Lewy bodies in surviving neurons that are enriched with α -synuclein protein. However, the exact etiology and precise cause of PD has yet to be fully characterized, but involves dysfunction of numerous processes,

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including mitochondrial function, calcium homeostasis, dopamine (DA) homeostasis, autophagy, and proteostasis (Kalia and Lang, 2015).

Mitochondrial dysfunction has emerged as one of the key mechanisms underlying the pathogenesis of both sporadic PD and familial Parkinsonism (For more details on PD and mitochondrial dysfunction see the reviews by Giannoccaro 2017 and Larsen 2018 (Giannoccaro et al., 2017; Larsen et al., 2018). Specifically, the mitochondrial complex I activity is decreased by 40% in the substantia nigra region of the midbrain in PD patients, and complex I subunits are selectively reduced (Bindoff et al., 1989; Hattori et al., 1991; Schapira et al., 1990). Interestingly, complex I inhibitors such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone induce a clinical syndrome mimicking PD phenotypes in both human and non-human primates (Beal, 2003; Dauer and Przedborski, 2003). Further evidences for the involvement of mitochondrial dysfunction in PD pathogenesis comes from the fact that several disease-related genes such as *PINK1*, *Parkin*, *DJ1* are linked to mitochondrial pathways (Bose and Beal, 2016). Vulnerability of SNc DA neurons in PD is in part due to their particular bioenergetics and morphological characteristics. SNc DA neurons have a higher energy demand for normal function than those that are less vulnerable due to their long and highly-branched, unmyelinated axonal arbors (Pissadaki and Bolam, 2013). SNc DA neurons have a higher basal rate of oxidative phosphorylation (OXPHOS) which may confer a further increase in risk (Pacelli et al., 2015).

Mutations in the LRRK2 gene (PARK8) are the most prevalent causes of the late-onset autosomal dominant type of PD (Paisan-Ruiz et al., 2004; Zimprich et al., 2004), accounting for 5-6% of familial and 1-2% of sporadic PD cases (Bardien et al., 2011; Farrer et al., 2005; Gilks et al., 2005; Hardy, 2010). Six LRRK2 mutations have a proven pathogenicity (Ross et al., 2011): R1441C/G, N1437H, Y1699C, G2019S and I2020T. Recently, it is shown that LRRK2 contributes to the risk of sporadic PD (Nalls et al., 2014). Importantly, in most LRRK2 mutation carriers, the clinical and pathological features are indistinguishable from those of sporadic PD, demonstrating an unprecedentedly significant role of LRRK2 in PD pathogenesis (Gosal et al., 2005).

LRRK2 is a multifunctional complex protein, 2527-amino-acids long with multiple domains, including a leucine-rich repeat (LRR), a ROC-COR GTPase, a mitogen-activated protein kinase, and WD40 domains. Not surprisingly, it participates in a broad range of cellular activities, and extensive studies suggest that LRRK2 pathogenesis involves diverse signaling pathways and cellular processes such as cytoskeleton remodeling, vesicular trafficking, autophagy, mitochondria dynamics and quality control, protein translation (Cookson, 2010; Price et al., 2018; Roosen and Cookson, 2016; Taymans et al., 2015). The most frequent mutation, G2019S, found in the kinase domain, shows increased LRRK2 kinase activity (West et al., 2005).

LRRK2 interacts with a number of key regulators of mitochondrial fission/fusion, co-localizing with them either in the cytosol or on mitochondrial membranes, indicating that it has multiple regulatory roles (Stafa et al., 2014; Wang et al., 2012). Thus, LRRK2 might directly affect mitochondrial function in addition to indirectly regulating it through

autophagy or cytoskeletal dynamics. This hypothesis is of great interest as mitochondrial dysfunction is central to PD pathogenesis (Beal, 2005; Bose and Beal, 2016). A growing body of evidence supports a role for LRRK2 in mitochondrial function. Mitochondrial dysfunctions (higher oxidative stress, reduced mitochondria membrane potential and decreased ATP production, mitochondria DNA damage, elongated mitochondria, mitochondrial fragmentation, mitophagy) were observed in postmortem human tissues from LRRK2-linked PD patients, various animal models of G2019S-LRRK2 PD (Table 1) (Cooper et al., 2012; Mortiboys et al., 2010; Sanders et al., 2014; Yue et al., 2015) and cellular models of the disease (Cherra et al., 2013; Niu et al., 2012; Su and Qi, 2013; Wang et al., 2012). Exactly how LRRK2 mutations could lead to mitochondrial dysfunction is not yet clear, but recent advances have provided a number of clues (Fig. 1). In this review, we discuss our understanding of how LRRK2 mutations perturb mitochondrial function, ultimately contributing to PD pathogenesis.

2. Subcellular localization of LRRK2

LRRK2 normally exists as a dimeric structure minimally mediated via its ROC domain, and dimerization is required for its kinase activity and localization to cellular membranes (Berger et al., 2010; Deng et al., 2008; Greggio et al., 2008; Sen et al., 2009). The WD40 domain also appears to be important for dimerization and kinase activity (Jorgensen et al., 2009). Although the majority of LRRK2 protein is present in the cytoplasm, about 10% of LRRK2 is present in the mitochondrial fraction of cells over-expressing the protein and is associated with the mitochondrial outer membrane in rodent brains (Biskup et al., 2006; West et al., 2005). In rat primary cortical neuronal cultures, confocal images showed a partial overlap of LRRK2 immunoreactivity with mitochondrial and lysosomal markers (Biskup et al., 2006). Ultrastructural analysis revealed that LRRK2 is associated with intracellular membranes, including lysosomes, transport vesicles, and mitochondria in rodent brains. Thus, the specific association of a fraction of LRRK2 with mitochondria and its ability to induce mitochondria-dependent apoptosis (Cui et al., 2011; Iaccarino et al., 2007), raise the possibility that LRRK2 may compromise mitochondrial function when over-expressed or mutated leading to PD pathogenesis (Biskup et al., 2006).

3. LRRK2 and mitochondrial oxidative stress

Oxidative stress is the result of disequilibrium between excessive production of reactive oxygen species (ROS) and limited antioxidant defenses. ROS can lead to oxidative damage of proteins, DNA, and lipids (Raha and Robinson, 2000). Mitochondria generate most of the ROS as a byproduct of OXPHOS by the respiratory chain complex. Superoxide anion, which is produced mainly by mitochondrial complexes I and III of the electron transport chain, is highly reactive and can easily cross the inner mitochondrial membrane, where it can be reduced to H₂O₂. Familial PD cases have unequivocally been found to be related to mitochondrial complex I dysfunction (Betarbet et al., 2000; Dauer and Przedborski, 2003; Ved et al., 2005). The PD-susceptible SNc DA neurons in mouse primary culture showed elevated OXPHOS and increased ROS production (Pacelli et al., 2015). One of the probable reasons could be the large axonal arborization of the SNc DA neurons. SNc DA neurons

display an increased density of mitochondria and an elevated ATP production, which are factors contributing to ROS (Pacelli et al., 2015).

Multiple studies have demonstrated that LRRK2 mutant is associated with an increased susceptibility to oxidative stress, leading to increased cell death (Cooper et al., 2012; Imai et al., 2008; Mendivil-Perez et al., 2016; Ng et al., 2009; Nguyen et al., 2011; Pereira et al., 2014; Reinhardt et al., 2013). Rotenone is a specific inhibitor that binds to the ubiquinone binding site of mitochondria complex I, thus preventing electron transfer via flavin mononucleotide (FMN) to coenzyme Q10. Consequently, interruption of the OXPHOS chain concomitantly generates ROS such as superoxide and hydrogen peroxide. LRRK2 G2019S-expressing flies display reduced lifespan and increased sensitivity to rotenone (Ng et al., 2009). Rotenone induces DNA fragmentation, loss of mitochondrial membrane potential, and intracellular ROS generation in nerve-like differentiated cells carrying the G2019S mutation, and this could be reversed by LRRK2 kinase inhibitor (Mendivil-Perez et al., 2016). Moreover, multiple groups have demonstrated increased susceptibility to oxidative stress in LRRK2 mutant iPSC-derived DA neurons (Nguyen et al., 2011) and neurons (Cooper et al., 2012).

The intrinsic cellular redox state is also influenced by LRRK2 mutations in some model systems. Neural stem cells carrying the R1441G mutation displayed higher oxidative stress, increased rates of cell death, and impaired neuronal differentiation (Bahnassawy et al., 2013). The basal oxygen consumption rate (OCR) is reduced in iPSC-derived neural cells from PD patients carrying the homozygous G2019S mutation and the heterozygous R1441C mutation in LRRK2 when compared to healthy controls (Cooper et al., 2012). Notably, these mitochondria defects can be rescued by a LRRK2 inhibitor (Cooper et al., 2012). Finally, enhanced mitochondrial DNA damage is found in iPSC-derived neural cells from patients carrying the G2019S mutation (Howlett et al., 2017; Sanders et al., 2014). DNA damage could both cause and result from oxidative stress.

On the other hand, pathogenic LRRK2 mutations can decrease the antioxidant defenses of mitochondria through several different mechanisms. It is reported that LRRK2 kinase mutant G2019S significantly increased phosphorylation of peroxiredoxin 3 (PRDX3), the most important scavenger of hydrogen peroxide in the mitochondria, compared to the wild-type. The increase in PRDX3 phosphorylation was associated with decreased peroxidase activity in the *Drosophila* brain (Angeles et al., 2014). Both motor dysfunction and mitochondrial degeneration present in LRRK2 mutants were ameliorated by PRDX3 (Angeles et al., 2014). Another possibility for mutant LRRK2 to decrease the antioxidant defenses of mitochondria came from hyper-phosphorylation of 4E-BP. 4E-BP1 is an inhibitor of translation that has been implicated in mediating the survival response to oxidative stress. Hyper-phosphorylation of 4E-BP in vivo can lead to reduced oxidative stress resistance and dopaminergic neurodegeneration (Imai et al., 2008; Tain et al., 2009). Finally, LRRK2 mutant may affect neuronal uncoupling proteins (UCPs) which are crucial for reducing the production of ROS and consequent oxidative stress (Conti et al., 2005). Expression of UCP2, which has been identified as the cause of mitochondrial proton leakage in fibroblasts from LRRK2 PD patients with the G2019S mutation (Papkovskaia et al., 2012), is upregulated in response to elevated ROS generation in affected mutation carriers.

Restoration of mitochondrial membrane potential by the UCP inhibitor genipin confirmed the role of UCPs in this mechanism (Grunewald et al., 2014; Papkovskaia et al., 2012).

Interestingly, studies in *C. elegans* (Saha et al., 2009; Samann et al., 2009) and *Drosophila* (Venderova et al., 2009) suggest an antagonistic effect of the LRRK2 and PINK1 genes (Samann et al., 2009). PINK1 exerts directly or indirectly an inhibitory effect on LRRK2 in fibroblasts or iPSC-derived DA neurons from PD patients with PINK1 mutations (Azkona et al., 2016). Ectopic expression of human Parkin in LRRK2 G2019S-expressing flies provides significant protection against DAergic neurodegeneration that occurs with age or in response to rotenone (Venderova et al., 2009). Notably, Parkin appears to interact with LRRK2 physically in vitro (Smith et al., 2005).

4. LRRK2 and mitochondrial dynamics and quality control

4.1. LRRK2 and mitochondrial fission and fusion

Mitochondria are dynamic organelles that constantly fuse and divide. These processes, collectively termed mitochondrial dynamics, are important for mitochondrial inheritance and for the maintenance of mitochondrial functions. The dynamic balance of fission and fusion contributes to mitochondrial health. These processes help transmitting energy across long distances within the cell, which are required for axonal and synaptic functions (Baloh et al., 2007; Chen et al., 2007; Hoppins et al., 2007). Any perturbation from these dynamic processes would lead to disease phenotypes. The process of fission and fusion is regulated by molecular machinery that includes dynamin-related GTPases and WD40 repeat-containing proteins. Since the LRRK2 protein contains both GTPase and WD40 domains, it could potentially serve as a scaffold during mitochondrial fission and fusion events.

LRRK2 mutations associated with PD have been shown to alter mitochondrial fusion/fission but with conflicting results. Fibroblasts derived from human PD patients with the G2019S mutation have elongated mitochondria (Mortiboys et al., 2010). Homo LRRK2 G2019S knock-in mice display progressive changes in mitochondria that are consistent with arrested fission (Yue et al., 2015). Conversely, most studies show that LRRK2 mutants cause fragmentation of mitochondria (Grunewald et al., 2014; Niu et al., 2012; Smith et al., 2016; Su and Qi, 2013; Wang et al., 2012). Interconnectivity of mitochondria is reduced in fibroblast culture from PD patients carrying the G2019S mutation as compared to control subjects (Grunewald et al., 2014). Smith and colleagues reported that PD-derived fibroblasts displayed a fragmented mitochondrial network which could be attenuated by a LRRK2 inhibitor (Smith et al., 2016). Over-expression of LRRK2 G2019S mutant can induce mitochondrial fragmentation in primary cortical neurons through interacting with dynamin-like protein 1 (DLP1, a mitochondrial fission protein) (Niu et al., 2012). Along the same line, human dopaminergic neuroblastoma cell line SH-SY5Y expressing LRRK2 mutants (G2019S and R1441C) exhibits severe mitochondrial fragmentation with shorter and smaller mitochondria observed in electron micrographs (Wang et al., 2012). The mechanistic investigation revealed that LRRK2 regulates mitochondrial dynamics through direct interaction with DLP1. Similar results were observed by Su and Qi in PD patient fibroblasts, wherein mitochondrial fission was accelerated by LRRK2 G2019S mutant by recruiting the dynamin-related protein 1 (DRP1) to the mitochondria (Su and Qi, 2013). Notably, the

kinase activity of LRRK2 is required for its interaction with DRP1 and mitochondrial fragmentation in these studies (Smith et al., 2016; Su and Qi, 2013; Wang et al., 2012). In a recent investigation, a novel LRRK2 variant E193K identified in an Italian family, was found to alter LRRK2 binding to DRP1 thus affecting fission (Perez Carrion et al., 2018). Further, optic atrophy 1 (OPA1, a protein controlling mitochondria fusion) levels were reported to be reduced in G2019S PD patient brains (Stafa et al., 2014).

Another recent and very intriguing finding has implicated the role of lysosomal RAB7 in mitochondrial fission (Wong et al., 2018). The study demonstrated the existence of Mitochondria-lysosome contacts and the contacts can regulate mitochondrial fission via RAB7 GTP hydrolysis (Wong et al., 2018). Since RAB7 is one of the substrates of LRRK2 (Beilina et al., 2014), it is plausible that LRRK2 mutants affect mitochondrial dynamics in PD via regulating RAB GTP hydrolysis.

4.3. LRRK2 and mitophagy

Autophagy is a key cellular catabolic process wherein the cytosolic components, including mainly dysfunctional organelles, misfolded proteins, and surplus or unnecessary cytoplasmic contents are transported to lysosomes for digestion. Mitophagy describes the clearance of damaged mitochondria. Dysregulation of mitophagy plays important roles in neurodegenerative diseases (Vives-Bauza and Przedborski, 2011). There is substantial evidence suggesting that LRRK2 regulates autophagy (Beilina et al., 2014; Cherra et al., 2013; Cookson, 2016; Ferree et al., 2012; Hindle et al., 2013; Hsieh et al., 2016; Orenstein et al., 2013; Ramonet et al., 2011; Saha et al., 2015; Schapansky et al., 2014; Tong et al., 2012).

LRRK2 mutants have been shown to activate dendritic mitochondrial clearance by autophagy in cortical neuronal culture (Cherra et al., 2013). Inhibition of LRRK2 impairs autophagy by altering autophagosome-lysosome fusion, causes DRP1-mediated mitochondrial fission, and induces mitophagy in SH-SY5Y (Saez-Atienzar et al., 2014). Interestingly, loss of mitochondrial membrane potential has been observed in fibroblasts from PD patients harboring the G2019S LRRK2 mutation (Su et al., 2015). This was accompanied by an increase in autophagic flux and higher expression of autophagy markers in LRRK2 mutants. In HeLa cells, expressing wild-type and mutant LRRK2 G2019S induced mitochondrial mass loss. Further investigation revealed that G2019S bound to and phosphorylated Bcl2, resulting in excessive mitophagy (Su et al., 2015). LRRK2 PD-patient-derived fibroblast lines displayed a more fragmented mitochondrial network and heightened mitophagy at baseline (Smith et al., 2016).

While the above evidence suggests that LRRK2 affects mitophagy via autophagy indirectly, studies from Xinnan Wang's group have demonstrated a direct role of LRRK2 in mitophagy (Hsieh et al., 2016). Miro is an outer mitochondrial membrane protein that anchors the microtubule motors kinesin and dynein to mitochondria. They reported that LRRK2 in iPSC-derived neurons causes the removal of damaged mitochondria by forming a complex with Miro, thereby promoting its displacement from damaged mitochondria (Hsieh et al., 2016). Mutant LRRK2 (G2019S) disrupts this complex, slows Miro removal and delays the subsequent mitophagy.

4.3. LRRK2 and mitochondrial trafficking

Axonal transport is critical for maintaining healthy neurons as neurons are highly polarized cells that utilize specific motor proteins to travel along cytoskeletons composed of microtubules. Defects in axonal transport can lead to disruption in energy homeostasis, impaired protein clearance pathways, neurite shortening, and eventual cell death (Fu and Holzbaur, 2014; Maday et al., 2014).

LRRK2 has been shown to interact with microtubules and cytoskeleton proteins (Beilina et al., 2014; Caesar et al., 2013; Law et al., 2014). Co-localization and ultrastructural analyses in primary neuronal cultures showed that LRRK2 interacts closely with microtubules in a well-ordered, periodic fashion, suggesting the existence of a LRRK2-binding site on microtubules or microtubule-bound proteins (Kett et al., 2012). Interestingly, it was found that the level of free tubulin is significantly increased in the brain extracts of LRRK2 knock-out mice (Gillardon, 2009), whereas it is dramatically decreased in the brain homogenates of LRRK2 wild-type and G2019S transgenic mice (Parisiadou et al., 2009). Thus LRRK2 might be a potential stabilizing protein for microtubule assembly. LRRK2 has been shown to physically interact with tubulin proteins via its GTPase domain; it phosphorylates them, thereby increasing tubulin polymerization in vitro (Gandhi et al., 2008; Gillardon, 2009). Consistent with this observation, microtubule assembly is impaired in mice overexpressing the wild-type or G2019S mutant LRRK2 (Lin et al., 2009). Another study suggests that G2019S LRRK2 expression may cause dendrite degeneration in *Drosophila* by promoting the phosphorylation of the microtubule-associated protein tau via GSK3 β homolog Shaggy (Lin et al., 2010).

Tubulin acetylation is a post-translational modification associated with microtubules stability and has a prevalent role in axonal microtubule structure and function (Esteves et al., 2014; Esteves et al., 2015; Godena et al., 2014). Acetylation of microtubules promotes microtubule-dependent trafficking (Reed et al., 2006). In isolated peripheral blood mononuclear cells from both sporadic PD and LRRK2 G2019 patients, it has been observed that tubulin acetylation is decreased when compared to age-matched healthy individuals (Esteves et al., 2015). Perturbed microtubule assembly has also been observed in vivo in postmortem brain tissue of LRRK2-associated PD patients, and in transgenic and viral-based rodent models expressing LRRK2 mutants (Dusonchet et al., 2011; Li et al., 2009; MacLeod et al., 2006; Melrose et al., 2010; Rajput et al., 2006; Zimprich et al., 2004). LRRK2, thus, seems to have a role in maintaining microtubule dynamics. Disturbances in the microtubule network would affect axonal transport including mitochondria trafficking. LRRK2 R1441C (Roc-COR) mutant inhibits axonal mitochondria transport as well as locomotion in *Drosophila* (Godena et al., 2014). The mutant LRRK2 R1441C and Y1699C inhibits microtubule acetylation, hampering axonal transport. Inhibiting histone deacetylases restores axonal transport and locomotion (Godena et al., 2014). Also, cells expressing the R1441C mutant display hampered mitochondrial transport, decreased number of mitochondria traveling in both anterograde and retrograde direction, and significantly decreased the total run length of mitochondria as compared to control. These aberrations could be attenuated by treatment with LRRK2-specific GTP-binding inhibitors (Thomas et al., 2016).

While the above evidence suggests that LRRK2 affects mitochondria trafficking indirectly by modulating microtubule stability, Wang and her colleagues demonstrate a direct role of LRRK2 in mitochondria trafficking in iPSC-derived neurons by interaction with Miro. LRRK2 removes damaged mitochondria by forming a complex with Miro, thereby promoting its displacement from damaged mitochondria (Hsieh et al., 2016). G2019S LRRK2 mutant disrupts this complex therefore, Miro remains on damaged mitochondria which keep trafficking. In summary, the experiments conducted so far show that axonal transport of mitochondria is affected by LRRK2 mutations, which might play an important role in PD pathogenesis. Notably, the defects could not be rescued by LRRK2 kinase inhibitors (Hsieh et al., 2016; Schwab et al., 2017; Thomas et al., 2016).

LRRK2 can also disturb mitochondrial homeostasis by affecting the PGC-1 α pathway. Genetic or pharmacological activation of the *Drosophila* PGC-1 α ortholog pargel is sufficient to rescue the disease phenotypes of LRRK2 genetic fly models of PD (Ng et al., 2017).

5. LRRK2 and calcium homeostasis

Mitochondria are involved in maintaining calcium homeostasis such as sequestering Ca²⁺ in neurons through the low affinity mitochondrial uniporter and its associated regulators (Patron et al., 2013). Perturbed calcium homeostasis has been suggested for the pathogenesis of PD. The PD-susceptible SNc DA neurons rely upon voltage-gated calcium channels for autonomous pacemaking, thus putting an excess metabolic burden in terms of ATP to expel the excess calcium in every round of depolarization (Surmeier et al., 2011). Some evidence suggests that constant and long-lasting elevations of cytosolic Ca²⁺ occurring in SNc DA neurons are directly leading to increased ROS production from mitochondria, thereby augmenting cell death sensitivity (Egnatchik et al., 2014; Guzman et al., 2010; Lemasters et al., 2009; Singh et al., 2018). During aging and in neurodegenerative disease processes, the ability of neurons to maintain an adequate energy level is compromised, thus impacting on Ca²⁺ homeostasis (Cali et al., 2014; Raffaello et al., 2016).

Studies analyzing the direct involvement of LRRK2 in calcium homeostasis are scarce. Cortical neurons expressing mutant LRRK2 have shown defects in Ca²⁺ buffering capacity, which results in impairments of mitochondrial function, degradation, and dendritic shortening. Accordingly, the inhibition of the L-type of Ca²⁺ channels or treatments with Ca²⁺ chelators revert the phenotype (Cherra et al., 2013). LRRK2 G2019S iPSC-derived sensory neurons display diminished calcium responses to KCl depolarization. These phenotypes could be partially rescued by treatment with LRRK2 kinase inhibitors (Schwab and Ebert, 2015).

Perturbed calcium homeostasis has been shown to play a role in LRRK2-induced autophagy. Overexpression of wild-type or G2019S LRRK2 in HEK-293 cells has been reported to activate the nicotinic acid/adenine dinucleotide phosphate (NAADP) receptors to cause Ca²⁺ efflux from lysosomes (Gomez-Suaga et al., 2012), which results in the induction of autophagy. Consequently, enhanced cytosolic Ca²⁺ could have downstream effects on other Ca²⁺-dependent cellular events.

Mitochondria are involved in maintaining calcium homeostasis such as sequestering Ca^{2+} in neurons through the low affinity mitochondrial calcium uniporter (MCU) and its associated regulators (Patron et al., 2013). There is some evidence to show PINK1 can influence the activity of mitochondrial Ca^{2+} transport systems (Marongiu et al., 2009), and inhibition of the MCU rescues dopaminergic neurons in PINK1-deficient Zebrafish (Soman et al., 2017). A recent study shows that pathogenic LRRK2 mutants cause increased dendritic and mitochondrial calcium uptake in cortical neurons and familial PD patient fibroblasts by upregulating MCU levels (Verma et al., 2017).

LRRK2 also targets the major presynaptic Ca influx pathway, the CaV2.1 channel, as a further mechanism to modulate intracellular calcium homeostasis. One study shows that LRRK2 stimulates CaV2.1 channels, resulting in an increase in Ca^{2+} current density (Bedford et al., 2016). Thus, targeting Ca^{2+} pathways that ultimately converge on mitochondria may represent attractive loci for early therapeutic intervention in PD (Guzman et al., 2010; Singh et al., 2018; Verma et al., 2017).

6. Concluding Remarks

LRRK2 pathogenic mutants are known to cause autosomal dominant PD. Research in the last 15 years has confirmed that pathogenic LRRK2 mutations cause mitochondrial dysfunction in a diverse range of experimental models including *C. elegans*, *Drosophila*, rodent brain tissues and primary cultures, human neuroblastoma cell lines, iPSC-derived neurons from PD patient, and PD patient brain tissues (Table 1). It is now generally accepted that mitochondrial dysfunction plays a significant role in the etiology and pathogenesis of PD. However, to date, most of the studies relating LRRK2 to mitochondrial dysfunction are correlative or performed in vitro. Thus, in vivo studies are required to validate these findings and to reveal the physiological relevance.

There are many questions that need to be explored in the future. To begin with, how does LRRK2 affect mitochondria? Is it a direct effect or an indirect effect through interacting with the microtubules thus affecting trafficking? Both mitochondria and lysosomes are affected by LRRK2 mutants, but it is still unclear in which organelles the damage starts and how it is then extended to affect the others. Does impaired autophagic-lysosomal pathway associated with LRRK2 mutations cause the accumulation of dysfunctional mitochondria; or does mitochondrial damage induced by LRRK2 mutations impact lysosomal function and biogenesis? What stimulates the interaction of LRRK2 with DRP1? How does LRRK2 affect MCU? Although recent studies have found a subset of Rab GTPases as LRRK2 substrates (Dodson et al., 2012; Steger et al., 2016), a continuing search for LRRK2 substrates and interactors, and associated downstream signaling pathways is of critical importance to address these key questions. Finally, it is important to justify whether the observed LRRK2 mutant phenotype is attributed to increased kinase activity or GTPase activity.

To conclude, extensive research is warranted to pinpoint the specific roles of LRRK2 mutants in causing neurodegeneration via mitochondrial dysfunction. It remains to be fully

clarified whether mitochondrial dysfunction represents a cause or a consequence of disease pathogenesis.

Acknowledgements/Conflict of interest disclosure

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Highlights

- Pathogenic LRRK2 mutations cause dopaminergic neurodegeneration
- Mitochondrial dysfunction is central to Parkinson's disease (PD) pathogenesis
- LRRK2 regulates cell survival and oxidative stress
- LRRK2 mutations affect mitochondrial dynamics, trafficking, and mitophagy

Fig 1: Diagram showing pathways and molecules affecting mitochondrial function.

Abbreviations: Bcl-2: B-cell lymphoma 2; DRP1: dynamin like protein; 4E-BP1: eukaryotic translation initiation factor 4E-binding protein 1; MCU: mitochondrial calcium uniporter; OPA1: optic atrophy 1; PRDX3: peroxiredoxin 3

Table 1.**LRRK2 mutations and mitochondrial dysfunction**

Model	LRRK2 variants	Mitochondrial oxidative stress	References
Yeast	G2019S R1441C	Increased ROS	Pereira et al., 2014
C. elegans	KO	Reduced oxidative stress in PINK1 loss of function allele background	Samann et al., 2009
C. elegans	G2019S	Increased vulnerability of DA neurons to ROT	Saha et al., 2009
Drosophila	G2019S	Increased sensitivity to ROT, rescued by Parkin	Ng et al., 2009
Drosophila	G2019S	Increased oxidative stress	Angeles et al., 2014
Drosophila	dLrrk	Regulates response to oxidative stress via 4E-BP phosphorylation	Imai et al., 2008; Tain et al., 2009
NLCs from PD patients	G2019S	Increased sensitivity to ROT rescued by LRRK2 inhibitors	Mendivil-Perez et al., 2016
NSCs from mice	R1441G	Higher oxidative stress	Bahnassawy et al., 2013
Rat midbrain neurons PD patients fibroblasts	G2019S	Increased mtDNA damage rescued by LRRK2 inhibitor	Howlett et al., 2017
PD patients fibroblasts	G2019S	UCP2 increased ROS increased	Grunewald et al. 2014
PD patients fibroblasts	G2019S	UCP4 mRNA up-regulated	Papkovskaia et al., 2016
PD patients fibroblasts	G2019S R1441C	Increased vulnerability to valinomycin	Smith et al., 2016
iPSCs-derived DA neurons from PD patients	G2019S	Increased sensitivity to oxidative stress	Nguyen et al., 2011
iPSCs-derived neurons from PD patients	G2019S	Increased sensitivity to ROT attenuated by LRRK2 inhibitor	Reinhardt et al., 2013
iPSCs-derived neurons from PD patients	G2019S	Increased oxidative damage	Sanders et al., 2014
iPSCs-derived neurons from PD patients	G2019S R1441C	Oxygen consumption decreased	Cooper et al., 2012
Model	LRRK2 Variants	Mitochondrial fission and fusion	References
Mouse cortical neuron cultures	G2019S	Increased fission	Niu et al., 2012
SH-SY5Y cells Rat cortical neuron cultures	G2019S R1441C	Increased mitochondrial fragmentation	Wang et al., 2012
Mouse brains	G2019S knock-in	Mitochondrial fission arrested	Yue et al., 2015
PD patients fibroblasts	G2019S	Elongated, interconnected mitochondria, reduced MMP and ATP production	Mortiboys et al., 2010
Hela cells PD patients fibroblasts	G2019S	Excessive mitochondrial fission which could be blocked by Drp1 inhibitor	Su and Qi, 2013
PD patients fibroblasts	G2019S R1441C	Increased mitochondrial fragmentation	Grunewald et al., 2014 Smith et al., 2016
PD patients fibroblasts	E193K	Abnormal mitochondrial fission	Carrion et al., 2018
PD patient brains	G2019S	Decreased OPA1	Stafa et al., 2014
Model	LRRK2 Variants	Mitophagy	References
SH-SY5Y cells	LRRK2 inhibitor	Promotes mitophagy	Saez-Atienzar et al., 2014
Mouse cortical neuron cultures	G2019S R1441C	Increased Mitophagy	Cherra et al., 2013

Model	LRRK2 variants	Mitochondrial oxidative stress	References
Mouse brains	G2019S	Increased number of autophagic vacuoles and damaged mitochondria	Ramonet et al., 2011
PD patients fibroblasts Rat DA neuron culture	G2019S	Excessive mitophagy	Su et al., 2015
PD patients fibroblasts	G2019S R1441C	Heightened mitophagy	Smith et al., 2016
iPSC-derived neurons from PD patients	G2019S	Delayed mitophagy	Hsieh et al., 2016
Model	LRRK2 Variants	Cytoskeleton dynamics and mitochondria trafficking	References
Cultured neurons from mice	G2019S	Decreased free tubulin	Parisiadou et al., 2009
Mice	LRRK2 KO	Increased free tubulin	Gillardon et al., 2009
HEK293T cells	R1441C,R1441G, Y1699C, I2020T	Increased association with microtubules	Kett et al., 2012
HEK293T cells	R1441G KO	Altered tubulin acetylation	Law et al., 2014
PBMC from PD patients	G2019S Sporadic PD	Decreased tubulin acetylation	Esteves et al., 2015
Mice	G2019S	Impaired microtubule assembly	Lin et al., 2009
Mouse Synaptoneurosome PD patient fibroblasts	R1441G G2019S	Destabilize F-actin	Caesar et al., 2015
Drosophila	G2019S	Increased tau phosphorylation	Lin et al., 2010
Mice	G2019S	Increased tau phosphorylation	Melrose et al., 2010
SH-SY5Y cells	R1441C	Hampered mitochondria transport	Thomas et al., 2016
Rat cortical neurons Drosophila	R1441C	Decreased mitochondria transport	Godena et al., 2014
iPSC-derived neurons from PD patients	G2019S	Decreased mitochondria transport	Hsieh et al., 2016
iPSC-derived DA neurons from PD patients	G2019S	Increased mitochondria mobility	Schwab et al., 2017

Abbreviations: HEK-293T: human embryonic kidney 293 cells; iPSC: induced pluripotent stem cell; NLC: nerve like differentiated cells; NSC: neural stem cell; PMBC: Peripheral blood mononuclear cells; ROT: rotenone; Drp1: dynamin related protein; OPA1: optic atrophy 1; UCP2: uncoupling protein 2; MMP: mitochondrial membrane potential; PINK-1: PTEN-induced kinase