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Review Article

Mitochondrial Dysfunction in Parkinson's Disease: Mechanistic Insights and Emerging Therapeutic Strategies

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Abstract

Mitochondrial dysfunction is a major contributor to multifactorial neurodegenerative disease, Parkinson's Disease (PD). The molecular links between mitochondrial dysfunction and the causes of PD are summarised here in light of our current knowledge. Using data from genetic and subjective studies, we identify the mitochondrial pathways impacted by α-synuclein aggregation, oxidative stress, dysregulated calcium signalling, and reduced mitophagy. Particular focus is on the link between mitochondria, lysosomes, and the endoplasmic reticulum as well as how these interorganelle interactions contribute to neuronal vulnerability.

Evidence gathered suggests a decline in oxidative phosphorylation, an increase in Reactive Oxygen Species (ROS) production, and the activation of programmed cell death pathways as mitochondrial dysfunction contributes to dopaminergic neuron death. Further modifications in the PINK1, Parkin, and other genes related to PD lead to additional alterations in the processes controlling mitochondrial quality, triggering neuroinflammation *via* the cGAS-STING and NLRP3 inflammasome pathways.

Identifying the principal unifying mechanism in the pathophysiology of PD as mitochondrial malfunction provides new therapeutic options. Among the most promising treatments are increased mitophagy, enhanced mitochondrial biogenesis, and reduced oxidative stress especially *via* gene therapy, PGC-1α activation, and mitochondrial-targeted antioxidants.

Keywords: Pulmonary disease; Neurodegenerative disease; Antioxidants; Gene therapy

Introduction

With up to 2% of persons over 60 afflicted, PD is the most common neurodegenerative disease, restricting motor ability. The clinical diagnosis of PD depends on the presence of motor symptoms sensitive to levodopa-for instance, bradykinesia, resting tremor, or rigidity. Non-motor symptoms, including sleep issues, melancholy, autonomic dysfunction, and olfactory impairment, often accompany motor symptoms. Even if PD is fairly common, there are currently no known treatments to stop its progression; this exposes a significant lack of understanding of how the disease progresses [1,2].

From a neuropathological perspective, PD is distinguished by two main features: The selective death of certain neurons in particular brain regions, like the degeneration of dopaminergic neurons in the Substantia Nigra pars Compacta (SNc), and the accumulation of eosinophilic alpha-Synuclein (aSYN) positive Lewy bodies. Postmortem human PD brain studies show that Lewy Pathology (LP) is not consistently present over the brain, even in the advanced stages of the disease, but is rather found in particular sensitive areas, showing a patchy distribution [3, 4]. Though certain brain regions the olfactory bulb, SNc, locus coeruleus, amygdala, pedunculopontine nucleus, and dorsal motor nucleus of vagus are known to be more vulnerable to LP, determining the exact order and extent of LP development has been challenging.

Lewy Neuropathy (LN) affects other body parts besides influencing many regions of the peripheral nervous system, including nerve fibres in the skin, heart, and oesophagus. Research using experimental Parkinson's disease models have demonstrated that misfolded α-Synuclein (aSYN) can pass between cells. These results have helped to confirm the hypothesis that dangerous aSYN aggregates may similarly spread between brain regions connected by synapses in humans, hence supporting the progressive development of LN throughout the central nervous system [5,6].

Although LN distribution has been somewhat thoroughly mapped, the spatiotemporal patterns of neuron loss in damaged regions are still unknown. Although it has been well established and directly associated with the onset of motor symptoms in Parkinson's disease, a thorough assessment of the degree of neurodegeneration throughout the brain is still missing. Furthermore, research on the amount of cell loss have produced rather ambiguous results [7]. It is important to differentiate between intracellular elements raising LP buildup risk in neurons and those directly causing neurodegeneration as there is not a clear association between LP development and neuronal death [8,9].

Among the significant pathological mechanisms found so far [10,11] are impaired protein homeostasis, proteasomal and lysosomal degradation system malfunction, protein and membrane transport defects, neurotransmission-affecting synaptic dysfunction, neuroinflammation, and mitochondrial dysfunction. Among these factors, mitochondrial dysfunction is known to be one of the most important pathological features of Parkinson's disease. Neurons are particularly reliant on preserving the functional integrity of mitochondria, as they are so essential in keeping cellular metabolism and survival going. This review gathers data on mitochondrial dysfunction in inherited and idiopathic Parkinson's disease, investigates the complex connection between mitochondrial stress and aSYN aggregation, and emphasises important mitochondrial pathways involved in neurodegeneration in light of our present understanding of illness aetiology. We also evaluate historical and current therapeutic approaches for addressing mitochondrial dysfunction in an effort to stop the course of the disease and identify current knowledge gaps [12-14].

The vulnerability of dopaminergic neurons to mitochondrial dysfunction

Essential organelles of cells, mitochondria serve many vital roles. Their main job is to produce Adenosine Triphosphate (ATP) by oxidative phosphorylation. Mitochondria also have a role in calcium signalling, heme (a constituent of haemoglobin) and lipids production, and apoptosis, which is the controlled process of cell death [15,16]. These organelles undergo mitophagy, motility inside the cell, fission, and fusion to preserve their proper operation. These processes involve many proteins, and mutations in them might disrupt the mitochondrial equilibrium, causing cellular malfunction and the onset of illnesses, including PD [17,18].

Mitochondria are crucial for correct neuronal operation. Because of their complex, polarised structure, mitochondria need to be unequally distributed among neurons according to local energy needs. Where metabolic activity is at its highest, their highest concentrations are discovered in the nodes of Ranvier as well as in the pre and postsynaptic terminals. Many important neuronal activities, including neurotransmitter uptake and recycling, calcium homeostasis control, actin cytoskeletal development, axonal transport, synaptic vesicle transport, and maintenance of electrochemical gradients, depend on mitochondrial ATP generation [19,20].

The highly specialized structure of dopaminergic neurons especially emphasizes the need for exact coordination of mitochondrial dynamics across many different neural areas. Mitochondrial trafficking, which employs retrograde transport to carry aged or damaged mitochondria from synapses back to the soma for later mitophagy and anterograde transport to deliver functioning mitochondria to regions with greater energy demands, hence ensuring efficient nerve signal transmission [21,22].

Most mitochondrial fusion, the process of fusing damaged organelles with good ones to restore their function, happens in the soma. Particularly when the damage is unevenly dispersed, mitochondrial fission frequently comes before mitophagy and so produces both normal and damaged mitochondrial fragments [23,24].

Because of their complex structure and great energy demands, dopaminergic neurons are particularly sensitive to mitochondrial damage. Other risk variables are low levels of complex I of the Electron Transport Chain (ETC), which is necessary for the first stage of oxidative phosphorylation, and the buildup of oxidized dopamine

caused by mitochondrial oxidative stress. Furthermore, exacerbating mitochondrial dysfunction is increased calcium entry *via* L-type channels, which may also cause oxidative stress in the mitochondria [25-27].

Processes of neuronal death in PD

The loss of dopaminergic cells, which contributes to the onset of PD symptoms, is linked to mitochondrial dysfunction. The main result of this malfunction is a drop in ATP production. The primary driver of neuronal apoptosis [28] is, however, an increase in Reactive Oxygen Species (ROS) levels, not a bioenergetic failure brought on by lower ATP levels.

Usually, producing lower ROS levels is oxidative phosphorylation, which is partially controlled by antioxidant enzymes. A rise in ROS corresponds with a decline in the activity of complex I in the Electron Transport Chain (ETC). In PD patients, complex I activity is reduced by 25%-30%, accompanied by a concomitant decrease in its expression in dopaminergic neurons. This rise in ROS levels is worsened by hampered electron transport from complex I to ubiquinone in the ETC, which leads to an elevated conversion of molecular oxygen to superoxide radicals [29,30].

Excessive ROS levels can damage a wide spectrum of biological macromolecules, including proteins, lipids, and DNA. More injury to complex I leads to a vicious cycle of rising ROS levels. Additionally, dysfunction of ETC results in changes in the activity of other protein complexes involved in cellular respiration [31,32]. Studies show that oxidative phosphorylation is compromised at every step of electron transport in the ETC, hence aggravating mitochondrial dysregulation [33] and decreasing expression of complex II–IV and ATP synthase subunits.

ROS directly trigger apoptosis by damaging mitochondrial membrane proteins such as OPA1 and cardiolipin.

This harm prevents cytochrome C from being released into the cytoplasm. Cytochrome C binds to Apoptotic Protease Activating Factor 1 (APAF1) to create the heptameric molecule known as the apoptosome. This sets off the caspase cycle, which results in cell death [34]. Besides mitochondrial-triggered apoptosis, other pathways, including autophagy, necroptosis, ferroptosis, parthanatos, and pyroptosis, can also cause neuronal death in Parkinson's disease. Usually, the recycling of damaged organelles, known as autophagy, enables cells to survive in harsh circumstances. But in Parkinson's disease, it sometimes kills cells, thereby speeding up neurodegeneration [35,36].

Another road in PD, known as parthanatos, is mediated by the overactivation of Poly (ADP-ribose) Polymerase (PARP-1) produced by DNA damage induced by Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). Movement of the mitochondrial protein Apoptosis-Inducing Factor (AIF) from the mitochondria to the nucleus is a prominent indicator of parthanatos observed in neurons of PD patients [37,38]. Models of PD show that blocking PARP-1 prevents neuronal death and neurotoxicity triggered by α-synuclein. Another process helping to cause neuron death in PD, ferroptosis is distinguished by heightened lipid peroxidation induced by iron accumulation [39,40].

Models of PD have revealed that several neurotoxins start various cell death processes. Especially following 48 hours of exposure of neurons to 6OHDA and MPP+ and 24 hours of exposure to rotenone, necroptosis starts. Necroptosis is the creation of the necrosome, a complicated structure composed of RIPK1, RIPK3, FADD, and an inactive form of caspase 8. The phosphorylation of Mixed-Chain Kinase Domain-Like Pseudokinase (MLKL), which causes its migration to the cell membrane and heightened membrane permeability, is the consequence of this complex [41-43].

One of the primary processes causing neuroinflammation in Parkinson's disease is thought to be pyroptosis. The NLRP3 inflammasome is activated when its pyrin domain identifies Damage-Associated Molecular Patterns (DAMPs) such as mitochondrial DNA (mtDNA), cardiolipin, and cytochrome c, which are generated under oxidative stress circumstances [44,45]. Recruitment of the adaptor protein ASC and procaspase-1 upon NLRP3 inflammasome activation causes autoproteolysis and the synthesis of active caspase-1. Activated caspase-1 not only breaks gasdermin D and releases its N-terminal fragment, but it also stimulates the synthesis of the inflammatory cytokines IL-1β and IL-18. This part causes pores in the plasma membrane, which stimulates cytokine release and causes pyroptosis, an inflammatory form of programmed cell death [46,47].

A crucial link between α-synuclein pathology and mitochondrial dysfunction

Although mutations in *PARK* genes could explain

mitochondrial dysfunction in some Parkinson's disease patients, the underlying causes of idiopathic Parkinson's disease are debatable. Experimental findings from investigations on separated mitochondria and rats, however, indicate that one of the main causes of mitochondrial dysfunction is aSYN pathology. Monomeric aSYN regulates the alpha subunit of the mitochondrial ATP synthase under ordinary circumstances [48,49]. Studies in mice with aSYN knockout which express lower ATP synthase efficiency and lower ATP levels support this. Other investigations with aSYN-null mice have revealed complex I deficiency as well as alterations in neuronal mitochondrial membrane architecture [50,51].

Research have shown that excessive aSYN protein in the form of overexpressed monomers or oligomers and fibers lowers the activity of mitochondrial Complex I (CI), dissipates mitochondrial membrane potential, and raises oxidative stress. Studies demonstrating a dose-dependent inhibition of CI by aSYN pathology draw more attention to this impact on CI activity. Observations of aSYN knockout mice that were resistant to MPTP-induced toxicity have pointed to a direct effect of aSYN on CI function [52,53]. Overexpression of human aSYN in normal mice or by use of transgenic mice carrying the SNCA A30P mutation backed this data indicating that MPTP toxicity is increased. The CI inhibitor rotenone has also yielded comparable results. The pathology of aSYN, nevertheless, seems to have an impact other than only CI. Pathological aSYN oligomers can also disrupt mitochondrial function by interacting with the ATP synthase subunit alpha and causing the opening of the mitochondrial permeability transition pore [54,55]. Moreover, aSYN oligomers have been shown to interact with the outer mitochondrial membrane protein TOM20, so disrupting the import of mitochondrial proteins and resulting in ETC dysfunction, greater ROS, and loss of mitochondrial membrane potential. Another reported consequence of aSYN pathology, which is vital for calcium exchange, is disruption of the link between mitochondria and the Endoplasmic Reticulum (ER), which can further aggravate mitochondrial respiration by causing dysregulated intracellular calcium levels [56,57].

Taken together, these findings suggest that multiple independent mechanisms exist by which aSYN pathology can provoke mitochondrial dysfunction. Moreover, many of these pathways converge on a common pathological phenotype characterized by reduced mitochondrial respiration, disrupted mitochondrial membrane potential, and increased cellular and mitochondrial ROS.

Mitochondrial damage-induced inflammation in PD

Initial findings that hinted at a connection between TFAM shedding, the release of mtDNA, and inflammation were derived from basic research not directly related to PD. In studies using Mouse Embryonic Fibroblasts (MEFs), a partial knockout of the tfam gene was used to artificially induce stress on Mitochondrial DNA (mtDNA). This stress, caused by insufficient tfam, resulted in mtDNA leaking out of the mitochondria due to improper packaging.

mtDNA can act as a DAMP in the cytoplasm, therefore activating inflammatory signalling through the cGAS/STING pathway [58,59]. The escape of mitochondrial DAMPs during apoptosis is made possible by the mitochondrial permeability transition pore. It has been shown that the formation of BAK/BAX or VDAC macropores on the outer mitochondrial membrane helps with mitochondrial herniation and the following liberation of mtDNA. Adding ubiquitin to BAK, a PD-associated protein, could help to avoid pore formation, the release of cytochrome c, and the beginning of apoptosis by enhancing BAK's ability to stop pore formation. Encouragement of the efficient elimination of damaged mitochondria helps to lower the inflammatory risk. A study using a Parkin knockout "mutator" mouse model further supported the specific roles of Parkin and PINK1 in inflammation brought on by mitochondrial damage [60,61]. This model shows that increased amounts of circulating cell-free mtDNA (ccf mtDNA) and a number of serum cytokines were linked with the buildup of mtDNA variations in the absence of PARKIN. Lowering the levels of the Stimulator of Interferon Genes (STING), which controls the activation of the DNA inflammasome, on the other hand, was enough to stop the motor impairments and dopaminergic neuron loss formerly seen in these mice, indicating that inflammation caused these effects. In a previous study on a small group of PD patients with Parkin mutations, high inflammatory indicators were seen [62,63]. Moreover, Parkin/PINK1 has been shown to modulate cell cycle progression by influencing the downstream target of cGAS/STING pathway, TANK-Binding Kinase 1 (TBK1), at impaired mitochondria. Parkin/PINK1 traps TBK1 during mitophagy when it is concentrated at mitochondria, hence terminating

mitosis. On the contrary, the lack of Parkin or PINK1 was connected to increased cell proliferation in mice. Furthermore, the NOD-, LRR-, and NLRP3 have been identified as targets of cGAS/STING signaling, whereby mitochondrial dysfunction and raised ROS directly activate the inflammasome [64,65]. Treatment of LPS-primed mouse microglia with the mitochondrial complex I inhibitor rotenone dose-dependently activated NLRP3, produced ASC specks, and caused processing of pro-interleukin-1β. NLRP3 inflammasome activation has been related with improved Parkin-mediated tethering between the ER and mitochondria, leading to mitochondrial calcium overload and inhibition of mitophagy [66].

Apart from their contributions in innate immunity, Parkin and PINK1 might also have roles in regulating the adaptive immune response. Experiments on mice lacking either parkin or pink1, by exposing them to the bacterial endotoxin LPS or an intestinal infection with gram-negative bacteria, induced the production of MDVs [67,68]. These MDVs transport mitochondrial antigens to the plasma membrane for presentation on Major Histocompatibility Complex Class I (MHC I) molecules. The cellular levels of Sorting Nexin 9 (Snx9) are regulated through a proteasome-dependent mechanism involving parkin, which is essential for the production of MDVs and the presentation of mitochondrial antigens. Collectively, these findings indicate important roles of Parkin and PINK1 in the induction of mitophagy, regulation of immunological responses, and cell-cycle control, especially in the context of PD [69].

Link between mitochondria, lysosomes and Er and its impact on calcium homeostasis

There is ample evidence that lysosomal degradation failure is one of the reasons for the buildup of dysfunctional mitochondria in PD. Studies showed that lysosomal functions are disrupted by mutations in the genes *SNCA* and *LRRK2*. Further, in neurons derived from iPSCs with DJ-1 mutations, mitochondrial stress was found to cause accumulation of oxidized dopamine, which further led to lysosomal dysfunction and aggregation of alpha-synuclein [70,71].

Apart from the interconnection between lysosomes and mitochondria, the ER plays a role in the interaction between different cellular organelles related to PD. The mitochondria-associated membrane has been altered in several Parkinson's disease models. Alpha-synuclein, for instance, was localized at MAMs, and toxic SNCA variants are associated with an increase in mitochondrial fragmentation [72,73].

Additionally, calcium homeostasis relies on coordinated communication between the mitochondria, lysosomes, and ER. A calcium-dependent decrease in ATP production was associated with disrupted communication between the ER and mitochondria in neurons from individuals with a triplication mutation and mice that overexpress SNCA. Furthermore, some of the genes associated with familial PD suggest that DJ-1, PARKIN, PINK1, and LRRK2 may be implicated in calcium pathways [74,75].

Studies performed using isradipine, a calcium channel blocker, have proved the protective role of this agent in dopaminergic neurons, further highlighting the significance of calcium homeostasis in the pathophysiology of PD. This occurs as a result of reduced mitochondrial turnover and mass, together with reduced oxidative stress [76].

Mitochondrial therapy for Parkinson's disease

Understanding how mitochondrial dysfunction contributes to the pathophysiology of Parkinson's disease has sparked the development of new therapeutics. Translating these promising mitochondrial targets, uncovered *via* research, into realistic therapy choices for patients with both familial and sporadic Parkinson's disease offers a daunting issue for researchers in this field. As a result, many strategies have been created to enhance Parkinson's disease mitochondrial activity [77].

Gene therapy

The idea of using gene therapy to replace diseased DNA with healthy DNA first emerged in 1972. As science and technology have developed, this technique has become more complex and complicated, but its basic principles remain unchanged. Lentivirus and recombinant AAV are two of the most widely used viral vectors now employed to precisely deliver genetic material into cells in order to influence the expression of specific genes [78,79]. With regard to Parkinson's disease, gene therapy aims to accomplish a range of objectives such as the restoration of dopamine production, the enhancement of neurotrophic support, and the modulation of communication between distinct brain neural networks. Parkinson's disease treatments also include interfering with key aspects of the mitochondrial pathway in order to halt neurodegeneration. Among these is PGC-

1α, a transcriptional coactivator that controls the expression of genes responsible for mitochondrial synthesis and antioxidant defense. This represents a critical component of neuroprotective approaches employed to treat PD since patients suffering from the disease express lower levels of PGC-1α [80,81]. Moreover, the genetic manipulation technique CRISPR-CAS9 is capable of correcting gene mutations responsible for specific symptoms of the disease and may even be able to edit DNA in germ cells, thus preventing future generations from developing genetic Parkinson's disease [82,83].

Antioxidant therapies

It has been observed that during the progression of PD, there is mitochondrial malfunctioning of neurons as reflected by reduced ATP synthesis, lower expression of the respiratory chain complex, and enhanced ROS formation. It is already documented that mitochondria in poor health generate more ROS than those in better health. Moreover, the mitochondria of neuronal cells regenerate very slowly and are particularly prone to oxidative stress. This oxidative stress generates free radicals, which may be toxic to the structure and function of neural cells, and possibly weaken the antioxidant defenses to promote neurodegeneration [84,85].

In a MPTP mouse model of PD, resveratrol exhibits antioxidant properties and has shown promise in treating motor dysfunction. Resveratrol was also shown in cell culture studies to be capable of blunting MPP+-induced mitochondrial dysfunction and apoptosis *via* the AKT/GSK-3β pathway. Though Coenzyme Q10 (CoQ10) is another antioxidant known to enhance the activity of complexes I and II within the electron transport chain, meta-analyses have reported that supplementation with CoQ10 has no symptomatic benefit and does not significantly delay the functional decline in PD patients [86,87]. Based on its capability to alleviate MPTP-induced neurotoxicity and block the disruption of electron transfer from complex I, CoQ10 has been suggested to provide benefit only in a particular subgroup of PD patients, namely those individuals with a "mitochondrial form of PD." In comparison with other general antioxidants, MitoQ has displayed greater efficacy at preventing mitochondrial oxidative damage. MitoQ has been found to protect against 6-OHDA-induced mitochondrial dysfunction both *in vitro* and in vivo in models of PD, possibly through a mechanism involving PGC-1α-mediated up-regulation of MFN2 expression [88,89].

The health benefits of saffron and its bioactive constituents are well recognized, in view of their antioxidant properties, which can restore the activity of antioxidant enzymes such as Superoxide Dismutase (SOD), Glutathione S-Transferase (GST), and catalase. In addition to reducing ROS, this increase in glutathione and total thiol levels might be a promising therapeutic approach to the improvement of motor symptoms in PD [90,91]. N-Acetylcysteine (NAC) is a powerful free oxygen radical scavenger that maintains sulfhydryl groups in a reduced state and restores neuronal Glutathione (GSH) levels. The therapeutic potential of modulating neuronal GSH metabolism in PD is emphasized by the fact that the normalization of GSH levels can decrease oxidative stress and cell death, considering the link between the death of dopaminergic neurons, oxidative stress, and GSH depletion [92,93].

Interestingly, various antioxidants such as resveratrol and vitamin E inhibit the activities of DNA methyltransferases and histone deacetylases, thereby affecting DNA methylation and histone acetylation. The close link between oxidative stress, mitochondrial dysfunction, and Parkinson's disease pathology underlines therapeutic approaches for Parkinson's disease focusing on inhibiting excessive ROS production and promoting mitochondrial function by antioxidant therapy [94,95].

Enhanced mitochondrial biogenesis

Maintaining mitochondrial stability in cells calls for interaction between the nuclear and mitochondrial genomes, a really complex mechanism known as mitochondrial biogenesis. Reduced ROS generation is possible with a great many healthy mitochondria. Genome-wide studies showing reduced expression of the main mitochondrial biogenesis regulator PGC-1α in Parkinson's disease patients compared with healthy controls [96,97] underlined that mitochondrial biogenesis has a significant function in the pathogenesis of Parkinson's disease. Further research revealed mitophagy issues in dopamine-producing neurons devoid of the Parkin gene, mostly caused by mitochondrial biogenesis defects brought on by increased PARIS, hence lowering PGC-1α. Parkin helps to degrade and synthesize mitochondria. Therefore, treatment of Parkinson's disease and neuroprotection could reasonably include enhanced mitochondrial biogenesis [98,99]. Though there are many

strategies, it is important to center on the AMPK-SIRT1-PGC-1α route to boost mitochondrial biogenesis. In different animal models of Parkinson's disease, activation of PGC-1α has been demonstrated to be neuroprotective. Bezafibrate, an activator of all types of PPARs, raised PGC-1α level and protected mouse models of neurodegenerative diseases. While inhibiting the D1 receptor causes a reversal, activation of the dopamine D1 receptor has been shown to stimulate mitochondrial biogenesis in a rat model of Parkinson's disease. The introduction of exogenous mitochondria, mitochondrial transplantation is a fresh treatment option for Parkinson's disease that has demonstrated promising therapeutic effects [100-102].

Enhancing mitophagy

The development of PD depends much on mitophagy. Studies on PD and LBD patients have shown higher mitophagy in the neurons, including one employing an ultrastructural analysis. Through high-throughput drug screening using dopaminergic neurons generated from iPSCs of PD patients with PARKIN or PINK1 mutations, 320 compounds were screened to discover chemicals that increase the turnover of depolarized mitochondria. Four active chemicals were found. Other possible methods to cause mitophagy include increasing Parkin and PINK1 and suppressing USP30 and USP14. Abundant in mitochondria, melatonin promotes the oxidation of cardiolipin and the recovery of mitophagy in PD. Given these factors, one possible therapeutic approach for PD [103,104] is to emphasize mitophagy enhancement. Certain of these substances have demonstrated efficacy in iPSCs produced from idiopathic PD patients with deficient mitochondrial clearance [105,106] and have also helped to alleviate motor impairments in Drosophila models of PINK1 deficiency.

Conclusion

A leading cause of Parkinson's disease is mitochondrial dysfunction, which links genetic predisposition, α-synuclein aggregation, and neuroinflammation. The great vulnerability of dopaminergic neurons is underlined by the intricate disruption of mitophagy, calcium regulation, and mitochondrial respiration. The interplay between lysosomes, mitochondria, and the endoplasmic reticulum adds complexity to the degenerative cascade. While current therapies remain largely symptomatic, growing insights into mitochondrial biology have spurred the development of innovative therapeutic strategies-ranging from antioxidant interventions and PGC-1α activators to mitophagy-enhancing compounds and gene-editing approaches. These efforts highlight mitochondria not only as a central pathological hub but also as a tractable therapeutic target. Future research focusing on personalized mitochondrial therapies may provide a realistic path toward slowing or halting neurodegeneration in Parkinson's disease.

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