

The Mitochondrial Interactome in Parkinson's and Huntington's Diseases

Harshit Gouri^{1*}, Yavnika Bararia² and Vidushi Malhotra³

¹Department of Chemistry, University of Delhi, Delhi, India; ²Department of Physiotherapy, KR Mangalam University, Gurugram, Haryana, India; ³GMIS, Denpasar, Bali, Indonesia

*Correspondence to: Harshit Gouri, Department of Chemistry, University of Delhi, Delhi 110007, India. ORCID: <https://orcid.org/0009-0006-4507-8989>. Tel: +91-8630381523, E-mail: harshitgouri123@gmail.com

Citation of this article: Gouri H, Bararia Y, Malhotra V. The Mitochondrial Interactome in Parkinson's and Huntington's Diseases. *Nat Cell Sci* 2025;3(3):e00017. doi: 10.61474/ncs.2025.00017.

Abstract

Mitochondrial dysfunction is a central driver of neurodegeneration in Parkinson's disease (PD) and Huntington's disease (HD). This review synthesizes evidence on the convergence of genetic mutations and environmental toxicants on mitochondrial pathways to promote pathology and critically evaluates emerging mitochondria-targeted therapies. We highlight the impact of mutations in *PINK1*, *PRKN*, *LRRK2*, *GBA*, and *HTT*, alongside exposures to agents such as rotenone, paraquat, MPTP, heavy metals, and solvents, in disrupting mitochondrial integrity. Key mechanisms include impaired oxidative phosphorylation, calcium dysregulation, reactive oxygen species accumulation, defective mitophagy, and altered fission–fusion dynamics. We further emphasize the synergistic interplay between genetic vulnerability and environmental insults, positioning the mitochondrial interactome as a unifying framework for understanding PD and HD pathogenesis. We assess therapeutic strategies, such as mitophagy enhancers, dynamin-related protein 1 inhibitors, and mitochondria-targeted antioxidants, while highlighting significant translational challenges, including poor brain penetrance and variable patient responses. Finally, we propose a precision medicine approach, leveraging patient-derived induced pluripotent stem cells, advanced imaging modalities, and multi-omics biomarker discovery to facilitate early detection and individualized interventions. By integrating mechanistic, toxicological, and therapeutic perspectives, this review underscores the pivotal role of mitochondria and identifies them as a promising target for disease-modifying therapies in PD and HD.

Keywords: Neurodegenerative diseases; Parkinson's disease; Huntington's disease; Mitochondrial interactome; Mitophagy; Environmental toxins.

Introduction

Neurodegenerative disorders such as Parkinson's disease (PD) and Huntington's disease (HD) are progressive and debilitating conditions characterized by selective neuronal loss and central nervous system dysfunction.¹ Despite distinct genetic etiologies and clinical presentations, both diseases share a central pathological hallmark: mitochondrial dysfunction. As central hubs of energy metabolism, redox regulation, calcium buffering, and cell death signaling, mitochondria are particularly critical for neurons, which have high metabolic demands and limited regenerative capacity.^{2,3} Early studies of mitochondrial involvement in neurodegeneration focused on discrete processes such as deficits in adenosine triphosphate (ATP) production or increased oxidative stress.⁴ However, it is now clear that mitochondria do not operate in isolation but are dynamically regulated by a complex network of genetic, environmental, and intracellular signals.⁵ This network, referred to herein as the mitochondri-

al interactome, encompasses both intrinsic factors, such as mutations in nuclear and mitochondrial genes, and extrinsic influences, including exposure to neurotoxicants and inflammation.⁶ Disruptions to this tightly regulated system can trigger a cascade of pathological events, ultimately leading to neuronal injury and death.⁷ In PD, mutations in genes such as *PINK1*, *PRKN* (Parkin), *DJ-1*, and *LRRK2* disrupt key aspects of mitochondrial quality control, including mitophagy, redox homeostasis, and mitochondrial dynamics.⁸ These genetic vulnerabilities are exacerbated by environmental toxins such as rotenone, paraquat, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (structures shown in Fig. 1), which inhibit mitochondrial respiratory complexes and potentiate oxidative stress.^{9–12}

Similarly, in HD, the expanded Cytosine–Adenine–Guanine trinucleotide (CAG) repeat in the *HTT* gene produces a mutant huntingtin protein, which disrupts mitochondrial trafficking, oxidative phosphorylation, and calcium handling.¹³ Although environmental links in HD are less well defined than

Received: May 30, 2025 | Revised: August 29, 2025 | Accepted: September 20, 2025 | Published online: September 30, 2025



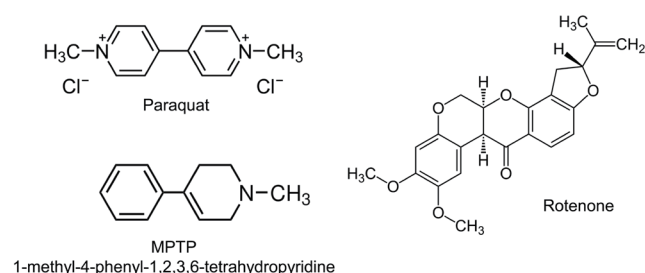


Fig. 1. Structure of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), Rotenone, Paraquat (Structures created using ChemDraw). The mitochondrial neurotoxins MPTP, Rotenone, and Paraquat are commonly used in experimental models of Parkinson's disease, where they inhibit mitochondrial respiratory complexes, disrupt redox balance, and induce oxidative stress, thereby phenocopying the mitochondrial quality control deficits caused by mutations in genes such as *PINK1*, *PRKN*, *DJ-1*, and *LRRK2*.^{10–12}

in PD, accumulating evidence suggests that factors such as metal exposure, stress, and dietary deficiencies may modulate disease progression via mitochondrial pathways.³

Moreover, mitochondrial dysfunction in PD and HD extends beyond organellar defects to include impaired signaling, biogenesis, proteostasis, and inter-organelle communication. These disruptions collectively compromise cellular energy homeostasis, exacerbate excitotoxic and inflammatory stress, and promote the accumulation of toxic proteins. Mitochondria thus serve as both sensors and amplifiers of neuropathological stress, integrating genetic susceptibilities and environmental exposures.⁹ This review aims to integrate

current knowledge on how genetic mutations, environmental toxicants, and mitochondrial signaling pathways converge in the pathogenesis of PD and HD. By framing neurodegeneration through the lens of the mitochondrial interactome, we seek to highlight shared molecular mechanisms, identify potential therapeutic targets, and propose new directions for precision medicine approaches in neurodegenerative disease management.

Mitochondrial function in neurons

Neurons are uniquely reliant on mitochondria due to their polarized structure, terminal differentiation, and high metabolic activity. Sustained ATP generation and tight regulation of calcium are essential for synaptic transmission, plasticity, and survival (Fig. 2).^{14–18} Even subtle perturbations in mitochondrial function can undermine neuronal viability, rendering mitochondria central players in the pathogenesis of neurodegenerative diseases such as PD and HD.^{3,6} Importantly, mitochondrial dysfunction is not confined to neurons. Glial cells—including astrocytes, oligodendrocytes, and microglia—also exhibit impaired bioenergetics, redox imbalance, and altered mitochondrial signaling, which exacerbate neuroinflammation, impair metabolic support, and accelerate disease progression.^{19,20} In astrocytes, deficits in mitochondrial metabolism reduce glutamate clearance and lactate shuttling to neurons, while in microglia, altered mitochondrial dynamics drive excessive production of pro-inflammatory cytokines.^{21–23} A critical determinant of mitochondrial health across both neuronal and non-neu-

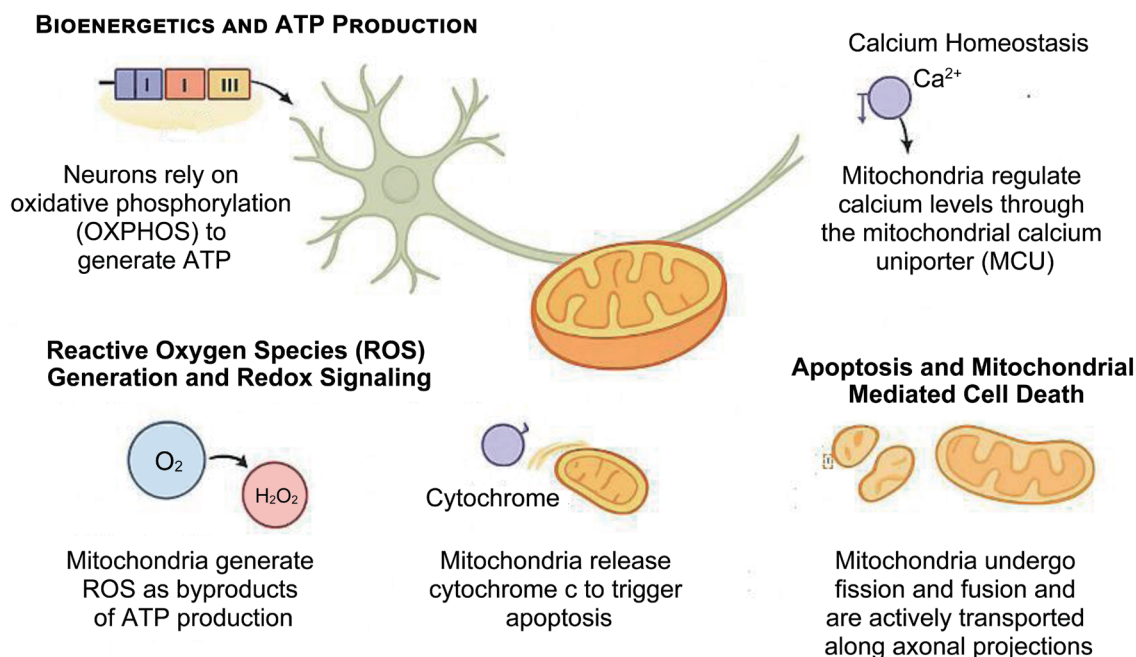


Fig. 2. Mitochondrial function in neurons. This schematic illustrates the major roles of mitochondria in neurons. Mitochondria sustain neuronal activity through oxidative phosphorylation (OXPHOS)-mediated adenosine triphosphate (ATP) production, regulate intracellular calcium via the mitochondrial calcium uniporter (MCU), and modulate redox signaling by generating reactive oxygen species (ROS). Mitochondria also govern intrinsic apoptosis by releasing cytochrome c and maintain their own health via dynamic processes such as fission, fusion, and motility. Disregulation of these functions contributes to neuronal vulnerability in neurodegenerative diseases such as Parkinson's disease and Huntington's disease.^{16–18}

ronal populations is the mitochondrial membrane potential ($\Delta\Psi_m$). This electrochemical gradient is essential for oxidative phosphorylation, calcium buffering, and regulation of reactive oxygen species.^{24,25} Recent studies demonstrate that collapse of $\Delta\Psi_m$ occurs as an early event in PD and HD, preceding overt neurodegeneration, and has been detected in patient-derived induced pluripotent stem cell (iPSC) models and advanced neuroimaging studies. Thus, $\Delta\Psi_m$ has emerged as a sensitive biomarker for mitochondrial dysfunction and a potential therapeutic target in neurodegenerative disorders.^{26–28}

Bioenergetics and ATP production

Neurons rely heavily on oxidative phosphorylation for energy. Mitochondria generate ATP primarily via the electron transport chain (ETC), located in the inner mitochondrial membrane. Electrons derived from Nicotinamide Adenine Dinucleotide (NADH) and Flavin Adenine Dinucleotide (FADH_2) are transferred through complexes I–IV, creating a proton gradient that drives ATP synthesis through complex V (ATP synthase).^{29,30} Disruptions in ETC function, particularly at complexes I and III, are well documented in PD and HD, leading to decreased ATP output, synaptic failure and neuronal death.³¹

Calcium homeostasis

Mitochondria regulate intracellular calcium (Ca^{2+}) by rapidly sequestering it through the mitochondrial calcium uniporter (MCU), especially at endoplasmic reticulum (ER)-mitochondria contact sites. This buffering stabilizes synaptic activity and prevents cytotoxic Ca^{2+} overload.³² In neurodegenerative contexts, mitochondrial Ca^{2+} dysregulation can trigger opening of the mitochondrial permeability transition pore (mPTP), leading to membrane depolarization, swelling, and apoptotic or necrotic death.³²

Reactive oxygen species (ROS) generation and redox signaling

As a byproduct of electron leakage in the ETC, mitochondria generate reactive oxygen species (ROS), including superoxide and hydrogen peroxide.^{33,34} At physiological levels, ROS act as signaling molecules, but excessive ROS can oxidize lipids, proteins, and nucleic acids, contributing to oxidative stress. Elevated ROS is observed in both PD and HD and is exacerbated by toxins such as rotenone and paraquat.³⁵ Endogenous antioxidant defenses (e.g., superoxide dismutase, glutathione) often become overwhelmed, further driving neurodegeneration.^{36,37}

Apoptosis and mitochondria-mediated cell death

Mitochondria are key regulators of intrinsic apoptosis. Upon mitochondrial outer membrane permeabilization (MOMP), cytochrome c is released into the cytosol, triggering activation of caspase-9 and downstream effector caspases.³⁸ In PD and HD, pro-apoptotic proteins such as BCL2-associated X (BAX) and p53 upregulated modulator of apoptosis (PUMA) are upregulated, while anti-apoptotic factors like B-cell lymphoma 2 (BCL-2) are downregulated, tipping the balance toward cell death. Aggregates of mutant huntingtin and α -synuclein can directly compromise mitochondrial

membranes, exacerbating cell vulnerability to apoptosis.^{35,39}

Mitochondrial dynamics: fission, fusion, and motility

Mitochondria are highly dynamic organelles that undergo continuous cycles of fission and fusion, regulated by GTPases such as dynamin-related protein 1 (DRP1) (fission) and mitofusin 1/2 (MFN1/2) and optic atrophy 1 (OPA1) (fusion).^{40,41} These processes maintain mitochondrial integrity, facilitate content exchange, and ensure distribution along axons and dendrites. In PD, hyperactivation of DRP1 and fragmentation of mitochondria are observed, while in HD, trafficking defects impair the delivery of mitochondria to synapses, disrupting local energy supply.^{42–44}

Mitophagy and quality control

Mitophagy, the selective autophagic degradation of damaged mitochondria, is essential for mitochondrial quality control.⁴⁵ It is orchestrated by the PINK1-Parkin pathway, which labels dysfunctional mitochondria for degradation.^{46,47} Loss-of-function mutations in *PINK1* or *PRKN* impair mitophagy, leading to the accumulation of dysfunctional organelles, a hallmark of familial PD.⁴⁸ Similarly, in HD, mutant huntingtin interferes with autophagosome formation and mitochondrial turnover, exacerbating energy deficits and oxidative stress.⁴⁹

Genetic mutations and mitochondrial vulnerability in Parkinson's and Huntington's diseases

Neurodegenerative disorders such as PD and HD are increasingly understood not only through their proteinopathy-driven frameworks but also through the lens of mitochondrial vulnerability, where genetic mutations directly compromise organelle function. Advances in genomics and molecular neuroscience have revealed that several PD- and HD-associated genes converge on mitochondrial quality control, dynamics, and bioenergetics, underscoring a common mechanistic foundation (discussed in Table 1).^{8,50,51}

PTEN-induced putative kinase 1 (PINK1) and Parkin: Guardians of mitophagy in PD

Mutations in *PINK1* and *Parkin* (*PRKN*) are among the most well-characterized genetic causes of early-onset PD. Under physiological conditions, *PINK1* is imported into healthy mitochondria and degraded. However, when mitochondrial membrane potential is lost, *PINK1* accumulates on the outer mitochondrial membrane (OMM),⁵² where it recruits and activates the E3 ubiquitin ligase *Parkin*. *Parkin* ubiquitinates several OMM proteins (e.g., *VDAC1*, *Mfn2*), marking the organelle for selective degradation via mitophagy.^{53,54} In PD, loss-of-function mutations in *PINK1* or *Parkin* impair this surveillance mechanism, leading to the accumulation of damaged mitochondria, elevated ROS, and apoptotic sensitivity in dopaminergic neurons of the substantia nigra.⁵⁵ Recent cryo-EM studies have elucidated the conformational activation of *Parkin* by phosphorylated ubiquitin and *PINK1*, reinforcing the “feed-forward” loop essential for mitochondrial clearance. Additionally, mitophagy-independent roles for *Parkin* in mitochondrial-derived vesicle formation and redox homeostasis have emerged, expanding its functional repertoire.⁵⁶

Table 1. Mitochondrial dysfunction in Parkinson's disease (PD) and Huntington's disease (HD)

Characteristic	PD	HD
Impaired mitophagy	Mutations in <i>PINK1</i> and <i>Parkin</i> impair clearance of dysfunctional mitochondria	Mutant huntingtin (<i>mHTT</i>) downregulates autophagy-related genes, reducing mitophagy efficiency
Abnormal fission/Fusion balance	LRRK2 enhances DRP1-mediated mitochondrial fragmentation	<i>mHTT</i> disrupts expression of fission and fusion proteins, leading to abnormal dynamics
Defective axonal transport	LRRK2 interferes with the Miro–Milton complex, impairing mitochondrial trafficking	<i>mHTT</i> binds to motor protein complexes, disrupting axonal mitochondrial transport
Disruption of respiratory chain complex I	α -Synuclein aggregation inhibits complex I activity, impairing oxidative phosphorylation	<i>mHTT</i> reduces transcription of complex I subunits, lowering respiratory efficiency
Increased oxidative stress and calcium sensitivity	<i>PINK1</i> , <i>Parkin</i> , LRRK2, and α -synuclein mutations increase reactive oxygen species (ROS) and calcium sensitivity	<i>mHTT</i> promotes ROS production and exacerbates calcium dysregulation

This table summarizes key mitochondrial defects implicated in PD and HD pathogenesis. Distinct genetic and protein alterations in each disease impair mitophagy, mitochondrial dynamics, axonal transport, and respiratory chain activity, ultimately promoting oxidative stress and calcium dysregulation. DRP1, dynamin-related protein 1; HD, Huntington's disease; LRRK2, leucine-rich repeat kinase 2; *Parkin* (PRKN), E3 ubiquitin ligase *Parkin*; PD, Parkinson's disease; *PINK1*, PTEN-induced putative kinase 1.

Leucine-rich repeat kinase 2 (LRRK2): Modulator of mitochondrial dynamics

LRRK2 is the most common genetic contributor to autosomal dominant PD.^{57,58} The G2019S mutation increases its kinase activity and alters several downstream processes, including mitochondrial fission, motility, and autophagy. LRRK2 interacts with DRP1, facilitating mitochondrial fragmentation.^{58,59} In parallel, mutant LRRK2 disrupts mitochondrial trafficking along axons by impairing the Miro–Milton–kinesin complex.⁶⁰ Furthermore, mutant LRRK2 suppresses mitophagy by interfering with Rab GTPases-mediated vesicular transport. LRRK2 inhibitors (e.g., DNL201, BIIB122) are in clinical trials, aiming to restore mitochondrial homeostasis.^{59,61} In vitro studies confirm that LRRK2 kinase inhibition enhances mitophagy and preserves mitochondrial network integrity.⁶²

α -Synuclein: A structural stressor on mitochondria

Although *SNCA* mutations are less common, duplications, triplications, and point mutations (e.g., A53T, E46K) in the gene encoding α -synuclein cause familial PD. Aggregated α -synuclein associates with mitochondrial membranes, particularly mitochondria-associated ER membranes, where it disrupts calcium signaling and bioenergetics.⁶³ α -Synuclein interferes with complex I activity, enhances mitochondrial fragmentation, and blocks mitophagic flux.⁶⁴ Moreover, it interacts with cardiolipin in the inner mitochondrial membrane, potentially altering cristae structure and triggering cytochrome c release.^{65,66} Single-molecule biophysics techniques now show that α -synuclein oligomers form lipid pores in mitochondrial membranes, permitting uncontrolled ion flux and loss of membrane potential.^{67,68}

GBA: Lysosomal–mitochondrial crosstalk in PD

Variants in the *GBA* gene, encoding the lysosomal enzyme glucocerebrosidase, represent one of the most prevalent genetic risk factors for PD, affecting 5–15% of patients.^{69,70} Loss-of-function mutations impair lysosomal degradation of α -synuclein and disrupt sphingolipid metabolism, establishing a pathological feedback loop between lysosomal stress, α -synuclein accumulation, and mitochondrial dysfunction.^{70,71} GBA deficiency lowers mitochondrial membrane potential and

reduces complex I activity, thereby compounding bioenergetic deficits. Clinically, *GBA*-associated PD is often characterized by earlier onset, more rapid progression, and higher rates of cognitive decline compared to sporadic PD, highlighting lysosomal–mitochondrial crosstalk as a central pathogenic axis in PD.^{70,72}

Mutant Huntingtin and mitochondrial dysregulation in HD

HD is caused by an expanded CAG repeat in the *HTT* gene, resulting in mutant huntingtin (*mHTT*) with an elongated polyglutamine (polyQ) tract.^{47,73} This toxic gain-of-function protein disrupts multiple cellular pathways, with mitochondria among the earliest and most severely affected organelles.⁷⁴ *mHTT* impairs axonal mitochondrial transport, decreases the expression of mitochondrial fission/fusion proteins (e.g., MFN1, OPA1), and inhibits peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α), the master regulator of mitochondrial biogenesis.^{75,76} It also binds the outer mitochondrial membrane and promotes mPTP opening, increasing vulnerability to calcium and oxidative stress. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) mediated excision of the expanded CAG tract in HD iPSC-derived neurons has been shown to restore mitochondrial respiration and dynamics, demonstrating a direct gene-organelle pathological axis (as shown in Fig. 3).^{77,78}

This schematic illustrates how key genetic mutations associated with Parkinson's disease (PD) and Huntington's disease (HD) converge on mitochondrial dysfunction, leading to neuronal vulnerability. In PD, mutations in *PINK1*, *Parkin* (PRKN), LRRK2, *SNCA* (α -synuclein), and *GBA* disrupt mitophagy, mitochondrial dynamics, trafficking, and redox balance. In HD, the mutant *HTT* protein impairs mitochondrial biogenesis by interfering with PGC-1 α , alters fission/fusion dynamics (affecting MFN1/OPA1), disrupts calcium handling, and promotes mitochondrial permeability transition pore (mPTP) opening. These molecular perturbations lead to impaired mitophagy, defective biogenesis, calcium dyshomeostasis, and fragmented mitochondrial networks. Ultimately, the pathological consequences include energy deficits, oxidative stress, neuroinflammation, and neuronal death, central to disease progression.^{1,5,79}

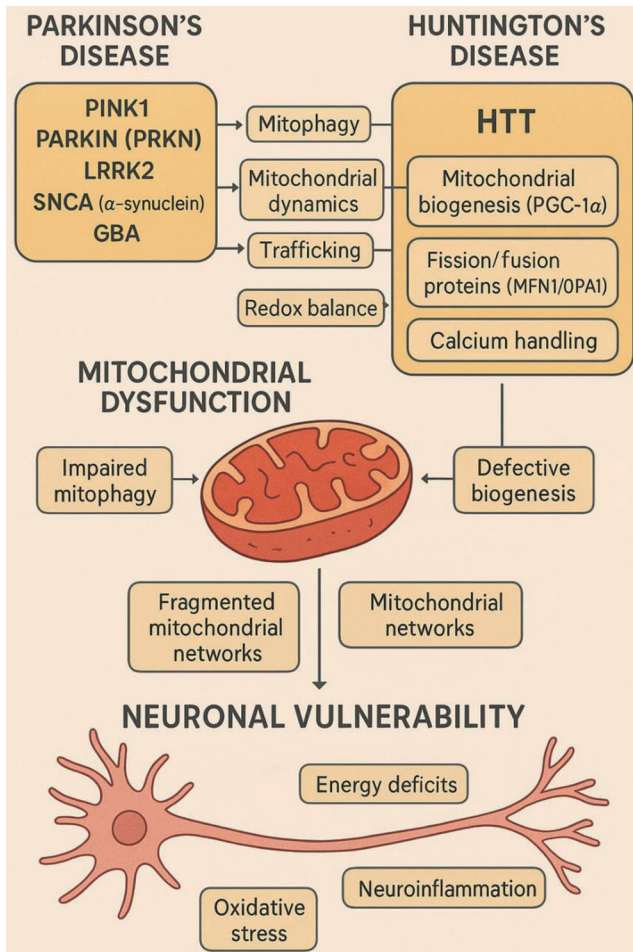


Fig. 3. Genetic mutations linking mitochondrial dysfunction to Parkinson's and Huntington's diseases. GBA, glucosylceramidase beta; HTT, Huntingtin; LRRK2, leucine-rich repeat kinase 2; MFN1, mitofusin 1; OPA1, optic atrophy 1; PARKIN, E3 ubiquitin-protein ligase parkin; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1- α ; PINK1, PTEN-induced kinase 1; SNCA, synuclein alpha (α -synuclein).

The interplay between environmental toxins and genetic predispositions

The development and progression of neurodegenerative diseases such as PD and HD reflect a complex interplay between genetic susceptibility and environmental exposures.^{80,81} While monogenic mutations in genes such as *PINK1*, *PRKN*, *LRRK2*, and *HTT* establish a molecular predisposition, environmental toxins often precipitate or accelerate the clinical disease. Experimental and epidemiological studies consistently show that genetically vulnerable neurons exhibit heightened sensitivity to environmental stressors. For instance, dopaminergic neurons lacking *PINK1* or *Parkin* exhibit exaggerated mitochondrial depolarization, mitophagy failure, and ROS accumulation upon exposure to pesticides such as rotenone or paraquat.^{82,83} Similarly, mutant *LRRK2* (G2019S) knock-in mice display exacerbated mitochondrial fragmentation and dopaminergic cell loss when challenged with trichloroethylene, an industrial solvent linked to PD in

occupational settings (Fig. 4).^{83–85}

Environmental toxins not only damage mitochondria directly but also intersect with the molecular pathways already dysregulated by genetic mutations. Several pesticides and industrial compounds impair autophagic flux and lysosomal degradation, thereby exacerbating mitophagic deficits in *Parkin*-deficient cells.⁸³ Heavy metals such as manganese and cadmium downregulate the transcription of mitochondrial biogenesis regulators, including *PGC-1 α* and nuclear respiratory factor 1, both of which are already repressed in HD due to mutant huntingtin-mediated transcriptional interference.⁸⁶ Furthermore, airborne particulate matter and polycyclic aromatic hydrocarbons (PAHs) can hyperactivate *DRP1* to enhance mitochondrial fission, aggravating the fragmentation already driven by mutant *LRRK2* or *mHTT*.⁸⁷ These findings support a “multiple hit” hypothesis, whereby environmental stressors magnify the pathological effects of disease-associated gene variants, often pushing mitochondrial function beyond a recoverable threshold.⁸⁸ A summary of the pathological effects associated with these genes is provided in Table 2.

Beyond direct molecular interactions, environmental toxins may modulate the expression of mitochondrial genes through epigenetic alterations.⁸⁹ For example, chronic exposure to pollutants like dieldrin and benzo[a]pyrene activates histone deacetylases, suppressing the transcription of anti-oxidant enzymes and mitochondrial transcription factors.⁹⁰ In brain samples from PD patients with known toxin exposure, DNA methylation of nuclear-encoded mitochondrial genes such as *TFAM* and *MFN2* has been observed, further implicating epigenetic remodeling in disease pathogenesis. These modifications may establish persistent mitochondrial defects that remain even after exposure ends, creating a latent risk for neurodegeneration.⁹¹ The intersection between gene mutations and environmental insults is crucial for developing personalized therapeutic approaches. Patients harboring mutations in mitophagy-related genes may benefit from treatments that enhance lysosomal degradation or support mitochondrial biogenesis.⁹² *Nrf2* pathway activators such as sulforaphane or dimethyl fumarate have shown promise in restoring redox homeostasis and enhancing mitochondrial resilience in toxin-exposed, genetically predisposed neurons. Small-molecule inhibitors of *DRP1*, such as Mdivi-1, are under investigation for their potential to reverse mitochondrial fragmentation induced by both genetic mutations and environmental factors.⁹³ These insights reinforce the need for precision medicine approaches that consider a patient's genetic profile and environmental exposure history.

As shown in Table 3, quantitative data from epidemiological and experimental studies reinforce the strong link between environmental toxins and neurodegenerative risk. For instance, agricultural workers with long-term exposure to paraquat or rotenone exhibit a 2–3-fold increase in PD incidence. This is consistent with rodent models in which low-dose, chronic administration reproduces nigrostriatal degeneration and α -synuclein aggregation.^{94,95} Similarly, industrial exposure to trichloroethylene is associated with a markedly elevated PD risk, a finding mirrored in murine studies showing mitochondrial fragmentation and dopaminergic loss at doses of 200–400 mg/kg/day.^{96,97} Heavy metals such as manganese and cadmium show clear dose-dependent neurotoxicity in both humans and animal models, with el-

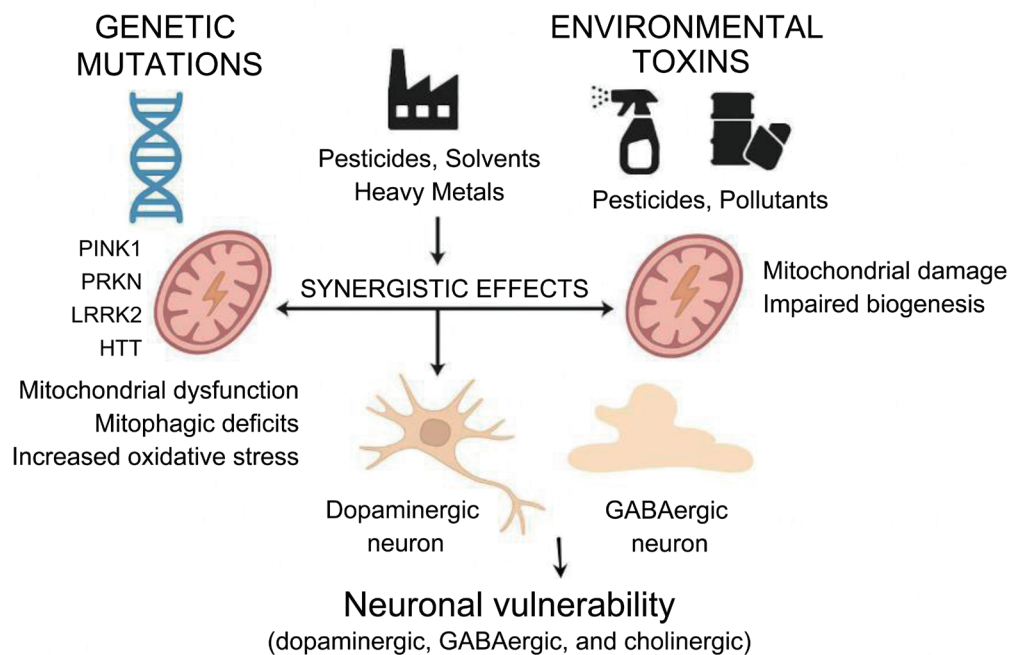


Fig. 4. Synergistic interactions between genetic mutations and environmental toxins in neurodegeneration. Genetic mutations in genes such as *PINK1*, *PRKN*, *LRRK2*, and *HTT* disrupt mitochondrial quality control by impairing mitophagy and increasing oxidative stress. Simultaneously, exposure to environmental toxins—including pesticides, solvents, heavy metals, and airborne pollutants—damages mitochondrial directly, reduces biogenesis, and drives epigenetic alterations. These two factors act synergistically to exacerbate mitochondrial dysfunction and oxidative stress, leading to dopaminergic neuron damage and progression of neurodegenerative diseases such as PD and HD.^{84,85} GABA, gamma-aminobutyric acid; HD, Huntington's disease; HTT, Huntingtin gene; PD, Parkinson's disease. *LRRK2*, leucine-rich repeat kinase 2; *Parkin* (*PRKN*), E3 ubiquitin ligase Parkin; *PINK1*, PTEN-induced putative kinase 1.

evated blood or urinary levels correlating with impaired mitochondrial biogenesis and motor dysfunction.^{87,98} Chronic airborne pollutants, particularly PM2.5 and PAHs, also present a significant epidemiological risk, linked to increased PD incidence and mitochondrial gene methylation changes.^{99,100} Collectively, these quantitative findings support a dose-response relationship in which even moderate, sustained exposure can synergize with genetic predispositions to drive neurodegenerative pathology.

Beyond mitochondrial impairment, environmental toxins disrupt other cellular systems that contribute to neurodegeneration. Several pesticides and heavy metals can induce ER stress, triggering the unfolded protein response and perturbing calcium homeostasis, which further sensitizes neurons to apoptotic signaling.¹⁰¹ Toxins such as dieldrin have been shown to impair lysosomal function and autophagic flux, exacerbating mitophagy deficits already present in *PINK1*- and *Parkin*-mutant backgrounds. Chronic exposure to airborne pollutants (PM2.5, PAHs) and manganese also activates microglial inflammatory cascades, leading to sustained release of pro-inflammatory cytokines (e.g., Tumor Necrosis Factor Alpha (TNF- α), Interleukin-1 Beta (IL-1 β)) and reactive oxygen species.^{102,103} This neuroinflammatory milieu not only damages neurons directly but also amplifies ER and mitochondrial stress, establishing a vicious cycle of cellular dysfunction.¹⁰⁴ These findings underscore that the pathogenic synergy between genetic predisposition and environmental

exposure extends beyond mitochondria to include ER stress responses, lysosomal degradation pathways, and neuroinflammatory signaling. Together, these interconnected dysfunctions accelerate the progression of PD and HD.

Therapeutic targeting of mitochondrial dysfunction in PD and HD

Given the central role of mitochondrial dysfunction in the pathogenesis of both PD and HD, mitochondria have emerged as critical therapeutic targets (Fig. 5a, b).¹⁰⁵ Unlike traditional symptomatic treatments, which primarily modulate neurotransmitter levels, mitochondrial-targeted therapies aim to reverse or mitigate upstream cellular pathology, offering the potential for disease modification.¹⁰⁶ A key therapeutic strategy involves restoring mitophagy—the selective autophagic degradation of dysfunctional mitochondria—which is compromised in PD due to mutations in *PINK1* and *Parkin*, and in HD due to mHTT-mediated inhibition of autophagic flux.¹⁰⁷ Several pharmacological agents are being developed to enhance *PINK1*-*Parkin* signaling or bypass defective steps.¹⁰⁸ For instance, small molecules such as KTP601 can stabilize *PINK1* on the outer mitochondrial membrane, while others mimic phosphorylated ubiquitin to activate *Parkin*. AMP-activated protein kinase activators like metformin and 5-aminoimidazole-4-carboxamide ribonucle-

Table 2. Gene–mitochondrial dysfunction–pathology links in PD and HD

Gene/Protein	Disease	Mitochondrial dysfunction	Pathological consequences
PINK1	PD	Impaired mitophagy due to failed mitochondrial membrane potential sensing	Accumulation of damaged mitochondria, oxidative stress, dopaminergic neuron loss
Parkin (PRKN)	PD	Defective ubiquitination of outer mitochondrial membrane proteins	Failure of mitochondrial clearance, increased ROS, apoptosis
LRRK2	PD	Hyperactive fission, disrupted trafficking, inhibition of mitophagy	Mitochondrial fragmentation, reduced energy production, neuroinflammation
α-Synuclein	PD	Binds mitochondrial membranes, disrupts complex I and MAMs	Mitochondrial swelling, cristae disruption, calcium dysregulation
HTT (mutant huntingtin)	HD	Inhibits mitochondrial biogenesis, impairs dynamics and trafficking	Decreased ATP production, mitochondrial fragmentation, synaptic failure
PGC-1α	HD	Transcriptional repression of mitochondrial biogenesis regulators	Energy deficit, increased oxidative stress, neuronal degeneration
MFN1 / OPA1	Both	Downregulated, impairing fusion and cristae maintenance	Fragmented mitochondria, loss of membrane potential, apoptosis
DRP1	Both	Hyperactivated (especially in PD and HD models)	Excessive fission, mitochondrial fragmentation, neurodegeneration

Table 2 Summarizes the relationships between key genetic mutations and their impact on mitochondrial function in PD and HD. The table highlights how mutations in specific genes disrupt mitochondrial processes—such as mitophagy, fission–fusion dynamics, axonal transport, and respiratory chain function—and outlines the resulting pathological consequences, such as oxidative stress, neuronal vulnerability, and neurodegeneration. ATP, adenosine triphosphate; DRP1, dynamin-related protein 1; HD, Huntington’s disease; LRRK2, leucine-rich repeat kinase 2; MAMs, mitochondria-associated membranes; MFN1, mitofusins 1; OPA1, optic atrophy 1; Parkin (PRKN), E3 ubiquitin ligase Parkin; PD, Parkinson’s disease; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species.

otide (AICAR) have been shown to stimulate both mitophagy and mitochondrial biogenesis in preclinical PD models, even with impaired PINK1-Parkin signaling. Despite strong pre-clinical data, translating these findings has proven challeng-

ing. Mitophagy enhancers and metabolic modulators often face significant hurdles, such as poor pharmacokinetics, uncertain dosing regimens, and variable target engagement in human neurons, which have limited their clinical advance-

Table 3. Quantitative evidence linking environmental toxins to neurodegenerative disease risk

Toxin / Pollutant	Typical exposure levels	Epidemiological data (human)	Experimental dose–response (model systems)	Key Pathological outcomes
Paraquat (herbicide)	Agricultural workers: >20 days/year use	2–3× higher PD risk vs non-exposed	Rodents: 10 mg/kg i.p. twice weekly → progressive dopaminergic neuron loss	Oxidative stress, mitochondrial depolarization, α-synuclein aggregation
Rotenone (pesticide)	Farm workers, chronic occupational contact	~70% ↑ PD incidence in exposed individuals	2–3 mg/kg/day oral/rodent → PD-like motor deficits	Complex I inhibition, ROS generation, nigrostriatal degeneration
Trichloroethylene (TCE, solvent)	Industrial settings: ≥25 ppm for >5 years	6× higher PD risk among exposed workers	200–400 mg/kg/day in mice → mitochondrial dysfunction & α-syn aggregation	Mitochondrial fragmentation, dopaminergic cell loss
Manganese (Mn, welding fumes)	Blood Mn >10 µg/L in welders	Elevated PD-like symptoms & motor deficits	Rodents: 15–50 mg/kg MnCl ₂ → impaired motor function	Inhibition of mitochondrial biogenesis, basal ganglia accumulation
Cadmium (Cd)	Urinary Cd >1 µg/g creatinine	Associated with cognitive decline & PD-like motor impairment	Chronic exposure in rodents (1–5 mg/kg) → mitochondrial DNA damage	Suppression of PGC-1α, NRF1, oxidative stress
Air pollution (PM2.5, PAHs)	Urban PM2.5 >12 µg/m ³ ; PAHs ~10–20 ng/m ³ roadside	1.2–1.5× ↑ PD risk with chronic PM exposure	Long-term inhalation in mice → neuroinflammation & α-syn upregulation	Epigenetic changes (DNA methylation of TFAM, MFN2), enhanced DRP1-mediated fission

Table 3 summarizes representative exposure levels, epidemiological associations, and dose–response findings from experimental models for major environmental toxins implicated in PD and HD. Data highlight the concordance between human studies and preclinical models, underscoring how chronic or occupational exposure to pesticides, solvents, heavy metals, and air pollutants can precipitate mitochondrial dysfunction and neurodegeneration, especially in genetically susceptible individuals. DRP1, dynamin-related protein 1; HD, Huntington’s disease; MFN2, mitofusin 2; NRF1, nuclear respiratory factor 1; PAHs, polycyclic aromatic hydrocarbons; PD, Parkinson’s disease; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PM, particulate matter; ROS, reactive oxygen species; TFAM, mitochondrial transcription factor A.

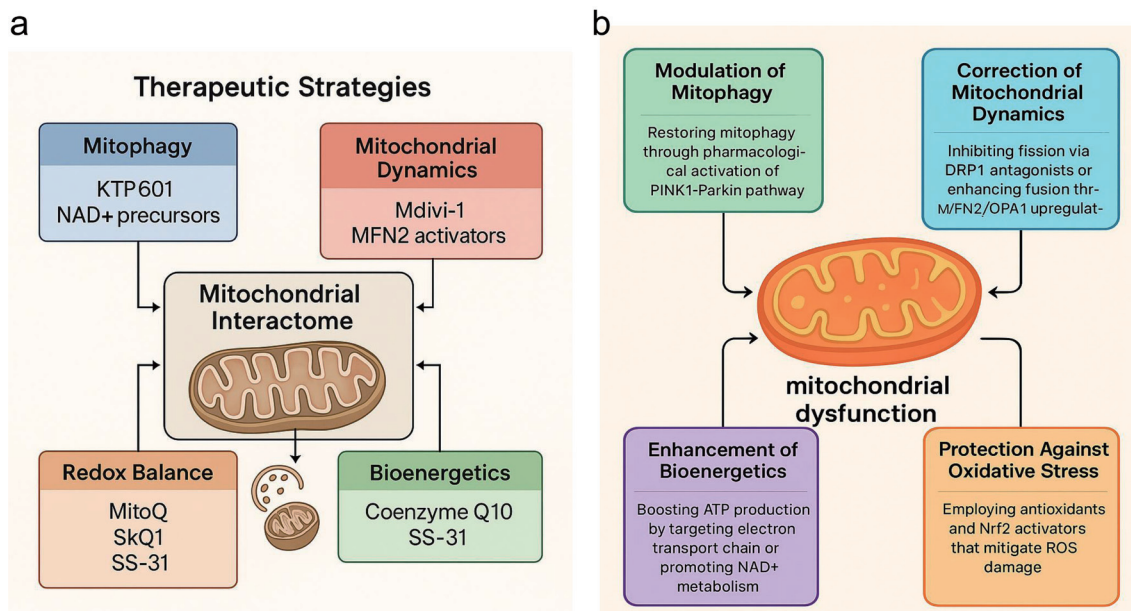


Fig. 5. Mitochondrial dysfunction and therapeutic strategies in Parkinson's and Huntington's diseases. Figure created using Biorender and Napkin AI. (a) Therapeutic Strategies: Emerging mitochondria-targeted interventions address these pathological mechanisms. Approaches include restoring mitophagy (KTP601, NAD⁺ precursors), modulating mitochondrial dynamics (Mdivi-1, MFN2 activators), enhancing redox balance (MitoQ, SkQ1, SS-31), and improving bioenergetics (Coenzyme Q10, SS-31). Together, these strategies highlight mitochondria as a central therapeutic target in neurodegenerative disease modification. (b) Pathophysiological Basis: Mitochondrial dysfunction contributes to neuronal vulnerability in PD and HD through several interconnected pathways: impaired mitophagy, altered dynamics, redox imbalance, and compromised bioenergetics. These disruptions amplify oxidative stress, energy failure, and progressive neurodegeneration. ATP, adenosine triphosphate; HD, Huntington's disease; MFN2, mitofusin 2; NAD⁺, nicotinamide adenine dinucleotide (oxidized form); OPA1, optic atrophy 1; PD, Parkinson's disease; ROS, reactive oxygen species.

ment.^{109–111} Another therapeutic axis involves modulating mitochondrial dynamics—specifically, correcting the imbalance between fission and fusion.¹¹² Excessive fission, common in both PD and HD, contributes to bioenergetic decline and pro-apoptotic signaling. Pharmacological inhibitors of DRP1, such as Mdivi-1, can reduce mitochondrial fragmentation and preserve neuronal viability.¹¹³ In HD models, enhancing the expression of fusion-promoting proteins like MFN2 and OPA1 through gene therapy or small molecules has shown promise in restoring mitochondrial morphology and improving ATP production.¹¹⁴ However, Mdivi-1 and related DRP1 inhibitors have not progressed to human trials due to off-target effects and safety concerns, underlining the difficulties in developing safe modulators of mitochondrial dynamics.^{115,116} At the genetic level, CRISPR/Cas9 technologies are being employed to correct the pathogenic *HTT* expansions or to knock down hyperactive mutant *LRRK2* alleles. These approaches have successfully restored mitochondrial respiration and dynamics in patient-derived iPSC models, presenting a promising avenue for precision therapeutics.¹¹⁷

Improving mitochondrial bioenergetics remains a cornerstone of therapeutic development. Agents such as coenzyme Q10 and creatine, though showing mixed results in large-scale trials, have demonstrated the ability to enhance electron transport chain activity and buffer ATP levels in early-stage PD and HD, as shown in Figure 5a.¹¹⁸ More recently, targeting NAD⁺ metabolism with compounds like nicotinamide riboside and nicotinamide mononucleotide has gained attention. These compounds boost sirtuin activity and PGC-1 α -mediated biogenesis, thereby enhancing mitochon-

drial resilience to oxidative and metabolic stress. However, translating these strategies has proven challenging. Large-scale clinical trials of coenzyme Q10 and creatine in PD and HD yielded disappointing results, showing no significant disease-modifying benefits despite strong biochemical rationale and early pilot data. These failures highlight challenges related to brain penetrance, trial design, and the possibility that mitochondrial rescue may only be effective during specific disease stages or in particular genetic subgroups.^{119–122} Mitochondria-targeted antioxidants represent another promising avenue.¹²³ Unlike conventional antioxidants, compounds such as MitoQ, SkQ1, and SS-31 are designed to accumulate within mitochondria, where they neutralize ROS at the source and stabilize mitochondrial membranes. These molecules have shown promise in reducing lipid peroxidation and preserving mitochondrial potential in animal models and are currently undergoing clinical evaluation.^{119,124,125} Parallel strategies involve activating Nrf2 pathway—a master regulator of antioxidant and detoxification responses. Nrf2 activators like dimethyl fumarate upregulate cellular defenses and improve mitochondrial morphology and function in both PD and HD models. While early-phase trials are ongoing, their long-term efficacy and safety remain uncertain. These translational gaps underscore the need for precision medicine approaches, integrating patient-derived iPSCs, multi-omics biomarkers, and advanced imaging to identify patients most likely to benefit from mitochondria-targeted therapies.^{25,126}

Cutting-edge approaches such as mitochondrial transplantation and nanomedicine represent the next frontier. Mitochondrial transplantation involves the direct transfer

of healthy mitochondria into damaged neurons, a strategy that has shown neuroprotective effects in rodent models of PD.¹²⁷ Complementarily, nanocarrier systems, including liposomes and cerium oxide nanoparticles, are being engineered to deliver antioxidants, gene-editing tools, or even intact mitochondria across the blood–brain barrier. While challenges remain concerning immune compatibility, targeted delivery, and long-term integration, these novel platforms underscore a future in which mitochondria-centric interventions may transform the therapeutic landscape of neurodegenerative diseases.¹¹⁷

Limitations and future directions

Despite significant advances, important gaps remain in understanding the mitochondrial interactome in neurodegeneration. Mechanistic connections between specific gene mutations (e.g., *PINK1*, *PRKN*, *LRRK2*, *GBA*, and *HTT*) and mitochondrial dysfunction are still incompletely mapped, particularly across different neuronal subtypes. Human data on long-term epigenetic consequences of environmental exposures are scarce, and standardized biomarkers for mitochondrial dysfunction are lacking, hindering both early diagnosis and therapeutic monitoring. Furthermore, most evidence derives from PD and HD models, which may not fully represent mitochondrial dynamics in other neurodegenerative diseases such as Alzheimer's disease or ALS. Future research should focus on (i) patient-derived iPSC models and advanced imaging modalities to capture disease heterogeneity, (ii) multi-omics approaches to discover reliable, clinically translatable mitochondrial biomarkers, (iii) integrative studies that assess the combined impact of genetics, environment, and organelle cross-talk (ER stress, lysosomal impairment, neuroinflammation), and (iv) translational efforts to improve brain penetrance and specificity of mitochondria-targeted therapeutics. Collaborative, cross-disease studies will be crucial to validate the mitochondrial interactome as a unifying framework and accelerate the development of precision therapies.

Conclusions

This review positions mitochondria at the center of PD and HD pathogenesis, where genetic mutations and environmental exposures converge to disrupt cellular homeostasis. By mapping the mitochondrial interactome, we identify actionable therapeutic nodes, including impaired mitophagy, fission–fusion imbalance, and oxidative stress, that represent actionable therapeutic nodes. Promising strategies that move beyond symptomatic management include mitochondria-targeted antioxidants (e.g., MitoQ, SS-31), DRP1 inhibitors (e.g., Mdivi-1), NAD⁺ boosters (e.g., nicotinamide riboside, nicotinamide mononucleotide), and gene-editing techniques for mutations in genes such as *LRRK2* and *HTT*. Combining these approaches with precision medicine tools—such as iPSC-based modeling, advanced imaging, and biomarker-guided patient stratification—will be essential to overcome translational barriers. Mitochondria represent not only a shared vulnerability in PD and HD but also a promising focal point for therapeutic development. Harnessing mechanistic insights into the mitochondrial interactome

can pave the way for individualized, mitochondria-centered interventions with the potential to alter disease progression and improve patient outcomes.

Acknowledgments

None.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Study concept and design (HG, YB), acquisition of data (HG), analysis and interpretation of data (HG, YB), drafting of the manuscript (HG), critical revision of the manuscript for important intellectual content (HG, YB, VM), framing and refinement of specific sections (VM), visualization including design and preparation of figures (HG, YB), and study supervision (YB, VM). All authors have made significant contributions to this work and have approved the final manuscript.

References

- [1] Franco-Iborra S, Vila M, Perier C. Mitochondrial Quality Control in Neurodegenerative Diseases: Focus on Parkinson's Disease and Huntington's Disease. *Front Neurosci* 2018;12:342. doi:10.3389/fnins.2018.00342, PMID:29875626.
- [2] Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. *J Pharmacol Exp Ther* 2012;342(3):619–630. doi:10.1124/jpet.112.192138, PMID:22700435.
- [3] Mohamed Yusoff AA, Mohd Khair SZN. Unraveling mitochondrial dysfunction: comprehensive perspectives on its impact on neurodegenerative diseases. *Rev Neurosci* 2025;36(1):53–90. doi:10.1515/revneuro-2024-0080, PMID:39174305.
- [4] Arun S, Liu L, Donmez G. Mitochondrial Biology and Neurological Diseases. *Curr Neuroparmacol* 2016;14(2):143–154. doi:10.2174/1570159x13666150703154541, PMID:26903445.
- [5] Golpich M, Amini E, Mohamed Z, Azman Ali R, Mohamed Ibrahim N, Ahmadiani A. Mitochondrial Dysfunction and Biogenesis in Neurodegenerative diseases: Pathogenesis and Treatment. *CNS Neurosci Ther* 2017;23(1):5–22. doi:10.1111/cns.12655, PMID:27873462.
- [6] Nicoletti V, Palermo G, Del Prete E, Mancuso M, Ceravolo R. Understanding the Multiple Role of Mitochondria in Parkinson's Disease and Related Disorders: Lesson From Genetics and Protein-Interaction Network. *Front Cell Dev Biol* 2021;9:636506. doi:10.3389/fcell.2021.636506, PMID:33869180.
- [7] Lezi E, Swerdlow RH. Mitochondria in neurodegeneration. *Adv Exp Med Biol* 2012;942:269–286. doi:10.1007/978-94-007-2869-1_12, PMID:22399427.
- [8] Trinh D, Israwi AR, Arathoon LR, Gleave JA, Nash JE. The multifaceted role of mitochondria in the pathology of Parkinson's disease. *J Neurochem* 2021;156(6):715–752. doi:10.1111/jnc.15154, PMID:33616931.
- [9] Rego AC, Cardoso SM, Oliveira CR. Molecular Pathways of Mitochondrial Dysfunction in Neurodegeneration: the Paradigms of Parkinson's and Huntington's Diseases. In: Malva JO, Rego AC, Cunha RA, Oliveira CR (eds). *Interaction Between Neurons and Glia in Aging and Disease*. Boston, MA: Springer; 2007:193–219. doi:10.1007/978-0-

- 387-70830-0_9.
- [10] Lanaro R, Costa JL, Fernandes LC, Resende RR, Tavares MF. Detection of paraquat in oral fluid, plasma, and urine by capillary electrophoresis for diagnosis of acute poisoning. *J Anal Toxicol* 2011;35(5):274–279. doi:10.1093/anatox/35.5.274, PMID:21619722.
- [11] Kotake Y. [Tetrahydroisoquinoline derivatives as possible Parkinson's disease-inducing substances]. *Yakugaku Zasshi* 2002;122(11):975–982. doi:10.1248/yakushi.122.975, PMID:12440154.
- [12] Caboni P, Sarais G, Vargiu S, De Luca MA, Garau VL, Ibba A, *et al.* LC–MS–MS Determination of Rotenone, Deguelin, and Rotenolone in Human Serum. *Chroma* 2008;68(9):739–745. doi:10.1365/s10337-008-0830-0.
- [13] Carmo C, Naia L, Lopes C, Rego AC. Mitochondrial Dysfunction in Huntington's Disease. *Adv Exp Med Biol* 2018;1049:59–83. doi:10.1007/978-3-319-71779-1_3, PMID:29427098.
- [14] Godoy JA, Rios JA, Picón-Pagès P, Herrera-Fernández V, Swaby B, Crepin G, *et al.* Mitostasis, Calcium and Free Radicals in Health, Aging and Neurodegeneration. *Biomolecules* 2021;11(7):1012. doi:10.3390/biom11071012, PMID:34356637.
- [15] Li S, Sheng ZH. Regulation of Synaptic Transmission through Mitochondrial Positioning and Metabolism. In: Jonas EA (ed). *The Oxford Handbook of Mitochondria*. Oxford: Oxford University Press; 2024. doi:10.1093/oxfordhb/9780190932183.013.13.
- [16] Walters GC, Usachev YM. Mitochondrial calcium cycling in neuronal function and neurodegeneration. *Front Cell Dev Biol* 2023;11:1094356. doi:10.3389/fcell.2023.1094356, PMID:36760367.
- [17] Kausar S, Wang F, Cui H. The Role of Mitochondria in Reactive Oxygen Species Generation and Its Implications for Neurodegenerative Diseases. *Cells* 2018;7(12):274. doi:10.3390/cells7120274, PMID:30563029.
- [18] Mattson MP, Gleichmann M, Cheng A. Mitochondria in neuroplasticity and neurological disorders. *Neuron* 2008;60(5):748–766. doi:10.1016/j.neuron.2008.10.010, PMID:19081372.
- [19] Palpagama TH, Waldvogel HJ, Faull RLM, Kwakowsky A. The Role of Microglia and Astrocytes in Huntington's Disease. *Front Mol Neurosci* 2019;12:258. doi:10.3389/fnmol.2019.00258, PMID:31708741.
- [20] Joshi AU, Minhas PS, Liddelaw SA, Haileselassie B, Andreasson KI, Dorn GW 2nd, *et al.* Fragmented mitochondria released from microglia trigger A1 astrocytic response and propagate inflammatory neurodegeneration. *Nat Neurosci* 2019;22(10):1635–1648. doi:10.1038/s41593-019-0486-0, PMID:31551592.
- [21] Araujo APB, Vargas G, Hayashide LS, Matias I, Andrade CBV, de Carvalho JJ, *et al.* Aging promotes an increase in mitochondrial fragmentation in astrocytes. *Front Cell Neurosci* 2024;18:1496163. doi:10.3389/fncel.2024.1496163, PMID:39703460.
- [22] López-Molina L, Pereda-Velarde A, di Franco N, Aerts I, Sebastià E, Valls-Roca L, *et al.* Mitochondria from huntington's disease striatal astrocytes are hypermetabolic and compromise neuronal branching. *Cell Commun Signal* 2025;23(1):341. doi:10.1186/s12964-025-02341-6, PMID:40671084.
- [23] Dos Santos MP, Leocadio VE, de Sá Hayashide L, Marques M, Carvalho CF, Galina A, *et al.* Lipopolysaccharide Induces Mitochondrial Fragmentation and Energetic Shift in Reactive Microglia: Evidence for a Cell-Autonomous Program of Metabolic Plasticity. *Toxins (Basel)* 2025;17(6):293. doi:10.3390/toxins17060293, PMID:40559871.
- [24] Uddin MH, Rumman M, Sarowar T. Mitochondrial Dysfunction in Huntington Disease. *Antioxidants and Functional Foods for Neurodegenerative Disorders*, 1st Ed. Boca Raton: CRC Press; 2021:151–174. doi:10.1201/9780429319310-12.
- [25] Ebadpour N, Mahmoudi M, Kamal Kheder R, Abavisani M, Baridjavadi Z, Abdollahi N, *et al.* From mitochondrial dysfunction to neuroinflammation in Parkinson's disease: Pathogenesis and mitochondrial therapeutic approaches. *Int Immunopharmacol* 2024;142(Pt A):113015. doi:10.1016/j.intimp.2024.113015, PMID:39222583.
- [26] Cerantonio A, Citrigno L, Greco BM, De Benedittis S, Passarino G, Maletta R, *et al.* The Role of Mitochondrial Copy Number in Neurodegenerative Diseases: Present Insights and Future Directions. *Int J Mol Sci* 2024;25(11):6062. doi:10.3390/ijms25116062, PMID:38892250.
- [27] Zink A, Conrad J, Telugu NS, Diecke S, Heinz A, Wanker E, *et al.* Assessment of Ethanol-Induced Toxicity on iPSC-Derived Human Neurons Using a Novel High-Throughput Mitochondrial Neuronal Health (MNH) Assay. *Front Cell Dev Biol* 2020;8:590540. doi:10.3389/fcell.2020.590540, PMID:33224955.
- [28] Luo HM, Xu J, Huang DX, Chen YQ, Liu YZ, Li YJ, *et al.* Mitochondrial dysfunction of induced pluripotent stem cells-based neurodegenerative disease modeling and therapeutic strategy. *Front Cell Dev Biol* 2022;10:1030390. doi:10.3389/fcell.2022.1030390, PMID:36478742.
- [29] Bhagavan NV, Ha CE. Electron Transport Chain, Oxidative Phosphorylation, and Other Oxygen-Consuming Systems. *Essentials of Medical Biochemistry*. Burlington, MA: Elsevier; 2011:135–150. doi:10.1016/B978-0-12-095461-2.00013-8.
- [30] Heales SJ, Gegg ME, Clark JB. Oxidative phosphorylation: structure, function, and intermediary metabolism. *Int Rev Neurobiol* 2002;53:25–56. doi:10.1016/s0074-7742(02)53003-8, PMID:12512336.
- [31] Seager R, Lee L, Henley JM, Wilkinson KA. Mechanisms and roles of mitochondrial localisation and dynamics in neuronal function. *Neuronal Signal* 2020;4(2):NS20200008. doi:10.1042/NS20200008, PMID:32714603.
- [32] Nicholls DG, Budd SL. Mitochondria and neuronal survival. *Physiol Rev* 2000;80(1):315–360. doi:10.1152/physrev.2000.80.1.315, PMID:10617771.
- [33] Federico A, Cardaioli E, Da Pozzo P, Formichi P, Gallus GN, Radi E. Mitochondria, oxidative stress and neurodegeneration. *J Neurol Sci* 2012;322(1-2):254–262. doi:10.1016/j.jns.2012.05.030, PMID:22669122.
- [34] Hernansanz-Agustín P, Enríquez JA. Generation of Reactive Oxygen Species by Mitochondria. *Antioxidants (Basel)* 2021;10(3):415. doi:10.3390/antiox10030415, PMID:33803273.
- [35] Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. *Free Radic Biol Med* 2010;48(6):749–762. doi:10.1016/j.freeradbiomed.2009.12.022, PMID:20045723.
- [36] Napolitano G, Fasciolo G, Di Meo S, Venditti P. Mitochondrial redox biology: Reactive species production and antioxidant defenses. In: de Oliveira MR (ed). *Mitochondrial Physiology and Vegetal Molecules*. London: Academic Press; 2021:105–125. doi:10.1016/B978-0-12-821562-3.00053-8.
- [37] Averill-Bates D. Reactive oxygen species and cell signaling. Review. *Biochim Biophys Acta Mol Cell Res* 2024;1871(2):119573. doi:10.1016/j.bbamcr.2023.119573, PMID:37949302.
- [38] El-Osta H, Circu ML. Mitochondrial ROS and apoptosis. In: Buhlman L (ed). *Mitochondrial Mechanisms of Degeneration and Repair in Parkinson's Disease*. Cham: Springer International Publishing; 2016:1–23. doi:10.1007/978-3-319-42139-1_1.
- [39] Patten DA, Germain M, Kelly MA, Slack RS. Reactive oxygen species: stuck in the middle of neurodegeneration. *J Alzheimers Dis* 2010;20(Suppl 2):S357–S367. doi:10.3233/JAD-2010-100498, PMID:20421690.
- [40] Tilokani L, Nagashima S, Paupe V, Prudent J. Mitochondrial dynamics: overview of molecular mechanisms. *Essays Biochem* 2018;62(3):341–360. doi:10.1042/EBC20170104, PMID:30030364.
- [41] Chan DC. Fusion and fission: interlinked processes critical for mitochondrial health. *Annu Rev Genet* 2012;46:265–287. doi:10.1146/annurev-genet-110410-132529, PMID:22934639.
- [42] Green A, Hossain T, Eckmann DM. Mitochondrial dynamics involves molecular and mechanical events in motility, fusion and fission. *Front Cell Dev Biol* 2022;10:1010232. doi:10.3389/fcell.2022.1010232, PMID:36340034.
- [43] Suárez-Rivero JM, Villanueva-Paz M, de la Cruz-Ojeda P, de la Mata M, Cotán D, Oropesa-Ávila M, *et al.* Mitochondrial Dynamics in Mitochondrial Diseases. *Diseases* 2016;5(1):1. doi:10.3390/diseases5010001, PMID:28933354.
- [44] Chen H, Chan DC. Mitochondrial dynamics—fusion, fission, movement, and mitophagy—in neurodegenerative diseases. *Hum Mol Genet* 2009;18(R2):R169–R176. doi:10.1093/hmg/ddp326, PMID:19808793.
- [45] Narendra D, Walker JE, Youle R. Mitochondrial quality control mediated by PINK1 and Parkin: links to parkinsonism. *Cold Spring Harb Perspect Biol* 2012;4(11):a011338. doi:10.1101/cshperspect.a011338, PMID:23125018.
- [46] Bader V, Winklhofer KF. PINK1 and Parkin: team players in stress-induced mitophagy. *Biol Chem* 2020;401(6-7):891–899. doi:10.1515/

- hsz-2020-0135, PMID:32297878.
- [47] Han R, Liu Y, Li S, Li XJ, Yang W. PINK1-PRKN mediated mitophagy: differences between in vitro and in vivo models. *Autophagy* 2023; 19(5):1396–1405. doi:10.1080/15548627.2022.2139080, PMID:362 82767.
 - [48] Imberechts D, Vandenbergh W. Defects in PINK-PRKN-PARK7/DJ-1-dependent mitophagy and autosomal recessive Parkinson disease. *Autophagy* 2023;19(6):1872–1873. doi:10.1080/15548627.2022.213 9129, PMID:36282786.
 - [49] Franco-Iborra S, Plaza-Zabala A, Montpeyo M, Sebastian D, Vila M, Martinez-Vicente M. Mutant HTT (huntingtin) impairs mitophagy in a cellular model of Huntington disease. *Autophagy* 2021;17(3):672–689. doi:10.1080/15548627.2020.1728096, PMID:32093570.
 - [50] Chaturvedi RK, Flint Beal M. Mitochondrial diseases of the brain. *Free Radic Biol Med* 2013;63:1–29. doi:10.1016/j.freeradbiomed.2013.03.018, PMID:23567191.
 - [51] Chaturvedi RK, Beal MF. Mitochondria targeted therapeutic approaches in Parkinson's and Huntington's diseases. *Mol Cell Neurosci* 2013;55:101–114. doi:10.1016/j.mcn.2012.11.011, PMID:23220289.
 - [52] Eldeeb MA, Fallahi A, Soumbasis A, Bayne AN, Trempe JF, Fon EA. Mitochondrial import stress and PINK1-mediated mitophagy: the role of the PINK1-TOMM-TIMM23 supercomplex. *Autophagy* 2024;20(8):1903–1905. doi:10.1080/15548627.2024.2340399, PMID:38597070.
 - [53] Vizziello M, Borellini L, Franco G, Ardolino G. Disruption of Mitochondrial Homeostasis: The Role of PINK1 in Parkinson's Disease. *Cells* 2021;10(11):3022. doi:10.3390/cells10113022, PMID:34831247.
 - [54] Eldeeb MA, Ragheb MA. N-degron-mediated degradation and regulation of mitochondrial PINK1 kinase. *Curr Genet* 2020;66(4):693–701. doi:10.1007/s00294-020-01062-2, PMID:32157382.
 - [55] Jin SM, Youle RJ. PINK1- and Parkin-mediated mitophagy at a glance. *J Cell Sci* 2012;125(Pt 4):795–799. doi:10.1242/jcs.093849, PMID:22448035.
 - [56] Riley BE, Olzmann JA. A polyubiquitin chain reaction: parkin recruitment to damaged mitochondria. *PLoS Genet* 2015;11(1):e1004952. doi:10.1371/journal.pgen.1004952, PMID:25612006.
 - [57] Singh A, Zhi L, Zhang H. LRRK2 and mitochondria: Recent advances and current views. *Brain Res* 2019;1702:96–104. doi:10.1016/j.brainres.2018.06.010, PMID:29894679.
 - [58] Wang X, Yan MH, Fujioka H, Liu J, Wilson-Delfosse A, Chen SG, *et al.* LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLP1. *Hum Mol Genet* 2012;21(9):1931–1944. doi:10.1093/hmg/dds003, PMID:22228096.
 - [59] Bonello F, Hassoun SM, Mouton-Liger F, Shin YS, Muscat A, Tesson C, *et al.* LRRK2 impairs PINK1/Parkin-dependent mitophagy via its kinase activity: pathologic insights into Parkinson's disease. *Hum Mol Genet* 2019;28(10):1645–1660. doi:10.1093/hmg/ddz004, PMID:30629163.
 - [60] Boecker CA. The Role of LRRK2 in Intracellular Organelle Dynamics. *J Mol Biol* 2023;435(12):167998. doi:10.1016/j.jmb.2023.167998, PMID:36764357.
 - [61] Esteves AR, Cardoso SM. LRRK2 at the Crossroad Between Autophagy and Microtubule Trafficking: Insights into Parkinson's Disease. *Neuroscientist* 2017;23(1):16–26. doi:10.1177/1073858415616558, PMID:26740081.
 - [62] Vermilyea SC, Emborg ME. In Vitro Modeling of Leucine-Rich Repeat Kinase 2 G2019S-Mediated Parkinson's Disease Pathology. *Stem Cells Dev* 2018;27(14):960–967. doi:10.1089/scd.2017.0286, PMID:29402177.
 - [63] Guardia-Laguarta C, Area-Gomez E, Rüb C, Liu Y, Magrané J, Becker D, *et al.* α -Synuclein is localized to mitochondria-associated ER membranes. *J Neurosci* 2014;34(1):249–259. doi:10.1523/JNEUROSCI.2507-13.2014, PMID:24381286.
 - [64] Nakamura K. α -Synuclein and mitochondria: partners in crime? *Neurotherapeutics* 2013;10(3):391–399. doi:10.1007/s13311-013-0182-9, PMID:23512373.
 - [65] Ghio S, Camilleri A, Caruana M, Ruf VC, Schmidt F, Leonov A, *et al.* Cardiolipin Promotes Pore-Forming Activity of Alpha-Synuclein Oligomers in Mitochondrial Membranes. *ACS Chem Neurosci* 2019;10(8):3815–3829. doi:10.1021/acscchemneuro.9b00320, PMID:31356747.
 - [66] Choi ML, Chappard A, Singh BP, MacLachlan C, Rodrigues M, Fedotova EI, *et al.* Pathological structural conversion of α -synuclein at the mitochondria induces neuronal toxicity. *Nat Neurosci* 2022;25(9):1134–1148. doi:10.1038/s41593-022-01140-3, PMID:36042314.
 - [67] Simitsi AM, Koros C, Stefanis L. Alpha-synuclein gene and Parkinson's disease. In: Martin CR, Preedy VR (eds). *Genetics, Neurology, Behavior, and Diet in Parkinson's Disease*. London: Academic Press; 2020:19–34. doi:10.1016/B978-0-12-815950-7.00002-3.
 - [68] Protter D, Lang C, Cooper AA. α -Synuclein and Mitochondrial Dysfunction: A Pathogenic Partnership in Parkinson's Disease? *Parkinsons Dis* 2012;2012:829207. doi:10.1155/2012/829207, PMID:22737587.
 - [69] Gegg ME, Menozzi E, Schapira AHV. Glucocerebrosidase-associated Parkinson disease: Pathogenic mechanisms and potential drug treatments. *Neurobiol Dis* 2022;166:105663. doi:10.1016/j.nbd.2022.105663, PMID:35183702.
 - [70] Gegg ME, Schapira AHV. The role of glucocerebrosidase in Parkinson disease pathogenesis. *FEBS J* 2018;285(19):3591–3603. doi:10.1111/febs.14393, PMID:29385658.
 - [71] Pradas E, Martinez-Vicente M. The Consequences of GBA Deficiency in the Autophagy-Lysosome System in Parkinson's Disease Associated with GBA. *Cells* 2023;12(1):191. doi:10.3390/cells12010191, PMID:36611984.
 - [72] Smith L, Schapira AHV. GBA Variants and Parkinson Disease: Mechanisms and Treatments. *Cells* 2022;11(8):1261. doi:10.3390/cells11081261, PMID:35455941.
 - [73] Bossy-Wetzel E, Petrilli A, Knott AB. Mutant huntingtin and mitochondrial dysfunction. *Trends Neurosci* 2008;31(12):609–616. doi:10.1016/j.tins.2008.09.004, PMID:18951640.
 - [74] Shirendeb U, Reddy AP, Manczak M, Calkins MJ, Mao P, Tagle DA, *et al.* Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington's disease: implications for selective neuronal damage. *Hum Mol Genet* 2011;20(7):1438–1455. doi:10.1093/hmg/ddr024, PMID:21257639.
 - [75] Jin YN, Johnson GV. The interrelationship between mitochondrial dysfunction and transcriptional dysregulation in Huntington disease. *J Bioenerg Biomembr* 2010;42(3):199–205. doi:10.1007/s10863-010-9286-7, PMID:20556492.
 - [76] Sharma A, Behl T, Sharma L, Aelya L, Bungau S. Mitochondrial Dysfunction in Huntington's Disease: Pathogenesis and Therapeutic Opportunities. *Curr Drug Targets* 2021;22(14):1637–1667. doi:10.2174/1389450122666210224105945, PMID:33655829.
 - [77] Lopes C, Tang Y, Anjo SI, Manadas B, Onofre I, de Almeida LP, *et al.* Mitochondrial and Redox Modifications in Huntington Disease Induced Pluripotent Stem Cells Rescued by CRISPR/Cas9 CAGs Targeting. *Front Cell Dev Biol* 2020;8:576592. doi:10.3389/fcell.2020.576592, PMID:33072759.
 - [78] Tobore TO. Towards a comprehensive understanding of the contributions of mitochondrial dysfunction and oxidative stress in the pathogenesis and pathophysiology of Huntington's disease. *J Neurosci Res* 2019;97(11):1455–1468. doi:10.1002/jnr.24492, PMID:31304621.
 - [79] Li W, Fu Y, Halliday GM, Sue CM. PARK Genes Link Mitochondrial Dysfunction and Alpha-Synuclein Pathology in Sporadic Parkinson's Disease. *Front Cell Dev Biol* 2021;9:612476. doi:10.3389/fcell.2021.612476, PMID:34295884.
 - [80] Polito L, Greco A, Seripa D. Genetic Profile, Environmental Exposure, and Their Interaction in Parkinson's Disease. *Parkinsons Dis* 2016;2016:6465793. doi:10.1155/2016/6465793, PMID:26942037.
 - [81] Qidwai T. Neurodegenerative Diseases Involve Multifactorial Interplay of Genetics and Environmental Factors. *Neurodegenerative Diseases: Multifactorial Degenerative Processes, Biomarkers and Therapeutic Approaches* (First Edition). Sharjah: Bentham Science Publishers; 2022:1–12. doi:10.2174/9789815040913122010003.
 - [82] Tsuboi Y. Environmental-genetic interactions in the pathogenesis of Parkinson's disease. *Exp Neurobiol* 2012;21(3):123–128. doi:10.5607/en.2012.21.3.123, PMID:23055790.
 - [83] Helley MP, Pinnell J, Sportelli C, Tieu K. Mitochondria: A Common Target for Genetic Mutations and Environmental Toxicants in Parkinson's Disease. *Front Genet* 2017;8:177. doi:10.3389/fgene.2017.00177, PMID:29204154.
 - [84] Kwakye GF, McMinimy RA, Aschner M. Disease-Toxicant Interactions in Parkinson's Disease Neuropathology. *Neurochem Res* 2017; 42(6):1772–1786. doi:10.1007/s11064-016-2052-4, PMID:27613618.

- [85] Chin-Chan M, Navarro-Yepes J, Quintanilla-Vega B. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. *Front Cell Neurosci* 2015;9:124. doi:10.3389/fncel.2015.00124, PMID:25914621.
- [86] Goldman SM. Environmental toxins and Parkinson's disease. *Annu Rev Pharmacol Toxicol* 2014;54:141–164. doi:10.1146/annurev-pharmtox-011613-135937, PMID:24050700.
- [87] Reddam A, McLarnan S, Kupsc A. Environmental Chemical Exposures and Mitochondrial Dysfunction: a Review of Recent Literature. *Curr Environ Health Rep* 2022;9(4):631–649. doi:10.1007/s40572-022-00371-7, PMID:35902457.
- [88] Huang M, Barges-Carot A, Riaz Z, Wickham H, Zenitsky G, Jin H, *et al.* Impact of Environmental Risk Factors on Mitochondrial Dysfunction, Neuroinflammation, Protein Misfolding, and Oxidative Stress in the Etiopathogenesis of Parkinson's Disease. *Int J Mol Sci* 2022;23(18):10808. doi:10.3390/ijms231810808, PMID:36142718.
- [89] Fernagut PO. Etiology and Progression of Parkinson's Disease: Cross-Talk Between Environmental Factors and Genetic Vulnerability. In: Steiner H, Tseng KY (eds). *Handbook of Behavioral Neuroscience*. Vol. 24. 2016:803–819. doi:10.1016/B978-0-12-802206-1.00040-4.
- [90] Martínez-García GG, Mariño G. Autophagy role in environmental pollutants exposure. *Prog Mol Biol Transl Sci* 2020;172:257–291. doi:10.1016/bs.pmbts.2020.02.003, PMID:32620245.
- [91] Zuo M, Ye M, Lin H, Liao S, Xing X, Liu J, *et al.* Mitochondrial Dysfunction in Environmental Toxicology: Mechanisms, Impacts, and Health Implications. *Chem Res Toxicol* 2024;37(11):1794–1806. doi:10.1021/acs.chemrestox.4c00328, PMID:39485318.
- [92] Andersen J. Development of Mitophagy-inducing Small Molecules as Therapeutics for Aging and Alzheimer's Disease. In: Baudry M (ed). *IABS Forum 2023. International Association of Biomedical Sciences (IABS); 2023*. doi:10.59566/iabs.2023.p002.
- [93] Aman Y, Ryan B, Torsetnes SB, Knapskog AB, Watne LO, McEwan WA, *et al.* Enhancing mitophagy as a therapeutic approach for neurodegenerative diseases. *Int Rev Neurobiol* 2020;155:169–202. doi:10.1016/bs.irn.2020.02.008, PMID:32854854.
- [94] Paul K, Cockburn M, Bronstein J, Walker DJ, Jones D, Ritz B. Agricultural pesticide exposure related to metabolic changes in Parkinson's disease patients. *ISEE Conference Abstracts* 2022;2022(1). doi:10.1289/isee.2022.O-OP-199.
- [95] Sukadi AA, Fitriani DY, Khoe LC. Parkinson's in Farmers, Could it be Caused by the Paraquat Herbicide Exposure? *The Indonesian Journal of Community and Occupational Medicine* 2022;2(1):58–65. doi:10.53773/ijcom.v2i1.44.58-65.
- [96] De Miranda BR, Castro SL, Rocha EM, Bodle CR, Johnson KE, Greenamyre JT. The industrial solvent trichloroethylene induces LRRK2 kinase activity and dopaminergic neurodegeneration in a rat model of Parkinson's disease. *Neurobiol Dis* 2021;153:105312. doi:10.1016/j.nbd.2021.105312, PMID:33636387.
- [97] Adamson A, Ilieva N, Stone WJ, De Miranda BR. Low-dose inhalation exposure to trichloroethylene induces dopaminergic neurodegeneration in rodents. *Toxicol Sci* 2023;196(2):218–228. doi:10.1093/toxsci/kfad090, PMID:37669148.
- [98] Ahmed G, Rahaman MS, Perez E, Khan KM. Associations of Environmental Exposure to Arsenic, Manganese, Lead, and Cadmium with Alzheimer's Disease: A Review of Recent Evidence from Mechanistic Studies. *J Xenobiot* 2025;15(2):47. doi:10.3390/jox15020047, PMID:40278152.
- [99] Pardo M, Qiu X, Zimmermann R, Rudich Y. Particulate Matter Toxicity Is Nrf2 and Mitochondria Dependent: The Roles of Metals and Polycyclic Aromatic Hydrocarbons. *Chem Res Toxicol* 2020;33(5):1110–1120. doi:10.1021/acs.chemrestox.0c00007, PMID:32302097.
- [100] Gavito-Covarrubias D, Ramírez-Díaz I, Guzmán-Linares J, Limón ID, Manuel-Sánchez DM, Molina-Herrera A, *et al.* Epigenetic mechanisms of particulate matter exposure: air pollution and hazards on human health. *Front Genet* 2023;14:1306600. doi:10.3389/fgene.2023.1306600, PMID:38299096.
- [101] Merighi A, Lissi L. Endoplasmic Reticulum Stress Signaling and Neuronal Cell Death. *Int J Mol Sci* 2022;23(23):15186. doi:10.3390/ijms232315186, PMID:36499512.
- [102] Song J, Han K, Wang Y, Qu R, Liu Y, Wang S, *et al.* Microglial Activation and Oxidative Stress in PM(2.5)-Induced Neurodegenerative Disorders. *Antioxidants (Basel)* 2022;11(8):1482. doi:10.3390/antiox11081482, PMID:36009201.
- [103] Lane M, Oyster E, Luo Y, Wang H. The Effects of Air Pollution on Neurological Diseases: A Narrative Review on Causes and Mechanisms. *Toxics* 2025;13(3):207. doi:10.3390/toxics13030207, PMID:40137534.
- [104] Kunwar OK, Singh S. Neuroinflammation and neurodegeneration in Huntington's disease: genetic hallmarks, role of metals and organophosphates. *Neurogenetics* 2025;26(1):21. doi:10.1007/s10048-025-00801-2, PMID:39820855.
- [105] Hirose M. Review: Precision mitochondrial medicine — R0/PR2. Review: Precision mitochondrial medicine 2022. doi:10.1017/pcm.2022.8.pr2.
- [106] Pal C. Targeting mitochondria with small molecules: A promising strategy for combating Parkinson's disease. *Mitochondrion* 2024;79:101971. doi:10.1016/j.mito.2024.101971, PMID:39357561.
- [107] Zheng Q, Liu H, Gao Y, Cao G, Wang Y, Li Z. Ameliorating Mitochondrial Dysfunction for the Therapy of Parkinson's Disease. *Small* 2024;20(29):e2311571. doi:10.1002/sml.202311571, PMID:3835823.
- [108] Gao XY, Yang T, Gu Y, Sun XH. Mitochondrial Dysfunction in Parkinson's Disease: From Mechanistic Insights to Therapy. *Front Aging Neurosci* 2022;14:885500. doi:10.3389/fnagi.2022.885500, PMID:35795234.
- [109] Miller S, Muqit MMK. Therapeutic approaches to enhance PINK1/Parkin mediated mitophagy for the treatment of Parkinson's disease. *Neurosci Lett* 2019;705:7–13. doi:10.1016/j.neulet.2019.04.029, PMID:30995519.
- [110] Antico O, Thompson PW, Hertz NT, Muqit MMK, Parton LE. Targeting mitophagy in neurodegenerative diseases. *Nat Rev Drug Discov* 2025;24(4):276–299. doi:10.1038/s41573-024-01105-0, PMID:39809929.
- [111] Dhar KS, Townsend B, Montgomery AP, Danon JJ, Pagan JK, Kassios M. Enhancing CNS mitophagy: drug development and disease-relevant models. *Trends Pharmacol Sci* 2024;45(11):982–996. doi:10.1016/j.tips.2024.09.002, PMID:39419743.
- [112] Gleave JA, Perri PD, Nash JE. Mitochondrial dysfunction in Parkinson's disease: a possible target for neuroprotection. *Front Biol* 2014;9:489–503. doi:10.1007/s11515-014-1337-8.
- [113] Ghosh D, Kumar A. Harnessing Mitophagy for Therapeutic Advances in Aging and Chronic Neurodegenerative Diseases. *Neuroglia* 2024;5(4):391–409. doi:10.3390/neuroglia5040026.
- [114] Guo X, Disatnik MH, Monbureau M, Shamloo M, Mochly-Rosen D, Qi X. Inhibition of mitochondrial fragmentation diminishes Huntington's disease-associated neurodegeneration. *J Clin Invest* 2013;123(12):5371–5388. doi:10.1172/JCI70911, PMID:24231356.
- [115] Bordt EA, Clerc P, Roelofs BA, Saladino AJ, Tretter L, Adam-Vizi V, *et al.* The Putative Drp1 Inhibitor mdivi-1 Is a Reversible Mitochondrial Complex I Inhibitor that Modulates Reactive Oxygen Species. *Dev Cell* 2017;40(6):583–594.e6. doi:10.1016/j.devcel.2017.02.020, PMID:28350990.
- [116] Rosdah AA, Abbott BM, Langendorf CG, Deng Y, Truong JQ, Waddell HMM, *et al.* A novel small molecule inhibitor of human Drp1. *Sci Rep* 2022;12(1):21531. doi:10.1038/s41598-022-25464-z, PMID:36513726.
- [117] Su YC, Qi X. Inhibition of excessive mitochondrial fission reduced aberrant autophagy and neuronal damage caused by LRRK2 G2019S mutation. *Hum Mol Genet* 2013;22(22):4545–4561. doi:10.1093/hmg/ddt301, PMID:23813973.
- [118] Bhatti GK, Gupta A, Pahwa P, Khullar N, Singh S, Navik U, *et al.* Targeting mitochondrial bioenergetics as a promising therapeutic strategy in metabolic and neurodegenerative diseases. *Biomed J* 2022;45(5):733–748. doi:10.1016/j.bj.2022.05.002, PMID:35568318.
- [119] Shinn LJ, Lagalwar S. Treating Neurodegenerative Disease with Antioxidants: Efficacy of the Bioactive Phenol Resveratrol and Mitochondrial-Targeted MitoQ and SkQ. *Antioxidants (Basel)* 2021;10(4):573. doi:10.3390/antiox10040573, PMID:33917835.
- [120] Fields M, Marcuzzi A, Gonelli A, Celeghini C, Maximova N, Rimondi E. Mitochondria-Targeted Antioxidants, an Innovative Class of Antioxidant Compounds for Neurodegenerative Diseases: Perspectives and Limitations. *Int J Mol Sci* 2023;24(4):3739. doi:10.3390/

- ijms24043739, PMID:36835150.
- [121] Jiang Q, Yin J, Chen J, Ma X, Wu M, Liu G, *et al.* Mitochondria-Targeted Antioxidants: A Step towards Disease Treatment. *Oxid Med Cell Longev* 2020;2020:8837893. doi:10.1155/2020/8837893, PMID:33354280.
- [122] Travessa AM, Rodrigues FB, Mestre TA, Ferreira JJ. Fifteen Years of Clinical Trials in Huntington's Disease: A Very Low Clinical Drug Development Success Rate. *J Huntingtons Dis* 2017;6(2):157–163. doi:10.3233/JHD-170245, PMID:28671135.
- [123] Beal MF, Manfredi G, Damiano M, Hervias I, Sirianni A, Vijayvergiya C, *et al.* Symposium S13: Role of Mitochondria in Neurodegeneration. *J Neurochem* 2004;90(Suppl 1):S8–S8. doi:10.1111/j.1471-4159.2004.02653.x.
- [124] Bobermin LD, Bezerra CCR, Krebs-Rosa J, Da Silva VF, Schmitz I, de Souza Almeida RR, *et al.* Signaling Mechanisms Underlying the Glial protective Effects of Guanosine Against Glucose Deprivation-Induced Glial Dysfunction. *Neurochem Res* 2025;50(4):240. doi:10.1007/s11064-025-04498-5, PMID:40690058.
- [125] Rahman MM, Tumpa MAA, Rahaman MS, Islam F, Sutradhar PR, Ahmed M, *et al.* Emerging Promise of Therapeutic Approaches Targeting Mitochondria in Neurodegenerative Disorders. *Curr Neuroparmacol* 2023;21(5):1081–1099. doi:10.2174/1570159X21666230316150559, PMID:36927428.
- [126] Stellon D, Talbot J, Hewitt AW, King AE, Cook AL. Seeing Neurodegeneration in a New Light Using Genetically Encoded Fluorescent Biosensors and iPSCs. *Int J Mol Sci* 2023;24(2):1766. doi:10.3390/ijms24021766, PMID:36675282.
- [127] Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. *Ann Neurol* 2003;53(Suppl 3):S39–S47. doi:10.1002/ana.10479, PMID:12666097.