

Mitophagy Dysfunction in Neurodegenerative Diseases: Molecular Mechanisms, Disease-Specific Pathways and Therapeutic Targets

Nidhi Saraswat^{*1}, Dr Abhay Singh², Dr. Yogesh Dnyandeo Narkhede³, Dr. Yash Partap⁴, Ms. Maneesha Bhardwaj⁵

¹Assistant Professor (Pharmacology) Mangalaytan University, Aligarh, Uttar Pradesh. Email: nidhisaraswat106@gmail.com

²Assistant Professor Department of Transfusion Medicine, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, 206130, Email: abhayspggi@gmail.com

³M. S. Shalya (General and Laparoscopic Surgeon), Assistant Professor SSAM Medical College, Pune. Email: dryogeshnarkhede10@gmail.com

⁴Department - School of Allied and Healthcare Sciences GNA University, Phagwara Rd, Punjab-144401, Email: yash.partap@gnauniversity.edu.in

⁵Assistant Professor Faculty of Pharmaceutical Sciences, The ICFAL University, Himachal Pradesh. Email: bhardwajmeesha@gmail.com

*Corresponding Author: Nidhi Saraswat, Mail: nidhisaraswat106@gmail.com

Abstract

Mitophagy is a specific type of autophagy that is crucial for neuronal survival and for the maintenance of mitochondrial quality. Dysfunction of it leads to the progression of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. This review discusses major pathways of mitophagy, including PINK1-Parkin and Parkin-independent pathways, as well as disease-specific alterations in these pathways. Impaired removal of mitochondria promotes oxidative stress, energy failure, protein aggregation, neuroinflammation and neuronal apoptosis. Emerging treatments, such as urolithin A, rapamycin, nicotinamide riboside and gene-based approaches, may restore mitochondrial homeostasis. Nevertheless, the lack of tools to monitor mitophagic activity and disease-specific responses, as well as limited clinical evidence, hinders therapeutic translation. Elucidation of these mechanisms may facilitate the creation of specific therapies for neurodegenerative disorders.

Keywords: Mitophagy, Neurodegenerative diseases, Mitochondrial Dysfunction, Therapeutic Targets.

1. Introduction

Macroautophagy, an evolutionarily conserved mechanism, encompasses the lysosomal breakdown and recycling of cellular constituents. Mitophagy is a form of macroautophagy that specifically directs mitochondria to lysosomes for their destruction (Uoselis et al., 2023). Mitophagy is initiated when mitochondrial impairment surpasses the effectiveness of alternative quality and quantity control mechanisms, or when mitochondria are eliminated for cellular metabolic functions (Wang et al., 2023). The removal of mitochondria through mitophagy is crucial in various processes, including inflammation, metabolic shifts, and cellular reprogramming (Wang et al., 2026).

Mitochondria are vital organelles that govern cellular metabolism, maintain homeostasis, and manage stress responses. Impaired mitochondria not only fail to generate ATP and other biosynthetic compounds but also emit elevated quantities of "reactive oxygen species (ROS)". If reactive oxygen species are not eliminated promptly and build up within cells, it will lead to programmed cell death (Zorov et al., 2014). Mitophagy preserves mitochondria in an ideal state by eliminating defective or surplus mitochondria. The equilibrium of mitochondrial homeostasis is maintained through a balance of degradation and biogenesis, which may be disturbed by unregulated mitophagy. This results in a suboptimal mitochondrial condition, causing disorders of the neurological system, cardiovascular system, lungs, liver, kidneys, skeletal muscle, and more. The prompt and precise elimination of mitochondria is essential for cellular viability in response to alterations in developmental, bioenergetic, and environmental factors (Pickles et al., 2018).

Neurodegenerative illness refers to a category of ailments characterised by the gradual and persistent deterioration of nerve tissue, predominantly affecting the elderly, and marked by the targeted degeneration and depletion of central neurons (Jellinger, 2010). In neurons, if impaired mitochondria are not adequately eliminated through mitophagy, reactive oxygen species, nitrogen oxides, and various oxidising agents will be generated. These oxidising agents can induce a range of neurodegenerative disorders, including "Alzheimer's disease (AD)", "Parkinson's disease (PD)", "Amyotrophic lateral sclerosis (ALS)", and "Huntington's disease (HD)", among others (Lu et al., 2023).

Despite the diversity in lesion locations and etiologies of various ailments, neuronal degeneration remains their unifying factor. Significantly, compromised mitophagy could lead to the emergence or exacerbation of certain neurodegenerative disorders, rendering strategies aimed at enhancing mitophagy a plausible treatment option for these conditions (Lyu et al., 2024) (Ahmad and Siddiqui, 2022).

2. Molecular Mechanisms of Mitophagy in Neurons

Mitophagy does not occur through a single molecular pathway. Neurons have evolved a number of mechanisms to recognize and get rid of damaged mitochondria. The best-characterised pathway is the “PTEN-induced putative kinase 1 (PINK1)–Parkin pathway, in which mitochondrial depolarisation induces PINK1 stabilisation on the “outer mitochondrial membrane (OMM)”, followed by the recruitment of Parkin, ubiquitination of mitochondrial proteins, recruitment of autophagy receptors and lysosomal degradation of the damaged organelle (Truban et al., 2017). Besides this ubiquitin-dependent mechanism, mitochondria can be targeted for autophagic degradation via receptor-mediated pathways involving proteins like BCL2/adenovirus E1B 19-kDa-interacting protein 3 (BNIP3)”, “FUN14 domain-containing protein 1 (FUNDC1)”, BNIP3-like/NIX (BNIP3L) and BCL2-like 13 (BCL2L13) (Wang et al., 2023). These pathways may act in parallel or independently of PINK1–Parkin signalling and could become especially relevant under specific metabolic or cellular stress conditions.

2.1 PINK1–Parkin pathway

The PINK1–Parkin is the best-characterised pathway of selective mitochondrial clearance and has provided a major molecular framework for understanding mitophagy in neurons. PINK1 is a serine/threonine protein kinase that functions as a sensor of mitochondrial damage, and Parkin is a cytosolic E3 ubiquitin ligase that is activated and recruited to damaged mitochondria. Mutations in PINK1 and PRKN (encoding Parkin) have been linked to inherited forms of PD, emphasising the significance of this pathway in neuronal mitochondrial quality control (Pickrell and Youle, 2015a) (Trinh and Farrer, 2013).

2.1.1 PINK1 Stabilisation on Damaged Mitochondria

Under physiological conditions, PINK1 is continuously imported into healthy mitochondria in a manner dependent on mitochondrial membrane potential ($\Delta\Psi_m$). Upon mitochondrial import, PINK1 is proteolytically processed and degraded. Under basal conditions, PINK1 levels are very low. This mechanism prevents mitophagy from being activated unnecessarily in healthy mitochondria (Wang et al., 2023).

Mitochondrial damage, especially loss of mitochondrial membrane potential, inhibits PINK1 import into the inner mitochondrial membrane. Full-length PINK1 thus accumulates on OMM, where it serves as an initiating signal for mitochondrial quality control. Thus, the accumulation of PINK1 provides a molecular link between mitochondrial damage and the activation of selective autophagy (Pickrell and Youle, 2015a) (Lazarou et al., 2015). PINK1 accumulation is therefore considered an early molecular event in the recognition of damaged mitochondria.

2.1.2 PINK1-Mediated Ubiquitin Phosphorylation

Once PINK1 is stabilised on damaged mitochondria, it phosphorylates ubiquitin on serine 65 (Ser65). PINK1 also phosphorylates the analogous Ser65 residue in the ubiquitin-like domain of Parkin. Phosphorylated ubiquitin is a crucial molecular signal for the activation and amplification of Parkin-dependent mitophagy (Koyano et al., 2014).

Phosphorylated ubiquitin may facilitate Parkin activation, and activated Parkin produces additional ubiquitin chains on mitochondrial surface proteins. This establishes a positive-feedback loop whereby phospho-ubiquitin produced by PINK1 promotes Parkin activation and ubiquitination by Parkin generates more substrate for PINK1 phosphorylation. This can amplify a relatively local mitochondrial damage signal to a strong mitophagic response (Koyano et al., 2014) (Pickrell and Youle, 2015b).

2.1.3 Recruitment and Activation of Parkin

Under normal conditions, Parkin is mainly present in the cytosol in an autoinhibited state. Mitochondrial damage results in PINK1-dependent phosphorylation of ubiquitin and Parkin, leading to conformational changes that activate Parkin and recruit it to the OMM. Activated Parkin acts as an E3 ubiquitin ligase to stimulate ubiquitination of several OMM proteins (Chin and Li, 2016).

Experimental studies demonstrated that Parkin is selectively recruited to mitochondria following mitochondrial depolarisation and facilitates their autophagic elimination. This finding identified Parkin as a key regulator of damage-induced mitochondrial clearance. Thus, recruitment of Parkin is a key point between sensing of mitochondrial damage and initiation of selective mitochondrial degradation (Narendra et al., 2008).

2.1.4 Ubiquitination of Outer Mitochondrial Membrane Proteins

Upon activation, Parkin ubiquitinates a number of proteins on the OMM. These include proteins involved in mitochondrial dynamics and transport, such as mitofusins, and other mitochondrial surface proteins. The ubiquitin chains then serve as molecular signals to promote recruitment of selective autophagy machinery (Youle and Narendra, 2011).

PINK1 and Parkin are not acting independently but cooperatively. PINK1 is the first to detect the damaged mitochondria and produces phospho-ubiquitin, and Parkin amplifies the ubiquitination signal on the surface of

the mitochondria. Such amplification allows for subsequent recruitment of autophagy receptors and the formation of autophagic structures around the damaged mitochondrion (Truban et al., 2017).

2.1.5 Recruitment of Mitophagy Receptors

Ubiquitinated mitochondria are recognised by selective autophagy receptors, which bridge the damaged organelle to the autophagic machinery. The main receptors involved in PINK1–Parkin-mediated mitophagy are “optineurin (OPTN)”, nuclear dot protein 52 kDa (NDP52/CALCO2), p62/SQSTM1, TAX1BP1 and NBR1. Among them, OPTN and NDP52 have been identified as crucial receptors for initiation of PINK1-Parkin-dependent mitophagy(Lazarou et al., 2015).

OPTN and NDP52 have ubiquitin-binding domains that enable them to interact with ubiquitinated mitochondria. They also bind to ATG8-family proteins, including LC3 and GABARAP proteins, during the formation of autophagic membranes. These interactions allow autophagy receptors to act as molecular bridges connecting damaged mitochondria to the autophagic machinery(Heo et al., 2015)(Lazarou et al., 2015).

Importantly, NDP52 and OPTN can recruit autophagy initiation factors upstream of the ULK1 complex, including WIPI1, ULK1 and DFCP1, to mitochondria. Therefore, mitophagy receptors are not only passive cargo adaptors, but they can also actively contribute to the initiation and progression of autophagosome formation(Lazarou et al., 2015).

2.1.6 Formation of the Mitophagosome

The damaged mitochondrion is then associated with a developing isolation membrane known as the phagophore, following the recruitment of autophagy receptors. The phagophore expands around the damaged mitochondrion, eventually enclosing it in a double membrane structure called the mitophagosome. LC3 lipidation and recruitment of ATG proteins are key steps in this process. Phagophore LC3/GABARAP proteins bind to LC3-interacting regions in mitophagy receptors, allowing selective sequestration of damaged mitochondria into the growing autophagosome(Youle and Narendra, 2011).

2.1.7 Fusion with Lysosomes and Mitochondrial Degradation

The last step of mitophagy is the fusion of the mitophagosome with lysosomes. The fusion results in an autolysosomal compartment in which mitochondrial proteins, lipids, membranes and mitochondrial DNA are degraded by lysosomal hydrolases. The degradation products can then be recycled and used by the cell(Mary et al., 2023).

Mitophagic flux to be successful needs to have lysosomal degradation finished. Note that the presence of mitophagy-related proteins or the formation of autophagosomes does not always indicate the complete degradation of mitochondria. Therefore, ideally, mitophagy assessment should differentiate between pathway initiation and the successful completion of mitochondrial clearance(Basak and Holzbaur, 2025a),(Youle and Narendra, 2011). This distinction is especially critical for neurons as mitochondrial trafficking, localisation, and turnover vary among neuronal compartments. Emerging evidence suggests that neuronal mitophagy is spatially regulated and cannot always be explained by mechanisms observed in non-neuronal cell lines.

2.2 Parkin-Independent Mitophagy

Whereas PINK1-Parkin-dependent mitophagy has been studied extensively, mitochondria can also be eliminated in a Parkin-independent manner. Parkin-independent routes are mediated by mitochondrial proteins that function as mitophagy receptors and bind directly to the autophagy machinery. Major receptors are BNIP3, NIX/BNIP3L, FUNDC1, BCL2L13, FKBP8 and other proteins that can connect mitochondria to ATG8-family proteins(Choubey et al., 2021a)(Springer and Macleod, 2016).

These pathways represent alternative mitochondrial quality-control mechanisms and may be particularly important during hypoxia, metabolic stress, mitochondrial stress, or when the canonical PINK1-Parkin pathway is insufficient. The evidence available suggests that neuronal mitophagy is not a linear signalling cascade, but rather a network of overlapping and context-dependent pathways(Basak and Holzbaur, 2025a).

2.3 BNIP3- and NIX/BNIP3L-Mediated Mitophagy

BNIP3 and NIX/BNIP3L are mitophagy receptors on the outer mitochondrial membrane. Both proteins contain “LC3-interacting regions (LIRs)” that bind directly to LC3 and other ATG8-family proteins on autophagic membranes. BNIP3 and NIX are induced or activated by cellular stress, in particular hypoxia and metabolic changes. Interaction with LC3 promotes mitochondrial recruitment to developing autophagosomal membranes and facilitates mitochondrial engulfment(D’Arcy, 2024). NIX is best characterized in physiological mitochondrial clearance during cellular differentiation, while BNIP3 plays important roles in stress-associated mitochondrial turnover. The BNIP3/NIX pathway suggests that mitochondrial damage does not always need to be sensed through PINK1 stabilisation and Parkin recruitment. Rather, some stress-induced receptors can couple the mitochondria and autophagy machinery directly(Tang et al., 2025).

2.4 FUNDC1-Mediated Mitophagy

FUNDC1 is a hypoxia-regulated OMM protein that functions as a mitophagy receptor. Like BNIP3 and NIX, FUNDC1 has an LIR motif that mediates its interaction with LC3. However, reversible phosphorylation of specific residues regulates its ability to induce mitophagy. Under normoxic conditions FUNDC1 is phosphorylated and maintained in a relatively inactive state. Changes in the phosphorylation status of FUNDC1 in hypoxia increase its interaction with LC3 and promote the recruitment of mitochondria to autophagic membranes(Liu et al., 2012).

FUNDC1-mediated mitophagy therefore provides a mechanism through which mitochondrial clearance can be coupled to cellular oxygen availability. This pathway highlights the importance of post-translational regulation in determining whether mitochondrial receptors can engage the autophagy machinery(Zhang, 2021).

2.5 BCL2L13-Mediated Mitophagy

BCL2L13 is another outer-membrane mitochondrial protein that can induce mitophagy by interacting with the autophagy machinery. It has an LC3-interacting region and can promote mitochondrial fragmentation and subsequent sequestration of mitochondria in autophagic structures(Choubey et al., 2021b). BCL2L13-mediated mitophagy is considered a Parkin-independent pathway and represents an alternative route for mitochondrial clearance. Its activity may be especially relevant when mitochondrial damage or cellular stress activates mitophagy without strong PINK1–Parkin signaling(Youle and Narendra, 2011).

2.6 Regulation of Mitophagy by Mitochondrial Dynamics

Mitochondrial dynamics such as fission and fusion are highly correlated with mitophagy. Mitochondrial fission produces smaller mitochondrial fragments that may help in segregating damaged mitochondrial regions from otherwise healthy mitochondrial networks. Mitochondrial fusion, in contrast, allows functional mitochondria to share mitochondrial components and metabolites, thereby contributing to mitochondrial resilience(Wang et al., 2022). The balance between fission, fusion, mitochondrial transport and mitophagy is particularly important in neurons, as mitochondria must be distributed over long cellular distances and maintained at sites of high energy demand, including synapses(Youle and Van Der Bliek, 2012).

Moreover, several aspects of mitochondrial dynamics also cross-talk with mitophagy signalling. One example is Parkin-mediated ubiquitination of mitofusins, which can promote their removal and affect mitochondrial network organisation. Therefore, mitochondrial fragmentation and selective mitochondrial degradation should be viewed as interrelated mitochondrial quality control mechanisms instead of independent processes(Gustafsson and Dorn, 2018).

2.7 Regulation of Mitophagy by Cellular Stress

Cellular conditions dynamically regulate mitophagy. Loss of mitochondrial membrane potential is a major trigger for PINK1 stabilisation. Hypoxia can activate receptor-mediated pathways involving BNIP3, NIX and FUNDC1. Oxidative stress, nutrient availability, calcium imbalance and alterations in cellular energy status can also affect mitochondrial turnover(Wang et al., 2023). Mitochondrial damage caused by stress is particularly important in neurons, as excessive mitochondrial ROS and impaired ATP production could impair synaptic function and neuronal survival. Thus, appropriate induction of mitophagy allows removal of damaged mitochondria before they become a major source of oxidative and metabolic stress(Islam, 2017).

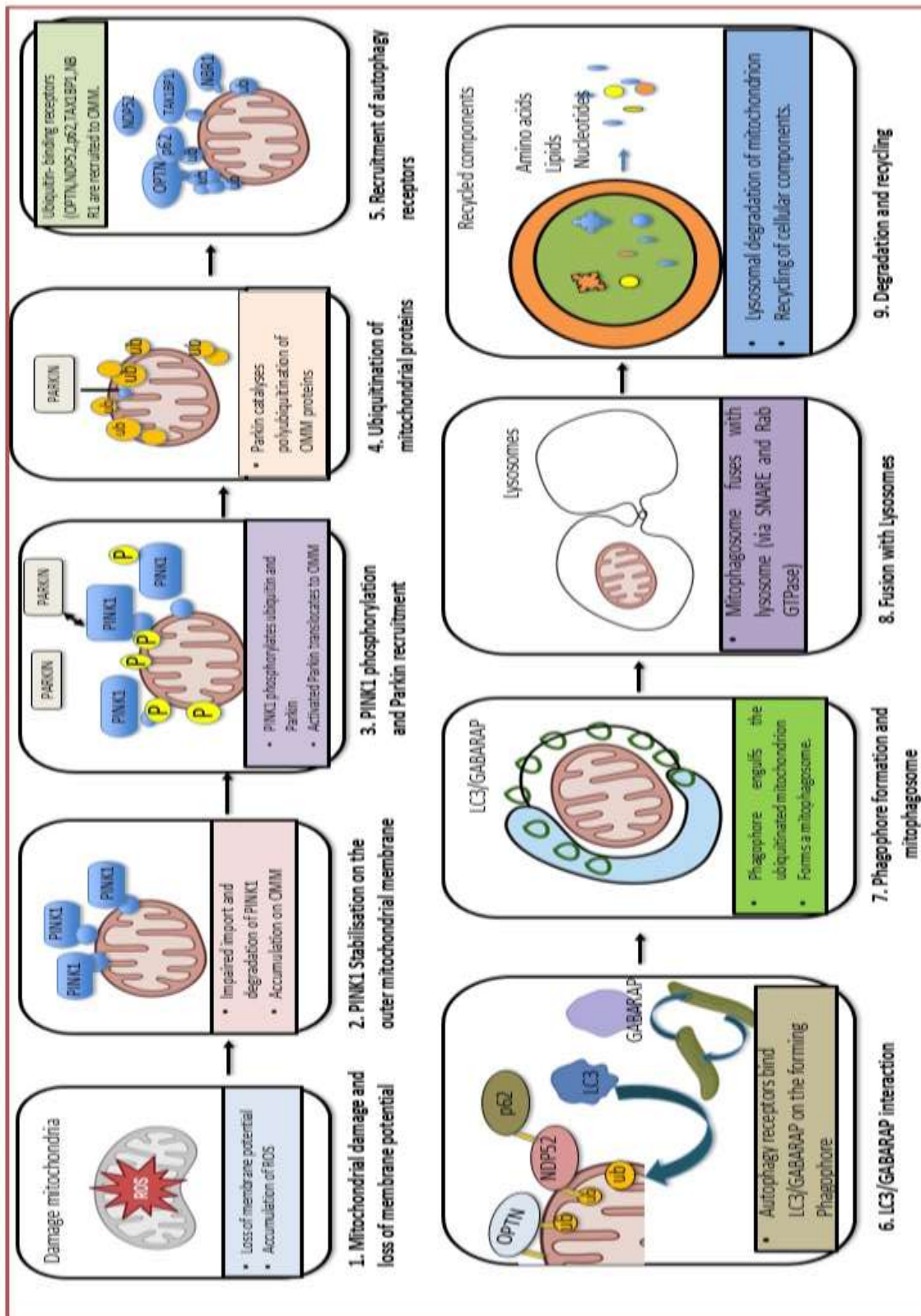


Figure 1: It depicts the PINK1-PARKIN pathway.

But mitophagy must be strictly regulated. Overzealous elimination of mitochondria may compromise cellular energy production, while insufficient clearance of mitochondria can lead to the accumulation of dysfunctional mitochondria. Thus, neuronal survival depends on a proper balance between mitochondrial damage, repair, biogenesis and selective mitochondrial degradation (Novak, 2012).

3. Mitophagy Dysfunction in Major Neurodegenerative Diseases

3.1 Alzheimer's disease

AD is induced by the degeneration of neurons and synapses, marked by the atypical accumulation of β -amyloid ($A\beta$) and the buildup of hyperphosphorylated Tau protein (pTau). The primary clinical characteristic is the deterioration of the cerebral cortex, leading to memory impairment and cognitive deficits (E. Liu et al., 2024). Electron microscopy has revealed specific changes in the mitochondrial ultrastructure of AD sufferers in contrast to healthy individuals (Baloyannis, 2006). Recent research indicates that the accumulation of $A\beta$ is pivotal in initiating mitochondrial impairment in AD. As a result, treatment approaches aimed at improving mitochondrial function and maintaining mitochondrial integrity are becoming increasingly popular for addressing neurological illnesses, such as AD (Chen and Yan, 2010).

Recent research indicates that the accumulation of $A\beta$ is pivotal in initiating mitochondrial impairment in AD. As a result, treatment approaches aimed at improving mitochondrial function and maintaining mitochondrial integrity are becoming increasingly popular for addressing neurological illnesses, such as AD (Wang et al., 2020). Mitochondrial impairment, as shown, may occur prior to the buildup of $A\beta$ aggregates. Properly operating mitochondria can diminish the abnormal processing of "amyloid precursor protein (APP)" and the accumulation of $A\beta$ plaques (Ye et al., 2015). Furthermore, the cytosolic Parkin in the brains of AD patients diminishes as the condition advances, resulting in the atypical buildup of PINK1. The overexpression of Parkin successfully reinstates mitophagy. Furthermore, it diminishes the buildup of impaired mitochondria. The reinstatement of mitophagy promotes the suppression and diminishment of $A\beta$ plaques, eradication of tau hyperphosphorylation, and avoidance of cognitive impairment (Roßner et al., 2022).

The atypical buildup of tau protein also impairs the process of mitophagy. The N-terminal tau fragment exhibits a stable affinity for Parkin and cytosolic "ubiquitin C-terminal hydrolase L1 (UCHL-1)", resulting in the aberrant localization of Parkin and UCHL-1 to mitochondria and subsequent excessive mitochondrial degradation and synaptic loss, contributing to the onset of AD (Corsetti et al., 2015). Brains of AD patients demonstrate heightened aggregation of mitochondrial proteins such as COXIV and Tomm20, which correlates with elevated Tau levels. Furthermore, a study indicated diminished concentrations of the autophagy indicators ATG5, Beclin1, ATG12, ULK1, along with mitophagy markers like Optineurin, BNIP3L, FUNDC1 and BNIP3 in the cerebral tissues of AD patients (Ganguly et al., 2024). The aggregation of tau may potentially hinder mitophagy by directly integrating into the mitochondrial membrane, leading to heightened mitochondrial membrane potential, diminished Parkin recruitment, and escalated neuronal toxicity (Hu et al., 2016).

Significantly, in both $A\beta$ and tau C. elegans models of Alzheimer's, urolithin A-induced mitophagy was shown to ameliorate memory deficits via processes reliant on PINK1, "Parkinson's disease-related-1 (PDR-1)", or DAF-16/FOXO-regulated germline-tumour affecting-1 (DCT-1) (Fang et al., 2019). Currently, it has been demonstrated that the gradual degeneration of functioning neurons is a significant pathogenic characteristic of AD. For instance, it has been documented that evident neuronal apoptosis may manifest in the initial phase of AD. Simultaneously, inadequate ATP synthesis resulting from compromised mitophagy may increase the vulnerability of neuronal cells to apoptosis-inducing proteins and expedite their demise. In contrast to other brain cells, neurons exhibit a greater reliance on ATP generated by the oxidative phosphorylation process of mitochondria. Mitochondrial failure can directly lead to neuronal death, impairing their abilities to receive, integrate, transmit, and conduct information (Lu et al., 2023).

In summary, dysfunctional mitophagy promotes the elevation of Alzheimer's disease-associated pathological proteins, including the buildup of $A\beta$ and Tau protein phosphorylation, heightens neuronal apoptosis, and disrupts cerebral energy metabolism, thereby hastening the onset and progression of AD (Reddy and Oliver, 2019a). Currently, no medication can evidently postpone or avert AD, as it is a progressive neurological disorder influenced by numerous causes. Fortunately, current research suggests that mitophagy inducers can eliminate dysfunctional mitochondria and bolster their capacity to withstand oxidative stress, so enhancing mitochondrial function and postponing the progression of AD (Ghosh and Kumar, 2024). In the AD mouse model, the addition of NAD⁺ precursors (such as nicotinamide) can enhance mitochondrial performance, diminish $A\beta$ accumulation and Tau protein phosphorylation, thereby ameliorating cognitive impairments in mice. Consequently, additional investigation into the correlation between mitophagy dysfunction and AD may yield novel insights for the targeted modulation of mitophagy and amelioration of neuropathological alterations in Alzheimer's, thus ensuring informed clinical choices for therapeutic approaches to neurodegenerative disorders (Liu et al., 2013).

3.2 Parkinson's disease

PD results from the deterioration of dopaminergic neurons within the substantia nigra. The primary symptoms are heightened muscle tension across the body, sluggish movements, and expressionless facial features, frequently accompanied by static tremors (Fahn, 2003). The manifestation of PD is associated with alterations in several critical proteins, including α -Synuclein (α -syn), "leucine-rich repeat kinase 2 (LRRK2)", "protein DJ-1 (DJ-1)", "F-Box protein 7 (Fbxo7)", and "vacuolar protein sorting 35 (VPS35)" (Zhang et al., 2018).

Investigations revealed that in the PD animal model, mitochondria exhibited enlargement and edema, indicating a potential mitophagy dysfunction. α -syn has been documented to provoke neuronal demise by enhancing mitophagy in A53T mutant mice (Wang et al., 2023). In yeast cells, the deleterious effects of α -syn can be conveyed via mitophagy facilitated by Sir2, the yeast equivalent of mammalian SIRT1 (Kumari et al., 2026). Subsequent research indicated that Fbxo7, α -syn, LRRK2, VPS35 and DJ-1 influence the onset of PD via mechanisms associated with Parkin-mediated mitophagy (Huang et al., 2025). For instance, the overproduction of the A53T α -syn mutant triggers p38 MAPK activation, resulting in the phosphorylation of Parkin at serine 131, ultimately leading to mitochondrial impairment and neuronal demise (Wang et al., 2023).

Furthermore, these proteins facilitate mitophagy via other pathways. The G2019S mutation in LRRK2 may impede the expulsion of Miro from the outer mitochondrial membrane, therefore postponing mitochondrial stasis and mitophagy (Bonello et al., 2019). The mutation additionally enhances the phosphorylation of RAB10 at threonine 73 in PD patients, consequently reducing the accumulation of OPTN on depolarised mitochondria and hindering depolarisation-induced mitophagy (Wauters et al., 2020). LRRK2 kinase inhibitors rectify the mitophagy defect caused by G2019S without reliance on the PINK1-Parkin pathway. These findings indicate that PD-associated proteins may influence the progression of PD by modifying mitophagy, which can be rectified using pharmacological agents, thus paving the way for novel therapeutic strategies for PD (X. Le Wang et al., 2021).

Research has indicated that alterations in either PINK1 or Parkin can result in the manifestation of genetic Parkinson's. The lack of PINK1 or Parkin leads to dysfunctional mitophagy, heightened oxidative stress, and the buildup of substantial toxic materials, resulting in mitochondrial impairment in the mesencephalic SN and ultimately causing the demise of dopaminergic neurons (Sever and Erbaş, 2024). Consequently, pharmacological strategies targeting the modulation of PINK1/Parkin signalling should prove beneficial in the management of PD. Significantly, nitrosative stress constitutes a critical pathogenic characteristic in PD. Collectively, it is evident that mitochondrial impairment resulting from mitophagy abnormalities is a significant contributor to the development of PD. Consequently, sustaining mitophagy at an optimal level with small-molecule modulators presents a promising approach for PD treatment; however, this complex therapeutic strategy needs additional investigation into the correlation between mitophagy and Parkinson's (Zhang et al., 2016).

3.3 Huntington's disease

Until recently, there was unexpectedly scant data explicitly associating mitophagy with HD. It is a neurological condition associated with the deterioration of motor coordination. The origin of HD is associated with mutations in the gene that encodes "Huntington (Htt)", primarily distinguished by an additional sequence of "polyglutamine (polyQ)" repeats at the N-terminus of the Htt protein (Gatto et al., 2020). Expanded polyQ repeats exhibit aberrant interactions with "glyceraldehyde-3-phosphate dehydrogenase" (GAPDH, an enzyme involved in glycolysis), diminishing the activation of GAPDH-mediated mitophagy (Hwang et al., 2015). Moreover, elongated polyQ repeats disrupt the assembly of ULK1/PtdIns3K and the interaction with OPTN/NDP52, thereby influencing the initiation of mitophagy and the recruitment of LC3 to mitochondria (Wang et al., 2023). Impairments in mitophagy lead to the buildup of dysfunctional mitochondria and heightened cellular death, facilitating the advancement of HD. Consequently, the swift and efficient removal of impaired mitochondria is crucial (Sawant et al., 2021). Augmenting the PINK1-Parkin-driven mitophagy mechanism can bolster mitochondrial integrity and provide neuroprotection in Huntington's disease. Significantly, the hyperactivation of mitophagy facilitates the progression of Huntington's disease (Khalil et al., 2015). VCP, a class II ATPase, has the ability to associate with mutant Htt and aggregate in mitochondria, leading to excessive activation of PINK1-Parkin-mediated mitophagy and, eventually, neuronal demise (Doblado et al., 2021).

Shirendeb et al. discovered that mHtt engaged with mitochondrial "dynamin-related protein 1 (Drp1)", which augmented the GTPase activity of Drp1, leading to excessive mitochondrial fragmentation and irregular distribution (Shirendeb et al., 2012). Recent studies have indicated that the advancement of HD may initiate when nonviable or deteriorating mitochondria are not eliminated. Notably, alterations in the quantity and dimensions of mitochondria were detected in HD, contingent upon grade. Moreover, it was demonstrated that the mitochondrial architecture of neurons impacted by HD was compromised, diminished in size, and more spherical, with disrupted cristae. Furthermore, studies involving cellular and animal models of HD indicate that

both nuclear and mitochondrial DNA sustain damage, so reinforcing the link between mitophagy impairment and the development of HD(Lu et al., 2023).

3.4 Amyotrophic lateral sclerosis

While the prevalence of ALS is lower than that of AD or PD, it remains a lethal and untreatable condition marked by the targeted degradation of motor neurons, resulting in escalating muscular weakening and mortality from respiratory failure. Alterations in many genes play a role in the advancement of ALS(Verma et al., 2025). Mutant “Superoxide dismutase (SOD1)” inhibits the retrograde transport of mitochondria within neurons. It additionally consolidates and sequesters OPTN, obstructing the development of mitophagosomes and subsequently mitophagy flux. The cumulative impacts result in the accumulation of impaired mitochondria at axon terminals, diminishing neuronal viability(Andersen, 2006). Reports indicate that the Parkin-mediated mitophagy pathway is stimulated in the ALS mutant SOD1 murine model (Palomo et al., 2018). The simultaneous deletion of PINK1 and Parkin leads to the accumulation of impaired mitochondria, diminishing mitochondrial efficacy and resulting in the deterioration of ALS neuromuscular connections(Rogers et al., 2017). In contrast, Palomo et al. indicated that the deletion of the Parkin gene in the SOD1-G93A animal model diminishes mitochondrial loss and postpones the advancement of ALS. Nevertheless, as far, no credible rationale has been provided for these inconsistencies(Palomo et al., 2018).

Genetic alterations in autophagy-regulating genes, including the ubiquitin-binding proteins OPTN and SQSTM1/p62, as well as the kinase TBK1, have been documented in individuals with ALS(Ramesh and Pandey, 2017). In instances of mitochondrial impairment, OPTN is attracted to ubiquitinated mitochondria subsequent to Parkin activation, and commences the assembly of autophagosomes, a mechanism supported by the development of a sheet-like condensate on the injured organelle's surface(Qiu et al., 2022). An ALS-related mutation in the ubiquitin-binding domain of OPTN was discovered to obstruct the recruitment of OPTN to impaired mitochondria, impeding mitophagy(Moore and Holzbaur, 2016). Likewise, certain pathogenic variants of TBK1 seen in ALS patients adversely affect kinase activity or dimerization, hence impairing mitophagy. SQSTM1, also known as p62, is a structural protein with well-defined functions in autophagy(Beckers and Van Damme, 2025). p62 is additionally summoned to impaired mitochondria, where it generates condensates that are separate from those produced by OPTN, yet it colocalizes with NEMO. 2–3% of ALS instances have a genetic association with mutations in the p62 gene, which has been observed to colocalize with TDP-43 aggregates in the brain and spinal cord inclusions of individuals with ALS(Harding et al., 2023). Nonetheless, it has still to be ascertained if mutations in p62 provoke ALS via impairments in mitophagy or through alternative autophagic mechanisms like aggrephagy, although new studies indicate that p62 is not essential for this pathway in neuronal cells. Conversely, p62 is essential for lysophagy, and mutations linked to ALS impede the removal of impaired lysosomes in cell cultures; nevertheless, additional research is necessary to elucidate a pathogenic mechanism in motor neurons(Gallagher and Holzbaur, 2023).

Predominantly, the majority of research on mitophagy inside the nervous system emphasizes molecular etiology and prospective therapeutic options for neurological disorders. Nonetheless, debates persist regarding the focus of mitophagy, the precise mechanisms of receptor-mediated mitophagy, variations in research and environmental contexts, the balance of drawbacks versus benefits in illness therapy, and the optimal strategies to address these issues. The future research challenge lies in developing improved models to comprehend the impacts of mitophagy, prevalent signaling pathways, and mitochondrial abnormalities on the pathogenic mechanisms of neurodegenerative disorders(Lu et al., 2023). Additionally, agents that selectively promote or suppress mitophagy may be employed in the model to examine the alterations in mitophagy and its correlation with the onset and progression of illnesses. Furthermore, the outcomes of focusing on mitophagy in prolonged chronic neurological disorders remain ambiguous, and there is a deficiency of comprehensive and stringent studies on short-term acute neurological conditions. These issues require resolution in next studies(Picca et al., 2023).

4. Molecular Links Between Mitophagy Dysfunction and Neurodegeneration

4.1 Mitophagy and oxidative stress

Oxidative stress arises when the generation of Reactive oxygen species markedly escalates, surpassing the antioxidant enzyme capacity of a cell. ROS are generated as a secondary result of metabolic processes within mitochondria (Singh et al., 2019). A β has been identified as a factor that enhances the generation of ROS by mitochondria through the formation of coordination complexes with metal ions (Cu and Fe) in the brain (Roy et al., 2023). In AD brains, elevated ROS generation results from a lack of cytochrome c oxidase in the

mitochondrial electron transport chain. Reactive oxygen species (ROS) encompass both radical and non-radical forms of oxygen, including superoxide radical anion (O_2^-), peroxynitrite ($ONOO^-$), nitric oxide (NO), hydrogen peroxide (H_2O_2) and hydroxyl radical (HO) (Misrani et al., 2021). An imbalance in the generation and breakdown of ROS can lead to oxidative stress, as these species can oxidise nucleic acids (DNA and RNA), proteins, and lipids, ultimately harming neuronal cells (Li et al., 2013).

Numerous investigations have demonstrated that reactive oxygen species contribute to cellular damage in the context of ageing and several neurodegenerative disorders. With advancing age, elevated levels of ROS have been correlated with the buildup of impaired mitochondria. Oxidative stress induces alterations in mitochondrial DNA (Cui et al., 2012). The alterations in mtDNA that arise with ageing and are not passed down are referred to as somatic mutations. These mtDNA mutations are linked to impaired OXPHOS functionality, as mtDNAs are known to encode enzymes utilised in the ETC, hence harming mitochondria and ultimately resulting in diminished ATP synthesis (McKenzie et al., 2004). ROS also harm proteins and lipids related to bioenergetics, including cardiolipin present in the inner membrane. Consequently, neurones succumb to apoptosis or necrosis over time due to insufficient energy supply or heightened oxidative stress, ultimately contributing to the onset and advancement of neuroinflammation and neurodegenerative disorders.

Furthermore, elevated levels of ROS are linked to the induction of senescence in many cells by causing damage and the reduction of telomere length in nuclear DNA, as well as through ROS-driven cellular signalling mechanisms (Stojanovic et al., 2025). Oxidative stress and the resulting significant rise in its by-products have been extensively documented in AD. These oxidised biomolecular by-products exhibit greater stability and are thus utilised as reactive oxygen species markers in tracking the advancement of Alzheimer's. Neuronal mitochondria are adversely affected by oxidative stress, resulting in their gradual deterioration. Elevated oxidative stress is significant as it harms mitochondria, leading to neuronal dysfunction (Facecchia et al., 2011). Oxidative stress additionally harms mtDNA, thereby impairing the respiratory complexes. The excessive generation of reactive oxygen species leads to mitochondrial impairment via oxidative stress. This detrimental loop of reduced ATP synthesis resulting from impaired OXPHOS, heightened oxidative stress, mitochondrial impairment, and cellular demise is characteristic of Alzheimer's disease advancement (Butterfield and Halliwell, 2019).

In PD, the aberrant expression of Drp1 and Mfn2 may induce a change in the mitochondrial network toward fragmentation. With the passage of time, these structural modifications impede ATP supply to synapses and hinder standard mitophagy (Arias-Carrión et al., 2026). Achieving equilibrium between fusion and fission is crucial for satisfying regional energy requirements and isolating critically impaired organelles for removal. Dysregulated mitochondrial dynamics consequently establishes a foundation for neuronal stress and hastens pathogenic processes (Chan, 2020).

When mitochondria incur damage or experience a loss of membrane potential, mitophagy mechanisms—especially those facilitated by PINK1 and Parkin—are accountable for their targeted elimination. Dysfunction of these systems leads to the buildup of impaired organelles that emit ROS, proteotoxic fragments, and pro-apoptotic elements (Ashrafi and Schwarz, 2012). Genes related with Parkinson's disease significantly suggest impaired mitophagy, as mutations in PINK1 or Parkin diminish the capacity to ubiquitinate and eliminate damaged mitochondria. Disruptions in this route can increase the loss of dopaminergic neurones, even in intermittent PD (Malpartida et al., 2021).

Furthermore, intramitochondrial proteases and chaperones sustain proteostasis by either refolding or destroying improperly folded proteins. In ALS, mutated SOD1 or TDP-43 may cluster within the intermembrane space, disrupting import channels and proteolytic activity (Chauhan et al., 2025). In Huntington's disease, mutated huntingtin can disrupt autophagic processes, obstructing the removal of harmful protein fragments. Consequently, the quality-control framework—comprising mitophagy, proteostasis, and mitochondrial import—arises as a pivotal arena in neurodegeneration, wherein disease-specific proteins interfere with standard clearance processes (Yang, 2025).

An expanding collection of research associates persistent neuroinflammation with mitochondrial deterioration across all principal neurodegenerative disorders. Impaired mitochondria emit alarmins such as mtDNA, cytochrome c, and cardiolipin, functioning as “damage-associated molecular patterns (DAMPs)” to stimulate microglia and astrocytes (Lin et al., 2022). Activated glial cells generate pro-inflammatory cytokines (such as IL-6, TNF- α , IL-1 β) and reactive nitrogen species (such as nitric oxide), which further impair mitochondrial function. As time progresses, a feedforward loop develops; augmented mitochondrial damage results in elevated DAMP release, amplifying inflammation and worsening neuronal stress (Müller et al., 2025).

In ALS, the activation of microglia frequently occurs prior to the noticeable loss of motor neurones, indicating an initial interaction between innate immune responses and the metabolic requirements of susceptible neurones. The significance of chronic inflammation in Parkinson's, Huntington's and Alzheimer's disease is

increasingly acknowledged, especially the notion that glial dysfunction exacerbates mitochondrial stress, propelling the transition from minor impairment to overt neuronal death (Rodríguez and Mahy, 2017).

Excessive calcium in neurones can be fatal, and mitochondria are essential in regulating cytosolic Ca^{2+} during excitatory occurrences. At certain contact points between the endoplasmic reticulum and mitochondria, referred to as MAMs, the transport of calcium is meticulously controlled. Nevertheless, in situations like AD or ALS, alterations in mitochondrial-associated membranes facilitate excessive calcium absorption by mitochondria. Increased Ca^{2+} concentrations can activate the mPTP, disrupt membrane potential, and initiate apoptosis or necrosis (Truong et al., 2025).

Parkinson's disease may additionally entail modified coupling between the endoplasmic reticulum and mitochondria, intensifying calcium dysregulation and oxidative stress in dopaminergic neurones (Gómez-Suaga et al., 2018). Familial ALS mutations in TDP-43 or fused in sarcoma (FUS) disrupt standard protein management at MAMs, underscoring the susceptibility of these subcellular junctions in pathological conditions. Excessive or sustained influx of calcium leads to the release of apoptotic agents such as cytochrome c from mitochondria, resulting in irreversible neuronal degeneration (Scarian et al., 2022)

4.2 Mitophagy and protein aggregation

Protein misfolding and aggregation are hallmark pathological features of several neurodegenerative diseases including Alzheimer's, Parkinson's, Huntington's disease and amyotrophic lateral sclerosis (Ciechanover and Kwon, 2015). Key pathological proteins include amyloid- β ($\text{A}\beta$) and hyperphosphorylated tau in AD, α -synuclein in PD, mutant huntingtin in HD, and TDP-43 and mutant SOD1 in ALS (Ciurea et al., 2023). Increasing evidence suggests that mitochondrial dysfunction and defective mitophagy are tightly associated with the accumulation and toxicity of these misfolded proteins. Importantly, the relationship between mitophagy and protein aggregation seems to be reciprocal, as impaired mitochondrial clearance promotes conditions favourable for protein aggregation and pathological protein aggregates interfere with mitochondrial quality-control mechanisms. Such interaction may create a positive feedback cycle that contributes to neuronal dysfunction and degeneration (Basak and Holzbaur, 2025b) (Tanaka, 2020a).

Mitochondria are especially sensitive to the damage caused by misfolded proteins and the associated cellular stress. Pathological protein accumulation impairs mitochondrial respiration, affects mitochondrial membrane potential, increases the generation of ROS and interferes with mitochondrial dynamics. These changes can either activate or impair mitophagy depending on the degree and duration of mitochondrial stress. Under physiological conditions, mitophagy acts to clear damaged mitochondria, thus limiting the accumulation of dysfunctional organelles that can generate excessive ROS and other stress signals. However, if mitophagy is insufficient or defective, damaged mitochondria remain in neurones and can further exacerbate oxidative and proteostatic stress (Liu et al., 2017).

The ubiquitin–autophagy system provides an important mechanistic link between protein aggregation and mitophagy. p62/SQSTM1 is an autophagy adaptor that recognises ubiquitinated cargo and is involved in aggregate clearance and mitochondrial quality control (Katsuragi et al., 2015). p62 can bind to ubiquitinated proteins and to LC3 to promote the delivery of such proteins to autophagosomes. It may also be involved in Parkin-dependent mitochondrial ubiquitination and mitophagy. Thus, interference with p62-mediated autophagy may influence both clearance of protein aggregates and damaged mitochondria (Johansen and Lamark, 2011).

Alpha-synuclein in Parkinson's disease serves as an important example of the interaction between protein aggregation and mitochondrial quality control. Misfolded and aggregated α -synuclein is a major component of Lewy bodies and has been implicated in mitochondrial dysfunction, oxidative stress and altered mitochondrial dynamics (Pozo Devoto and Falzone, 2017). Experimental evidence suggests that pathological α -synuclein can interfere with mitochondrial homeostasis and autophagic pathways, while defective mitochondrial quality control may create an intracellular environment favouring α -synuclein accumulation and toxicity (Feng et al., 2021) (Shen and Dettmer, 2024). Thus, the relationship between α -synuclein and mitochondrial quality control is complex and may involve reciprocal effects rather than a simple one-way pathway.

Another mechanism connecting defective mitophagy to protein aggregation is mitochondrial oxidative stress. Dysfunctional mitochondria can produce excess ROS that can oxidatively modify cellular proteins and increase their propensity to misfold or aggregate. Mitochondrial dysfunction and oxidative stress have been linked to α -synuclein aggregation in PD, and α -synuclein accumulation might further disrupt mitochondrial function. Similar interactions between mitochondrial dysfunction, oxidative stress and pathological protein accumulation have been described in other neurodegenerative conditions (Tanaka, 2020a) (Feng et al., 2021).

Mitochondrial dysfunction has been implicated in both $\text{A}\beta$ and tau pathology in Alzheimer's. Mitochondrial dysfunction and oxidative stress are associated with the accumulation of $\text{A}\beta$, whereas tau pathology is associated with mitochondrial transport and bioenergetic failure (Reddy and Oliver, 2019b). Mitochondrial

dysfunction and oxidative stress may, in contrast, contribute to abnormal protein processing and aggregation. Mitophagy is only part of this complex network, but the failure to clear damaged mitochondria may exacerbate the cellular stress induced by A β and tau pathology. Thus, defective mitophagy and pathological protein aggregation may constitute a self-sustaining pathological feedback loop. This interaction is especially important in long-lived neurones, where efficient removal of both damaged mitochondria and misfolded proteins is required to maintain cellular homeostasis. However, the exact role of this relationship differs between neurodegenerative diseases and is still a subject of intense research (Long et al., 2026).

4.3 Mitophagy and neuroinflammation

There is growing evidence suggesting that mitophagy acts as a safeguard against the triggering of inflammatory reactions due to the release of mtDNA. Upon the release of mtDNA into the cytoplasm, it may operate as a “danger-associated molecular pattern (DAMP)” capable of initiating inflammatory pathways. Extracellular mtDNA can incite inflammation via the cGAS-STING signalling cascade and/or by the stimulation of the NLRP3 inflammasome (Tong et al., 2022)(Marchi et al., 2022). Significantly, the concentrations of cGAS and STING, as well as the interferon regulatory transcription factor IRF3, are elevated in these tissues(Basit et al., 2020).

In neuroblastoma cells, the absence of PINK1 correlates with elevated mRNA levels for interleukins and chemokines such as IL-6, IL-1a, IL-1b, IL-8, MMP-3, and IFN-b. Patients with Parkinson's disease possessing mutations in the PRKN gene exhibit increased concentrations of IL-6, IL-1b, CCL2, and CCL4 in their serum. The absence of Parkin in Mutator mice, which gather mutations in mitochondrial DNA, results in the buildup of inflammatory substances such as IL-6, IL-13, IFN β 1, IL-12, CCL2, and CCL4 in the bloodstream. Significantly, the absence of STING can reinstate baseline levels and ameliorate both the motor impairments and the depletion of dopaminergic neurones observed in Parkin-mutator mice. These investigations suggest that proficient mitophagy mitigates the neuroinflammatory reactions linked to the release of mitoDNA into the cytosol (Liu et al., 2022)(Vizziello et al., 2021).

4.4 Mitophagy and neuronal apoptosis

Neuronal apoptosis is a key mechanism involved in the progressive loss of neurones in neurodegenerative diseases. Mitochondria are central to the regulation of intrinsic apoptosis because mitochondrial damage can lead to mitochondrial outer membrane permeabilisation, release of pro-apoptotic proteins, initiation of caspases, and ultimately cell death. Mitophagy acts upstream of these events by selectively eliminating damaged mitochondria and limiting the accumulation of mitochondria capable of initiating apoptotic signalling. Thus, balanced mitophagy may in turn be neuroprotective by preserving mitochondrial integrity and preventing inappropriate activation of mitochondrial apoptotic pathways (Basak and Holzbaur, 2025c)(Tanaka, 2020b).

Mitochondrial damage is frequently associated with the loss of mitochondrial membrane potential, excessive ROS production, dysregulated calcium, and impaired ATP generation. If the extent of mitochondrial damage exceeds what the mitochondrial quality-control mechanisms can handle, the mitochondrial outer membrane can become permeable, releasing apoptogenic factors such as cytochrome c into the cytosol. Cytochrome c then participates in apoptosome formation and the activation of caspase-9. Activation of executioner caspases such as caspase-3 then follows, eventually resulting in apoptotic cell death (Bock and Tait, 2020).

Mitophagy can potentially counteract this process by removing damaged mitochondria even before the point of no return. In this context, the PINK1-Parkin pathway is especially important. After mitochondrial damage, PINK1 accumulation and Parkin activation promote ubiquitination and subsequent autophagic clearance of damaged mitochondria. Mitophagy may reduce ROS production and the probability of mitochondrial apoptotic signalling by decreasing the intracellular pool of damaged mitochondria (Youle and Narendra, 2010).

Therefore, the relationship between mitophagy and apoptosis is closely related to the degree and duration of mitochondrial damage. Mild mitochondrial damage can trigger mitophagy as a defensive reaction, enabling the cell to get rid of defective mitochondria and re-establish mitochondrial homeostasis. Conversely, severe or persistent mitochondrial damage can outstrip mitophagic capacity, leading to accumulation of dysfunctional mitochondria, oxidative stress, mitochondrial membrane permeabilisation and activation of apoptotic pathways (Zong et al., 2024a).

Mitochondrial dynamics are also involved in mitophagy-apoptosis crosstalk. Excessive mitochondrial fragmentation may increase the number of damaged mitochondrial fragments and promote apoptotic signalling if mitochondrial quality control is not sufficient. In contrast, proper removal of mitochondria prevents accumulation of dysfunctional mitochondrial fragments. Thus, mitophagy, mitochondrial fission/fusion and apoptosis should be viewed as interconnected elements of mitochondrial homeostasis rather than as separate processes (B. H. Liu et al., 2024).

The PINK1–Parkin system exemplifies an important link between mitochondrial quality control and neuronal survival. PINK1 and Parkin are involved in the removal of damaged mitochondria and disruption of this

pathway has been linked to increased mitochondrial dysfunction and neuronal vulnerability. However, experimental evidence also suggests a more complex relationship between PINK1/Parkin-mediated mitophagy and neuronal survival than a simple linear pathway. It has been shown that spatial and temporal regulation of mitophagy in neurones is different from commonly used immortalised cell models and studies in appropriate neuronal systems are essential (Whitworth and Pallanck, 2017)(Grenier et al., 2013).

Mitophagy may also cross-talk with apoptotic signalling through oxidative stress and inflammatory pathways. Damaged mitochondria release mitochondrial components and ROS that induce cellular stress responses and defective mitophagy may allow these signals to persist. In neurodegenerative diseases, this may establish a cellular environment in which mitochondrial dysfunction, inflammation, and neuronal death support each other. Recent studies in neurones have found links between defective mitochondrial clearance and inflammatory signalling pathways, thus extending the role of mitophagy beyond simple mitochondrial degradation (Basak et al., 2026).

Mitophagy and neuronal apoptosis are two closely linked processes that determine neuronal fate following mitochondrial injury. Effective mitophagy supports mitochondrial quality and neuronal survival. Inadequate mitochondrial clearance may result in the accumulation of damaged mitochondria and promote apoptotic signalling. However, mitophagy should not be considered as a paradigmatic antiapoptotic mechanism since excessive mitochondrial removal may in itself compromise cellular bioenergetics. Therefore, the balance between mitochondrial damage, mitophagy, mitochondrial biogenesis and apoptotic signalling should be kept at an appropriate level for neuronal homeostasis (Basak and Holzbaur, 2025c)(Tanaka, 2020b)(Youle and Narendra, 2010).

5. Therapeutic Modulation of Mitophagy

5.1 Pharmacological modulators

Drugs that act on mitophagy have great potential to improve the treatment of neurodegenerative diseases and ageing. Various compounds such as urolithin A, NAD⁺ precursors and rapamycin have been modulated and improve mitophagy and mitochondrial function.

Mitophagy modulator	Mechanism / molecular target	Experimental model	Major findings relevant to neurodegeneration	Evidence type	Reference
Urolithin A (UA)	Gut microbiota-derived metabolite; promotes mitophagy and mitochondrial quality control, including lysosomal/autophagic pathways	Healthy elderly humans; aged animals	UA was safe and bioavailable in elderly individuals and altered plasma acylcarnitines and skeletal-muscle mitochondrial gene expression, indicating improved mitochondrial/cellular health	Human clinical trial	(Andreux et al., 2019)
Urolithin A (UA)	Stimulates mitophagy and improves lysosomal function	AD transgenic mouse models	Improved learning, memory and olfactory function; reduced A β and tau pathology; enhanced long-term potentiation; restored mitophagy and lysosomal function	Animal study	(Hou et al., 2024)
Rapamycin	mTOR inhibition → enhanced autophagy/mitophagy; increases Parkin-mediated mitochondrial clearance	APP/PS1 mice	Increased Parkin-mediated mitophagy and mitophagosome-lysosome fusion; improved learning, memory and synaptic plasticity; reduced oxidative stress and apoptosis; improved	Animal study	(H. Wang et al., 2021)

			mitochondrial function		
Rapamycin	mTOR inhibition → activation of mitophagy/PINK1–Parkin pathway	5×FAD mice	Enhanced mitophagy, reduced neuronal loss and mitochondrial dysfunction, and improved cognitive function; facilitated clearance of Aβ and damaged mitochondria	Animal study	(Zheng et al., 2024)
Nicotinamide riboside (NR)	NAD ⁺ precursor → increases NAD ⁺ availability; regulates AMPK/SIRT3 and mitochondrial quality-control pathways	POLG-mutant iPSC-derived astrocytes	NR improved defective mitophagy and mitochondrial dysfunction; effects involved PINK1/Parkin and AKT/mTOR/AMPK/ULK1 signaling	Cellular study	(Chen et al., 2021)
Nicotinamide riboside (NR)	NAD ⁺ augmentation → AMPK–SIRT3 signaling; improves mitochondrial metabolism	LPS-stimulated microglia	Reduced inflammatory responses, restored mitochondrial respiration and reduced metabolic dysfunction through AMPK–SIRT3 signaling	Cellular study	(Moon et al., 2025)

5.2 Natural compounds

Dietary Polyphenols: Polyphenols are naturally occurring substances found in fruits, vegetables and other plant-based meals that have been shown to improve mitophagy and protect against mitochondrial dysfunction (Davinelli et al., 2020). Compounds such as resveratrol, quercetin and curcumin have been shown to increase mitophagy, reduce oxidative stress and improve cognitive performance in animal studies. Quercetin is a natural flavonoid with anti-inflammatory and antioxidant activities that markedly lowers microglial inflammation by induction of mitophagy. It inhibits the growth of microglial cells and suppresses the generation of inflammatory substances and the activation of the NF-κB pathway and NLRP3 inflammasome. Quercetin inhibits the activation of the NLRP3 inflammasome by enhancing the clearance of injured mitochondria via mitophagy, hence decreasing mtROS buildup (Stacchiotti and Corsetti, 2020)(Han et al., 2021).

These dietary polyphenols are being studied in animal models for their potential to counteract the effects of ageing and neurodegenerative diseases, but their clinical efficacy in humans is unknown (Grabska-Kobyłecka et al., 2023). These dietary polyphenols are being investigated in animal models for their potential to prevent the effects of ageing and neurodegenerative diseases, but their therapeutic utility in humans remains uncertain. The key issue is bioavailability, as the absorption and metabolism of polyphenols depend on their chemical structure and interactions with gut bacteria. There are little in vivo data and the concentrations used in the in vitro experiments are unlikely to be achieved in humans. There is also a lack of knowledge about synergistic effects with other plant chemicals. But further studies are needed to investigate the safety of high consumption of polyphenols. More clinical trials are needed to assess the therapeutic potential of polyphenols in mitochondrial dysfunction and age-related illnesses (Crozier et al., 2009)(Husain et al., 2022).

5.3 Gene-based approaches

Mitophagy is a promising strategy to directly modify mitophagy to treat neurodegenerative illnesses and minimise ageing-related mitochondrial malfunction. Recent breakthroughs in genetic engineering and delivery methods have paved new paths for tailored therapeutics to improve mitophagy (Yang et al., 2026).

PINK1 and Parkin Gene Therapy: Mutations in the PINK1 and Parkin genes have been associated with faulty mitophagy and impaired mitochondrial function, especially with neurodegenerative illnesses such as PD. Gene

therapy techniques delivering functional copies of these genes have shown promise in restoring mitophagy and enhancing mitochondrial health. Mitochondrial abnormalities were corrected, neuroinflammation ameliorated and motor function improved in PD models following delivery of PINK1 or Parkin genes in animal models (Pickrell and Youle, 2015c)

5.4 Mitochondria-targeted approaches

Mitochondrial Transplantation: This involves the transfer of healthy mitochondria from donor cells to recipient cells with malfunctioning mitochondria. Mitochondrial transplantation has been promising in mending tissue damage in neurological and other illnesses and modulating the regulation of neuroinflammation. Despite promising studies, the mechanisms driving the absorption of mitochondria into neurons are still unknown (Zong et al., 2024b). Mitochondrial malfunction is a hallmark of neurodegenerative illnesses including Parkinson's, Alzheimer's and ALS. This leads to cellular energy deficiencies, and therefore mitochondrial transplantation is a possible therapeutic method to restore cellular function in these conditions (Ore et al., 2024). Mitochondrial transplantation is successful in a number of criteria including the quality of isolated mitochondria, the protocol of delivery and the ability of recipient cells to ingest and integrate these mitochondria. The origin and status of the mitochondria are of paramount relevance since only intact functional mitochondria can restore bioenergetic balance of the recipient cells. The mode of delivery is also critical, and should be able to transport the mitochondria to the target cells in an intact state. Finally, recipient cells must be able to internalise the transplanted mitochondria and integrate them into their endogenous mitochondrial network to gain therapeutic effect (Chang et al., 2019).

Recent research indicates that exogenous mitochondria can be delivered into animal tissue cells for therapeutic purposes through local or intravenous injection. Mitochondrial transfer is a normal mechanism in the brain, whereby damaged mitochondria are transferred from neurones to astrocytes for destruction and recycling. Astrocytes then supply functioning mitochondria for neuronal uptake. This physiological mechanism provides a solid rationale for mitotherapy for neurological illnesses associated with mitochondrial malfunction (Henrich and Scheiblich, 2026). The first investigation to demonstrate the potential for therapy of unmodified mitochondria in AD was carried out in a mouse model produced by intracerebroventricular injection of A β peptide (Wadan et al., 2025). Freshly isolated human mitochondria administered intravascularly from HeLa cells effectively restored cognitive function in AD mice to approaching that of non-AD mice. Neuronal damage and gliosis were greater in the hippocampus of untreated mice compared to treated AD mice. Improved mitochondrial function was associated with increased activity of important enzymes involved in energy metabolism, such as CS of the Krebs cycle and "cytochrome c oxidase (COX)", the fourth complex of the electron transport chain (Weidling and Swerdlow, 2020)(Wadan et al., 2025).

PD is a promising strategy to enhance mitochondrial function via mitotherapy. Several studies have demonstrated that infusion or transplantation of freshly isolated mitochondria significantly improves mitochondrial function (Chang et al., 2019). These studies showed that mitochondrial transplantation enhanced the expression of mitochondrial proteins and precursor metabolites which in turn increased energy production and cellular respiration. When cells are given transplanted mitochondria, studies show that they have less ROS and make more ATP. Moreover, MPTP rat model studies have shown upregulation of ETC activity, restoration of cellular apoptosis and necrosis processes, and reduction of ROS levels following mitochondrial injection. The findings suggest the therapeutic potential of intravenous or intracerebral injection of mitochondria (Shi et al., 2017). Mitochondrial donation has been observed in a wide range of human and animal tissues. This process involves the replacement of dysfunctional mitochondria with healthy ones and is a promising strategy for the treatment of mitochondrial disorders. Mitochondrial donation has been linked to the healing of injured cells, better activity of OXPHOS, greater ATP production, and improved mitochondrial function. Recently, a new notion has been introduced in the transplantation of cellular parts such as mitochondrial organelles to promote healing and functionality of the cell (Gomzikova et al., 2021). Xenogeneic mitochondrial transplantation has been shown to restore mitochondrial respiration in human mitochondrial DNA-deficient cells in vitro (Singh et al., 2026).

But there are hurdles to clear before mitochondrial transplantation can be used in the clinic. This includes: optimisation of yield and purity of mitochondria, protocol development for long-term storage of mitochondria and prevention of transplant rejection. There is a risk of mitochondrial rejection; foreign mitochondria detected by the immune system might be a non-self signal that induces an inflammatory response. One potential way to address this is autologous mitochondrial transplantation where the mitochondria are derived from the patient (McCully et al., 2016). But for people with congenital mitochondrial abnormalities, other options might be needed, such as mitochondria from close maternal relatives or gene-editing methods (D'Amato et al., 2023).

To summarise, mitochondrial transplantation is a novel therapeutic approach for the treatment of diseases caused by mitochondrial dysfunction. However, despite the great progress that has been made in understanding the mechanisms of mitochondrial transfer, further studies are needed to improve the techniques and address the existing challenges. Further advances in this field could lead to the application of mitochondrial transplantation as a potential treatment for many mitochondrial diseases and thus to considerable clinical benefits soon enough.

6. Challenges and Future Perspectives

Although mitophagy is emerging as a possible therapeutic target in neurodegenerative diseases, there are a number of challenges. First, mitophagy is controlled by several PINK1/Parkin-dependent and Parkin-independent pathways, whose contribution varies between neuronal types and disease conditions. Thus, generalised activation of mitophagy might not always be useful, and the proper degree and timing of mitophagy modulation must be determined (Dhar et al., 2024).

A second major challenge is the lack of reliable methods for measuring mitophagy flux in the central nervous system. Alone, changes in levels of PINK1, Parkin, LC3 or p62 do not confirm effective mitochondrial degradation. Therefore, disease-relevant neuronal models, live-cell imaging and validated mitophagy-flux biomarkers are required to improve the translation of experimental findings to clinical studies (Dhar et al., 2024)(Dagda and Rice, 2017).

Most mitophagy modulators that are currently being explored, such as urolithin A, rapamycin, and other autophagy-inducing compounds, have shown benefits primarily in cellular and animal models. For example, rapamycin induced Parkin-mediated mitophagy and ameliorated cognitive and mitochondrial abnormalities in APP/PS1 mice and urolithin A has shown safety and modulation of mitochondrial biomarkers in humans. Nevertheless, evidence for disease-modifying efficacy in patients with neurodegenerative diseases remains limited (Wang et al., 2021).

Therefore, future studies should aim at the development of selective mitophagy modulators, disease-specific delivery systems, and clinically relevant biomarkers. Recent advances in PINK1 activators and USP30 inhibitors are particularly promising, as these approaches target the selective enhancement of mitochondrial quality control and have begun entering early clinical development. Patient-derived neuronal models and combination strategies targeting mitophagy together with oxidative stress, neuroinflammation or mitochondrial biogenesis may further enhance therapeutic efficacy (Antico et al., 2025).

7. Conclusion

Mitophagy is a key mitochondrial quality control process that maintains neuronal energy metabolism and cellular homeostasis. Its dysregulation results in accumulation of damaged mitochondria, oxidative stress, neuroinflammation, protein aggregation and neuronal death in major neurodegenerative diseases (Yang et al., 2023).

The PINK1/Parkin pathway and other alternative receptor-mediated mitophagy pathways are important molecular targets for therapeutic intervention. Preclinical studies with mitophagy modulators such as urolithin A, rapamycin and spermidine have shown promising neuroprotective effects, but their clinical efficacy and long-term safety are yet to be established (Li et al., 2023).

So overall, restoring mitophagy rather than enhancing it may be a better therapeutic strategy." Future studies combining selective mitophagy modulation, reliable biomarkers, disease-specific models and targeted drug delivery may help to facilitate the development of clinically effective therapies for neurodegenerative disease (Dhar et al., 2024).

References

1. Ahmad, M.O., Siddiqui, S.T., 2022. The Internet of Things for Healthcare: Benefits, Applications, Challenges, Use Cases and Future Directions. *Lect. Notes Networks Syst.* 318, 527–537. https://doi.org/10.1007/978-981-16-5689-7_46/SAVE-RESEARCH
2. Andersen, P.M., 2006. Amyotrophic lateral sclerosis associated with mutations in the CuZn superoxide dismutase gene. *Curr. Neurol. Neurosci. Reports* 2006 61 6, 37–46. <https://doi.org/10.1007/S11910-996-0008-9>
3. Andreux, P.A., Blanco-Bose, W., Ryu, D., Burdet, F., Ibberson, M., Aebischer, P., Auwerx, J., Singh, A., Rinsch, C., 2019. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. *Nat. Metab.* 2019 16 1, 595–603.

- <https://doi.org/10.1038/s42255-019-0073-4>
4. Antico, O., Thompson, P., ... N.H.-N. reviews D., 2025, undefined, n.d. Targeting mitophagy in neurodegenerative diseases. *nature.com* Antico, PW Thompson, NT Hertz, MMK Muqit, LE Parton *Nature Rev. Drug Discov.* 2025 • *nature.com*.
 5. Arias-Carrión, O., Guerra-Crespo, M., Soto-Rojas, L.O., Valle, Y., Ortega-Robles, E., Ortuño-Sahagún, D., 2026. Mitochondrial resilience: a convergent framework for pathogenesis and neuroprotection in Parkinson's disease. *Front. Pharmacol.* 17, 1886917. <https://doi.org/10.3389/FPHAR.2026.1886917>
 6. Ashrafi, G., Schwarz, T.L., 2012. The pathways of mitophagy for quality control and clearance of mitochondria. *Cell Death Differ.* 2013 201 20, 31–42. <https://doi.org/10.1038/cdd.2012.81>
 7. Baloyannis, S.J., 2006. Mitochondrial alterations in Alzheimer's disease. *J. Alzheimer's Dis.* 9, 119–126. <https://doi.org/10.3233/JAD-2006-9204;PAGE:STRING:ARTICLE/CHAPTER>
 8. Basak, B., Holzbaur, E.L.F., 2025a. Mitophagy in Neurons: Mechanisms Regulating Mitochondrial Turnover and Neuronal Homeostasis. *J. Mol. Biol.* 437. <https://doi.org/10.1016/J.JMB.2025.169161>
 9. Basak, B., Holzbaur, E.L.F., 2025b. Mitophagy in Neurons: Mechanisms Regulating Mitochondrial Turnover and Neuronal Homeostasis. *J. Mol. Biol.* 437. <https://doi.org/10.1016/j.jmb.2025.169161>
 10. Basak, B., Holzbaur, E.L.F., 2025c. Mitophagy in Neurons: Mechanisms Regulating Mitochondrial Turnover and Neuronal Homeostasis. *J. Mol. Biol.* 437, 169161. <https://doi.org/10.1016/J.JMB.2025.169161>
 11. Basak, B., Riley, J.F., Nataraj, N.M., Holzbaur, E.L., 2026. Mitophagy in neuronal health and disease: from mechanisms to neurodegeneration. *J. Clin. Invest.* 136. <https://doi.org/10.1172/JCI199847>
 12. Basit, A., Cho, M.G., Kim, E.Y., Kwon, D., Kang, S.J., Lee, J.H., 2020. The cGAS/STING/TBK1/IRF3 innate immunity pathway maintains chromosomal stability through regulation of p21 levels. *Exp. Mol. Med.* 2020 524 52, 643–657. <https://doi.org/10.1038/s12276-020-0416-y>
 13. Beckers, J., Van Damme, P., 2025. The role of autophagy in the pathogenesis and treatment of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). *Autophagy Reports* 4. <https://doi.org/10.1080/27694127.2025.2474796>
 14. Bock, F.J., Tait, S.W.G., 2020. Mitochondria as multifaceted regulators of cell death. *Nat. Rev. Mol. Cell Biol.* 21, 85–100. <https://doi.org/10.1038/S41580-019-0173-8>
 15. Bonello, F., Hassoun, S.M., Mouton-Liger, F., Shin, Y.S., Muscat, A., Tesson, C., Lesage, S., Beart, P.M., Brice, A., Krupp, J., Corvol, J.C., Corti, O., 2019. LRRK2 impairs PINK1/Parkin-dependent mitophagy via its kinase activity: pathologic insights into Parkinson's disease. *Hum. Mol. Genet.* 28, 1645–1660. <https://doi.org/10.1093/HMG/DDZ004>
 16. Butterfield, D.A., Halliwell, B., 2019. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat. Rev. Neurosci.* 2019 203 20, 148–160. <https://doi.org/10.1038/s41583-019-0132-6>
 17. Chan, D.C., 2020. Mitochondrial Dynamics and Its Involvement in Disease. *Annu. Rev. Pathol. Mech. Dis.* 15, 235–259. <https://doi.org/10.1146/ANNUREV-PATHMECHDIS-012419-032711/CITE/REFWORKS>
 18. Chang, C.Y., Liang, M.Z., Chen, L., 2019. Current progress of mitochondrial transplantation that promotes neuronal regeneration. *Transl. Neurodegener.* 2019 81 8, 17-. <https://doi.org/10.1186/S40035-019-0158-8>
 19. Chauhan, S., Maan, P., Panghal, A., 2025. TDP-43 Proteinopathies in ALS and FTLD: Mechanistic Insights and Therapeutic Approaches. *CNS Neurol. Disord. - Drug Targets* 24. <https://doi.org/10.2174/0118715273374466250617085832/CITE/REFWORKS>
 20. Chen, A., Kristiansen, C.K., Hong, Y., Kianian, A., Fang, E.F., Sullivan, G.J., Wang, J., Li, X., Bindoff, L.A., Liang, K.X., 2021. Nicotinamide Riboside and Metformin Ameliorate Mitophagy Defect in Induced Pluripotent Stem Cell-Derived Astrocytes With POLG Mutations. *Front. Chen, CK Kristiansen, Y Hong, A Kianian, EF Fang, GJ Sullivan, J Wang, X Li, LA Bind. cell Dev. Biol.* 2021 • *frontiersin.org* 9. <https://doi.org/10.3389/FCELL.2021.737304/FULL>
 21. Chen, J.X., Yan, S.S., 2010. Role of mitochondrial amyloid- β in Alzheimer's disease. *J. Alzheimer's Dis.* 20, 569–578. <https://doi.org/10.3233/JAD-2010-100357;PAGE:STRING:ARTICLE/CHAPTER>
 22. Chin, L.S., Li, L., 2016. Ubiquitin phosphorylation in Parkinson's disease: Implications for pathogenesis and treatment. *Transl. Neurodegener.* 2015 51 5, 1-. <https://doi.org/10.1186/S40035-015-0049-6>
 23. Choubey, V., Zeb, A., Kaasik, A., 2021a. Molecular Mechanisms and Regulation of Mammalian Mitophagy. *Cells* 11. <https://doi.org/10.3390/CELLS11010038>
 24. Choubey, V., Zeb, A., Kaasik, A., 2021b. Molecular Mechanisms and Regulation of Mammalian Mitophagy. *Cells* 2022, Vol. 11, Page 38 11, 38. <https://doi.org/10.3390/CELLS11010038>
 25. Ciechanover, A., Kwon, Y.T., 2015. Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies. *Exp. Mol. Med.* 47, e147–e147.

- <https://doi.org/10.1038/EMM.2014.117>;SUBJMETA
26. Ciurea, A.V., Mohan, A.G., Covache-Busuioc, R.A., Costin, H.P., Glavan, L.A., Corlatescu, A.D., Saceleanu, V.M., 2023. Unraveling Molecular and Genetic Insights into Neurodegenerative Diseases: Advances in Understanding Alzheimer's, Parkinson's, and Huntington's Diseases and Amyotrophic Lateral Sclerosis. *Int. J. Mol. Sci.* 2023, Vol. 24, Page 10809 24, 10809. <https://doi.org/10.3390/IJMS241310809>
 27. Corsetti, V., Florenzano, F., Atlante, A., Bobba, A., Ciotti, M.T., Natale, F., Della Valle, F., Borreca, A., Manca, A., Meli, G., Ferraina, C., Feligioni, M., D'Aguanno, S., Bussani, R., Ammassari-Teule, M., Nicolin, V., Calissano, P., Amadoro, G., 2015. NH2-truncated human tau induces deregulated mitophagy in neurons by aberrant recruitment of Parkin and UCHL-1: implications in Alzheimer's disease. *Hum. Mol. Genet.* 24, 3058–3081. <https://doi.org/10.1093/HMG/DDV059>
 28. Crozier, A., Jaganath, I.B., Clifford, M.N., 2009. Dietary phenolics: chemistry, bioavailability and effects on health. *Nat. Prod. Rep.* 26, 1001–1043. <https://doi.org/10.1039/B802662A>
 29. Cui, H., Kong, Y., Zhang, H., 2012. Oxidative Stress, Mitochondrial Dysfunction, and Aging. *J. Signal Transduct.* 2012, 646354. <https://doi.org/10.1155/2012/646354>
 30. D'Amato, M., Morra, F., Di Meo, I., Tiranti, V., 2023. Mitochondrial Transplantation in Mitochondrial Medicine: Current Challenges and Future Perspectives. *Int. J. Mol. Sci.* 2023, Vol. 24, Page 1969 24, 1969. <https://doi.org/10.3390/IJMS24031969>
 31. D'Arcy, M.S., 2024. Mitophagy in health and disease. Molecular mechanisms, regulatory pathways, and therapeutic implications. *Apoptosis* 2024 299 29, 1415–1428. <https://doi.org/10.1007/S10495-024-01977-Y>
 32. Dagda, R.K., Rice, M., 2017. Protocols for assessing mitophagy in neuronal cell lines and primary neurons. *Neuromethods* 123, 249–277. https://doi.org/10.1007/978-1-4939-6890-9_13/SAVE-RESEARCH
 33. Davinelli, S., De Stefani, D., De Vivo, I., Scapagnini, G., 2020. Polyphenols as Caloric Restriction Mimetics Regulating Mitochondrial Biogenesis and Mitophagy. *Trends Endocrinol. Metab.* 31, 536–550. <https://doi.org/10.1016/j.tem.2020.02.011>
 34. Dhar, K., Townsend, B., ... A.M.-T. in, 2024, undefined, n.d. Enhancing CNS mitophagy: drug development and disease-relevant models. *cell.comKS Dhar, B Townsend, AP Montgomery, JJ Danon, JK Pagan, M KassiouTrends Pharmacol. Sci.* 2024•*cell.com*.
 35. Doblado, L., Lueck, C., Rey, C., Samhan-arias, A.K., Prieto, I., Stacchiotti, A., Monsalve, M., 2021. Mitophagy in Human Diseases. *Int. J. Mol. Sci.* 2021, Vol. 22, Page 3903 22, 3903. <https://doi.org/10.3390/IJMS22083903>
 36. Facecchia, K., Fochesato, L.A., Ray, S.D., Stohs, S.J., Pandey, S., 2011. Oxidative Toxicity in Neurodegenerative Diseases: Role of Mitochondrial Dysfunction and Therapeutic Strategies. *J. Toxicol.* 2011, 683728. <https://doi.org/10.1155/2011/683728>
 37. Fahn, S., 2003. Description of Parkinson's disease as a clinical syndrome. *Ann. N. Y. Acad. Sci.* 991, 1–14. <https://doi.org/10.1111/J.1749-6632.2003.TB07458.X>;ISSUE:ISSUE:DOI
 38. Fang, E.F., Hou, Y., Palikaras, K., Adriaanse, B.A., Kerr, J.S., Yang, B., Lautrup, S., Hasan-Olive, M.M., Caponio, D., Dan, X., Rocktäschel, P., Croteau, D.L., Akbari, M., Greig, N.H., Fladby, T., Nilsen, H., Cader, M.Z., Mattson, M.P., Tavernarakis, N., Bohr, V.A., 2019. Mitophagy inhibits amyloid- β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat. Neurosci.* 2019 223 22, 401–412. <https://doi.org/10.1038/s41593-018-0332-9>
 39. Feng, S.T., Wang, Z.Z., Yuan, Y.H., Sun, H.M., Chen, N.H., Zhang, Y., 2021. Update on the association between alpha-synuclein and tau with mitochondrial dysfunction: Implications for Parkinson's disease. *Eur. J. Neurosci.* 53, 2946–2959. <https://doi.org/10.1111/EJN.14699>
 40. Gallagher, E.R., Holzbaur, E.L.F., 2023. The selective autophagy adaptor p62/SQSTM1 forms phase condensates regulated by HSP27 that facilitate the clearance of damaged lysosomes via lysophagy. *Cell Rep.* 42. <https://doi.org/10.1016/J.CELREP.2023.112037>
 41. Ganguly, U., Carroll, T., Nehrke, K., Johnson, G.V.W., 2024. Mitochondrial Quality Control in Alzheimer's Disease: Insights from *Caenorhabditis elegans* Models. *Antioxidants* 2024, Vol. 13, Page 1343 13, 1343. <https://doi.org/10.3390/ANTIOX13111343>
 42. Gatto, E.M., Rojas, N.G., Persi, G., Etcheverry, J.L., Cesarini, M.E., Perandones, C., 2020. Huntington disease: Advances in the understanding of its mechanisms. *Clin. Park. Relat. Disord.* 3, 100056. <https://doi.org/10.1016/J.PRDOA.2020.100056>
 43. Ghosh, D., Kumar, A., 2024. Harnessing Mitophagy for Therapeutic Advances in Aging and Chronic Neurodegenerative Diseases. *Neuroglia* 2024, Vol. 5, Pages 391-409 5, 391–409. <https://doi.org/10.3390/NEUROGLIA5040026>

44. Gómez-Suaga, P., Bravo-San Pedro, J.M., González-Polo, R.A., Fuentes, J.M., Niso-Santano, M., 2018. ER-mitochondria signaling in Parkinson's disease. *Cell Death Dis.* 2018 93 9, 337-. <https://doi.org/10.1038/s41419-017-0079-3>
45. Gomzikova, M.O., James, V., Rizvanov, A.A., 2021. Mitochondria Donation by Mesenchymal Stem Cells: Current Understanding and Mitochondria Transplantation Strategies. *Front. Cell Dev. Biol.* 9, 653322. <https://doi.org/10.3389/FCELL.2021.653322/TEXT>
46. Grabska-Kobyłeczka, I., Szpakowski, P., Król, A., Książek-Winiarek, D., Kobyłeczki, A., Głabiński, A., Nowak, D., 2023. Polyphenols and Their Impact on the Prevention of Neurodegenerative Diseases and Development. *Nutr.* 2023, Vol. 15, Page 3454 15, 3454. <https://doi.org/10.3390/NU15153454>
47. Grenier, K., McLelland, G.L., Fon, E.A., 2013. Parkin- and PINK1-dependent mitophagy in neurons: Will the real pathway please stand up? *Front. Neurol.* 4 JUL, 52019. <https://doi.org/10.3389/FNEUR.2013.00100/TEXT>
48. Gustafsson, Å.B., Dorn, G.W., 2018. Evolving and Expanding the Roles of Mitophagy as a Homeostatic and Pathogenic Process. <https://doi.org/10.1152/physrev.00005.2018> 99, 853–892. <https://doi.org/10.1152/PHYSREV.00005.2018>
49. Han, X., Xu, T., Fang, Q., Zhang, H., Yue, L., Hu, G., Sun, L., 2021. Quercetin hinders microglial activation to alleviate neurotoxicity via the interplay between NLRP3 inflammasome and mitophagy. *Redox Biol.* 44, 102010. <https://doi.org/10.1016/J.REDOX.2021.102010>
50. Harding, O., Holzer, E., Riley, J.F., Martens, S., Holzbaur, E.L.F., 2023. Damaged mitochondria recruit the effector NEMO to activate NF-κB signaling. *Mol. Cell* 83, 3188-3204.e7. <https://doi.org/10.1016/j.molcel.2023.08.005>
51. Henrich, A., Scheiblich, H., 2026. Mobile Powerhouses: Mitochondria Transfer via Tunnelling Nanotubes in Brain Health and Neurodegenerative Diseases. *Eur. J. Neurosci.* 63, e70463. <https://doi.org/10.1111/EJN.70463>;REQUESTEDJOURNAL:JOURNAL:14609568;WGROU:STRING:PUBLICATION
52. Heo, J.M., Ordureau, A., Paulo, J.A., Rinehart, J., Harper, J.W., 2015. The PINK1-PARKIN Mitochondrial Ubiquitylation Pathway Drives a Program of OPTN/NDP52 Recruitment and TBK1 Activation to Promote Mitophagy. *Mol. Cell* 60, 7–20. <https://doi.org/10.1016/J.MOLCEL.2015.08.016>
53. Hou, Y., Chu, X., Park, J.H., Zhu, Q., Hussain, M., Li, Z., Madsen, H.B., Yang, B., Wei, Y., Wang, Y., Fang, E.F., Croteau, D.L., Bohr, V.A., 2024. Urolithin A improves Alzheimer's disease cognition and restores mitophagy and lysosomal functions. *Alzheimer's Dement.* 20, 4212–4233. <https://doi.org/10.1002/ALZ.13847>;WEBSITE:WEBSITE:ALZ-JOURNALS;WGROU:STRING:PUBLICATION
54. Hu, Y., Li, X.C., Wang, Z.H., Luo, Y., Zhang, X., Liu, X.P., Feng, Q., Wang, Q., Yue, Z., Chen, Z., Ye, K., Wang, J.Z., Liu, G.P., 2016. Tau accumulation impairs mitophagy via increasing mitochondrial membrane potential and reducing mitochondrial Parkin. *Oncotarget* 7, 17356. <https://doi.org/10.18632/ONCOTARGET.7861>
55. Huang, J., Pham, V.T., Fu, S., Huang, G., Liu, Y.G., Zheng, L., 2025. Mitophagy's impacts on cancer and neurodegenerative diseases: implications for future therapies. *J. Hematol. Oncol.* 2025 181 18, 78-. <https://doi.org/10.1186/S13045-025-01727-W>
56. Husain, A., Alouffi, S., Khanam, A., ... R.A.-I.J. of, 2022, undefined, n.d. Therapeutic efficacy of natural product 'C-phycoerythrin' in alleviating streptozotocin-induced diabetes via the inhibition of glycation reaction in rats. *mdpi.com* A Husain, S Alouffi, A Khanam, R Akasha, A Farooqui, S Ahmad International J. Mol. Sci. 2022•mdpi.com.
57. Hwang, S., Disatnik, M., Mochly-Rosen, D., 2015. Impaired GAPDH-induced mitophagy contributes to the pathology of Huntington's disease. *EMBO Mol. Med.* 7, 1307–1326. <https://doi.org/10.15252/EMMM.201505256/FIGURES/7>
58. Islam, M.T., 2017. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. *Neurol. Res.* 39, 73–82. <https://doi.org/10.1080/01616412.2016.1251711>
59. Jellinger, K.A., 2010. Basic mechanisms of neurodegeneration: A critical update. *J. Cell. Mol. Med.* 14, 457–487. <https://doi.org/10.1111/J.1582-4934.2010.01010.X>;PAGE:STRING:ARTICLE/CHAPTER
60. Johansen, T., Lamark, T., 2011. Selective autophagy mediated by autophagic adapter proteins. *Autophagy* 7, 279–296. <https://doi.org/10.4161/AUTO.7.3.14487>
61. Katsuragi, Y., Ichimura, Y., Komatsu, M., 2015. P62/SQSTM1 functions as a signaling hub and an autophagy adaptor. *FEBS J.* 282, 4672–4678. <https://doi.org/10.1111/FEBS.13540>;WEBSITE:WEBSITE:FEBS;PAGE:STRING:ARTICLE/CHAPTER
62. Khalil, B., El Fissi, N., Aouane, A., Cabirol-Pol, M.J., Rival, T., Liévens, J.C., 2015. PINK1-induced mitophagy promotes neuroprotection in Huntington's disease. *Cell Death Dis.* 2015 61 6, e1617–e1617.

- <https://doi.org/10.1038/cddis.2014.581>
63. Koyano, F., Okatsu, K., Kosako, H., Tamura, Y., Go, E., Kimura, M., Kimura, Y., Tsuchiya, H., Yoshihara, H., Hirokawa, T., Endo, T., Fon, E.A., Trempe, J.F., Saeki, Y., Tanaka, K., Matsuda, N., 2014. Ubiquitin is phosphorylated by PINK1 to activate parkin. *Nature* 510, 162–166. <https://doi.org/10.1038/NATURE13392>
 64. Kumari, S., Singh, H., Vaidya, S., Taliyan, R., 2026. Targeting Sirtuin Signaling in Parkinson's Disease and Neurodegeneration: Molecular Insights and Translational Potential. *Mol. Neurobiol.* 2026 631 63, 775-. <https://doi.org/10.1007/S12035-026-06062-W>
 65. Lazarou, M., Sliter, D.A., Kane, L.A., Sarraf, S.A., Wang, C., Burman, J.L., Sideris, D.P., Fogel, A.I., Youle, R.J., 2015. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature* 524, 309–314. <https://doi.org/10.1038/NATURE14893>
 66. Li, J., Wuliji, O., Li, W., Jiang, Z.G., Ghanbari, H.A., 2013. Oxidative Stress and Neurodegenerative Disorders. *Int. J. Mol. Sci.* 2013, Vol. 14, Pages 24438-24475 14, 24438–24475. <https://doi.org/10.3390/IJMS141224438>
 67. Li, J., Yang, D., Li, Z., Zhao, M., Wang, D., Sun, Z., ... P.W.-A. research, 2023, undefined, n.d. PINK1/Parkin-mediated mitophagy in neurodegenerative diseases. ElsevierJ Li, D Yang, Z Li, M Zhao, D Wang, Z Sun, P Wen, Y Dai, F Gou, Y Ji, D Zhao, L YangAgeing Res. Rev. 2023•Elsevier.
 68. Lin, M. miao, Liu, N., Qin, Z. hong, Wang, Y., 2022. Mitochondrial-derived damage-associated molecular patterns amplify neuroinflammation in neurodegenerative diseases. *Acta Pharmacol. Sin.* 2022 4310 43, 2439–2447. <https://doi.org/10.1038/s41401-022-00879-6>
 69. Liu, B.H., Xu, C.Z., Liu, Y., Lu, Z.L., Fu, T.L., Li, G.R., Deng, Y., Luo, G.Q., Ding, S., Li, N., Geng, Q., 2024. Mitochondrial quality control in human health and disease. *Mil. Med. Res.* 2024 111 11, 32-. <https://doi.org/10.1186/S40779-024-00536-5>
 70. Liu, D., Pitta, M., Jiang, H., Lee, J.H., Zhang, G., Chen, X., Kawamoto, E.M., Mattson, M.P., 2013. Nicotinamide forestalls pathology and cognitive decline in Alzheimer mice: evidence for improved neuronal bioenergetics and autophagy procession. *Neurobiol. Aging* 34, 1564–1580. <https://doi.org/10.1016/J.NEUROBIOLAGING.2012.11.020>
 71. Liu, E., Zhang, Y., Wang, J.Z., 2024. Updates in Alzheimer's disease: from basic research to diagnosis and therapies. *Transl. Neurodegener.* 2024 131 13, 45-. <https://doi.org/10.1186/S40035-024-00432-X>
 72. Liu, H., Dai, C., Fan, Y., Guo, B., Ren, K., Sun, T., Wang, W., 2017. From autophagy to mitophagy: the roles of P62 in neurodegenerative diseases. *J. Bioenerg. Biomembr.* 49, 413–422. <https://doi.org/10.1007/S10863-017-9727-7>
 73. Liu, L., Feng, D., Chen, G., Chen, M., Zheng, Q., Song, P., Ma, Q., Zhu, C., Wang, R., Qi, W., Huang, L., Xue, P., Li, B., Wang, X., Jin, H., Wang, J., Yang, F., Liu, P., Zhu, Y., Sui, S., Chen, Q., 2012. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. *Nat. Cell Biol.* 14, 177–185. <https://doi.org/10.1038/NCB2422>
 74. Liu, T.W., Chen, C.M., Chang, K.H., 2022. Biomarker of Neuroinflammation in Parkinson's Disease. *Int. J. Mol. Sci.* 2022, Vol. 23, Page 4148 23, 4148. <https://doi.org/10.3390/IJMS23084148>
 75. Long, W., Yuan, M., Wang, S., Tan, X., Gao, L.C., 2026. The mitophagy-inflammasome axis: a shared pathological hub in Alzheimer's and Parkinson's diseases. *Transl. Neurodegener.* 2026 151 15, 38-. <https://doi.org/10.1186/S40035-026-00578-W>
 76. Lu, Y., Li, Z., Zhang, S., Zhang, T., Liu, Y., Zhang, L., 2023. Cellular mitophagy: Mechanism, roles in diseases and small molecule pharmacological regulation. *Theranostics* 13, 736. <https://doi.org/10.7150/THNO.79876>
 77. Lyu, Y., Meng, Z., Hu, Y., Jiang, B., Yang, J., Chen, Y., Zhou, J., Li, M., Wang, H., 2024. Mechanisms of mitophagy and oxidative stress in cerebral ischemia–reperfusion, vascular dementia, and Alzheimer's disease. *Front. Mol. Neurosci.* 17, 1394932. <https://doi.org/10.3389/FNMOL.2024.1394932/FULL>
 78. Malpartida, A.B., Williamson, M., Narendra, D.P., Wade-Martins, R., Ryan, B.J., 2021. Mitochondrial Dysfunction and Mitophagy in Parkinson's Disease: From Mechanism to Therapy. *Trends Biochem. Sci.* 46, 329–343. <https://doi.org/10.1016/j.tibs.2020.11.007>
 79. Marchi, S., Guilbaud, E., Tait, S.W.G., Yamazaki, T., Galluzzi, L., 2022. Mitochondrial control of inflammation. *Nat. Rev. Immunol.* 2022 233 23, 159–173. <https://doi.org/10.1038/s41577-022-00760-x>
 80. Mary, A., Eysert, F., Checler, F., Chami, M., 2023. Mitophagy in Alzheimer's disease: Molecular defects and therapeutic approaches. *Mol. Psychiatry* 28, 202–216. <https://doi.org/10.1038/S41380-022-01631-6;TECHMETA>
 81. McCully, J.D., Levitsky, S., Nido, P.J. del, Cowan, D.B., 2016. Mitochondrial transplantation for therapeutic use. *Clin. Transl. Med.* 5, e16. <https://doi.org/10.1186/S40169-016-0095-4>

82. McKenzie, M., Liolitsa, D., Hanna, M.G., 2004. Mitochondrial Disease: Mutations and Mechanisms. *Neurochem. Res.* 29, 589–600. <https://doi.org/10.1023/B:NERE.0000014829.42364.DD/METRICS>
83. Misrani, A., Tabassum, S., Yang, L., 2021. Mitochondrial Dysfunction and Oxidative Stress in Alzheimer's Disease. *Front. Aging Neurosci.* 13, 617588. <https://doi.org/10.3389/FNAGI.2021.617588/FULL>
84. Moon, C.Y., Park, J., Shin, E.J., Kang, H., 2025. Nicotinamide riboside abrogates lipopolysaccharide-induced inflammation and mitochondrial dysfunction in microglia through the AMP-activated protein kinase-sirtuin. *ElsevierCY Moon, J Park. EJ Shin, H KangFood Biosci.* 2025•Elsevier 63. <https://doi.org/10.1016/J.FBIO.2024.105799>
85. Moore, A.S., Holzbaur, E.L.F., 2016. Dynamic recruitment and activation of ALS-associated TBK1 with its target optineurin are required for efficient mitophagy. *Proc. Natl. Acad. Sci.* 113, E3349–E3358. <https://doi.org/10.1073/PNAS.1523810113>
86. Müller, L., Di Benedetto, S., Müller, V., 2025. The dual nature of neuroinflammation in networked brain. *Front. Immunol.* 16, 1659947. <https://doi.org/10.3389/FIMMU.2025.1659947/FULL>
87. Narendra, D., Tanaka, A., Suen, D.F., Youle, R.J., 2008. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J. Cell Biol.* 183, 795–803. <https://doi.org/10.1083/JCB.200809125>
88. Novak, I., 2012. Mitophagy: A complex mechanism of mitochondrial removal. *Antioxidants Redox Signal.* 17, 794–802. <https://doi.org/10.1089/ARS.2011.4407;JOURNAL:JOURNAL:AREA;WGROU:STRING:PUBLICATION>
89. Ore, A., Angelastro, J.M., Giulivi, C., 2024. Integrating Mitochondrial Biology into Innovative Cell Therapies for Neurodegenerative Diseases. *Brain Sci.* 2024, Vol. 14, Page 899 14, 899. <https://doi.org/10.3390/BRAINSCI14090899>
90. Palomo, G.M., Granatiero, V., Kawamata, H., Konrad, C., Kim, M., Arreguin, A.J., Zhao, D., Milner, T.A., Manfredi, G., 2018. Parkin is a disease modifier in the mutant SOD1 mouse model of ALS. *EMBO Mol. Med.* 10, EMM201808888-. <https://doi.org/10.15252/EMMM.201808888/FIGURES/13>
91. Picca, A., Faltg, J., Auwerx, J., Ferrucci, L., D'Amico, D., 2023. Mitophagy in human health, ageing and disease. *Nat. Metab.* 2023 512 5, 2047–2061. <https://doi.org/10.1038/s42255-023-00930-8>
92. Pickles, S., Vigié, P., Youle, R.J., 2018. Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. *Curr. Biol.* 28, R170–R185. <https://doi.org/10.1016/J.CUB.2018.01.004>
93. Pickrell, A.M., Youle, R.J., 2015a. The roles of PINK1, Parkin, and mitochondrial fidelity in parkinson's disease. *Neuron* 85, 257–273. <https://doi.org/10.1016/j.neuron.2014.12.007>
94. Pickrell, A.M., Youle, R.J., 2015b. The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron* 85, 257–273. <https://doi.org/10.1016/J.NEURON.2014.12.007>
95. Pickrell, A.M., Youle, R.J., 2015c. The roles of PINK1, Parkin, and mitochondrial fidelity in parkinson's disease. *Neuron* 85, 257–273. <https://doi.org/10.1016/j.neuron.2014.12.007>
96. Pozo Devoto, V.M., Falzone, T.L., 2017. Mitochondrial dynamics in Parkinson's disease: a role for α -synuclein? *Dis. Model. Mech.* 10, 1075–1087. <https://doi.org/10.1242/DMM.026294>
97. Qiu, Y., Wang, Jincheng, Li, H., Yang, B., Wang, Jiajia, He, Q., Weng, Q., 2022. Emerging views of OPTN (optineurin) function in the autophagic process associated with disease. *Autophagy* 18, 73–85. <https://doi.org/10.1080/15548627.2021.1908722>
98. Ramesh, N., Pandey, U.B., 2017. Autophagy dysregulation in ALS: When protein aggregates get out of hand. *Front. Mol. Neurosci.* 10, 285028. <https://doi.org/10.3389/FNMOL.2017.00263/FULL>
99. Reddy, P.H., Oliver, D.M.A., 2019a. Amyloid Beta and Phosphorylated Tau-Induced Defective Autophagy and Mitophagy in Alzheimer's Disease. *Cells* 2019, Vol. 8, Page 488 8, 488. <https://doi.org/10.3390/CELLS8050488>
100. Reddy, P.H., Oliver, D.M.A., 2019b. Amyloid Beta and Phosphorylated Tau-Induced Defective Autophagy and Mitophagy in Alzheimer's Disease. *Cells* 2019, Vol. 8, Page 488 8, 488. <https://doi.org/10.3390/CELLS8050488>
101. Rodríguez, M., Mahy, N., 2017. Neuron-Microglia Interactions in Motor Neuron Degeneration. The Inflammatory Hypothesis in Amyotrophic Lateral Sclerosis Revisited. *Curr. Med. Chem.* 23, 4753–4772. <https://doi.org/10.2174/0929867324666161123091314/CITE/REFWORKS>
102. Rogers, R.S., Tungtur, S., Tanaka, T., Nadeau, L.L., Badawi, Y., Wang, H., Ni, H.M., Ding, W.X., Nishimune, H., 2017. Impaired mitophagy plays a role in denervation of neuromuscular junctions in ALS mice. *Front. Neurosci.* 11, 271352. <https://doi.org/10.3389/FNINS.2017.00473/TEXT>
103. Roßner, S., Schilling, S., Hutter-Paier, B., Checler, F., Alves Da Costa, C., 2022. Parkin as a Molecular Bridge Linking Alzheimer's and Parkinson's Diseases? *Biomol.* 2022, Vol. 12, Page 559 12, 559. <https://doi.org/10.3390/BIOM12040559>

104. Roy, R.G., Mandal, P.K., Maroon, J.C., 2023. Oxidative Stress Occurs Prior to Amyloid A β Plaque Formation and Tau Phosphorylation in Alzheimer's Disease: Role of Glutathione and Metal Ions. *ACS Chem. Neurosci.* 14, 2944. <https://doi.org/10.1021/ACSCHEMNEURO.3C00486>
105. Sawant, N., Morton, H., Kshirsagar, S., Reddy, A.P., Reddy, P.H., 2021. Mitochondrial Abnormalities and Synaptic Damage in Huntington's Disease: a Focus on Defective Mitophagy and Mitochondria-Targeted Therapeutics. *Mol. Neurobiol.* 2021 5812 58, 6350–6377. <https://doi.org/10.1007/S12035-021-02556-X>
106. Scarian, E., Fiamingo, G., Diamanti, L., Palmieri, I., Gagliardi, S., Pansarasa, O., 2022. The Role of VCP Mutations in the Spectrum of Amyotrophic Lateral Sclerosis—Frontotemporal Dementia. *Front. Neurol.* 13, 841394. <https://doi.org/10.3389/FNEUR.2022.841394/FULL>
107. Sever, T., Erbaş, O., 2024. The Role of the PINK1-Parkin Pathway in Mitophagy and Its Implications in Neurodegenerative Disorders. *J. Exp. Basic Med. Sci.* 5, 264–270. <https://doi.org/10.5606/JEBMS.2024.1103>
108. Shen, L., Dettmer, U., 2024. Alpha-Synuclein Effects on Mitochondrial Quality Control in Parkinson's Disease. *Biomolecules* 14. <https://doi.org/10.3390/BIOM14121649>
109. Shi, X., Zhao, M., Fu, C., Fu, A., 2017. Intravenous administration of mitochondria for treating experimental Parkinson's disease. *Mitochondrion* 34, 91–100. <https://doi.org/10.1016/J.MITO.2017.02.005>
110. Shirendeb, U.P., Calkins, M.J., Manczak, M., Anekonda, V., Dufour, B., McBride, J.L., Mao, P., Reddy, P.H., 2012. Mutant huntingtin's interaction with mitochondrial protein Drp1 impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in Huntington's disease. *Hum. Mol. Genet.* 21, 406–420. <https://doi.org/10.1093/HMG/DDR475>
111. Singh, A., Kukreti, R., Saso, L., Kukreti, S., 2019. Oxidative Stress: A Key Modulator in Neurodegenerative Diseases. *Mol.* 2019, Vol. 24, Page 1583 24, 1583. <https://doi.org/10.3390/MOLECULES24081583>
112. Singh, P., Tahavvori, A., Kuschner, C.E., Espin, B.B., Kazmi, J., Ramos, S. V., Yin, T., Hayashida, K., Ito-Hagiwara, K., Endo, Y., Yoshioka, K., Hagiwara, J., Sohi, A., Oropallo, A., Haddad, G., Li, T., Becker, L.B., Kim, J., 2026. Mitochondrial Transplantation as a Therapeutic Strategy for Inherited Mitochondrial Diseases. *Adv. Sci.* 13, e23368. <https://doi.org/10.1002/ADVS.202523368>;REQUESTEDJOURNAL:JOURNAL:21983844;WGROU:STRING: PUBLICATION
113. Springer, M.Z., Macleod, K.F., 2016. In Brief: Mitophagy: mechanisms and role in human disease. *J. Pathol.* 240, 253–255. <https://doi.org/10.1002/PATH.4774>
114. Stacchiotti, A., Corsetti, G., 2020. Natural Compounds and Autophagy: Allies Against Neurodegeneration. *Front. Cell Dev. Biol.* 8, 555409. <https://doi.org/10.3389/FCELL.2020.555409/FULL>
115. Stojanovic, B., Jovanovic, I., Dimitrijevic Stojanovic, M., Stojanovic, B.S., Kovacevic, V., Radosavljevic, I., Jovanovic, D., Miletic Kovacevic, M., Zornic, N., Arsic, A.A., Eric, S., Mirkovic, N., Nesic, J., Jakovljevic, S., Lazarevic, S., Milivojcevic Bevc, I., Milosevic, B., 2025. Oxidative Stress-Driven Cellular Senescence: Mechanistic Crosstalk and Therapeutic Horizons. *Antioxidants* 2025, Vol. 14, Page 987 14, 987. <https://doi.org/10.3390/ANTIOX14080987>
116. Tanaka, K., 2020a. The PINK1–Parkin axis: An Overview. *Neurosci. Res.* 159, 9–15. <https://doi.org/10.1016/j.neures.2020.01.006>
117. Tanaka, K., 2020b. The PINK1–Parkin axis: An Overview. *Neurosci. Res.* 159, 9–15. <https://doi.org/10.1016/J.NEURES.2020.01.006>
118. Tang, M., Outissint, I., Chen, Y., Gong, X., 2025. Comprehensive Insights Into Mitophagy: Mechanisms, Disease Associations, and Therapeutic Implications. *J. Cell. Biochem.* 126, e70056. <https://doi.org/10.1002/JCB.70056>
119. Tong, Y., Zhang, Z., Wang, S., 2022. Role of Mitochondria in Retinal Pigment Epithelial Aging and Degeneration. *Front. Aging* 3, 926627. <https://doi.org/10.3389/FRAGI.2022.926627/FULL>
120. Trinh, J., Farrer, M., 2013. Advances in the genetics of Parkinson disease. *Nat. Rev. Neurol.* 9, 445–454. <https://doi.org/10.1038/NRNEUROL.2013.132>
121. Truban, D., Hou, X., Caulfield, T.R., Fiesel, F.C., Springer, W., 2017. PINK1, Parkin, and Mitochondrial Quality Control: What can we Learn about Parkinson's Disease Pathobiology? *J. Parkinsons. Dis.* 7, 13–29. <https://doi.org/10.3233/JPD-160989>;WEBSITE:WEBSITE:SAGE;ISSUE:ISSUE:DOI
122. Truong, T.T., Singh, A.A., Bang, N. Van, Vu, N.M.H., Na, S., Choi, J., Oh, J., Mondal, S., 2025. Mitochondria-Associated Membrane Dysfunction in Neurodegeneration and Its Effects on Lipid Metabolism, Calcium Signaling, and Cell Fate. *Membr.* 2025, Vol. 15, Page 263 15, 263. <https://doi.org/10.3390/MEMBRANES15090263>
123. Uoselis, L., Nguyen, T.N., Lazarou, M., 2023. Mitochondrial degradation: Mitophagy and beyond. *Mol.*

- Cell 83, 3404–3420. <https://doi.org/10.1016/J.MOLCEL.2023.08.021>
124. Verma, M., Shukla, S., Shrivastava, S., Puranik, N., 2025. Neurodegenerative Disorder: An Overview. *Proteostasis Investig. Mol. Dyn. Neurodegener. Disord.* 1–37. https://doi.org/10.1007/978-981-96-6202-9_1/SAVE-RESEARCH
 125. Vizziello, M., Borellini, L., Franco, G., Ardolino, G., 2021. Disruption of Mitochondrial Homeostasis: The Role of PINK1 in Parkinson’s Disease. *Cells* 2021, Vol. 10, Page 3022 10, 3022. <https://doi.org/10.3390/CELLS10113022>
 126. Wadan, A.H.S., Shaaban, A.H., El-Sadek, M.Z., Mostafa, S.A., Moshref, A.S., El-Hussein, A., Ellakwa, D.E.S., Mehanny, S.S., 2025. Mitochondrial-based therapies for neurodegenerative diseases: a review of the current literature. *Naunyn-Schmiedeberg’s Arch. Pharmacol.* 2025 3989 398, 11357–11386. <https://doi.org/10.1007/S00210-025-04014-0>
 127. Wang, H., Fu, J., Xu, X., ... Z.Y.-T.J. of, 2021, undefined, n.d. Rapamycin activates mitophagy and alleviates cognitive and synaptic plasticity deficits in a mouse model of Alzheimer’s disease. *Acad. Wang, J Fu, X Xu, Z Yang, T ZhangThe Journals Gerontol. Ser. A*, 2021•academic.oup.com.
 128. Wang, H., Fu, J., Xu, X., Yang, Z., Zhang, T., 2021. Rapamycin activates mitophagy and alleviates cognitive and synaptic plasticity deficits in a mouse model of Alzheimer’s disease. *Acad. Wang, J Fu, X Xu, Z Yang, T ZhangThe Journals Gerontol. Ser. A*, 2021•academic.oup.com 76, 1707–1713. <https://doi.org/10.1093/GERONA/GLAB142>
 129. Wang, X. Le, Feng, S.T., Wang, Y.T., Yuan, Y.H., Li, Z.P., Chen, N.H., Wang, Z.Z., Zhang, Y., 2021. Mitophagy, a Form of Selective Autophagy, Plays an Essential Role in Mitochondrial Dynamics of Parkinson’s Disease. *Cell. Mol. Neurobiol.* 2021 425 42, 1321–1339. <https://doi.org/10.1007/S10571-021-01039-W>
 130. Wang, Q., Sun, Y., Li, T.Y., Auwerx, J., 2026. Mitophagy in the pathogenesis and management of disease. *Cell Res.* 2026 361 36, 11–37. <https://doi.org/10.1038/s41422-025-01203-7>
 131. Wang, S., Long, H., Hou, L., Feng, B., Ma, Z., Wu, Y., Zeng, Y., Cai, J., Zhang, D. wei, Zhao, G., 2023. The mitophagy pathway and its implications in human diseases. *Signal Transduct. Target. Ther.* 8, 304-. <https://doi.org/10.1038/S41392-023-01503-7;SUBJMETA>
 132. Wang, S., Tan, J., Miao, Y., Zhang, Q., 2022. Mitochondrial Dynamics, Mitophagy, and Mitochondria–Endoplasmic Reticulum Contact Sites Crosstalk Under Hypoxia. *Front. Cell Dev. Biol.* 10, 848214. <https://doi.org/10.3389/FCELL.2022.848214/FULL>
 133. Wang, W., Zhao, F., Ma, X., Perry, G., Zhu, X., 2020. Mitochondria dysfunction in the pathogenesis of Alzheimer’s disease: recent advances. *Mol. Neurodegener.* 2020 151 15, 30-. <https://doi.org/10.1186/S13024-020-00376-6>
 134. Wauters, F., Cornelissen, T., Imberechts, D., Martin, S., Koentjoro, B., Sue, C., Vangheluwe, P., Vandenberghe, W., 2020. LRRK2 mutations impair depolarization-induced mitophagy through inhibition of mitochondrial accumulation of RAB10. *Autophagy* 16, 203–222. <https://doi.org/10.1080/15548627.2019.1603548>
 135. Weidling, I.W., Swerdlow, R.H., 2020. Mitochondria in Alzheimer’s disease and their potential role in Alzheimer’s proteostasis. *Exp. Neurol.* 330, 113321. <https://doi.org/10.1016/J.EXPNEUROL.2020.113321>
 136. Whitworth, A.J., Pallanck, L.J., 2017. PINK1/Parkin mitophagy and neurodegeneration—what do we really know in vivo? *Curr. Opin. Genet. Dev.* 44, 47–53. <https://doi.org/10.1016/J.GDE.2017.01.016>
 137. Yang, H.M., 2025. Mitochondrial Dysfunction in Neurodegenerative Diseases. *Cells* 14, 276. <https://doi.org/10.3390/CELLS14040276>
 138. Yang, J., Li, J., Hou, X., Zheng, Y., Zhao, Z., Zhou, T., Jing, T., Kong, J., Zhang, G., Guo, Y., 2026. Targeting mitophagy for neuroprotection: mechanisms and therapeutic opportunities. *npj Aging* 2026 121 12, 122-. <https://doi.org/10.1038/s41514-026-00424-3>
 139. Yang, K., Yan, Y., Yu, A., Zhang, R., ... Y.Z.-N., 2023, undefined, n.d. Mitophagy in neurodegenerative disease pathogenesis. *pmc.ncbi.nlm.nih.gov* Yang, Y Yan, A Yu, R Zhang, Y Zhang, Z Qiu, Z Li, Q Zhang, S Wu, F LiNeural Regen. Res. 2023•pmc.ncbi.nlm.nih.gov.
 140. Ye, X., Sun, X., Starovoytov, V., Cai, Q., 2015. Parkin-mediated mitophagy in mutant hAPP neurons and Alzheimer’s disease patient brains. *Hum. Mol. Genet.* 24, 2938–2951. <https://doi.org/10.1093/HMG/DDV056>
 141. Youle, R.J., Narendra, D.P., 2011. Mechanisms of mitophagy. *Nat. Rev. Mol. Cell Biol.* 12, 9–14. <https://doi.org/10.1038/NRM3028>
 142. Youle, R.J., Narendra, D.P., 2010. Mechanisms of mitophagy. *Nat. Rev. Mol. Cell Biol.* 2011 121 12, 9–14. <https://doi.org/10.1038/nrm3028>
 143. Youle, R.J., Van Der Bliek, A.M., 2012. Mitochondrial fission, fusion, and stress. *Science* 337, 1062–1065.

- <https://doi.org/10.1126/SCIENCE.1219855>
144. Zhang, P.L., Chen, Y., Zhang, C.H., Wang, Y.X., Fernandez-Funez, P., 2018. Genetics of Parkinson's disease and related disorders. *J. Med. Genet.* 55, 73–80. <https://doi.org/10.1136/JMEDGENET-2017-105047>
145. Zhang, W., 2021. The mitophagy receptor FUN14 domain-containing 1 (FUNDC1): A promising biomarker and potential therapeutic target of human diseases. *Genes Dis.* 8, 640–654. <https://doi.org/10.1016/J.GENDIS.2020.08.011>
146. Zhang, Z., Liu, L., Jiang, X., Zhai, S., Xing, D., 2016. The Essential Role of Drp1 and Its Regulation by S-Nitrosylation of Parkin in Dopaminergic Neurodegeneration: Implications for Parkinson's Disease. *Antioxidants Redox Signal.* 25, 609–622. <https://doi.org/10.1089/ARS.2016.6634>;JOURNAL:JOURNAL:AREA;WGROU:STRING:PUBLICATION
147. Zheng, W., Li, K., Zhong, M., Wu, K., Zhou, L., Huang, J., Liu, L., Chen, Z., 2024. Mitophagy activation by rapamycin enhances mitochondrial function and cognition in 5× FAD mice. *ElsevierW Zheng, K Li, M Zhong, K Wu, L Zhou, J Huang, L Liu, Z ChenBehavioural Brain Res.* 2024•Elsevier 463. <https://doi.org/10.1016/J.BBR.2024.114889>
148. Zong, Y., Li, H., Liao, P., Chen, L., Pan, Y., Zheng, Y., Zhang, C., Liu, D., Zheng, M., Gao, J., 2024a. Mitochondrial dysfunction: mechanisms and advances in therapy. *Signal Transduct. Target. Ther.* 2024 91 9, 124-. <https://doi.org/10.1038/s41392-024-01839-8>
149. Zong, Y., Li, H., Liao, P., Chen, L., Pan, Y., Zheng, Y., Zhang, C., Liu, D., Zheng, M., Gao, J., 2024b. Mitochondrial dysfunction: mechanisms and advances in therapy. *Signal Transduct. Target. Ther.* 2024 91 9, 124-. <https://doi.org/10.1038/s41392-024-01839-8>
150. Zorov, D.B., Juhaszova, M., Sollott, S.J., 2014. Mitochondrial Reactive Oxygen Species (ROS) and ROS-Induced ROS Release. <https://doi.org/10.1152/physrev.00026.2013> 94, 909–950. <https://doi.org/10.1152/PHYSREV.00026.2013>