PINK1-regulated mitophagy dysfunction in the pathogenesis of Parkinson's disease (Review)

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Abstract. Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by the progressive loss of dopaminergic neurons in the substantia nigra and the accumulation of misfolded α-synuclein forming Lewy bodies. Emerging evidence highlights mitochondrial dysfunction as an important and early event in PD pathogenesis. Among the key regulators of mitochondrial quality control, PTEN-induced kinase 1 (PINK1) plays a pivotal role by initiating mitophagy, the selective clearance of damaged mitochondria. Under physiological conditions, PINK1 is rapidly degraded, whereas mitochondrial depolarization stabilizes PINK1 on the outer mitochondrial membrane, where it recruits and activates Parkin, an E3 ubiquitin ligase, to promote mitophagy. Loss-of-function mutations in PINK1 also disrupt this process, leading to the accumulation of dysfunctional mitochondria, oxidative stress, abnormal calcium homeostasis and neuronal apoptosis. Furthermore, PINK1 deficiency has been shown to exacerbate α-synuclein aggregation, impair synaptic transmission and activate neuroinflammatory pathways, collectively accelerating dopaminergic neurodegeneration. Therapeutic strategies aimed at restoring or enhancing PINK1-mediated mitophagy through pharmacological activation, gene delivery or modulation of parallel pathways-represent a promising avenue for PD intervention. Continued elucidation of the molecular functions of PINK1 will provide critical insights into mitochondrial homeostasis and novel therapeutic targets for PD.

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1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder of the central nervous system

(CNS), following Alzheimer's disease (1). Although the precise etiology of PD remains unclear, growing evidence indicates that both genetic and environmental factors contribute to its development, with aging recognized as a major risk factor (2). Epidemiological studies have shown that the incidence of PD ranges from 0.5 to 1% among individuals aged 65-69 years and increases to 1-3% in those aged ≥80 years, suggesting a strong age-related rise in disease prevalence (3,4). Notably, the global prevalence of PD is projected to double within the next three decades (5). The principal pathological hallmarks of PD include the progressive loss of dopaminergic neurons in the substantia nigra and the abnormal accumulation of α-synuclein (α-syn) within surviving neurons, leading to the formation of Lewy bodies (6). Dopaminergic neurons possess extensive and widely distributed axonal networks, dense synaptic connections and high intrinsic firing rates, features that impose substantial energy demands and render these cells particularly vulnerable to mitochondrial stress. In this context, mitochondrial quality control mechanisms are critical for sustaining neuronal survival and function (7-9).

Indeed, studies of familial PD-associated genes have demonstrated that mutations affecting key proteins involved in mitochondrial quality control can directly cause PD, providing compelling genetic evidence that mitophagy dysfunction contributes to PD pathogenesis (10,11). Among these pathways, PTEN-induced kinase 1 (PINK1)-mediated mitophagy has emerged as a major focus of current research (12). PINK1 interacts with multiple substrates to regulate mitochondrial function, playing dual roles in promoting mitochondrial clearance through mitophagy and maintaining mitochondrial homeostasis (13,14). Although PINK1-mediated mitophagy has been extensively reviewed, existing reviews remain narrowly focused on the canonical PINK1/Parkin pathway and leave several dimensions under-examined: The Parkin-independent functions of PINK1, the *in vitro-in vivo* discrepancy in detecting neuronal mitophagy and PINK1-independent, receptor-mediated mitophagy pathways. In the present review, these neglected dimensions are systematically covered and the competing explanations for the paradoxical observation that PINK1/Parkin knockout mice largely fail to recapitulate parkinsonian phenotypes are critically evaluated, an issue that remains unresolved and that is highlighted as a priority for future experimental work.

2. Causes of PD

PD is a prevalent, age-associated neurodegenerative disorder characterized primarily by the progressive loss of dopaminergic neurons in the substantia nigra and the accumulation of misfolded α-syn, which aggregates into Lewy bodies, two hallmark pathological features of the disease (15). The formation of Lewy bodies reflects an imbalance between the production and clearance of α-syn. Initially, soluble monomeric α-syn undergoes misfolding to form oligomeric intermediates, which subsequently assemble into amyloid fibrils and mature Lewy bodies. The accumulation of these aggregates has been associated with the onset and progression of PD pathology (16). These pathological processes disrupt neuronal signaling pathways, leading to the characteristic clinical manifestations of the disease (17).

As PD advances, several pathological mechanisms, including α-Syn misfolding, impaired dopamine metabolism, oxidative stress and neuronal apoptosis, interact synergistically, thereby accelerating neurodegeneration (18). Clinically, PD presents with both motor and non-motor symptoms. Motor symptoms include bradykinesia, muscular rigidity, resting tremor and postural instability, which primarily result from degeneration of the nigrostriatal dopaminergic pathway. Non-motor symptoms encompass cognitive impairment, autonomic dysfunction, psychiatric manifestations (such as anxiety and depression) and sleep disturbances (19).

3. Mechanism of mitophagy

Mitophagy selectively eliminates impaired, aged, dysfunctional or superfluous mitochondria, thereby reducing reactive oxygen species (ROS) generation and maintaining mitochondrial quality control (20). Proper mitophagic activity is essential for sustaining cellular homeostasis and neuronal survival. The process of mitophagy typically begins when mitochondria experience stress-induced damage or depolarization (21). Upon loss of mitochondrial membrane potential, a signaling cascade is activated that leads to the recruitment of autophagy machinery. Autophagy receptors interact with core autophagic components to form double-membraned autophagosomes, which encapsulate the damaged mitochondria (22). These autophagosomes subsequently fuse with lysosomes to form mitolysosomes, where the defective mitochondria are degraded and recycled (23,24).

Mitophagy is primarily triggered when mitochondria become damaged, depolarized or redundant (23). One of the main causes of mitophagy is the loss of mitochondrial membrane potential ($\Delta\psi m$), which is a key indicator of mitochondrial dysfunction (25). Under normal conditions, the kinase PINK1 is continuously imported into healthy mitochondria and degraded; however, when the membrane potential collapses, PINK1 accumulates on the outer mitochondrial membrane, where it recruits and activates the E3 ubiquitin ligase Parkin (26). Activated Parkin ubiquitinates numerous mitochondrial surface proteins, including mitofusin 1 (Mfn1), Mfn2 and voltage-dependent anion channel 1, marking the organelle for autophagic degradation (27). Another major cause of mitophagy is oxidative stress. Excessive production of ROS damages mitochondrial DNA, lipids and proteins, leading to functional impairment (20). To prevent the spread of oxidative damage, cells selectively eliminate these compromised mitochondria through mitophagy.

External agents and environmental factors can also cause mitophagy. Mitochondrial toxins such as rotenone, antimycin A and paraquat impair the electron transport chain (28,29). Some pharmaceuticals, including certain chemotherapeutic drugs and antiretroviral agents, exert mitochondrial toxicity that activates mitophagy as a protective response (30,31). Pathogen infection represents another trigger; numerous bacteria and viruses either induce mitophagy to promote host cell survival or inhibit it to evade immune detection (32,33). Finally, aging and chronic diseases are closely linked to altered mitophagy. With age, mitochondria accumulate mutations and oxidative damage, leading to increased mitophagic activity; however, excessive or insufficient mitophagy can both

be detrimental (34). Similarly, in metabolic disorders such as obesity, type 2 diabetes and non-alcoholic fatty liver disease, disrupted mitophagy exacerbates mitochondrial dysfunction and metabolic imbalance (35-37).

4. Mitophagy affects neuronal cellular function

Mitochondria perform numerous essential cellular functions, including ATP generation, cytosolic calcium buffering, lipid biosynthesis and the regulation of apoptosis and programmed cell death (38). Because mitochondria are responsible for energy production through oxidative phosphorylation and maintaining cellular redox balance, their dysfunction can lead to excessive oxidative stress, reduced ATP synthesis and impaired cell viability (39). Consequently, mitochondrial damage plays a pivotal role in the onset and progression of numerous neurodegenerative diseases (40). Mitochondria are also susceptible to oxidative injury; once damaged, they can generate excessive ROS, which further exacerbate oxidative stress, increase cellular toxicity, and ultimately trigger neuronal cell death (41).

To counteract these deleterious effects, cells have evolved a sophisticated mitochondrial quality control system such as mitochondrial biogenesis, mitochondrial dynamics and mitophagy, operating at both molecular and organellar levels (42). This system coordinates multiple repair and maintenance mechanisms to restore damaged mitochondria and preserve the structural and functional integrity of the mitochondrial network (43). When mitochondrial damage exceeds the repair capacity, cells activate a selective degradation process known as mitophagy, in which defective mitochondria are sequestered and eliminated through the autophagic pathway (44).

Mitophagy serves as the principal mechanism for maintaining mitochondrial homeostasis by selectively targeting damaged or aged mitochondria for lysosomal degradation. When PINK1-mediated mitophagy is impaired, defective mitochondria accumulate within neurons, leading to bioenergetic deficits, disrupted cellular signaling and impaired cytosolic calcium buffering (45). These pathological alterations ultimately culminate in neuronal dysfunction, apoptosis and neurodegeneration (46). Thus, mitophagy acts as the terminal safeguard of mitochondrial quality control. Failure of this process results in the accumulation of dysfunctional mitochondria, disrupted energy metabolism, and excessive oxidative stress, pathological events that have been causally linked to aging and multiple chronic neurodegenerative disorders, including PD (47).

5. PINK1-mediated mitophagy

The *PINK1* gene is located on chromosome 1 at position 1p36.12 and comprises eight exons with a total length of ~1.8 kb. The gene encodes a 581-amino acid serine/threonine kinase that is essential for maintaining mitochondrial function and structural integrity, highlighting the critical role of mitochondrial homeostasis in the pathogenesis of PD (48). The PINK1 protein contains several distinct structural domains: An N-terminal mitochondrial targeting sequence, a transmembrane domain, an N-terminal regulatory domain, a conserved serine/threonine kinase domain composed of N- and C-lobes and a C-terminal domain (49).

Extensive research over the past two decades has revealed that numerous *PARK* genes are closely associated with mitochondrial homeostasis, among which *PARK6* (encoding PINK1) and *PARK2* (encoding the E3 ubiquitin ligase Parkin) are the most prominent (50). Biochemical and genetic studies have demonstrated that PINK1 and Parkin function cooperatively within a common signaling pathway that governs mitophagy and, consequently, mitochondrial quality control (51,52). Activation of PINK1 represents one of the earliest and most critical steps in the mitophagic process (Fig. 1). Under physiological conditions, when mitochondria are healthy and maintain normal membrane potential, newly synthesized PINK1 is imported into the mitochondria, where it is cleaved by proteases such as presenilin-associated rhomboid-like protein (PARL) and subsequently degraded by the ubiquitin-proteasome system (53). In this state, PINK1 remains inactive, preventing the unnecessary removal of functional mitochondria.

Conversely, as shown in Fig. 1, when mitochondria become depolarized or otherwise damaged, PINK1 import is halted, and proteolytic cleavage by PARL is inhibited (54). As a result, full-length PINK1 accumulates and stabilizes on the outer mitochondrial membrane (OMM), where it undergoes autophosphorylation and becomes activated. Activated PINK1 then phosphorylates both ubiquitin and the Ser65 residue within the ubiquitin-like domain of Parkin, thereby recruiting cytosolic Parkin to the mitochondria and converting it into its active E3 ubiquitin ligase form (55). Activated Parkin catalyzes extensive ubiquitination of OMM proteins, marking damaged mitochondria for recognition by autophagy adaptor proteins such as optineurin and nuclear dot protein 52 kDa (56). These adaptors, in turn, recruit LC3-decorated autophagosomal membranes that envelop and target the defective mitochondria for lysosomal degradation (57).

6. PINK1-independent mitophagy pathways

Mitophagy is not exclusively governed by the PINK1/Parkin axis. In parallel, receptor-mediated, PINK1/Parkin-independent pathways eliminate mitochondria through OMM proteins that harbor LC3-interacting region motifs and directly recruit the autophagy machinery, bypassing the ubiquitin-dependent cascade. Representative receptors include FUN14 domain-containing protein 1, which mediates hypoxia-induced mitophagy through dephosphorylation-dependent LC3 binding (58); BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and its homolog NIX (also known as BNIP3L), which promote mitophagy under hypoxic conditions (59) and during programmed mitochondrial elimination such as erythroid maturation (60); and FK506-binding protein 8, which recruits LC3A to mediate Parkin-independent mitophagy (61). These receptor-mediated pathways are physiologically important in neurons and other post-mitotic cells and have been implicated in a range of neurodegenerative and metabolic disorders, such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (33,62). Acknowledging these parallel pathways provides a more complete account of mitophagy in PD,

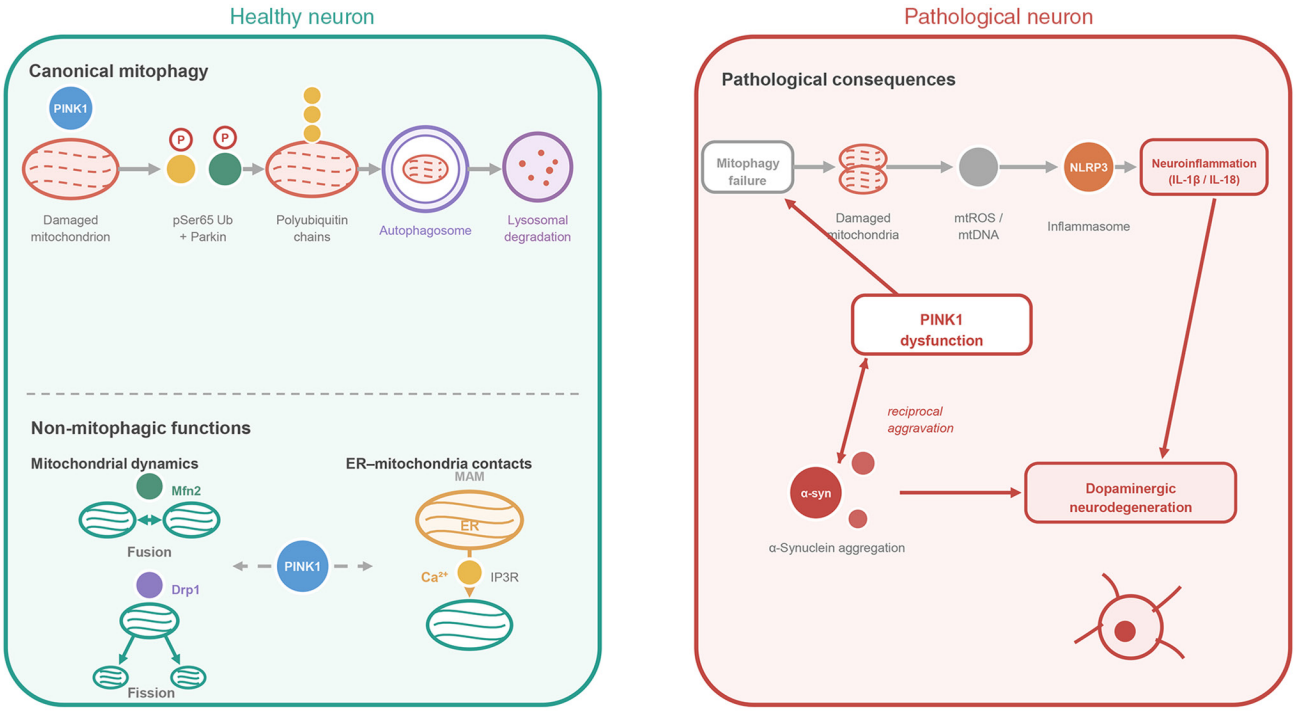


Figure 1. PINK1-regulated mitophagy and its pathological consequences in Parkinson's disease. Left (healthy neuron): PINK1 maintains mitochondrial quality control through canonical mitophagy, damaged mitochondria accumulate PINK1, recruit Parkin via pSer65 ubiquitin and are cleared through autophagosome-lysosome degradation. PINK1 also regulates mitochondrial dynamics (Mfn2-mediated fusion, Drp1-mediated fission) and ER-mitochondria contact sites (MAMs) via IP3R-Ca^{2+} signaling. Right (pathological neuron): PINK1 dysfunction impairs mitophagy, causing damaged mitochondria to accumulate. Released mtROS and mtDNA activate the NLRP3 inflammasome, triggering neuroinflammation (IL-1β/IL-18). PINK1 dysfunction also promotes α-synuclein aggregation, which reciprocally worsens PINK1 dysfunction, forming a vicious cycle that drives dopaminergic neurodegeneration. PINK1, PTEN-induced kinase 1; Mfn2, mitofusin 2; Drp1, dynamin-related protein 1; MAMs, mitochondria-associated membranes; IP3R, inositol 1,4,5-trisphosphate receptors; mtROS, mitochondrial reactive oxygen species; mtDNA, mitochondrial DNA.

corrects the misconception that mitophagy is synonymous with PINK1/Parkin signaling and offers plausible compensatory mechanisms when the canonical pathway is impaired (23).

7. PINK1 functional deficiency as a genetic etiology of PD

Mutations in *PINK1* represent the second most common cause of autosomal recessive PD and are associated with early-onset PD (63). The primary types of *PINK1* mutations include missense, nonsense and structural variants, with missense mutations being the most prevalent (64). For example, one study identified four *PINK1* variants, three missense mutations (c.832C>G, c.938C>T, and c.1220G>A) and one heterozygous deletion spanning exons 3 to 8 (65). Although these variants were found in the heterozygous rather than homozygous or compound heterozygous state, they may still exert pathogenic or susceptibility effects. Among these mutations, homozygous c.938C>T mutations have been identified in 29 Chinese mainland families with autosomal recessive early-onset PD (65).

Mutations in *PINK1* compromise its normal function, leading to reduced ATP production and excessive generation of ROS. The resulting oxidative stress exacerbates dopaminergic neuronal injury and promotes neurodegeneration through elevated ROS levels and loss of mitochondrial protection (52). Loss-of-function mutations in *PINK1* disrupt multiple mitochondrial quality control pathways, including those involved in mitophagy, mitochondrial dynamics and oxidative stress regulation (66). Beyond its role in mitophagy, PINK1 regulates mitochondrial dynamics independently of Parkin. It phosphorylates the outer-membrane GTPase mitofusin 2 (Mfn2), promoting mitochondrial fusion, and recruits the fission factor dynamin-related protein 1 to mitochondria under stress, thereby maintaining the balance between fusion and fission (67). Phosphorylated Mfn2 also functions as a substrate for Parkin, thereby coupling the mitochondrial dynamics machinery to the ubiquitin-dependent degradation of damaged mitochondria (67). Loss of PINK1 skews this balance toward excessive fragmentation, which impairs mitochondrial turnover and neuronal function. These defects act synergistically, particularly within energy-demanding dopaminergic neurons, to promote the accumulation of oxidative damage, metabolic collapse and apoptotic cell death, ultimately driving the progressive neurodegeneration characteristic of PD (68,69).

Beyond its direct impact on mitochondrial function, PINK1 deficiency also perturbs the structural and functional integrity of endoplasmic reticulum (ER) mitochondria contact sites, also known as mitochondria-associated membranes (MAMs) (4). These inter-organelle contact sites are essential for calcium signaling, phospholipid biosynthesis and the regulation of mitochondrial dynamics. Recent studies have shown that PINK1 plays a pivotal role in maintaining normal ER-mitochondria communication (70,71). Loss of PINK1 disrupts MAM structure and function, leading to intracellular calcium dyshomeostasis, altered lipid metabolism and secondary defects in mitochondrial fission-fusion balance (72). PINK1 and Parkin also regulate ER calcium release through inositol 1,4,5-trisphosphate receptors

(IP3Rs) (70). PINK1 deficiency dysregulates IP3R-mediated Ca^{2+} release, leading to mitochondrial calcium overload, opening of the mitochondrial permeability transition pore and activation of apoptotic signaling. Collectively, these alterations exacerbate cellular stress and sensitize dopaminergic neurons to degeneration. Directly linking these non-mitophagic functions to PD, PD-associated PINK1 and Parkin mutations disrupt MAM integrity and ER-mitochondrial Ca^{2+} transfer, and α-synuclein, which normally resides at MAMs, disrupts ER-mitochondrial contacts when pathologically mutated or aggregated (4). These non-mitophagic functions of PINK1 are tightly interconnected. Disruption of MAMs impairs ER-mitochondria calcium transfer and phospholipid exchange, which in turn contributes to aberrant lipid metabolism and calcium signaling dysregulation (72). Together with defective mitochondrial dynamics and mitophagy, these defects converge on a common endpoint, mitochondrial dysfunction, oxidative stress and heightened vulnerability of dopaminergic neurons, underscoring that PINK1 contributes to PD through multiple, mutually reinforcing mechanisms rather than through mitophagy alone (4,67).

8. PINK1-mediated mitophagy in the pathogenesis of PD

Mutations in *PINK1* identified in the primate brain and in human cellular models have been shown to diminish its kinase activity, reducing phosphorylation of downstream substrates that are critical for maintaining neuronal function and survival (73). Evidence suggests that it is specifically the kinase activity of PINK1, rather than its structural mitochondrial localization, that is indispensable for dopaminergic neuron viability in the primate brain (73). Consequently, the loss of PINK1 kinase function likely plays a pivotal role in the molecular pathogenesis of PD. In cellular models of PD, *PINK1* deficiency has been reported to abolish the reductive activity of mitochondrial complex I, an essential component of the oxidative phosphorylation system, thereby inducing mitochondrial dysfunction and dopaminergic neuronal death (67). These findings establish a mechanistic link between defective mitophagy, impaired energy metabolism, and neurodegeneration in PD.

Notably, despite the molecular evidence implicating PINK1 and Parkin in PD, animal model studies have yielded mixed results. In PINK1-mutant mice, a progressive reduction in mitochondrial precursor protein import has been observed, indicating compromised mitochondrial biogenesis and quality control (12). However, most *PINK1*- or *Parkin*-knockout mouse models fail to recapitulate the early-onset Parkinsonian phenotypes observed in humans carrying mutations in these genes because they lack significant dopaminergic neurodegeneration and the associated motor symptoms (74). Similarly, although *PINK1*- and *Parkin*-null *Drosophila* exhibit motor impairments and neuronal loss, they still demonstrate measurable levels of mitophagic activity under certain experimental conditions (75). These observations suggest that PINK1- and Parkin-independent mitophagy pathways may compensate for the loss of canonical signaling in some species or tissue contexts.

Collectively, these findings underscore an important caveat in interpreting PINK1/Parkin-mediated mitophagy as a single, overarching cause of PD. The failure of most PINK1- or Parkin-knockout mice to recapitulate dopaminergic neurodegeneration (74) indicates that, at least in rodents, loss of these genes alone is insufficient to trigger full PD pathology (75), likely owing to compensatory mitophagy pathways, species-specific differences in mitochondrial biology (73) and the relatively short lifespan and limited aging-related stress of laboratory mice (74). Accordingly, PINK1-mediated mitophagy is best understood as a key contributing mechanism that is especially consequential in the context of PINK1 mutations underlying familial early-onset PD, rather than a universal, obligatory cause of all PD. This refined perspective does not diminish the importance of PINK1-mediated mitophagy; rather, it aligns the proposed mechanism with the available *in vivo* evidence and highlights the need for complementary pathways and additional insults for PD to fully manifest.

A further layer of complexity concerns the well-documented discrepancy between *in vitro* and *in vivo* mitophagy. In cultured cells, mitophagy is readily induced by strong depolarizing agents such as carbonyl cyanide m-chlorophenyl hydrazone or combined oligomycin/antimycin A, whereas mitophagy in adult neurons *in vivo* is notoriously difficult to detect, even with sensitive reporters such as mito-QC and mt-Keima (76). This disparity arises from several technical and biological factors, including the limited spatiotemporal resolution of current reporters, the confinement of mitophagy largely to distal axonal compartments where damaged mitochondria are locally cleared and the rapid turnover of mitophagic intermediates, all of which complicate steady-state detection (76). Notably, this low and spatially restricted mitophagic flux does not imply functional irrelevance; rather, even modest, tightly regulated mitophagy is likely indispensable for the long-term maintenance of post-mitotic neurons, which must preserve mitochondrial fidelity over decades (25).

Recognizing this *in vitro-in vivo* discrepancy further supports viewing PINK1-mediated mitophagy as a key contributing mechanism whose magnitude and detectability vary with model system and assay sensitivity, rather than as a universally dominant process. These considerations carry direct implications for therapeutic development. First, the existence of PINK1- and Parkin-independent mitophagy pathways indicates that compensatory mechanisms may mask the consequences of PINK1 loss in rodents, and that these parallel pathways represent additional targets rather than grounds to discount the relevance of PINK1. Second, because PINK1 mutations are pathogenic primarily through loss of kinase activity rather than through structural mislocalization alone (73), the contribution of PINK1 to PD is not exclusively mitophagy-dependent, arguing for strategies that restore kinase signaling rather than merely enhancing bulk mitophagy. Third, and most notable for drug screening, conventional PINK1/Parkin-knockout mice may substantially underestimate the therapeutic window of PINK1 activators; preclinical evaluation should therefore be complemented by human induced pluripotent stem cell-derived neurons, primate models in which PINK1 kinase dysfunction reproducibly triggers neurodegeneration (73) and 'two-hit' models combining PINK1 deficiency with α-syn fibrils (77), which more faithfully capture the disease context in which PINK1 activation is most likely to be protective (3).

9. PINK1 dysfunction promotes the aggregation and propagation of α-syn

Multiple studies have demonstrated that the absence of functional PINK1 accelerates α-syn aggregation and propagation, thereby amplifying neurodegenerative pathology (77,78). In both cellular and animal models, loss of PINK1 renders endogenous α-syn more susceptible to misfolding and aggregation (77). For instance, following intracerebral injection of α-syn preformed fibrils, *PINK1*-knockout mice exhibit markedly increased levels of total and phosphorylated α-syn, pronounced formation of Lewy body-like aggregates and earlier onset of neuronal loss and motor dysfunction compared with wild-type controls (79). These findings suggest that impaired mitophagy in the absence of PINK1 facilitates the persistence of dysfunctional mitochondria and associated oxidative stress, creating a cellular environment conducive to α-syn aggregation.

Moreover, co-immunoprecipitation and proximity ligation assays have indicated a close spatial association between PINK1 and α-syn within cells, consistent with a direct or indirect interaction (80). These observations suggest that loss of PINK1 alters α-syn phosphorylation states and enhances its aggregation propensity, while pathological α-syn accumulation reciprocally destabilizes PINK1 and diminishes its kinase activity (80). Mechanistically, α-syn impairs PINK1 through multiple, non-mutually exclusive pathways. First, α-syn aggregates promote the degradation of PINK1 via the SIAH E3 ubiquitin ligase pathway, thereby reducing steady-state PINK1 protein levels (80). Second, α-syn oligomers induce the externalization of mitochondrial cardiolipin, which disrupts mitochondrial metabolism and compromises the depolarization-dependent stabilization of PINK1 on the outer mitochondrial membrane (17). Third, α-syn-induced oxidative stress destabilizes the kinase-active conformation of PINK1, diminishing its catalytic activity (79). Together, these mechanisms explain how α-syn reciprocally undermines the very mitophagy machinery that would otherwise facilitate its own clearance, although the relative contribution of each pathway remains to be fully delineated. This bidirectional interaction creates a vicious cycle in which PINK1 dysfunction promotes α-syn pathology, which in turn further impairs mitochondrial quality control, ultimately driving dopaminergic neuronal death and the progression of PD.

10. PINK1 dysfunction and neuroinflammation

As aforementioned, it has been confirmed that loss of PINK1 alters the phosphorylation state and aggregation propensity of α-syn, while pathological α-syn accumulation reciprocally destabilizes PINK1 and diminishes its kinase activity (79). These reciprocal interactions exacerbate mitochondrial dysfunction, promote oxidative stress and intensify inflammatory responses (79). Notably, these inflammatory effects are not confined to regions of neuronal loss but propagate throughout the CNS (79), suggesting that inflammation associated with PINK1 deficiency exhibits a systemic and self-perpetuating character. Increasing evidence links the PINK1-Parkin pathway to the regulation of microglial activation and the NLRP3 inflammasome. For instance, the NLRP3 inflammasome has been identified as a substrate of Parkin in neurons, and its activation is implicated in the progression of multiple neurodegenerative disorders, including PD (81).

Loss of PINK1 also promotes the activation of the NLRP3 inflammasome, a multiprotein cytoplasmic complex that activates caspase-1 upon sensing cellular danger signals, thereby inducing the maturation and secretion of pro-inflammatory cytokines such as IL-1β and IL-18 (82,83). Mechanistically, this activation is driven by mitochondrial dysfunction: PINK1 deficiency causes damaged mitochondria to accumulate and release mitochondrial reactive oxygen species and mitochondrial DNA, which serve as damage-associated molecular patterns that trigger NLRP3 inflammasome activation (84). This activation amplifies the inflammatory cascade, further exacerbating neuroinflammation, microglial overactivation and neuronal death (85). Thus, PINK1 dysfunction serves as a critical link between mitochondrial impairment and innate immune activation in the PD brain.

11. PINK1 dysfunction leads to selective neuronal death

Experimental evidence demonstrates that the loss of PINK1 leads to notable synaptic dysfunction in dopaminergic neurons (86). In *PINK1*-knockout mice, although the total number of dopaminergic neurons and striatal dopamine levels remain largely unchanged, amperometric recordings reveal a marked reduction in evoked dopamine release from striatal slices, along with decreased quantal size and release frequency of catecholamines in isolated chromaffin cells (87). These functional impairments precede overt neuronal loss, suggesting that synaptic transmission failure represents an early pathogenic event in PINK1-deficiency-induced neurodegeneration.

Ultrastructural studies have further elucidated the cellular mechanisms underlying neuronal death in PINK1 deficiency. Electron microscopy of *PINK1*-knockdown primate brains revealed degenerating neurons characterized by abundant lysosomes and phagocytic vacuoles but notably lacking overt mitochondrial structural abnormalities (73,88). This finding challenges the traditional paradigm that mitochondrial morphological disruption is the sole cause of neuronal death in PINK1 deficiency, suggesting that defective autophagy, lysosomal processing may also play a critical role. Moreover, loss of PINK1 extends its impact beyond dopaminergic systems, leading to abnormalities in neurotransmitter metabolism (89). In addition to dopamine, altered levels of γ-aminobutyric acid and glutamate have been observed following PINK1 deficiency (90). Dysregulation of these neurotransmitters further disrupts neuronal network function and contributes to widespread neurodegeneration.

12. Therapeutic strategies targeting PINK1-mediated mitophagy

Pharmacological strategies aim to reactivate PINK1/Parkin signaling or enhance mitophagy. The plant cytokinin kinetin, whose riboside triphosphate derivative kinetin triphosphate is phosphorylated by PINK1 and thereby amplifies the catalytic activity of even mutant PINK1 toward its substrate ubiquitin (91), was among the first small-molecule PINK1 activators described, although its precise mechanism has recently been revisited. In parallel, inhibition of the

mitochondrial deubiquitinase USP30, which removes ubiquitin from Parkin substrates and thereby limits mitophagy, has emerged as a strategy to enhance Parkin-dependent mitophagy (92). Broader mitophagy inducers, such as the naturally occurring compound urolithin A, have also been reported to stimulate mitophagy and confer neuroprotection in model systems (93).

Gene therapy approaches seek to restore wild-type PINK1 or Parkin expression in vulnerable neurons. Adeno-associated virus (AAV) vectors have been used to deliver PINK1 or Parkin in preclinical models, rescuing mitophagy and conferring neuroprotection (46). In rodents, AAV-mediated Parkin delivery protects nigral dopaminergic neurons against α-synuclein-, MPTP- and 6-hydroxydopamine-induced toxicity, and in non-human primates it attenuates α-synuclein-induced degeneration of dopaminergic terminals; PINK1-deficient models, including non-human primates with PINK1 loss-of-function, further establish the disease context for these gene therapies (52,73). Notably, a Phase I trial of kinetin triphosphate in PINK1-related PD was initiated in late 2025, and a first-in-human AAV9-PINK1 gene therapy trial is currently recruiting patients with biallelic PINK1 mutations (94).

Lifestyle-based interventions have also attracted considerable interest as accessible, low-risk approaches to enhance mitophagy. Aerobic exercise and caloric restriction activate the cellular energy sensor AMPK, which in turn stimulates the downstream kinase unc-51 like autophagy activating kinase 1 (ULK1) to drive mitophagy, thereby positioning PINK1 at the intersection of aging, exercise and dietary regulation in PD (57,94). Through this energy-sensing AMPK/ULK1 axis, endurance exercise promotes mitochondrial turnover and improves mitochondrial quality, while caloric restriction and dietary modulation engage convergent pathways that reinforce mitochondrial quality control (57,94). These observations suggest that exercise and dietary interventions may complement pharmacological and gene therapies and could form the basis of preventive strategies for at-risk populations.

Despite this progress, no PINK1- or mitophagy-targeting therapy has yet gained regulatory approval for PD (3), and most candidates remain in preclinical or early clinical evaluation. Principal obstacles include limited blood-brain barrier penetration, off-target effects, the low basal frequency of mitophagy in adult neurons and the difficulty of confirming target engagement in patients.

13. Summary

In summary, PINK1-mediated mitophagy is a critical mitochondrial surveillance mechanism whose dysfunction contributes to PD pathogenesis. Continued investigation into this pathway offers valuable insights into disease mechanisms and potential therapeutic interventions targeting mitochondrial quality control. Therapeutic strategies aimed at restoring or enhancing PINK1-mediated mitophagy, through small molecules, gene therapy or mitochondrial quality control modulators, represent a promising avenue for PD treatment. Nevertheless, as discussed in the preceding section, no PINK1- or mitophagy-targeting therapy has yet gained regulatory approval for PD, and most candidates remain in preclinical or early-stage clinical evaluation; these approaches should therefore be regarded as promising but still unproven, rather than as imminent treatments.

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Authors' contributions

HD, ZL, PZ and MM contributed to the manuscript conception and design. The first draft of the manuscript was written by HD, SL, ZZ, HA, YZhan, YZhao, YH, MC and HL. YZhao, HD, XH and HZ contributed to the systematic identification, screening and critical evaluation of the references cited in this manuscript, which constituted the acquisition and analysis of data for this review, and to figure visualization; XH and HZ also participated in drafting the relevant sections. ZL, YZhao, PZ and MM commented and critically revised previous versions of the manuscript. All authors have read and approved the final version of the manuscript. Data authentication not applicable.

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Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, DeepSeek (https://chat.deepseek.com/) was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K and Weintraub D: Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers 7: 47, 2021.

2. Pang SY, Ho PW, Liu HF, Leung CT, Li L, Chang EES, Ramsden DB and Ho SL: The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. Transl Neurodegener 8: 23, 2019.
3. Blagov AV, Goncharov AG, Babich OO, Larina VV, Orekhov AN and Melnichenko AA: Prospects for the development of pink1 and parkin activators for the treatment of Parkinson's disease. Pharmaceutics 14: 2514, 2022.
4. Barazzuol L, Giamogante F, Brini M and Calì T: PINK1/Parkin mediated mitophagy, Ca2+ signalling, and ER-Mitochondria contacts in Parkinson's disease. Int J Mol Sci 21: 1772, 2020.
5. Tolosa E, Garrido A, Scholz SW and Poewe W: Challenges in the diagnosis of Parkinson's disease. Lancet Neurol 20: 385-397, 2021.
6. Balestrino R and Schapira AHV: Parkinson disease. Eur J Neurol 27: 27-42, 2020.
7. Ge P, Dawson VL and Dawson TM: PINK1 and Parkin mitochondrial quality control: A source of regional vulnerability in Parkinson's disease. Mol Neurodegener 15: 20, 2020.
8. Zhu Y, Zhang J, Deng Q and Chen X: Mitophagy-associated programmed neuronal death and neuroinflammation. Front Immunol 15: 1460286, 2024.
9. Tang Y, Huang Y, Wan Z, Zhou B and Wu Z: Mitochondrial quality control links two seemingly unrelated neurodegenerative diseases. Autophagy 18: 2495-2497, 2022.
10. Song P, Peng W, Sauve V, Fakih R, Xie Z, Ysselstein D, Krainc T, Wong YC, Mencacci NE, Savas JN, *et al*: Parkinson's disease-linked parkin mutation disrupts recycling of synaptic vesicles in human dopaminergic neurons. Neuron 111: 3775-3788. e7, 2023.
11. Cherian A, K P D and Vijayaraghavan A: Parkinson's disease - genetic cause. Curr Opin Neurol 36: 292-301, 2023.
12. Vizziello M, Borellini L, Franco G and Ardolino G: Disruption of mitochondrial homeostasis: The role of PINK1 in Parkinson's disease. Cells 10: 3022, 2021.
13. Gonçalves FB and Morais VA: PINK1: A bridge between Mitochondria and Parkinson's disease. Life (Basel) 11: 371, 2021.
14. Quiles JM and Gustafsson ÅB: Mitochondrial quality control and cellular proteostasis: Two sides of the same coin. Front Physiol 11: 515, 2020.
15. Sung CC and Chung KKK: Age-dependent alpha-synuclein aggregation and Lewy body formation in Parkinson's disease. Neural Regen Res 20: 3533-3534, 2025.
16. Du XY, Xie XX and Liu RT: The role of α-synuclein oligomers in Parkinson's disease. Int J Mol Sci 21: 8645, 2020.
17. Lurette O, Martín-Jiménez R, Khan M, Sheta R, Jean S, Schofield M, Teixeira M, Rodriguez-Aller R, Perron I, Oueslati A and Hebert-Chatelain E: Aggregation of alpha-synuclein disrupts mitochondrial metabolism and induce mitophagy via cardiolipin externalization. Cell Death Dis 14: 729, 2023.
18. Bidesi NSR, Vang Andersen I, Windhorst AD, Shalgunov V and Herth MM: The role of neuroimaging in Parkinson's disease. J Neurochem 159: 660-689, 2021.
19. Cerri S, Mus L and Blandini F: Parkinson's disease in women and men: What's the difference? J Parkinsons Dis 9: 501-515, 2019.
20. Su L, Zhang J, Gomez H, Kellum JA and Peng Z: Mitochondria ROS and mitophagy in acute kidney injury. Autophagy 19: 401-414, 2023.
21. De Gaetano A, Gibellini L, Zanini G, Nasi M, Cossarizza A and Pinti M: Mitophagy and oxidative stress: The role of aging. Antioxidants (Basel) 10: 794, 2021.
22. Liu J, Ma H, Wu Z, Ji Y and Liang Y: The knowns and unknowns of membrane features and changes during autophagosome-lysosome/vacuole fusion. Int J Mol Sci 25: 11160, 2024.
23. Onishi M, Yamano K, Sato M, Matsuda N and Okamoto K: Molecular mechanisms and physiological functions of mitophagy. EMBO J 40: e104705, 2021.
24. Shen ZF, Li L, Zhu XM, Liu XH, Klionsky DJ and Lin FC: Current opinions on mitophagy in fungi. Autophagy 19: 747-757, 2023.
25. Han S, Zhang M, Jeong YY, Margolis DJ and Cai Q: The role of mitophagy in the regulation of mitochondrial energetic status in neurons. Autophagy 17: 4182-4201, 2021.
26. Wang XL, Feng ST, Wang ZZ, Yuan YH, Chen NH and Zhang Y: Parkin, an E3 ubiquitin ligase, plays an essential role in mitochondrial quality control in Parkinson's disease. Cell Mol Neurobiol 41: 1395-1411, 2021.
27. Park GH, Park JH and Chung KC: Precise control of mitophagy through ubiquitin proteasome system and deubiquitin proteases and their dysfunction in Parkinson's disease. BMB Rep 54: 592-600, 2021.
28. Rakhmatullina D, Ponomareva A, Gazizova N and Minibayeva F: Mitochondrial morphology and dynamics in Triticum aestivum roots in response to rotenone and antimycin A. Protoplasma 253: 1299-1308, 2016.
29. Zikaki K, Kiachaki E, Gaitanaki C and Aggeli IK: 'Villains' turning good: Antimycin A and rotenone, mitochondrial respiratory chain inhibitors, protect H9c2 cardiac cells against insults triggering the intrinsic apoptotic pathway. Int J Mol Sci 26: 2435, 2025.
30. Cheney L, Barbaro JM and Berman JW: Antiretroviral drugs impact autophagy with toxic outcomes. Cells 10: 909, 2021.
31. Martinez-Arroyo O, Gruevska A, Victor VM, González-Polo RA, Yakhine-Diop SMS, Fuentes JM, Esplugues JV, Blas-Garcia A and Apostolova N: Mitophagy in human astrocytes treated with the antiretroviral drug Efavirenz: Lack of evidence or evidence of the lack. Antiviral Res 168: 36-50, 2019.
32. Fu C, Cao N, Liu W, Zhang Z, Yang Z, Zhu W and Fan S: Crosstalk between mitophagy and innate immunity in viral infection. Front Microbiol 13: 1064045, 2022.
33. Wang S, Long H, Hou L, Feng B, Ma Z, Wu Y, Zeng Y, Cai J, Zhang DW and Zhao G: The mitophagy pathway and its implications in human diseases. Signal Transduct Target Ther 8: 304, 2023.
34. Chen G, Kroemer G and Kepp O: Mitophagy: An emerging role in aging and age-associated diseases. Front Cell Dev Biol 8: 200, 2020.
35. Miao MQ, Han YB and Liu L: Mitophagy in metabolic syndrome. J Clin Hypertens (Greenwich) 25: 397-403, 2023.
36. Jakubek P, Pakula B, Rossmeisl M, Pinton P, Rimessi A and Wieckowski MR: Autophagy alterations in obesity, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease: The evidence from human studies. Intern Emerg Med 19: 1473-1491, 2024.
37. Su Z, Guo Y, Huang X, Feng B, Tang L, Zheng G and Zhu Y: Phytochemicals: Targeting mitophagy to treat metabolic disorders. Front Cell Dev Biol 9: 686820, 2021.
38. Du H, Xu T, Yu S, Wu S and Zhang J: Mitochondrial metabolism and cancer therapeutic innovation. Signal Transduct Target Ther 10: 245, 2025.
39. Xu X, Pang Y and Fan X: Mitochondria in oxidative stress, inflammation and aging: From mechanisms to therapeutic advances. Signal Transduct Target Ther 10: 190, 2025.
40. Klemmensen MM, Borrowman SH, Pearce C, Pyles B and Chandra B: Mitochondrial dysfunction in neurodegenerative disorders. Neurotherapeutics 21: e00292, 2024.
41. Behl T, Makkar R, Sehgal A, Singh S, Sharma N, Zengin G, Bungau S, Andronie-Cioara FL, Munteanu MA, Brisc MC, *et al*: Current trends in neurodegeneration: Cross talks between oxidative stress, cell death, and inflammation. Int J Mol Sci 22: 7432, 2021.
42. Liu BH, Xu CZ, Liu Y, Lu ZL, Fu TL, Li GR, Deng Y, Luo GQ, Ding S, Li N and Geng Q: Mitochondrial quality control in human health and disease. Mil Med Res 11: 32, 2024.
43. Ye L, Fu X and Li Q: Mitochondrial quality control in health and disease. MedComm (2020) 6: e70319, 2025.
44. Ma L, Han T and Zhan YA: Mechanism and role of mitophagy in the development of severe infection. Cell Death Discov 10: 88, 2024.
45. Howden JH, Hakansson H, Nieto-Rostro M, McAdam R, Arber C, Brandon NJ and Kittler JT: Hexokinase 2 interacts with PINK1 to facilitate mitophagy in astrocytes and restrain inflammation-induced neurotoxicity. Cell Rep 44: 115809, 2025.
46. Li J, Yang D, Li Z, Zhao M, Wang D, Sun Z, Wen P, Dai Y, Gou F, Ji Y, *et al*: PINK1/Parkin-mediated mitophagy in neurodegenerative diseases. Ageing Res Rev 84: 101817, 2023.
47. Picca A, Faitg J, Auwerx J, Ferrucci L and D'Amico D: Mitophagy in human health, ageing and disease. Nat Metab 5: 2047-2061, 2023.
48. Koh H and Chung J: PINK1 as a molecular checkpoint in the maintenance of mitochondrial function and integrity. Mol Cells 34: 7-13, 2012.
49. Fiesel FC, Fričová D, Hayes CS, Coban MA, Hudec R, Bredenberg JM, Broadway BJ, Markham BN, Yan T, Boneski PK, *et al*: Substitution of PINK1 Gly411 modulates substrate receptivity and turnover. Autophagy 19: 1711-1732, 2023.

50. Dan H, Huang X, Liu Z, Wei B and Maslinda M: Mechanisms associated with PINK1 mutations in Parkinson's disease. F1000Res 14: 1138, 2025.
51. Pickrell AM and Youle RJ: The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. Neuron 85: 257-273, 2015.
52. Quinn PMJ, Moreira PI, Ambrósio AF and Alves CH: PINK1/PARKIN signalling in neurodegeneration and neuroinflammation. Acta Neuropathol Commun 8: 189, 2020.
53. Narendra DP and Youle RJ: The role of PINK1-Parkin in mitochondrial quality control. Nat Cell Biol 26: 1639-1651, 2024.
54. Sekine S: PINK1 import regulation at a crossroad of mitochondrial fate: The molecular mechanisms of PINK1 import. J Biochem 167: 217-224, 2020.
55. Tanaka K: The PINK1-Parkin axis: An overview. Neurosci Res 159: 9-15, 2020.
56. Wang C, Liu K, Cao J, Wang L, Zhao Q, Li Z, Zhang H, Chen Q and Zhao T: PINK1-mediated mitophagy maintains pluripotency through optineurin. Cell Prolif 54: e13034, 2021.
57. Iorio R, Celenza G and Petricca S: Mitophagy: Molecular mechanisms, new concepts on parkin activation and the emerging role of AMPK/ULK1 axis. Cells 11: 30, 2021.
58. Liu L, Feng D, Chen G, Chen M, Zheng Q, Song P, Ma Q, Zhu C, Wang R, Qi W, *et al*: Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol 14: 177-185, 2012.
59. Bellot G, Garcia-Medina R, Gounon P, Chiche J, Roux D, Pouysségur J and Mazure NM: Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains. Mol Cell Biol 29: 2570-2581, 2009.
60. Sandoval H, Thiagarajan P, Dasgupta SK, Schumacher A, Prchal JT, Chen M and Wang J: Essential role for Nix in autophagic maturation of erythroid cells. Nature 454: 232-235, 2008.
61. Bhujabal Z, Birgisdottir ÅB, Sjøttem E, Brenne HB, Øvervatn A, Habisov S, Kirkin V, Lamark T and Johansen T: FKBP8 recruits LC3A to mediate Parkin-independent mitophagy. EMBO Rep 18: 947-961, 2017.
62. Chu M, Tan M, Gan X, Cui S and Shi L: Targeting mitochondrial dysfunction in microglia: A new frontier for treating neurodegenerative diseases. Mol Neurobiol 63: 800, 2026.
63. Yin EP and Dieriks BV: Rethinking 'rare' PINK1 Parkinson's disease: A meta-analysis of geographical prevalence, phenotypic diversity, and α-synuclein pathology. J Parkinsons Dis 15: 41-65, 2025.
64. Krohn L, Grenn FP, Makarious MB, Kim JJ, Bandres-Ciga S, Roosen DA, Gan-Or Z, Nalls MA, Singleton AB and Blauwendraat C; International Parkinson's disease genomics consortium (IPDGC): Comprehensive assessment of PINK1 variants in Parkinson's disease. Neurobiol Aging 91: 168.e1-168.e5, 2020.
65. Zhang X, Zhang H, Liao B, Guo J, Xia K and Tang B: Mutation analysis of PINK1 gene in patients with early-onset Parkinsonism. Zhong Nan Da Xue Xue Bao Yi Xue Ban 36: 490-497, 2011.
66. Rüb C, Wilkening A and Voos W: Mitochondrial quality control by the Pink1/Parkin system. Cell Tissue Res 367: 111-123, 2017.
67. Chen X, Wang Q, Li S, Li XJ and Yang W: Mitochondrial-dependent and independent functions of PINK1. Front Cell Dev Biol 10: 954536, 2022.
68. Liu T, Kong X, Qiao J and Wei J: Decoding Parkinson's disease: The interplay of cell death pathways, oxidative stress, and therapeutic innovations. Redox Biol 85: 103787, 2025.
69. Xiao B, Kuruvilla J and Tan EK: Mitophagy and reactive oxygen species interplay in Parkinson's disease. NPJ Parkinsons Dis 8: 135, 2022.
70. Ham SJ, Yoo H, Woo D, Lee DH, Park KS and Chung J: PINK1 and Parkin regulate IP3R-mediated ER calcium release. Nat Commun 14: 5202, 2023.
71. Gelmetti V, De Rosa P, Torosantucci L, Marini ES, Romagnoli A, Di Rienzo M, Arena G, Vignone D, Fimia GM and Valente EM: PINK1 and BECN1 relocalize at mitochondria-associated membranes during mitophagy and promote ER-mitochondria tethering and autophagosome formation. Autophagy 13: 654-669, 2017.
72. Zhao WB and Sheng R: The correlation between mitochondria-associated endoplasmic reticulum membranes (MAMs) and Ca2+ transport in the pathogenesis of diseases. Acta Pharmacol Sin 46: 271-291, 2025.
73. Yang W, Guo X, Tu Z, Chen X, Han R, Liu Y, Yan S, Wang Q, Wang Z, Zhao X, *et al*: PINK1 kinase dysfunction triggers neurodegeneration in the primate brain without impacting mitochondrial homeostasis. Protein Cell 13: 26-46, 2022.
74. Paul S and Pickrell AM: Hidden phenotypes of PINK1/Parkin knockout mice. Biochim Biophys Acta Gen Subj 1865: 129871, 2021.
75. Julienne H, Buhl E, Leslie DS and Hodge JJL: Drosophila PINK1 and parkin loss-of-function mutants display a range of non-motor Parkinson's disease phenotypes. Neurobiol Dis 104: 15-23, 2017.
76. Han R, Liu Y, Li S, Li XJ and Yang W: PINK1-PRKN mediated mitophagy: Differences between in vitro and in vivo models. Autophagy 19: 1396-1405, 2023.
77. Creed RB and Goldberg MS: Enhanced susceptibility of PINK1 knockout rats to α-Synuclein fibrils. Neuroscience 437: 64-75, 2020.
78. Haque ME, Akther M, Azam S, Kim IS, Lin Y, Lee YH and Choi DK: Targeting alpha-synuclein aggregation and its role in mitochondrial dysfunction in Parkinson's disease. Br J Pharmacol 179: 23-45, 2022.
79. Nguyen TT, Kim YJ, Lai TT, Nguyen PT, Koh YH, Nguyen LTN, Ma HI and Kim YE: PTEN-Induced putative kinase 1 dysfunction accelerates synucleinopathy. J Parkinsons Dis 12: 1201-1217, 2022.
80. Abd Elghani F, Safory H, Hamza H, Savyon M, Farhoud M, Toren-Hershoviz M, Vitic Z, Ebanks K, Shani V, Bisharat S, *et al*: SIAH proteins regulate the degradation and intra-mitochondrial aggregation of PINK1: Implications for mitochondrial pathology in Parkinson's disease. Aging Cell 21: e13731, 2022.
81. Yan YQ, Zheng R, Liu Y, Ruan Y, Lin ZH, Xue NJ, Chen Y, Zhang BR and Pu JL: Parkin regulates microglial NLRP3 and represses neurodegeneration in Parkinson's disease. Aging Cell 22: e13834, 2023.
82. Song Y, Zhou Y and Zhou X: The role of mitophagy in innate immune responses triggered by mitochondrial stress. Cell Commun Signal 18: 186, 2020.
83. Haque ME, Akther M, Jakaria M, Kim IS, Azam S and Choi DK: Targeting the microglial NLRP3 inflammasome and its role in Parkinson's disease. Mov Disord 35: 20-33, 2020.
84. Zhang NP, Liu XJ, Xie L, Shen XZ and Wu J: Impaired mitophagy triggers NLRP3 inflammasome activation during the progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis. Lab Invest 99: 749-763, 2019.
85. Li J, Li J, Guo E, Wang Y, Yang M, Huo H, Shi Y and Zhao L: Pink1 deficiency enhances neurological deficits and inflammatory responses after intracerebral hemorrhage in mice. Neurotherapeutics 21: e00317, 2024.
86. Soman SK and Dagda RK: Role of cleaved PINK1 in neuronal development, synaptogenesis, and plasticity: Implications for Parkinson's disease. Front Neurosci 15: 769331, 2021.
87. Kitada T, Pisani A, Porter DR, Yamaguchi H, Tscherter A, Martella G, Bonsi P, Zhang C, Pothos EN and Shen J: Impaired dopamine release and synaptic plasticity in the striatum of PINK1-deficient mice. Proc Natl Acad Sci USA 104: 11441-11446, 2007.
88. Gautier CA, Kitada T and Shen J: Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc Natl Acad Sci USA 105: 11364-11369, 2008.
89. Bus C, Zizmare L, Feldkaemper M, Geisler S, Zarani M, Schaedler A, Klose F, Admard J, Mageean CJ, Arena G, *et al*: Human dopaminergic neurons lacking PINK1 exhibit disrupted dopamine metabolism related to vitamin B6 Co-Factors. iScience 23: 101797, 2020.
90. Alharbi B, Al-Kuraishy HM, Al-Gareeb AI, Elekhnawy E, Alharbi H, Alexiou A, Papadakis M and Batiha GE: Role of GABA pathway in motor and non-motor symptoms in Parkinson's disease: A bidirectional circuit. Eur J Med Res 29: 205, 2024.
91. Hertz NT, Berthet A, Sos ML, Thorn KS, Burlingame AL, Nakamura K and Shokat KM: A neo-substrate that amplifies catalytic activity of Parkinson's disease-related kinase PINK1. Cell 154: 737-747, 2013.
92. Bingol B, Tea JS, Phu L, Reichelt M, Bakalarski CE, Song Q, Foreman O, Kirkpatrick DS and Sheng M: The mitochondrial deubiquitinase USP30 opposes Parkin-mediated mitophagy. Nature 510: 370-375, 2014.
93. Ryu D, Mouchiroud L, Andreux PA, Katsyuba E, Moullan N, Nicolet-Dit-Félix AA, Williams EG, Jha P, Lo Sasso G, Huzard D, *et al*: Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nat Med 22: 879-888, 2016.
94. Lin Y and Wen DT: Pink1 at the crossroads of aging, exercise, and diet in Parkinson's disease: A mechanistic review. Front Aging Neurosci 18: 1738559, 2026.

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