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Review Article

Mitochondrial Regulation by PINK1-Parkin Signaling

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Two genes responsible for the juvenile Parkinson's disease (PD), *PINK1* and *Parkin*, have been implicated in mitochondrial quality control. The inactivation of *PINK1*, which encodes a mitochondrial kinase, leads to age-dependent mitochondrial degeneration in *Drosophila*. The phenotype is closely associated with the impairment of mitochondrial respiratory chain activity and defects in mitochondrial dynamics. *Drosophila* genetic studies have further revealed that PINK1 is an upstream regulator of Parkin and is involved in the mitochondrial dynamics and motility. A series of cell biological studies have given rise to a model in which the activation of PINK1 in damaged mitochondria induces the selective elimination of mitochondria in cooperation with Parkin through the ubiquitin-proteasome and autophagy machineries. Although the relevance of this pathway to PD etiology is still unclear, approaches using stem cells from patients and animal models will help to understand the significance of mitochondrial quality control by the PINK1-Parkin pathway in PD and in healthy individuals. Here I will review recent advances in our understanding of the PINK1-Parkin signaling and will discuss the roles of PINK1-Parkin signaling for mitochondrial maintenance and how the failure of this signaling leads to neurodegeneration.

1. Introduction

While eukaryotic cells have acquired the highly efficient power-generating system of aerobic respiration by incorporating mitochondria into the cytosol, they can suffer from problems related to uncontrollable oxidization. Nondividing cells or tissues with high energy demands in long-living animals require countermeasures against this issue because mitochondrial dysregulation has been implicated as one cause of neurodegeneration.

The neuropathology of Parkinson's disease, the second most common neurodegenerative disorder after Alzheimer's disease, is characterized by the degeneration of dopaminergic neurons in the midbrain. Mitochondrial dysfunction has long been a suspected cause of PD because the Parkinsonism-inducing neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is as a selective inhibitor of mitochondrial complex I. Reduced complex I activity has also been reported in autopsied brains and platelets from patients with sporadic PD [1–3], while mutations or polymorphisms in mitochondrial DNA are implicated in the genetic risk for PD [4]. Animals treated with a variety of mitochondrial toxins, including MPTP, 6-hydroxy-dopamine (6-OHDA), rotenone, and paraquat, partly recapitulate PD pathology, suggesting that mitochondrial dysfunction and oxidative stress are key elements in PD etiology [5].

The genetic study of PD cases, including familial ones, has furthered molecular approaches to the understanding the pathogenic mechanisms underlying neurodegeneration in PD. Among the identified monogenic and susceptibility genes, *Parkin*, *PINK1*, *DJ-1*, and *HtrA2/Omi* are implicated in mitochondrial regulation, and recent molecular genetic and cell biological studies have revealed that Parkin and PINK1 play essential roles in mitochondrial quality control. In this paper, we focus on the latest studies of mitochondrial quality control by PINK1-Parkin signaling, including mitophagy for damaged mitochondria, and discuss how the loss of function of these genes may lead to neurodegeneration. The relevance and importance of mitophagy in PD is also described in detail in [6]. The progress of research on a various types of mitophagy is well reviewed in [7].

2. Genetic Association between the PD Genes *Parkin* and *PINK1*

An autosomal recessive form of juvenile PD (AR-JP) linked to the *PARK2* locus, which is the major cause of juvenile PD, is caused by mutations in the *Parkin* gene [8]. The gene product contains a ubiquitin-like (Ubl) domain at the N-terminus and two RING fingers flanking a cysteine-rich domain, termed in between RING fingers (IBR), with ubiquitin ligase (E3) activity [9–11] (Figure 1). The RING-in-between-RING- (RBR-) containing E3 family proteins have recently been proposed to possess a hybrid E3 activity with properties of both HECT-type and RING-finger-type E3s [12, 13]. The Ubl domain has been shown to autoinhibit the C-terminal RBR-containing region intramolecularly [14]. Although several *Parkin*-deficient mouse lines have been generated; most of them did not fully recapitulate dopaminergic neurodegeneration, which hindered the determination of the pathophysiological role of the Parkin protein *in vivo* [15–18]. A breakthrough was achieved in genetic studies using *Drosophila* models for Parkin. Loss of the *Parkin* gene in *Drosophila* results in the massive degeneration of muscle tissues and a defect in spermatogenesis that is caused by mitochondrial degeneration [19, 20]. Similar mitochondrial phenotypes were found in *Drosophila* lacking *PINK1*, which is associated with another recessive form of juvenile PD and encodes a serine-threonine kinase with a mitochondrial targeting signal at the N-terminus [21–23] (Figure 1). Genetic epistasis studies have suggested that *PINK1* is upstream of *Parkin* and that these two genes are indispensable for the maintenance of mitochondrial functions in *Drosophila* [21–23].

3. PINK1 and Parkin Are Involved in the Regulation of Mitochondrial Dynamics

One phenotypic feature produced by the loss of *PINK1* is the accumulation of elongated or aggregated mitochondria in the flight muscles and the central dopaminergic neurons, which is closely associated with mitochondrial degeneration [23–26] (Figure 2). These mitochondrial defects cause age-dependent motor impairment and decreased sperm fertility. A similar morphological abnormality has been observed in *Parkin*-deficient flies, in which highly fused and swollen mitochondria with indistinct cristae are observed [26, 27] (Figure 2). Intriguingly, *PINK1* and *Parkin* mutant phenotypes are partly rescued by increased Drp1 activity, which is a component of the mitochondrial fission machinery, or by the reduced activity of Mitofusin (Mfn) or optic atrophy 1 (OPA1), which are involved in mitochondrial fusion events [24–26]. Abnormal mitochondrial morphology and dynamics are also observed in mammalian cultured cells and hippocampal and dopaminergic neurons [25, 28]. These findings suggest that PINK1 and Parkin are implicated in the regulation of mitochondrial morphology and the maintenance of mitochondrial function in both insects and mammals.

4. Parkin Is Involved in the Elimination of Damaged Mitochondria through the Mitophagy Pathway

Parkin is localized in the cytosol of cultured cells, but it remained unknown how Parkin regulates mitochondria. One cell biological study reported that when the mitochondrial membrane potential in cultured mammalian cells is disrupted by mitochondrial damaging reagents, such as carbonyl cyanide *m*-chlorophenylhydrazone (CCCP), Parkin is translocated to mitochondria with low membrane potential [29] (Figure 3). This translocation induces the LC3-mediated autophagic elimination of the damaged mitochondria, called mitophagy [29] (Figures 4 and 5). The mitochondrial accumulation of proteins that are poly-ubiquitinated with mainly Lys63-linked polyubiquitin and only a small portion of Lys48 linkages [30–32] recruits the ubiquitin- and LC3-binding adaptor protein p62/SQSTM1 [33–35] and ubiquitin-binding deacetylase HDAC6 [30] after Parkin translocation. Although the details of this mechanism are unresolved, Lys63-linked polyubiquitination may contribute to the proteasomal degradation of mitochondrial proteins [36] and the HDAC6- and/or p62-mediated sequestration of mitochondria [30, 31]. Depolarized mitochondria treated with CCCP or paraquat accumulate in the perinuclear compartment in a p62/SQSTM1-dependent manner [33–35], which is followed by the activation of autophagic isolation and subsequent lysosomal degradation of the mitochondria [29]. The clustering of ubiquitinated mitochondria by p62 and HDAC6 is reminiscent of the sequestration of ubiquitinated proteins, called aggresomes [37, 38]. The class III phosphatidylinositol 3-kinase (PI3K) complex activator Ambra1 and mitochondrial protein p32 are characterized as Parkin-binding partners involved in mitophagy and mitochondrial function [39, 40]. Ambra1 is recruited in a Parkin-dependent manner to perinuclear clusters of depolarized mitochondria and activates class III PI3K, which facilitates the autophagic elimination of mitochondria, a later stage of mitophagy. p32, which is primarily localized in the mitochondrial matrix, was shown to regulate the mitochondrial morphology and dynamics by decreasing the protein level of Parkin although the detailed molecular mechanism of p32 remains unclear [40]. p32 is suggested to support oxidative phosphorylation (OXPHOS) through the promotion of protein synthesis for mitochondrial respiratory complexes [41].

How is the autophagic machinery targeted to mitochondria? In yeast, the outer mitochondrial protein ATG32 is reported to recruit the autophagic machinery [44, 45]. Although there are no ATG32 homologs in higher animals, BNIP3 (BCL2 and adenovirus E1B 19 kDa-interacting protein 3) and NIX/BNIP3 like (BNIP3 L), which belong to the BH3-only mitochondrial protein family, induce both cell death [46–48] and mitophagy [49–51]. NIX is involved in programmed mitochondrial clearance by mitophagy during reticulocyte maturation [49, 52] and is reported to be required for Parkin translocation to depolarized mitochondria treated with CCCP [51]. However, it is unclear whether NIX is a key regulator of the PINK1-Parkin

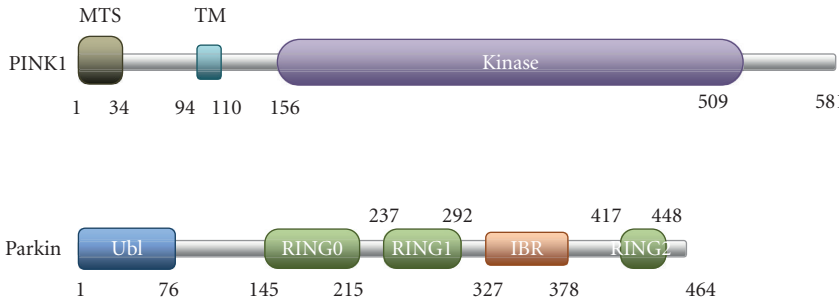

Figure 1: PINK1 and Parkin proteins. MTS, mitochondrial targeting sequence; TM, transmembrane domain; Ubl, ubiquitin-like domain; RING, Ring finger motif; IBR, in between RING fingers domain. RING0 has been characterized as a new domain with a similarity to conventional RING1 and RING2 domains [42]. The numbers correspond to the residue numbers for boundaries of the indicated domains.

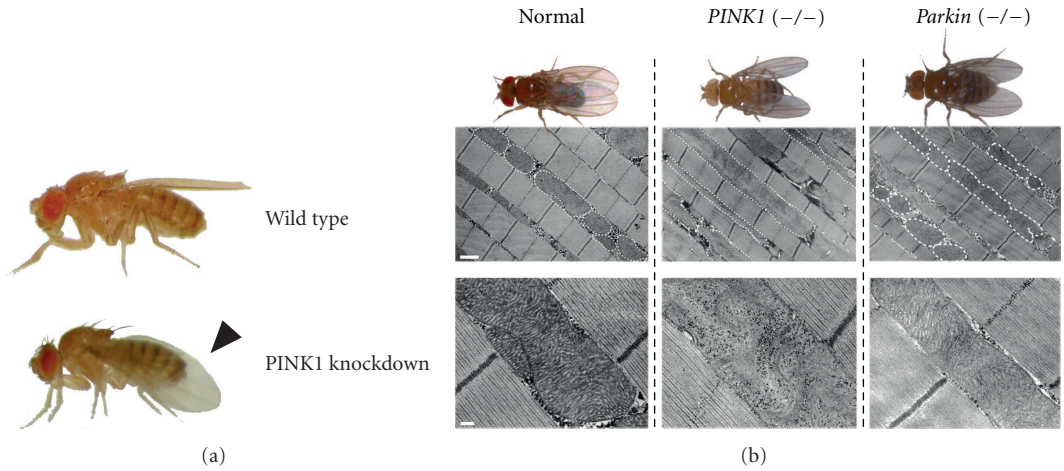

Figure 2: PINK1 and Parkin are required for the mitochondrial maintenance in *Drosophila melanogaster*. (a) Wings are kept in a horizontal position in wild-type fly (upper) while PINK1 knockdown in the muscles results in a drooped wing posture (arrowhead) due to the degeneration of the flight muscle mitochondria (lower). Data were adapted from [43]. (b) Transmission electron microscopy (TEM) analysis of the indirect flight muscle and morphology of mitochondria in 2-day-old adult flies. *PINK1*- and *Parkin*-deficient flies showed elongated and swollen mitochondria with indistinct cristae. Some mitochondria are outlined with broken lines to highlight morphology. Overhead view of wild-type (normal), *PINK1*- and *Parkin*-deficient flies is also shown. Scale bars = 1 μm in upper panels and 200 nm in lower. Original data were published in [27].

pathway because NIX-like proteins have not been found in *Drosophila*. In contrast, Nix has been characterized as a key mediator of a new type of mitochondrial quality control system, designated MALM (Mieap-induced accumulation of lysosome-like organelles within mitochondria) [53, 54]. MALM is involved in the selective degradation of oxidized mitochondrial proteins, which is performed by lysosome-like organelles independent of the PINK1-Parkin pathway.

5. PINK1 Regulates the Mitochondrial Translocation of Parkin

The translocation of Parkin from the cytosol to the mitochondria, which requires intact PINK1 with kinase activity, is an initial step of the mitophagy process in mammalian [33, 55–58] and *Drosophila* cultured cells [59] (Figure 6). Most of the pathogenic mutations found in PINK1 and Parkin compromise the mitochondrial translocation activity of Parkin, which was partly confirmed using a neuronal culture derived from iPS cells of *PINK1*-linked PD cases [60]. Thus, Parkin-mediated mitophagy may be closely associated with the etiology of juvenile PD caused by *PINK1* and *Parkin* mutations.

The E3 activity of Parkin is activated through an unknown mechanism after mitochondrial translocation, and it degrades several proteins localized in the mitochondrial outer membrane through the ubiquitin-proteasome pathway, which includes Mfn1 and Mfn2 [32, 61, 62], Drp1 [63], voltage-dependent anion channel 1 (VDAC1) [32, 33], and Bcl-2 [64]. The degradation of the mitochondrial elongation factor Mfn by Parkin, also observed in *Drosophila* cultured cells, contributes to the fragmentation of the mitochondria during mitophagy [59, 65]. This finding is consistent with observations in *Drosophila*, in which the loss of *PINK1* or *Parkin* leads to mitochondrial elongation, and a reduction of Mfn activity partly rescues the mitochondrial degeneration [24–26]. However, the elimination of Mfn by Parkin and the perinuclear aggregation of mitochondria by

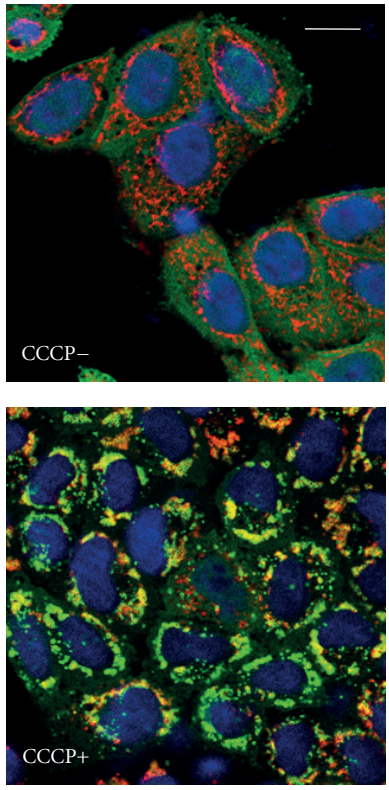

Figure 3: Mitochondrial translocation of Parkin. HeLa cells expressing GFP-tagged Parkin (green) were treated with (+) or without (–) 10 μM CCCP for 3 hrs to disrupt the mitochondrial membrane potential ($\Delta\psi$m). Parkin was moved to mitochondria upon the reduction of $\Delta\psi$m (stained with mitochondrial outer membrane protein Tom20 (red), counterstained with DAPI (blue) for the nucleus). Scale bar = 10 μm. Original data were provided by Shiba-Fukushima et al.

p62/SQSTM1 per se appear to be dispensable for mitophagy in mammalian cells [32, 34, 35], although the requirement of p62 is controversial [33]. As it is very likely that a p62-related protein NBR1 is also recruited to the damaged mitochondria in cultured mammalian cells, NBR1 may compensate the p62 function [32]. Mfn degradation and mitochondrial perinuclear clustering may prevent the refusion of damaged mitochondria with healthy mitochondria and the axonal transportation of damaged mitochondria [34, 61]. In addition, mitochondrial reorganization by the inactivation of Mfn and the recruitment of p62 may facilitate the isolation of mitochondria by the autophagosome [61].

6. Molecular Regulation of PINK1 and Parkin

PINK1 was originally isolated as one of the genes induced by the tumor suppressor PTEN, suggesting that the PI3K/AKT pathway negatively regulates *PINK1* expression [66]. Later, FoxO, a downstream component of the PI3K/AKT pathway, was shown to transactivate the mammalian *PINK1* promoter [67]. Although *PINK1* transcripts are abundantly expressed in cultured cells and several mitochondria-rich tissues, including the heart, skeletal muscle, and testis [66], it is difficult to detect endogenous PINK1 protein, which has made it challenging to elucidate the molecular action of PINK1. However, PINK1 turned out to be accumulated in depolarized mitochondria rapidly [55, 57, 58], suggesting that PINK1 is subjected to a posttranslational degradation (Figure 7). Several studies report that the rhomboid family protease presenilin-associated rhomboid-like protein (PARL), which is localized in the mitochondrial inner membrane (IM), processes PINK1 in a mitochondrial membrane potential-dependent manner [68–72]. Newly synthesized PINK1 in the cytosol is inserted into the IM, through the mitochondrial import activity of the Tom complex [73], and is cleaved in its putative transmembrane domain by PARL to generate the 52 kDa form of PINK1. The 52 kDa form is rapidly removed by a proteasome-dependent pathway, most likely after its release from the mitochondrial intermembrane space (IMS) to the cytosol [69–71].

Upon the depolarization of the mitochondrial membrane potential, IM insertion and the subsequent processing of PINK1 by PARL may be inhibited, leading to the accumulation of full-length PINK1 in the mitochondrial outer membrane (OM), most likely facing the cytosol [70, 71, 74]. However, it remains controversial whether the processing of PINK1 by PARL is required for Parkin recruitment upon depolarization of the mitochondria, and further studies will be necessary to completely resolve the topology changes of the processed forms of PINK1 [70, 72].

The accumulation and autophosphorylation of PINK1 likely stimulate its kinase activity, which is required for the mitochondrial translocation of Parkin [73, 75]. Although the detailed molecular mechanism through which PINK1 recruits Parkin to mitochondria remains unclear, our data suggest that the PINK1-dependent phosphorylation of Parkin in the Ubl domain is involved [76]. The phosphorylation of the Parkin Ubl domain by PINK1 may also contribute to the stimulation of Parkin E3 activity through the release of the RBR region from the autoinhibitory mechanism by the Ubl domain [77].

Parkin is also regulated at the transcriptional level. The unfolded protein response (UPR) transactivates Parkin transcripts [9, 78–80] through ATF4, a transcription factor that is involved in the unfolded protein response (UPR) [81]. Mitochondrial damage may induce the activation of the UPR [81, 82] and oxidative stress [83], leading to the upregulation of Parkin expression. In other stress contexts, such as γ-irradiation or hydrogen peroxide, p53 transactivates Parkin [84]. Conversely, Parkin is reported to suppress the transcription of p53 through the direct binding of Parkin to the *p53* promoter region, suggesting a negative feedback mechanism [85]. The p53-dependent induction of *Parkin* is implicated in the regulation of glucose metabolism because the loss of *Parkin* activates glycolysis and reduces mitochondrial respiration, leading to the Warburg effect [84]. This phenotype seems to be associated with the accumulating evidence from tumor cell lines and model animals that Parkin functions as a tumor suppressor. *Parkin* gene expression is downregulated or absent in ovarian [86–88] and breast tumors [89], acute lymphoblastic leukemia and chronic myeloid leukemia [90],

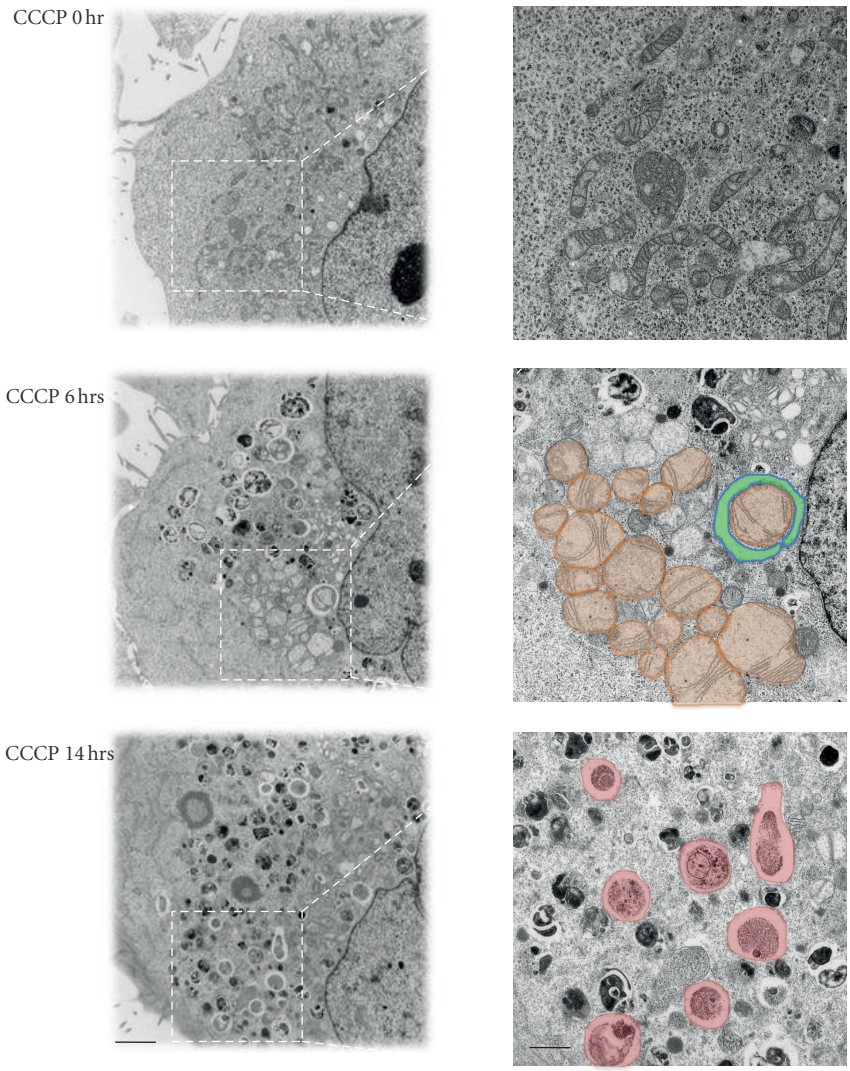

Figure 4: Ultramicroscopic analysis of mitophagy by Parkin. HeLa cells overexpressing Parkin were treated with CCCP for the indicated periods of time. Tubular mitochondria were seen in the cytoplasm before CCCP treatment. Swollen mitochondria (marked in orange) were observed in the perinuclear region of cytoplasm 6 hrs after CCCP treatment. The isolation membrane (green) encircling a swollen mitochondrion was also seen. Partially digested mitochondria in the lysosome-like vacuoles (red) were observed 14 hrs after CCCP treatment. Scale bars = 2 μm (left) and 500 nm (right). Original data were provided by Shiba-Fukushima et al.

colorectal cancers [91], non-small-cell lung cancer [92], glioblastoma [93], and tumor cell lines [94]. The inactivation of *Parkin* also leads to enhanced hepatocyte proliferation and the development of hepatic tumors with characteristics of hepatocellular carcinoma in mice [95] and humans [96].

7. PINK1 and Parkin Regulate Mitochondrial Motility

A variety of mitochondrial proteins are ubiquitinated and degraded through the ubiquitin-proteasome pathway after the mitochondrial translocation of Parkin [32]. It is not clear whether all of these proteins are ubiquitinated by Parkin. Among the mitochondrial proteins that are degraded, Mfn (see above) and Miro are well characterized as Parkin substrates. Miro family proteins contain two GTPase domains separated by a linker region containing putative calcium-binding EF hand motifs [97]. Miro is involved in microtubule-dependent mitochondrial transport through its binding partners Milton and kinesin heavy chain (KHC) [98–100]. Miro has been identified as one of the binding partners of PINK1 [101] and was isolated as a gene that modulates the phenotypes of *PINK1* mutant flies [102]. Two recent reports have demonstrated that Miro is degraded through the PINK1-Parkin pathway, which aids in the removal of damaged mitochondria from mitochondrial trafficking pathways [102, 103] (Figure 8). Wang et al. have also shown that the phosphorylation of Miro by PINK1 is a prerequisite for its degradation via Parkin [103], while another study failed to observe Miro phosphorylation or the requirement of this modification for Miro degradation [102].

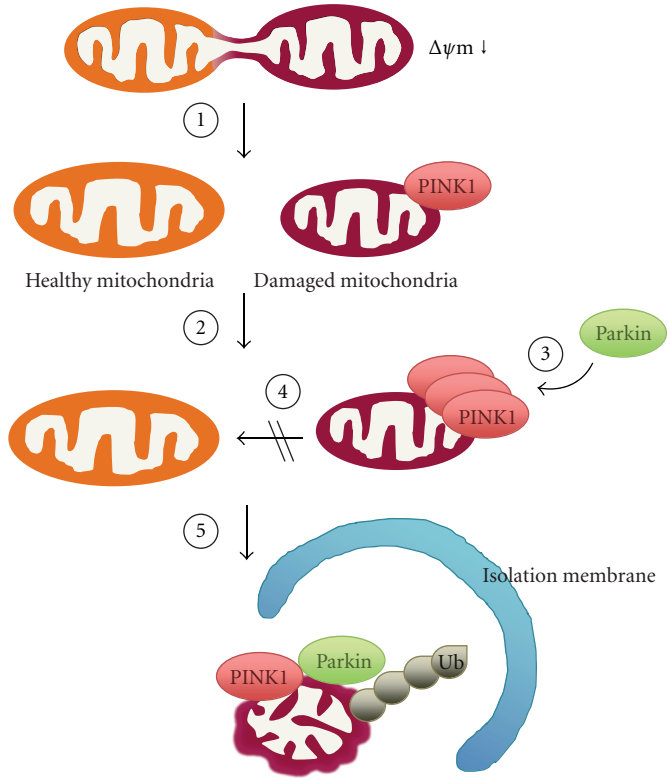

Figure 5: Mitophagy mediated by PINK1 and Parkin. Fusion/fission is required for the maintenance of a healthy mitochondrial population. Mitochondrial fusion is thought to require the exchange of a set of internal components, including copies of the mitochondrial genome, respiratory proteins, and metabolic products. Mitochondrial fission may play a role in the removal of damaged mitochondria (1, 2) with a reduced $\Delta\psi$m through an autophagy-lysosomal pathway, that is, "mitophagy." PINK1 is constitutively degraded in healthy mitochondria (see also Figure 3). Upon a decrease in $\Delta\psi$m, PINK1 is stabilized in the mitochondrial outer membrane (OM) (3). The accumulation of PINK1 induces the translocation of Parkin from the cytosol to the mitochondria (3), which leads to Parkin-dependent mitochondrial protein degradation, through which Mfn is degraded to prevent healthy mitochondria from refusing with damaged mitochondria (4). Parkin subsequently activates the autophagy machinery, which includes induction of the isolation membrane for autophagy (5).

8. Possible Involvement of DJ-1 and HtrA2 in the PINK1-Parkin Pathway

DJ-1, which exerts neuroprotective activities by scavenging hydrogen peroxide through self-oxidation, has been reported to be involved in mitochondrial maintenance [104–109]. Recently accumulated data suggest that DJ-1 functions in parallel to the PINK1-Parkin pathway to control mitochondrial activity in cultured cells [110, 111] and *Drosophila* [110, 112], while DJ-1/PINK1/Parkin triple knock-out mice exhibit no degenerative phenotypes in the nigrostriatal system [113]. In the context of mitophagy, however, reactive oxygen species (ROS) sensitize the mitochondrial translocation of Parkin in primary cultured neurons and other cells, and this sensitization is enhanced by the loss of DJ-1 [114]. A related finding has been reported that increased glutathione S-transferase activity protects dopaminergic neurons in *Parkin*-deficient flies, suggesting that ROS overproduction is an important component of the pathology of PINK1-Parkin defects [115].

Although the association between PD and the *HtrA2* gene, which encodes a mitochondrial serine protease and is involved in mitochondrion-dependent apoptosis [116–119], is disputed [120–122], the loss of the *HtrA2* gene leads to the selective loss of striatal neurons in mice, causing a Parkinsonian neurodegenerative phenotype [123]. It has been suggested that PINK1-dependent phosphorylation of HtrA2 enhances the protease activity of HtrA2, which is required for stress resistance [124]. In contrast, it has been shown that HtrA2 cleaves and inactivates Parkin under stress condition [125]. Genetic studies in *Drosophila* [126] and mice [127] do not suggest that HtrA2 is implicated in the PINK1-Parkin pathway.

9. Dysregulation of Mitochondrial Control and Possible Disease Relevance

Although PINK1-Parkin signaling appears to be conserved, at least between mammals and *Drosophila*, *PINK1*- and *Parkin*-deficient mice do not recapitulate the symptoms of PD. The molecular mechanism underlying mitochondrial quality control by the PINK1-Parkin pathway has been mostly characterized in cultured cells using mitochondria-damaging reagents. Therefore, the relevance of mitophagy

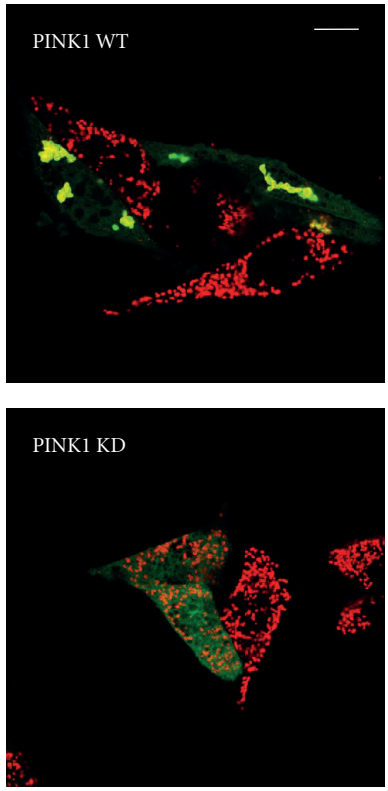

Figure 6: PINK1 kinase activity is required for the mitochondrial translocation of Parkin. Wild-type (WT) or kinase-dead (KD) PINK1 together with GFP-Parkin (green) was introduced in mouse embryonic fibroblasts derived from a *PINK1*-deficient mouse. GFP-Parkin was located on the mitochondria (red; Tom 20) in cells expressing PINK1 WT but not PINK1 KD after CCCP treatment. Scale bar = 10 μm. Original data were provided by Shiba-Fukushima et al.

observed in the cultured cells to PD etiology remains debatable. However, the accumulating evidence of mitochondrial abnormalities in animal models and PD patients has increased our understanding of the pathogenesis of the disease. It has been shown that mitochondrial populations harboring mutant mitochondrial genomes are selectively eliminated by Parkin [128]. The ubiquitination and elimination of Mfn do not occur in human fibroblasts derived from *PINK1*- and *Parkin*-linked PD patients following oxidative stress induction and depolarization treatment of the mitochondria [129]. Recent studies on *Parkin*- and *PINK1*-deficient mice have reported morphological and functional alterations of the mitochondria in neurons [130, 131] and astrocytes [132]. Like the muscle degeneration in *Drosophila*, the function of the heart, which depends on highly developed cardiac muscle mitochondria, is also impaired with increased oxidative stress in *PINK1* null mice [133]. Ischemic preconditioning has cardioprotective effects in heart failure models in which the mitochondrial translocation of Parkin is induced [134]. The deletion of *Parkin* in mice abolishes this effect [134]. Although the role of PINK1 and Parkin in the cardiac function of humans is yet unknown, it is worth noting that the prevalence of heart failure in elderly PD patients is twice that of elderly individuals without PD [135].

Interestingly, a missense mutation of the mitophagy-associated *PARL* gene found in PD cases abolishes PINK1 processing activity and subsequent Parkin-mediated mitophagy [72]. No polymorphisms in the *Miro* gene have been linked to PD to date [136], while the inactivation of Mfn2 but not Mfn1 in dopaminergic neurons of the mouse brain resulted in progressive degeneration of the nigrostriatal pathway, suggesting a functional difference between Mfn1 and Mfn2 in neurons [137, 138]. Mutations in Mfn2 cause the Charcot-Marie-Tooth disease type 2A, a peripheral nerve disorder characterized by a slowly progressive degeneration of the muscles of the extremities [139–141]. Mfn2 has been shown to be required for axonal mitochondrial transport by direct binding to Miro [142]. In this context, the mitochondrial fusion activity is not suggested to be essential for the mitochondrial transport because knockdown of OPA1, another protein for mitochondrial fusion, does not affect the mitochondrial motility [142].

10. Therapeutic Approach to the Mitochondrial Defects Caused by the Dysregulation of PINK1-Parkin Signaling

The impairment of mitochondrial complex I activity has been implicated in *PINK1*- and *Parkin*-linked PD cases and animal models [131, 143–148]. The addition of complex I and II substrates has been shown to improve the reduced respiration activity caused by inactivated PINK1 in cultured neurons [148]. The introduction of the yeast NADH dehydrogenase gene, which compensates for complex I activity, effectively rescues the *PINK1* mutant phenotype in *Drosophila* but does not ameliorate the *Parkin* phenotype, suggesting that the complex I regulation pathway is downstream of or parallel to PINK1 but upstream of Parkin [149].

A recent genetic screen using a *Drosophila PINK1* model isolated an enzyme producing vitamin K_2 as a strong modifier gene and revealed that vitamin K_2 functions as a mitochondrial electron carrier [150]. Because vitamin K_2 administration improves both *PINK1* and *Parkin* phenotypes in *Drosophila*, vitamin K_2 may be a promising therapy for general PD and *PINK1*- or *Parkin*-linked PD. The suppression of the mammalian target of rapamycin complex 1 (mTORC1) signaling for general protein translation [151–153] and stimulation of mitochondrial biogenesis [154, 155] may also be beneficial for the prevention of PD pathogenesis (Figure 9).

11. Conclusions

One of the neuropathological features of PD is the accumulation of protein inclusions called Lewy bodies, which implies a dysfunction of protein quality control regulated by the ubiquitin-proteasome and autophagy pathways. Indeed, some PD and PD-related genes are characterized as components of the protein quality control system (e.g., LRRK2 [157–162], ATP13A2 [163–166], HtrA2 [167, 168], and

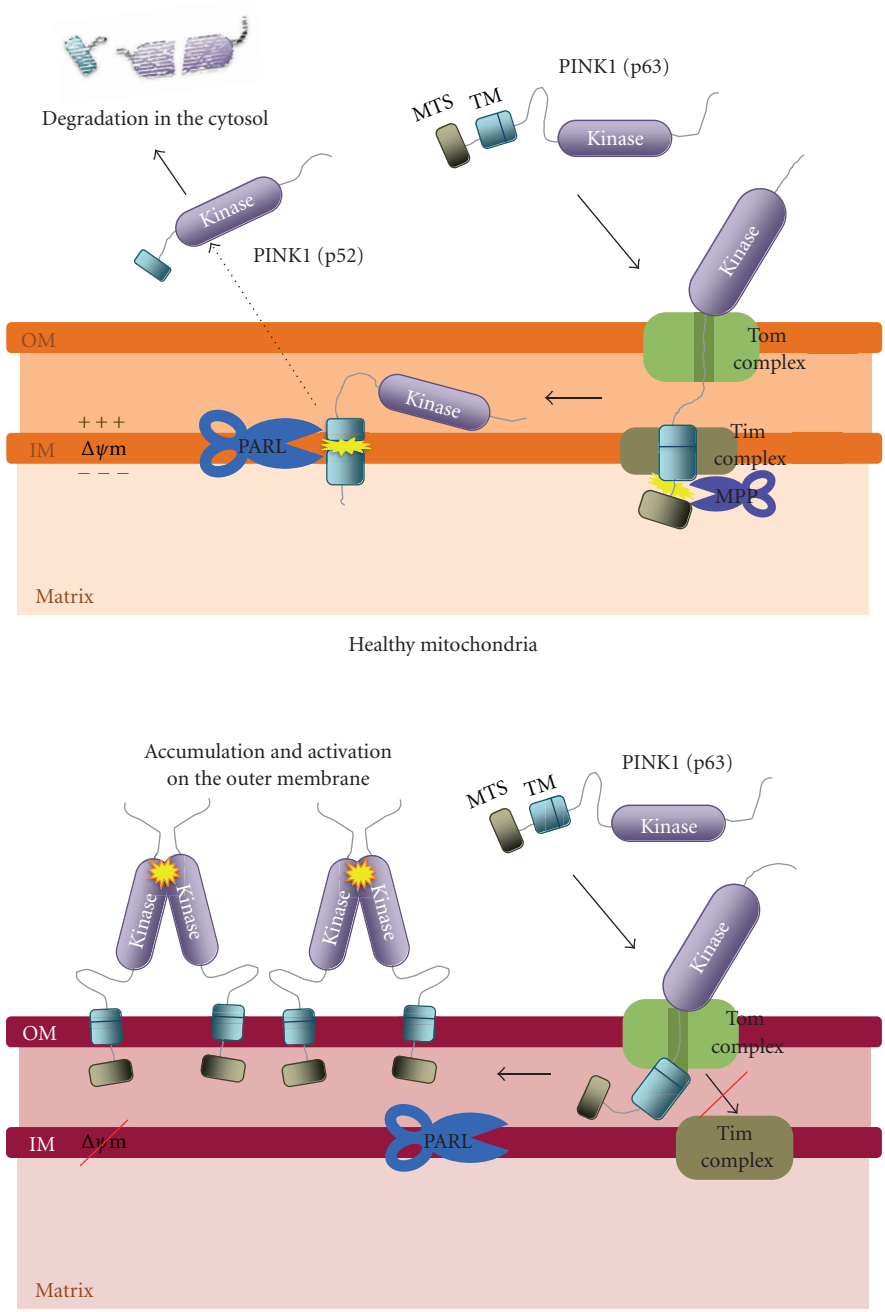

Figure 7: Proposed model of posttranslational processing of PINK1. Upper: newly synthesized PINK1 (p63) is targeted to the mitochondrial inner membrane (IM) via the Tom and Tim complexes. Full-length PINK1 is processed by mitochondrial processing protease (MPP), which cleaves the mitochondrial targeting sequence to generate the 60 kD form of PINK1 [130, 156]. PINK1 is then cleaved to a 52 kD form within the IM by PARL [68–71, 156]. The 52 kD PINK1 is released from the cytosol and degraded through proteasome activity. Lower: upon a decrease in $\Delta\psi$m, PINK1 is accumulated at the OM, most likely due to the inhibition of its transportation to the Tim complex.

FBXO7 [169, 170]) or abnormal proteins themselves (α-Synuclein [171–173], Tau [174–180]). In fission yeast, the impairment of the ubiquitin-proteasome pathway induces the accumulation of reactive oxygen species in mitochondria [181]. These mitochondria are removed from the autophagy pathway [181]. In a *Drosophila* model, it has been shown that mitochondria with accumulated misfolded proteins are also removed by Parkin [182]. The observation evokes endoplasmic-reticulum- (ER-) associated protein degradation (ERAD), which eliminates misfolded or unassembled proteins from the ER [183]. Intriguingly, a AAA+ ATPase p97/VCP, which is required for ERAD along with proteasome

Figure 8: Quarantine control of mitochondrial transportation by PINK1-Parkin signaling. Mitochondria are transported along the microtubule network through the Miro-Milton-KHC complex (1). In neurons, the transportation of healthy mitochondria to the nerve terminal ensures a stable energy supply for a variety of synaptic activities. PINK1 is activated in mitochondria with reduced $\Delta\psi$m and recruits Parkin, which results in Miro degradation; thus, damaged mitochondria are selectively removed from the mitochondrial transport machinery (2). These mitochondria may be further eliminated by PINK1-Parkin-mediated mitophagy.

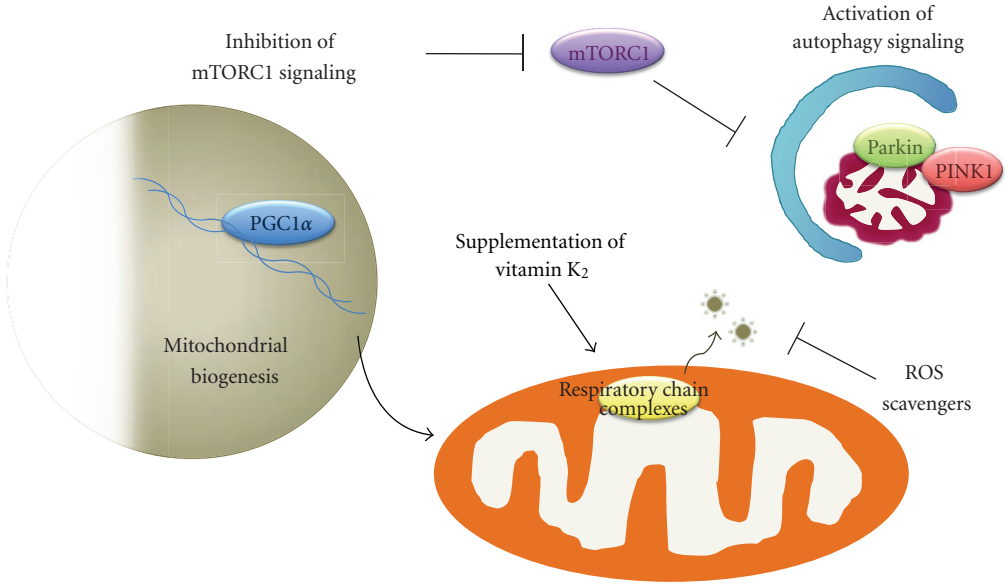

Figure 9: Signal pathways that modulate the PINK1-Parkin pathway. Inhibition of the mTORC1 pathway stimulates mitochondrial degeneration in *Drosophila*, while supplementation with vitamin K_2 or ROS scavengers ameliorates defects in respiratory chain activity. Increased mitochondrial biogenesis by the activation of peroxisome proliferator-activated receptor-γ coactivator- (PGC)-1α and autophagy machinery may improve mitochondrial activity.

activity, is involved in the elimination of proteins on the OM during mitophagy [61]. Thus, the pathways for protein quality control and mitochondrial maintenance are likely to be linked to each other.

Two gene products implicated in juvenile PD, PINK1 and Parkin, have recently been implicated in mitochondrial quality control. PINK1-Parkin-mediated mitophagy includes two major components: commitment to elimination by PINK1 and Parkin and execution of elimination by autophagy. While canonical autophagy components appear to be employed in the autophagy stage, the molecular mechanism through which PINK1 and Parkin signal the commitment to elimination remains largely unclear [29, 57, 152, 184]. This is obviously an important issue, and its resolution might lead to the identification of new genes associated with neurodegenerative disorders and new targets for a therapeutic approach to PD.

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