Chapter 6

Mitophagy Regulated by the PINK1-Parkin Pathway

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Additional information is available at the end of the chapter

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Abstract

Mitochondria play key roles in the cellular metabolism of lipids and iron as well as in cell death signaling. Mitochondrial dysregulation produces reactive oxygen species (ROS), which results in oxidative stress. Moreover, the accumulation of damaged mitochondria leads to cell death and tissue dysfunction. Mitochondrial maintenance involves mitophagy, a selective autophagy process that removes abnormal mitochondria. Parkinson's disease (PD) is a movement disorder caused by the specific loss of dopaminergic neurons in the substantia nigra of the midbrain. Two genes implicated in PD, *PINK1* and *Parkin*, regulate mitophagy in cultured cells. Reduction of the $\Delta\Psi m$ leads to activation of PINK1, which stimulates the recruitment of Parkin to the mitochondrial outer membrane of damaged mitochondria and activates Parkin's ubiquitin-ligase activity. Activated mitochondrial Parkin leads to the ubiquitination of mitochondrial proteins and subsequent mitophagy. This elaborate molecular mechanism was recently uncovered and the findings demonstrate the physiological and pathological roles of the PINK1-Parkin pathway. Here, we review these key findings on the molecular mechanism and ideas relevant to neurodegeneration caused by dysregulation of the PINK1-Parkin pathway.

Keywords: Dopaminergic neurons, mitochondria, Parkinson's disease, protein kinase, ubiquitin ligase

1. Introduction

In eukaryotic cells, mitochondria are highly efficient power-generating systems that perform aerobic respiration. Injured mitochondria leak ROS, resulting in oxidative stress and reduction of energy supply; this dysfunction eventually leads to cell death. Therefore, appropriate regulation of mitochondria is critical for vital activity and anti-aging. Mitochondrial dysregulation has indeed been implicated in various human diseases, including cancer, diabetes, myopathy, and a variety of neurodegenerative disorders such as amyotrophic lateral sclerosis

(ALS), Huntington's disease, neuropathy, and Parkinson's disease (PD). PD is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the midbrain. The motor symptoms of PD include tremor, rigidity, slowness of movement, and difficulty with ambulation. Although familial forms of PD are relatively rare cases, the identification of genes responsible for PD enables a better understanding of the molecular mechanisms underlying neurodegeneration. *Parkin* and *PINK1* mutations are associated with autosomal recessive forms of early-onset PD [1, 2]. A series of studies on *PINK1* and *Parkin* indicates that these two genes work in a coordinated manner in functions related to mitochondrial maintenance including mitochondria motility, proteasomal degradation of mitochondrial proteins, and selective mitochondrial autophagy (also known as mitophagy). These results strongly imply that dysregulation of mitochondria is one of the major factors in the etiology of PD. In this chapter, we focus on the latest studies that have made significant progress in elucidating the molecular mechanisms of mitochondrial quality control via the PINK1-Parkin pathway.

The selective degradation of mitochondria via an autophagic process was originally reported as mitophagy by J.J. Lamasters et al. [3]. In yeast, loss of the *MDM38* gene product, a component of the mitochondrial protein export machinery, reduces the content of respiratory chain complexes, elicits morphological mitochondrial changes, and disturbs mitochondrial K^+ homeostasis, resulting in mitophagy [4]. When mammalian reticulocytes mature into erythrocytes, mitochondria are removed by mitophagy [5]. In fertilized *C. elegans* oocytes, sperm-contributed mitochondria are selectively degraded by mitophagy [6, 7]. These observations indicate that mitophagy plays important roles in mitochondrial maintenance, differentiation, and developmental processes in eukaryotes.

2. Mitochondrial segregation and mitophagy

Damaged mitochondria are selectively segregated and degraded by mitophagy [3]. Mitochondrial morphology is maintained by mitochondrial fusion and fission. Mitofusin (Mfn) regulates or mediates mitochondrial fusion whereas Drp1 and Fis1 promote mitochondrial fission in mammals as well as in yeast [8]. Inhibition of Drp1 or Fis1 activity results in the suppression of mitophagy and the accumulation of oxidized mitochondrial proteins, leading to reduced respiration and impaired insulin secretion [9]. Orthologs of *Parkin* and *PINK1* have been identified in *Drosophila* [10–12]. Loss of *Drosophila PINK1* causes mitochondrial degeneration, resulting in male sterility, apoptotic muscle degeneration, and increased sensitivity to multiple stresses, including oxidative stress. Loss of *Drosophila Parkin* produces phenotypes similar to those elicited by the loss of *PINK1*, and Parkin overexpression rescues the mitochondrial defects observed in PINK1 mutant flies [11–13]. The *Drosophila* Parkin and PINK1 phenotypes are suppressed by increased Drp1 activity and are exacerbated by Opa1 or Mfn [14–16]. PINK1 and Parkin collaboratively ubiquitinate Mfn and the steady-state abundance of Mfn is inversely correlated with the activity of PINK1 and Parkin in *Drosophila* [17, 18]. Parkin also ubiquitinates Mfn1 and Mfn2 in mammalian cells, leading to proteasome- and p97/VCP-

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dependent degradation [19–21]. These reports indicate that PINK1 and Parkin positively regulate mitochondrial fission, which may facilitate mitochondrial clearance via mitophagy.

3. Parkin E3 ligase and ubiquitination

Parkin contains a ubiquitin-like (Ubl) domain at the *N*-terminus, RING-between-RING (RBR) domains at the *C*-terminus, and an atypical RING domain, RING0, in its linker region (Figure 1) [22–24].

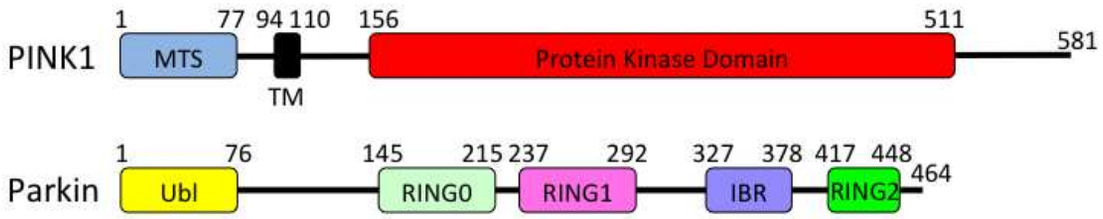

Figure 1. Schematic of PINK1 and Parkin proteins MTS: mitochondrial targeting sequence, TM: transmembrane region, Ubl: ubiquitin-like domain, RING: really interesting new gene domain, IBR: in between RING domain. Numbers indicate the positions in the amino acid sequence.

E3 ubiquitin ligases are roughly divided into two groups: RING finger-type E3 ligases and homologous to the E6AP carboxyl terminus (HECT)-type E3 ligases. HECT-type E3 ligases form a thioester intermediate between ubiquitin and a catalytic cysteine residue before transferring ubiquitin from E2 to a substrate. By contrast, RING finger-type E3 ligases mediate the direct transfer of ubiquitin from E2 to the substrate. Parkin, which was formerly classified as a RING finger-type E3 ligase, is now categorized as a HECT-RING hybrid E3-ligase [25, 26]. To activate Parkin, a ubiquitin-charged E2 associates with Parkin RING1 and ubiquitin is transferred from E2 to Cys431 in the RING2 domain of Parkin to form the HECT-like thioester intermediate [25–27]. Similar molecular behaviors were observed in other RBR proteins such as HHARI, and proteins containing a RBR domain are thought to be HECT-RING hybrid E3-ligases [25, 26].

PINK1 encodes a serine–threonine protein kinase with a mitochondrial targeting signal at the N-terminus (Figure 1) [2]. PINK1 is constitutively processed by mitochondrial proteases at the mitochondrial membrane of healthy mitochondria, resulting in proteasomal degradation [28–30]. The reduction in mitochondrial membrane potential ($\Delta\Psi m$) in damaged mitochondria leads to the accumulation and activation of PINK1 on the outer mitochondrial membrane [29]. Activated PINK1 recruits Parkin from the cytosol to mitochondria in response to decreased $\Delta\Psi m$. This action stimulates Parkin E3 activity, thereby promoting mitochondrial degradation via mitophagy [29, 31–35]. The Ubl domain in the N-terminal region of Parkin inhibits the E3 activity of Parkin by interacting with the RBR region [36]. PINK1 phosphorylates Ser65 in the Ubl domain of Parkin to activate Parkin E3 activity (Figure 2) [37–42]. Activated PINK1 also phosphorylates monomeric ubiquitin at Ser65 in the cytosol. Transient interaction with

phosphorylated ubiquitin leads to a conformational change in Parkin and subsequent activation of Parkin E3 activity [41, 43–45].

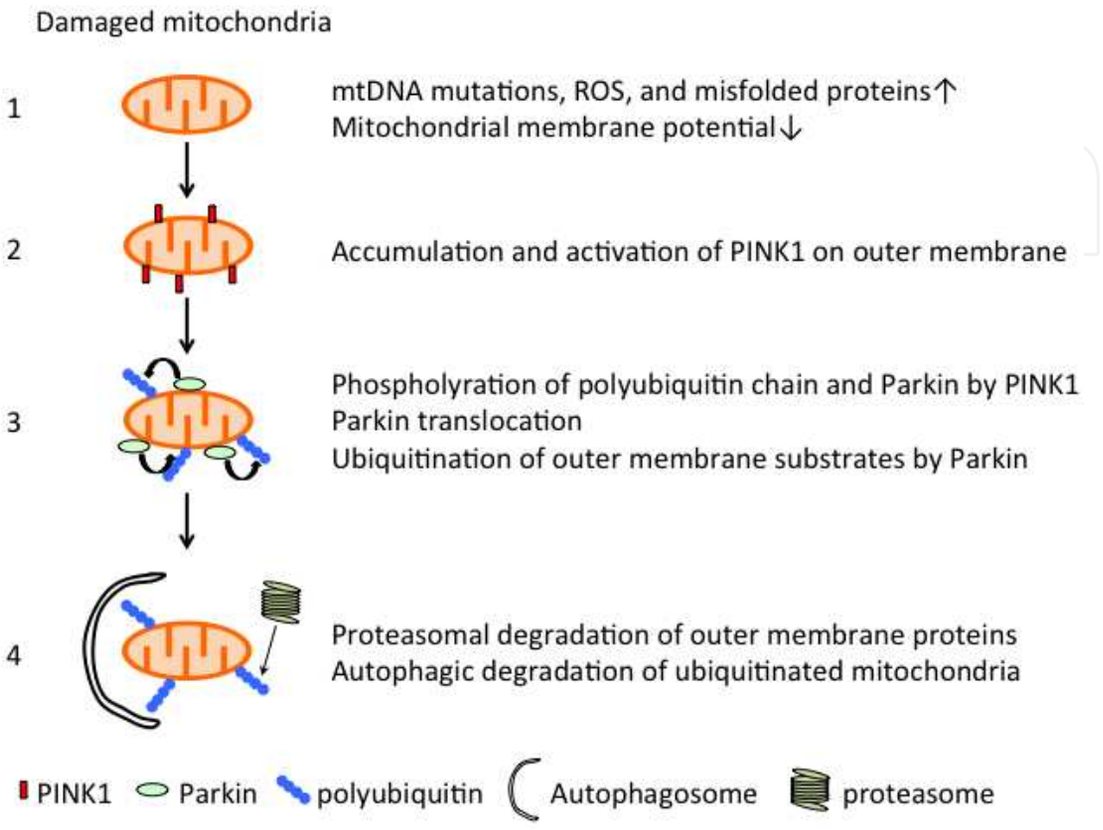

Figure 2. PINK1-Parkin-mediated mitophagy (1) Mitochondrial DNA (mtDNA) mutations, ROS overproduction and misfolded protein accumulation cause a reduction in ΔΨm. (2) PINK1, which is constitutively degraded under steady-state conditions, accumulates on damaged mitochondria. (3) Accumulated PINK1 activates itself and elicits mitochondrial translocation and Parkin activation through phosphorylation. Activated Parkin ubiquitinates substrates on mitochondria. (4) Polyubiquitinated proteins on the mitochondrial outer membrane are degraded by the proteasome, and damaged mitochondria are eliminated concurrently by mitophagy.

It has been reported that Parkin binds to four tandem-repeated mitochondrial ubiquitin chains, which mimic Lys63-linked polyubiquitin chains only when PINK1 is activated [46]. Subsequent reports have revealed that PINK1 phosphorylates mitochondrial polyubiquitin, resulting in Parkin activation and mitochondrial relocation (Figure 3) [41, 47]. While PINK1 phosphorylates both monoubiquitin and polyubiquitin, including Lys48- and Lys63-linked polyubiquitin chains, activated Parkin preferentially associates with Lys63-linked phosphorylated polyubiquitin chains on mitochondria [41]. Lys48-linked polyubiquitin chains are generally utilized as signals for proteasomal degradation [48], whereas Lys63-linked ubiquitin chains were first identified in yeast as atypical ubiquitin chains that respond to stress [49]. A variety of functions of Lys63-linked polyubiquitin chains were subsequently characterized, including the regulation of kinase activity, DNA damage response, signal transduction scaffolding, vesicular trafficking, and endocytosis [50]. Thus, the formation of Lys63-linked ubiquitin chains during mitophagy might have a critical role beyond Parkin recruitment [51].

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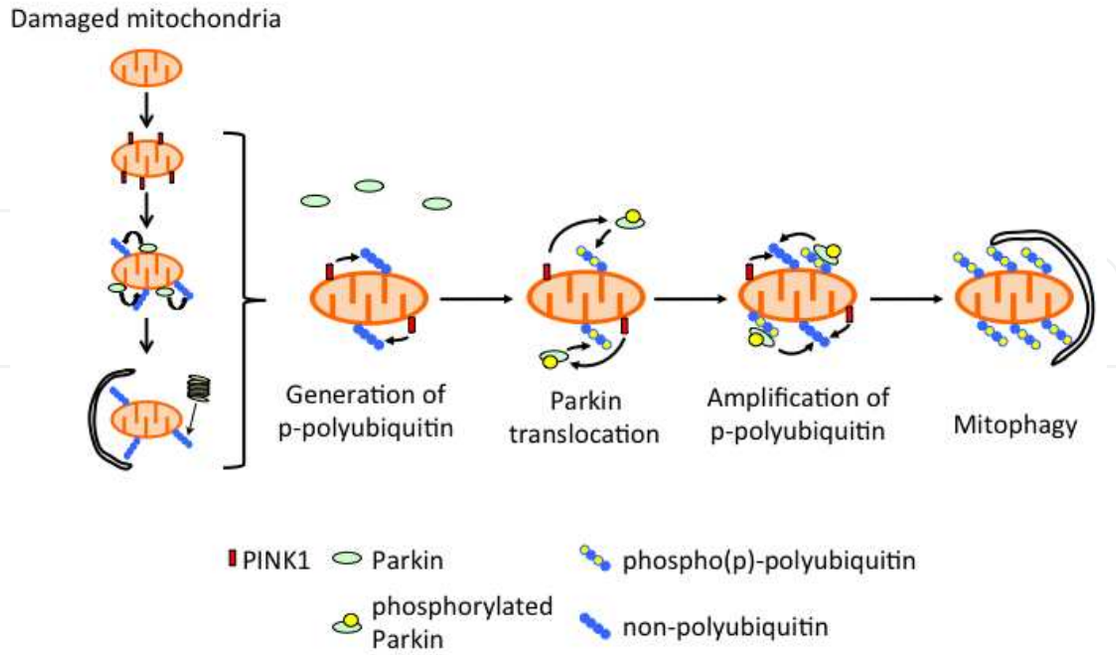

Figure 3. Amplification of phospho-polyubiquitin chain production achieves rapid Parkin translocation and activation Phospho-polyubiquitin chains on mitochondria are produced in collaboration with PINK1 and Parkin. The mechanism responsible for the formation of initial ubiquitin chains on mitochondria remains unresolved. The ubiquitin chains might be attached to outer membrane proteins via mitochondrial ubiquitin ligases other than Parkin. Alternatively, Parkin, which is activated by phospho-monoubiquitin in the cytosol, could attach ubiquitin chains to mitochondrial proteins. Phosphorylation of polyubiquitin chains by PINK1 promotes further Parkin activation and relocation to the mitochondrial outer membrane, amplifying the generation of phospho-polyubiquitin chains and subsequently recruiting autophagy machinery to ubiquitinated mitochondria.

Several reports have demonstrated that Parkin-interacting E2 enzymes mediate the ubiquitination reaction of Parkin. UBE2N is related to Parkin-mediated Lys63-linked ubiquitination [51, 52], whereas UBE2N, UBE2L3, and UBE2D2/3 synergistically contribute to Parkin-mediated mitophagy [53]. Knockdown of UBE2N, UBE2L3, or UBE2D2/3 but not UBE2A, UBE2S, or UBE2T significantly reduces autophagic clearance of depolarized mitochondria or Parkin E3 activity [53, 54]. However, recent reports indicate that the linkage property of polyubiquitination depends on Parkin itself rather than involved E2s [47], and that atypical Lys6- and Lys11-mediated polyubiquitination chains are also generated by Parkin and contribute to mitophagy [47, 55].

Deubiquitinating enzymes (DUBs) are also involved in PINK1-Parkin-mediated mitophagy. Because USP30 preferentially removes Lys6- and Lys11-linked ubiquitin chains generated by Parkin on damaged mitochondria, USP30 knockdown rescues the defective mitophagy caused by pathogenic mutations in Parkin [55, 56]. Moreover, knockdown of USP30 improves mitochondrial morphology in *Parkin*- or *PINK1*-deficient flies and protects them from the paraquat-induced reduction in dopamine, motor dysfunction, and shortened lifespan [56]. Conversely, USP8 removes Lys6-linked polyubiquitin on Parkin, which activates Parkin-mediated mitophagy [57]. As USP15 does not affect Parkin autoubiquitination and translocation to mitochondria, knockdown of CG8334, the closest homolog of USP15 in *Drosophila*,

largely rescues the altered mitochondrial morphology and the defective climbing ability in Parkin knockdown flies [58]. These findings could provide new therapeutic strategies for PD via the targeting of DUBs.

PINK1 and Parkin promote selective turnover of the respiratory chain complex in *Drosophila* independently of mitophagy pathway [59]. Quantitative Lys-ϵ-Gly-Gly (diGly) proteomics identified a variety of Parkin-dependent ubiquitinated proteins [47, 60]. Interestingly, the PINK1-Parkin pathway dynamically regulates protein ubiquitination levels in the mitochondrial outer and inner membranes, nucleus, cytoplasm, and cell membrane, suggesting that Parkin affects cellular events other than mitochondrial maintenance. Parkin-mediated xenophagy is one such example although it is unclear whether PINK1 is involved in this mechanism or not [61].

4. Regulators of PINK1

PINK1 stability is regulated by mitochondrial outer and inner membrane proteins, and upregulation of these proteins triggers PINK1 activation through dimerization and autophosphorylation (Figure 4) [62, 63]. PINK1 interacts with the translocase of the outer membrane (TOM) complex and is imported to the mitochondrial inner membrane [64, 65]. Under steady-state conditions, endogenous PINK1 is constitutively and rapidly degraded by the E3 ubiquitin ligases UBR1, UBR2, and UBR4 through the N-end rule pathway [30]. The PINK1 precursor is inserted into the mitochondrial inner membrane, where PINK1 is subjected to processing by mitochondrial proteases. The rhomboid family protease PARL, which is localized at the mitochondrial inner membrane, cleaves PINK1 at Ala103 in a ΔΨm-dependent manner [66–70]. Cleaved PINK1 is released to the cytosol or mitochondrial intermembrane space [70]. However, the molecular mechanism of its reverse transport from the mitochondria to the cytosol remains unclear. The mitochondrial processing peptidase and hetero dimeric matrix proteases m-AAA and ClpXP are also involved in PINK1 cleavage [71]. These reports indicate that mitochondrial inner and matrix proteases coordinately regulate PINK1 stability in a ΔΨm-dependent manner.

In *Drosophila*, loss of a PINK1-binding mitochondrial phosphatase PGAM5 improves the muscle degeneration, motor defects, and shorter lifespan caused by the loss of PINK1, suggesting that PGAM5 negatively regulates the PINK1 pathway related to mitochondrial maintenance [72]. PGAM5 knockout mice display PD-like motor dysfunction and progressive degeneration of dopaminergic neurons [73]. PGAM5S, a short form of PGAM5, recruits Drp1 and activates its GTPase activity by dephosphorylating Ser637 in Drp1, causing mitochondrial fragmentation [74]. Although the precise physiological and pathological roles of PGAM5 remain unclear, PGAM5 may play important roles in mitochondrial maintenance and PINK1-mediated mitophagy.

Lefebvre et al. identified ATPase inhibitory factor 1 (ATPIF1/IF1) as essential for Parkin translocation from cytosol to mitochondria and for mitophagy in cultured cells [75]. ATPF1

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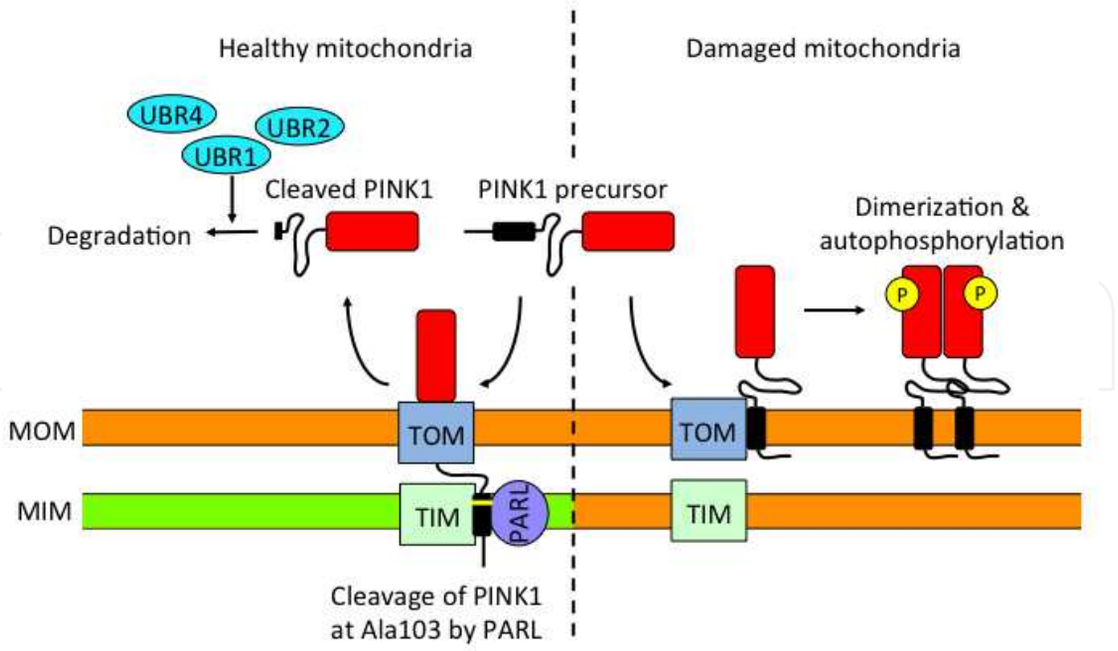

Figure 4. Molecular dynamics of PINK1 in healthy or damaged mitochondria In healthy mitochondria, PINK1 is imported by the TOM and TIM complexes to the mitochondrial inner membrane (MIM) and is processed by PARL, which in turn releases PINK1 into the cytosol. PINK1 is subjected to degradation by the ubiquitin ligases UBR1, UBR2, and UBR4. In damaged mitochondria, when PINK1 interacts with the TOM complex, it cannot be imported into the intermembrane space due to the loss of $\Delta\Psi m$. Instead, PINK1 accumulates on the mitochondrial outer membrane (MOM), which leads to the dimerization and autophosphorylation events that activate its kinase activity.

inhibits the reversal of F_1F_o-ATP synthase and promotes the reduction in $\Delta\Psi m$, resulting in the accumulation of PINK1 and the subsequent activation of mitophagy [75].

The master transcriptional factor for lipogenesis, sterol regulatory element binding transcription factor 1 (SREBF1), promotes Parkin translocation and mitophagy [76]. Although SREBF1 knockdown inhibits carbonyl cyanidem-chlorophenylhydrazone (CCCP)-induced PINK1 stabilization and Parkin translocation, the addition of excess amounts of cholesterol rescues these deficits, suggesting that SREBF1-dependent lipid synthesis may be a key factor in PINK1 stabilization [76].

5. Regulators of Parkin and mitophagy

Parkin-mediated ubiquitination of mitochondrial proteins initiates proteasomal and autophagic degradation, which involves a variety of regulators and ubiquitin- and/or LC3-binding proteins (Figure 5). The ubiquitin- and LC3-binding protein p62/SQSTM1 is required for Parkin-induced clustering of depolarized mitochondria to the perinuclear region [33, 77, 78]. Neighbor of BRCA1 gene 1 (NBR1), a functional homolog of p62, is also a ubiquitin-binding protein and is recruited to depolarized mitochondria in a PINK1-Parkin-dependent manner [79]. p62 and NBR1 expression levels coordinately change, suggesting a positive mutual regulatory relationship between p62 and NBR1 at least during viral infection [80]. Optineurin,

an autophagy receptor that binds to ubiquitinated mitochondria via ubiquitin-binding domains, is translocated to damaged mitochondria in a Parkin-dependent manner and recruits LC3 to induce mitochondrial degradation via autophagosomes [81]. However, optineurin and p62 are independently recruited to damaged mitochondria [81]. Tank-binding kinase 1 (TBK1) phosphorylates optineurin and p62, which enhances their binding affinity to LC3 and ubiquitin [82, 83]. Although TBK1 is activated downstream of Toll-like receptor 3 (TLR3) and the TLR4 signaling pathway, it is unknown which signaling event activates TBK1 during mitophagy [84]. Ambra1, an autophagy-promoting protein, is not required for Parkin translocation to depolarized mitochondria [85]. However, the interaction of Parkin with Ambra1 is potentiated during prolonged mitochondrial depolarization, resulting in the activation of the autophagy-associated class III phosphatidylinositol 3-kinase (PI3K) complex in mitochondria and their selective autophagic clearance [85].

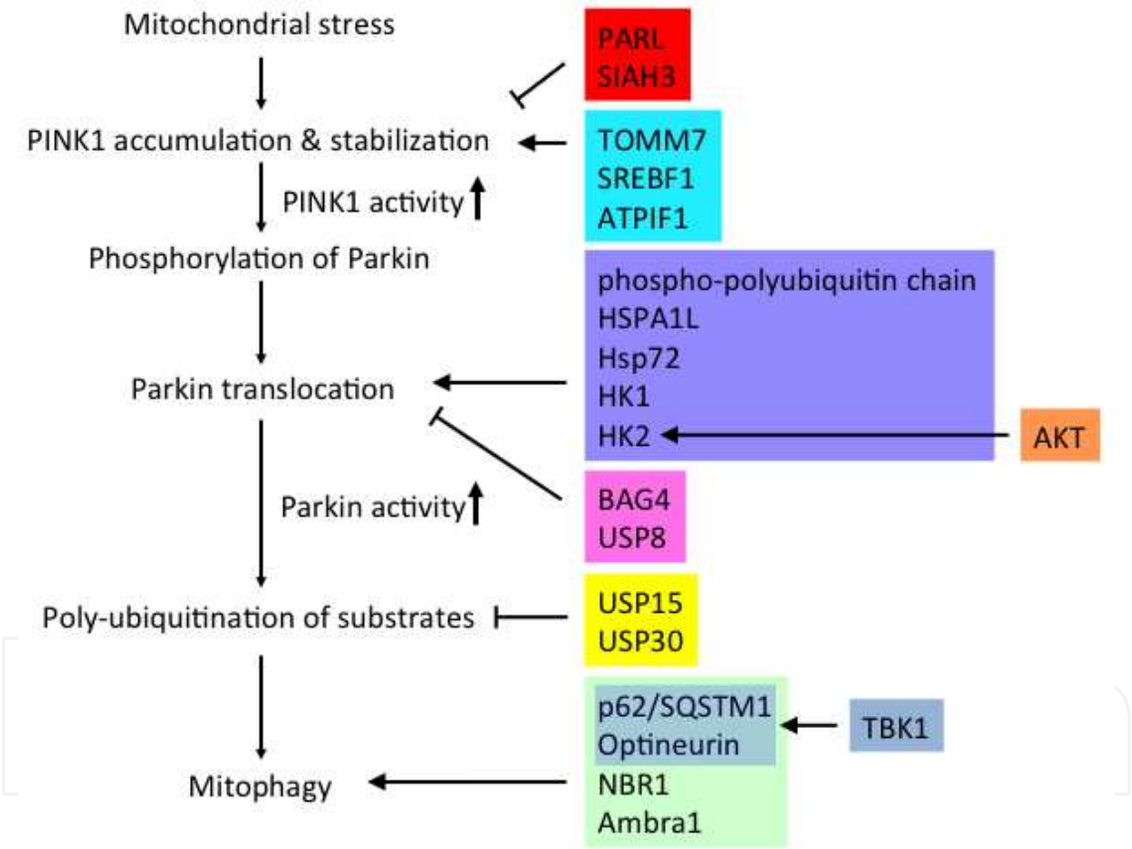

Figure 5. Regulators of the PINK1-Parkin pathway Various regulators of the PINK1-Parkin pathway have been characterized. ATPIF1, TOMM7, PARL, SIAH3, and SREBF1 are involved in PINK1 accumulation and stabilization on mitochondria. Mitochondrial phospho-polyubiquitin chain, HSPA1L, Hsp72, HK1, and HK2 promote Parkin translocation to mitochondria. HK2 activity is positively regulated by AKT signaling. By contrast, BAG4 and USP8 suppress Parkin translocation. The deubiquitinating enzymes USP15 and USP30 remove polyubiquitin from mitochondrial substrates of Parkin. The LC3- and ubiquitin-binding proteins p62/SQSTM1, NBR1, and optineurin link polyubiquitin on mitochondria to the autophagosome. TBK1 positively regulates the activities of p62/SQSTM1 and optineurin through phosphorylation. Ambra1 promotes autophagic clearance by activating the autophagy-associated class III phosphoinositide 3-kinase (PI3K) complex.

Recent genome-wide RNAi screens have also identified several regulators of PINK1 and Parkin. Hasson et al. found that TOMM7, one of the TOM components, is necessary for the accumulation of PINK1 and Parkin on damaged mitochondria and chaperone proteins, HSPA1L and BAG4, have mutually opposing roles in Parkin translocation [86]. TOMM7 knockout causes impaired PINK1 import into mitochondria by inhibiting the interaction of PINK1 with the TOM complex. Moreover, a mitochondrial E3 ligase SIAH3 inhibits PINK1 accumulation probably through ubiquitination-proteasome-dependent degradation, resulting in decreased Parkin translocation [86]. Another chaperone protein, Hsp72, rapidly translocates to depolarized mitochondria prior to Parkin recruitment and interacts with both Parkin and Mfn2 only after specific mitochondrial insults [87]. Myotubes in both Hsp72 knockout mice and Parkin knockout mice exhibit increased insulin resistance and reduced maximal respiration [87]. Furthermore, myotubes in Hsp72 knockout mice exhibit impaired CCCP-induced Mfn2 degradation and Parkin-mediated LC3-II accumulation, suggesting that Hsp72 is a positive regulator of Parkin in mitophagy [87].

McCoy et al. revealed that knockdown of hexokinase (HK)1 and HK2 inhibits Parkin translocation from the cytosol to the mitochondria [88]. Inhibition of AKT signaling attenuates Parkin recruitment to mitochondria and suppresses the translocation of HK2 to mitochondria, suggesting that AKT promotes Parkin relocation [88].

6. Mitochondrial motility regulated by PINK1-Parkin

PINK1 and Parkin regulate mitochondrial motility in addition to mitophagy, which appears to be particularly important for neuronal function. In neurons, mitochondria are transported from the cell body to nerve terminals. Mitochondrial Rho GTPase 1 (Miro1) regulates the microtubule-dependent transport of mitochondria along with Milton, kinesin, and dynein [89]. In *Drosophila*, knockdown of PINK1 or overexpression of Miro increases the mitochondrial length in larval motor neurons and the density within nerve terminals at larval neuromuscular junctions [90]. Similar to *Drosophila*, PINK1 or Parkin overexpression suppresses both retrograde and anterograde transport of mitochondria via Miro1 degradation in rat hippocampal axons [91]. Parkin Ser65 phosphorylation by PINK1 stimulates Lys27-linked polyubiquitination of Miro1 by Parkin [40, 92]. Mfn2, a Parkin substrate, is also involved in mitochondrial transport through binding to the Miro–Milton complex on mitochondria [93]. PINK1-Parkin is thought to keep damaged mitochondria away from nerve terminals by destroying the Miro–Milton complex, thereby facilitating the removal of mitochondria in the soma via mitophagy.

7. Mitochondria and PD

Respiratory complex I or NADH dehydrogenase activity is significantly reduced in the substantia nigra of PD patients [94–96], implying that selective dysregulation of complex I activity is a key component of PD pathogenesis. The fact that neurotoxin 1-methyl-4-phenylpyridinium (MPP^+) causes selective loss of dopaminergic neurons, which causes symptoms similar to Parkinsonism, reinforces this idea [97]. MPP^+ is produced by the monoamine oxidase (MAO)-

mediated oxidation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and is imported into dopaminergic neurons via dopamine reuptake systems [98, 99]. In dopaminergic neurons, MPP^+ is concentrated in the mitochondrial matrix and binds to NADH dehydrogenase, resulting in the inhibition of OXPHOS, ATP depletion, and dopaminergic neuron death [100].

In addition to PINK1 and Parkin, other genes that have been implicated in PD are also related to mitochondrial homeostasis. Mutations in DJ-1 are associated with early-onset PD [101, 102]. DJ-1 alleviates oxidative stress through its antioxidant activity and functions as a redox-sensitive molecular chaperone [103]. Loss of DJ-1 leads to abnormal mitochondrial phenotypes, including reduced $\Delta\Psi m$, increased fragmentation and accumulation of autophagic markers [104]. CHCHD2 was isolated as a novel PD-associated gene [105] and is thought to regulate OXPHOS in mitochondria [106]. PINK1 inhibition causes decreased dopaminergic neuron viability in *Drosophila* [13, 42] and the loss of Parkin causes dopaminergic neuron-specific mitochondrial dysfunction [107]. These reports suggest that PINK1 and Parkin play critical roles in mitochondrial maintenance and dopaminergic neuron survival. Dopaminergic neurons as well as other neurons and glia cells express MAOs, which are substrates of Parkin [47, 60, 108]. During the oxidization of cytosolic or vesicular dopamine by MAOs, ROS are generated. Thus, dysregulation of MAO levels in dopaminergic neurons may account for the vulnerability of dopaminergic neurons to oxidative stress and the selective degeneration of dopaminergic neurons.

8. Conclusions

Two genes implicated in PD, *PINK1* and *Parkin*, are involved in the clearance of damaged mitochondria. DJ-1 and CHCHD2, which are the other gene products associated with PD, are also involved in mitochondrial homeostasis. Accumulating evidence suggests that these PD-associated genes have multifaceted roles in mitochondria, including the regulation of mitochondrial motility and quality as well as redox and respiration regulation. Although the physiological and pathological significance of newly identified phosphorylated polyubiquitin chains in PD needs to be characterized further, a complete understanding of the PINK1-Parkin pathway and its modification via therapeutic intervention would provide an opportunity to overcome a variety of mitochondrial diseases as well as PD.

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