



OPEN ACCESS

EDITED BY

Judit Symmank,
University Hospital Jena, Germany

REVIEWED BY

Claudia Crosio,
University of Sassari, Italy
Mariaelena Repici,
Aston University, United Kingdom

*CORRESPONDENCE

Zhuohua Zhang
✉ zhangzhuohua@sklmg.edu.cn
Danling Wang
✉ danlingwang@usc.edu.cn

RECEIVED 29 October 2023

ACCEPTED 21 December 2023

PUBLISHED 11 January 2024

CITATION

Luo S, Wang D and Zhang Z (2024)
Post-translational modification
and mitochondrial function in Parkinson's
disease.
Front. Mol. Neurosci. 16:1329554.
doi: 10.3389/fnmol.2023.1329554

COPYRIGHT

© 2024 Luo, Wang and Zhang. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Post-translational modification and mitochondrial function in Parkinson's disease

Shishi Luo^{1,2,3}, Danling Wang^{1,2,3*} and Zhuohua Zhang^{1,2,4*}

¹Institute for Future Sciences, Hengyang Medical School, University of South China, Hengyang, Hunan, China, ²Key Laboratory of Rare Pediatric Diseases, Ministry of Education, Hengyang, Hunan, China, ³The Affiliated Changsha Central Hospital, Hengyang Medical School, University of South China, Changsha, Hunan, China, ⁴Institute of Molecular Precision Medicine, Xiangya Hospital, Key Laboratory of Molecular Precision Medicine of Hunan Province and Center for Medical Genetics, Hunan Key Laboratory of Medical Genetics, Central South University, Changsha, Hunan, China

Parkinson's disease (PD) is the second most common neurodegenerative disease with currently no cure. Most PD cases are sporadic, and about 5–10% of PD cases present a monogenic inheritance pattern. Mutations in more than 20 genes are associated with genetic forms of PD. Mitochondrial dysfunction is considered a prominent player in PD pathogenesis. Post-translational modifications (PTMs) allow rapid switching of protein functions and therefore impact various cellular functions including those related to mitochondria. Among the PD-associated genes, *Parkin*, *PINK1*, and *LRRK2* encode enzymes that directly involved in catalyzing PTM modifications of target proteins, while others like α -synuclein, *FBXO7*, *HTRA2*, *VPS35*, *CHCHD2*, and *DJ-1*, undergo substantial PTM modification, subsequently altering mitochondrial functions. Here, we summarize recent findings on major PTMs associated with PD-related proteins, as enzymes or substrates, that are shown to regulate important mitochondrial functions and discuss their involvement in PD pathogenesis. We will further highlight the significance of PTM-regulated mitochondrial functions in understanding PD etiology. Furthermore, we emphasize the potential for developing important biomarkers for PD through extensive research into PTMs.

KEYWORDS

Parkinson's disease, post-translational modification (PTM), mitochondrial function, ubiquitination, phosphorylation, acetylation, SUMOylation, s-nitrosylation

1 Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disease, affecting more than 10 million people worldwide (Kalia and Lang, 2015). Pathologically, PD is characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and the accumulation of aggregated α -synuclein in the form of intracellular inclusion called Lewy Body (LB) (Tanner, 1992). The manifestations of PD are chronic and progressive, with the main symptoms involving movement dysfunctions such as tremor, tonic, bradykinesia, and postural instability. Many patients also experience prodromal symptoms, including non-motor disturbances such as constipation, hyposmia, and mood disorders (Martinez-Martin et al., 2007; Lajoie et al., 2021). Currently, there is

no cure for PD. The available treatments only alleviate the movement symptoms with little effects on disease progression.

Most PD cases are sporadic, or idiopathic, with age and environmental exposures (such as pesticides, herbicides, heavy metal, and head injury) being the main known risk factors (Goldman, 2014; Ascherio and Schwarzschild, 2016). About 15% PD cases have a familial history, and about 5–10% of PD patients present a monogenic inheritance pattern (Hernandez et al., 2016). Mutations in at least 20 genes are identified to be linked with familial PD (Table 1). From which, dominantly associated genes such as *SNCA* (α -synuclein), *LRRK2*, and *VPS35*, as well as recessively associated genes like *PRKN* (*Parkin*), *DJ-1*, *GBA*, *PINK1*, *ATP13A2*, and *FBXO7*, are identified (Polymeropoulos et al., 1997; Kitada et al., 1998; Bonifati et al., 2003; Lwin et al., 2004; Valente et al., 2004; Gilks et al., 2005; Ramirez et al., 2006; Di Fonzo et al., 2009; Vilarino-Guell et al., 2011; Funayama et al., 2015). More than additional 90 genetic risk loci are shown to be associated with idiopathic PD (Bekris et al., 2010; Nalls et al., 2019). Individuals with genetic changes of those genes likely predispose to PD.

Human genetics have significantly contributed to our understanding of the molecular mechanisms of PD pathogenesis. Several key pathways, including those related to protein misfolding and aggregation, the ubiquitin-proteasomal system, autophagy, mitochondrial dysfunction, lysosomal abnormality, and vesicle trafficking, are revealed to PD (Henchcliffe and Beal, 2008; Meredith et al., 2009; Ebrahimi-Fakhari et al., 2012; Hunn et al., 2015; De Virgilio et al., 2016; Blumenreich et al., 2020). Of particular, mitochondrial dysfunction has long been implied in PD pathogenesis. Methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP), a mitochondrial complex I inhibitor, induces Parkinsonism in both human and animals (Langston et al., 1983). Multiple pesticides and herbicides are shown to induce parkinsonism via mitochondria-mediated mechanisms (Chen et al., 2017). A number of PD pathogenic monogenetic genes either encode mitochondrial proteins or regulate mitochondrial functions (Nicoletti et al., 2021). Genome-wide association studies (GWAS) also indicate that mitochondria-related processes are involved in both familiar and sporadic forms of PD (Billingsley et al., 2019).

Post-translational modifications (PTMs) refer to covalent chemical alterations of a protein after its synthesis. More than 400 types of PTMs are identified (Khoury et al., 2011). Some widely studied PTMs include phosphorylation, ubiquitination, methylation, acetylation, SUMOylation, etc. PTMs increase functional diversity of the modified protein, therefore modulate almost every aspect of cellular processes, including mitochondrial functions (Karve and Cheema, 2011; Stram and Payne, 2016). Among the PD-associated genes, *Parkin*, *PINK1*, and *LRRK2* encode enzymes that directly catalyze the PTM of target proteins while they are PTM modified themselves (Trempe et al., 2013; Eiyama and Okamoto, 2015; Taylor and Alessi, 2020). PD-related proteins like α -synuclein, *FBXO7*, *HTRA2*, *VPS35*, *CHCHD2*, and *DJ-1* either participate in or are heavily modified by PTMs (Mitsumoto et al., 2001; Plun-Favreau et al., 2007; Kang et al., 2012; Burchell et al., 2013; Tang et al., 2015; Meng et al., 2017). In this review, we aim to summarize the recent findings on major PTMs associated with PD-related proteins, either as enzymes or substrates, that have been shown to play significant roles in various mitochondrial functions, hence, PD pathogenesis.

2 Ubiquitination: regulating mitochondrial functions in Parkinson's disease

Ubiquitination is a PTM characterized by the covalent binding of ubiquitin (Ub) molecule to a specific target protein. This essential PTM primarily determines protein stability by marking the target protein for proteasomal degradation. However, it has also been reported to be able to enhance protein stability and regulate protein activities. Ubiquitination plays an essential role in maintaining normal mitochondrial functions. Dysregulated ubiquitination can cause mitochondrial dysfunctions. While the accumulation of misfolded and ubiquitinated α -synuclein has long been recognized as the toxic factor in PD brain pathology, evidence implicating the direct involvement of ubiquitination dysregulation in mitochondrial dysfunction and thus PD pathology emerged from the intensive study of PD associated *Parkin* and *PINK1*. As non-mitochondrial proteins, other PD-related proteins, such as *VPS35*, *FBXO7*, and *LRRKs*, are found to regulate mitochondrial functions by modifying ubiquitination process (Table 2).

2.1 Parkin-mediated ubiquitination and mitophagy

Mutations in *Parkin* gene are the most common genetic cause of juvenile-onset and early-onset PD (EOPD), defined by the appearance of PD symptoms in teens and before the age of 60 (Kitada et al., 1998). The *Parkin* gene encodes *Parkin*, an E3 ubiquitin ligase belonging to the RING-between-RING (RBR) family, which accepts Ub from the E2 enzyme and transfers it onto the target protein (Imai et al., 2000; Shimura et al., 2000; Zhang et al., 2000). By ubiquitinating various substrates, *Parkin* plays a central role in maintaining mitochondrial function and homeostasis (Palacino et al., 2004; Narendra et al., 2008).

The groundbreaking study illustrating *Parkin*'s role in mitophagy, the biological pathway that selectively eliminates defective mitochondria, was conducted by the Youle laboratory (Narendra et al., 2008). Later studies collectively reveal that *Parkin*-mediated mitophagy consists of three major steps: (1) initiation, the activation and translocation of *Parkin* onto the damaged mitochondria (Narendra et al., 2008; Matsuda et al., 2010); (2) priming, the cascade ubiquitination of various targets on the outer mitochondrial membrane (OMM) by *Parkin* (Tanaka et al., 2010; Chan et al., 2011; Sarraf et al., 2013); and (3) finishing, the lysosomal sequestration and degradation of heavily ubiquitinated mitochondria (Karbowski and Youle, 2011). Evidence suggests that the recruitment of *Parkin* to the damaged mitochondria is mediated by the binding of *Parkin* to the mitochondria-situated phosphorylated-Ub (phospho-Ub, pUb), which is formed by the kinase activity of *PINK1* (PTEN-induced putative kinase 1) (Xiong et al., 2009; Kane et al., 2014; Sauve et al., 2015). During the priming stage, *Parkin* ubiquitinates multiple proteins, showing a preference for OMM proteins including *Parkin* itself, *MFN1* and 2 (mitofusin 1 and 2), *MIRO1* and 2 (mitochondrial Rho GTPase 1 and 2), *VDAC1-3* (voltage-dependent anion channel 1–3), *CISD1* (CDGSH iron-sulfur domain 1), and *TOM 20, 40*, and

TABLE 1 Genes associated with familial PD.

	Gene	PARK locus	Alternative names	Inheritance	Type of parkinsonism
Widely validated	SNCA	PARK1, PARK4	NCAP	AD	Early/late onset, atypical
	PRKN	PARK2	Parkin	AR	Early onset, typical
	PINK1	PARK6	BRPK	AR	Early onset, typical
	DJ-1	PARK7	GATD2	AR	Early onset, typical
	LRRK2	PARK8	ROCO2, RIPK7	AD	Late onset, typical
	ATP13A2	PARK9	HSA9947, CLN12	AR	Juvenile onset, atypical
	PLA2G6	PARK14	PNPLA9, IPLA2	AR	Juvenile onset, atypical
	FBXO7	PARK15	FBX7	AR	Early onset, atypical
	VPS35	PARK17	MEM3	AD	Late onset, typical
	DNAJC6	PARK19	KIAA0473, DJC6	AR	Juvenile onset, atypical
	SYNJ1	PARK20	INPP5G	AR	Juvenile onset, atypical
	DNAJC13	PARK21	KIAA0678, RME8	AD	Late onset, typical
	VPS13C	PARK23	KIAA1421, BLTP5C	AR	Early onset, atypical
	POLG	-	POLG1, POLGA	AD	Early onset, atypical
Less validated	UCHL1	PARK5	PGP9.5	AD	Late onset, typical
	GIGYF2	PARK11	TNRC15, PERQ2, GYF2	AD	Late onset, typical
	HTRA2	PARK13	OMI	AD	Late onset, typical
	EIF4G1	PARK18	P220	AD	Late onset, typical
	CHCHD2	PARK22	C7orf17, MIX17B	AD	Late onset, typical
	PSAP	PARK24	GLBA, SAPI	AD	Late onset, typical

AD, autosomal dominant; AR, autosomal recessive; juvenile-onset, clinical symptom starting before 21 years; early-onset, clinical symptom starting between 20 and 60 years; late-onset, clinical symptom starting after 60 years; typical PD, PD cases presenting classical motor symptoms, with slow progression and good response to dopaminergic therapeutics; atypical PD, PD cases featuring prominent additional neurological signs, such as dementia, spasticity, dystonia, with or without abnormal ocular movements (Cherian and Vijayaraghavan, 2023); “-” means no answer.

70 (translocases of the outer membrane 20, 40, and 70) (Gegg et al., 2010; Lazarou et al., 2012; Sun et al., 2012; Ordureau et al., 2015; Liu et al., 2018; Lopez-Domenech et al., 2018). Ubiquitination of OMM proteins further promotes the recruitment of Ub-binding autophagy receptors such as P62/SQSTM1 (sequestosome 1), OPTN (optineurin), NDP52/CALCOCO2 (calcium-binding and coiled-coil domain-containing protein 2), and NBR1 (neighbor of Brca1). In turn, these receptors elicit the targeting of the damaged mitochondria to LC3-positive phagophores for lysosomal degradation (Figure 1; Heo et al., 2015; Ordureau et al., 2018; Padman et al., 2019).

Unlike many other E3 ligases that exhibit stringent substrate specificity, Parkin appears to be loose on substrate selectivity. In addition to the well-studied Parkin substrates, recent proteomic analyses have revealed that Parkin ubiquitinates an extensive large number of proteins (Rose et al., 2016; Martinez et al., 2017). After treatment with the mitochondrial uncoupler carbonyl cyanide *m*-chlorophenylhydrazone (CCCP) for extended hours, most OMM proteins are ubiquitinated without necessarily having functional consequences (Chan et al., 2011; Sarraf et al., 2013). In general, Parkin is activated by PINK1-mediated phosphorylation of its N-terminal ubiquitin-like domain. With the help of PINK1, ubiquitination on the OMM by Parkin leads to more pUb and consecutively greater Parkin recruitment and activation, creating a feed-forward loop to amplify the Parkin-mediated ubiquitination to the maximum (Ordureau et al., 2014). Using

artificial mitochondria-targeted proteins, Koyano et al. (2019) have found that the substrate specificity of Parkin is not determined by the amino-acid sequence within the substrate, but rather by the presence of pUb on the target protein (Durcan et al., 2012).

Proteomic analyses of purified mitochondria have revealed that Parkin produces a mixture of canonical and non-canonical Ub chains on damaged mitochondria. In general, Ub chains can form through any of the seven lysine (K6, K11, K27, K29, K33, K48, and K63) and the N-terminal methionine (Met1) (Kulathu and Komander, 2012; Akutsu et al., 2016). *In vitro*, Parkin ubiquitinates mitochondrial proteins with K6-, K11-, K48-, and K63-linked Ub chains to signal damaged mitochondria for mitophagy (Ordureau et al., 2014). Canonical K48-linked Ub chains are crucial for the proteasomal targeting and degradation of modified proteins (Manohar et al., 2019), while K63-linked Ub chains activate the autophagic machinery through recruiting autophagy adaptors like HDAC6 (histone deacetylase 6) and P62 (Seibenhener et al., 2004; Olzmann et al., 2007). Intriguingly, Parkin catalyzes certain degrees of K6- and K11-linked Ub chains on OMM proteins. Activity of Parkin-mediated mitophagy is impaired when either K6 or K11 Ub-linkage was inhibited by the expression of mutant Ub K6R or K11R, suggesting that K6- and K11-linked Ub chains positively regulate the mitophagy process (Durcan et al., 2014; Cunningham et al., 2015). Therefore, Parkin is considered a rather promiscuous E3 ligase that, once activated, ubiquitinates a broad range of proteins with a wide spectrum of Ub chains and amplifies the Ub signals via

TABLE 2 Ubiquitination of PD-related proteins and mitochondrial dysfunction.

PD-related protein		Enzyme	Substrate	Regulated mitochondrial function	References
Parkin	Directly involved in PTM enzymatic reaction	Parkin	Parkin	Activates mitophagy	Zhang et al., 2000
		Parkin	OMM proteins	Activates mitophagy	Gegg et al., 2010; Lazarou et al., 2012; Sun et al., 2012; Ordureau et al., 2015; Liu et al., 2018; Lopez-Domenech et al., 2018
		Parkin	Tollip	Promotes MDVs transport	Ryan et al., 2020
		Parkin	SNX9	Inhibits immune-related-MDVs formation	Matheoud et al., 2016
		Parkin	DRP1	Inhibits mitochondrial fission	Wang H. et al., 2011
		Parkin	MFN1	Inhibits mitochondrial fusion	Gegg et al., 2010
		Parkin	MFN2	Inhibits mitochondrial fusion, increases mitochondria-ER contacts	Gegg et al., 2010; Basso et al., 2018
		Parkin	PARIS	Promotes mitochondrial biogenesis	Siddiqui et al., 2016
		Parkin	MICU1	Maintains calcium homeostasis	Matteucci et al., 2018
	Parkin	MIRO	Increases mitochondria-ER contacts	Wang X. et al., 2011	
α -synuclein		SIAH-1	α -synuclein	Increases cytochrome c release	Lee et al., 2008
FBXO7		FBXO7	PINK1	Increases mitophagy	Liu et al., 2020
VPS35	Indirectly involved in PTM enzymatic reaction	MULAN	MFN2	Promotes mitochondrial fusion	Tang et al., 2015
LRRK2		PERK	MARCH5, MULAN, Parkin	Inhibits mitochondria-ER contacts	Toyofuku et al., 2020

Tollip, the endosomal adaptor Toll interacting protein; SNX9, sorting nexin 9; DRP1, dynamin-related protein 1; MFN1 and 2, mitofusin 1 and 2; PARIS, Parkin-interacting substrate; MICU1, mitochondrial calcium uptake 1; MIRO, mitochondrial Rho GTPase; PINK1, PTEN induced putative kinase 1; MULAN, mitochondrial E3 ubiquitin protein ligase 1; LRRK2, leucine-rich repeat kinase 2; MARCH5, membrane associated Ring-CH-type finger 5; ER, endoplasmic reticulum; MDV, mitochondrial-derived vesicle.

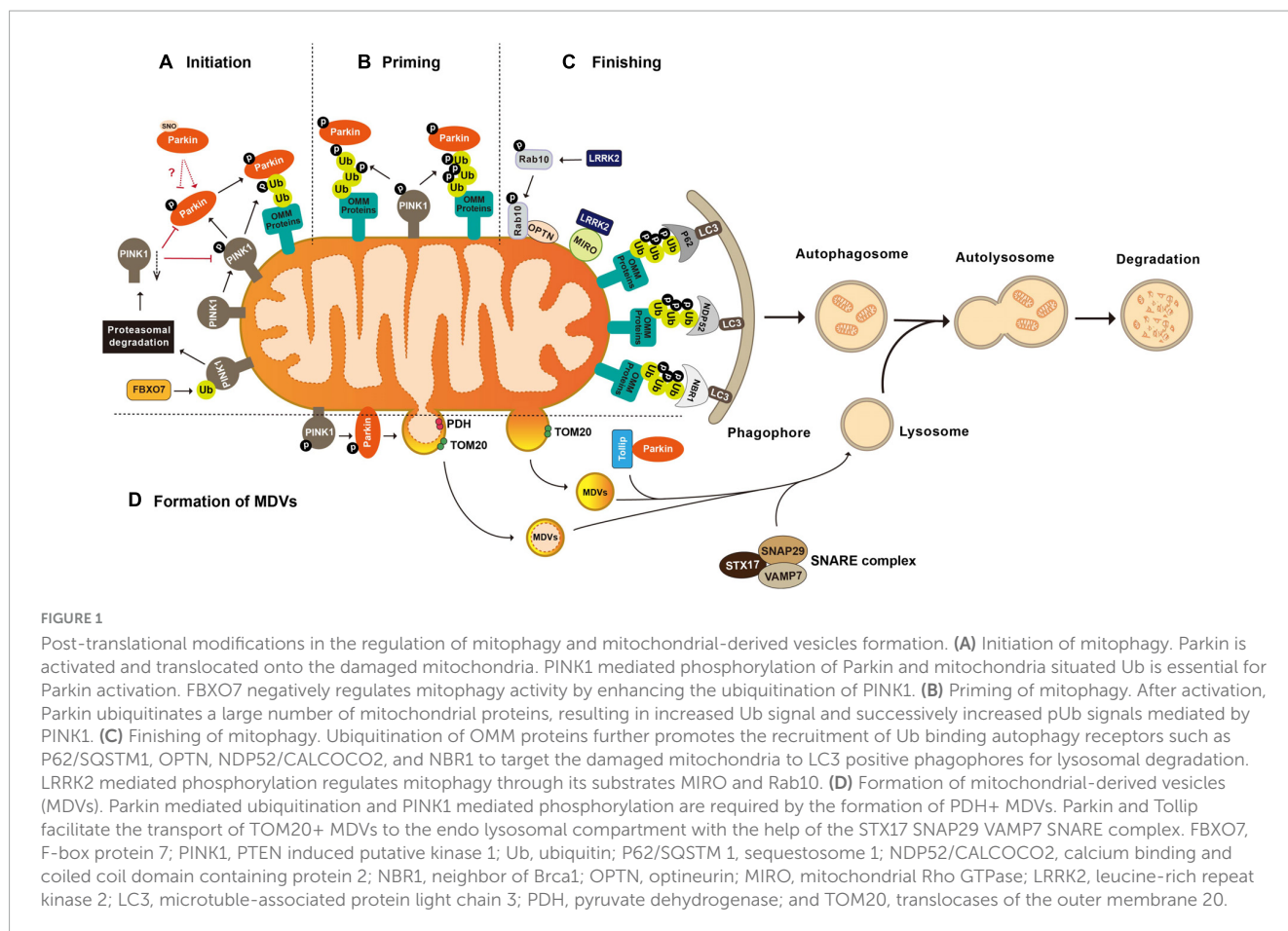
a positive-feedback manner to maximally ubiquitinated proteins on the damaged mitochondria.

Over 200 missense variants are identified in the *Parkin* gene, but only a small fraction has been clearly annotated to be pathogenic. Integrating clinical evidence with *in vitro* mitophagy activity, Yi et al. (2019) has conducted a systematic analysis of 51 Parkin variants, finding a correlation between the degree of mitophagy defect and the level of clinical manifestation. Among them, 13 Parkin variants are classified as pathogenic or likely pathogenic that all display severe mitophagy defects. Those variants designated as non-pathogenic show normal or near-normal mitophagy function (Yi et al., 2019). Likewise, Broadway et al. (2022) have investigated 10 rare Parkin mutants and found 7 with impaired mitophagy activity. These studies suggest that Parkin mediated mitophagy plays important roles in PD pathogenesis.

2.2 Parkin-mediated ubiquitination and mitochondrial-derived vesicles

In addition to mitophagy, an alternative mitochondrial quality control mechanism is via mitochondrial-derived vesicles (MDVs) (Cadete et al., 2016). With this, mitochondria transfer their defective mitochondrial contents to destination organelles, such as lysosomes, peroxisomes, and multivesicular bodies, for degradation via releasing vesicles with 70–150 nm in diameter (Futter et al., 1996; Soubannier et al., 2012a; Vasam et al., 2021; Rosina et al., 2022). Depending on the source of the mitochondrial stress,

MDVs derive from the inner mitochondrial membrane (IMM) as a double-membrane structure or from the OMM as a single-membrane vesicle (Konig et al., 2021; Popov, 2022; Heyn et al., 2023). Whether Parkin plays a preferential role in the formation of MDVs remains to be elucidated. *In vitro*, the formation of MDVs carrying inner membrane marker PDH (pyruvate dehydrogenase) is dependent on Parkin activity (McLelland et al., 2014; Ge et al., 2020). Targeting of Parkin-dependent MDVs to the later endo-lysosomal compartments is mediated by the ternary SNARE protein complex composed of STX17 (syntaxin 17), SNAP29 (synaptosome associated protein 29), and VAMP7 (vesicle-associated membrane protein 7) (Soubannier et al., 2012a; Juhasz, 2016; McLelland et al., 2016). Unlike those PDH-positive MDVs, the presence of MDVs containing only OMM marker like Tom20 is not affected by loss-of-function Parkin mutants T240R or C431S, indicating the independence of Parkin E3 ligase activity (Soubannier et al., 2012b). However, Parkin was found to coordinate with Tollip (the endosomal adaptor Toll interacting protein) to facilitate the transport of these single-membrane MDVs to the endo-lysosomal compartment, with the help of the STX17-SNAP29-VAMP7 SNARE complex (Figure 1; Ryan et al., 2020). In contrast, Parkin seems to inhibit the formation of a subtype of MDVs that plays important roles in immune cells related mitochondrial antigen presentation (MitAP) through triggering ubiquitination and proteasomal degradation of SNX9 (sorting nexin 9) (Matheoud et al., 2016). Thus, Parkin-mediated ubiquitination potentially link between mitochondrial dysfunction and neuroinflammation in PD (Sliter et al., 2018). Consistently, Parkin-null mice show



excessive inflammation due to STING-dependent (stimulator-of-interferon-genes dependent) pro-inflammation activity and increased vulnerability to inflammation-induced degeneration (Frank-Cannon et al., 2008; Sliter et al., 2018).

2.3 Parkin-mediated ubiquitination and other mitochondrial functions

2.3.1 Parkin-mediated ubiquitination and mitochondrial dynamics

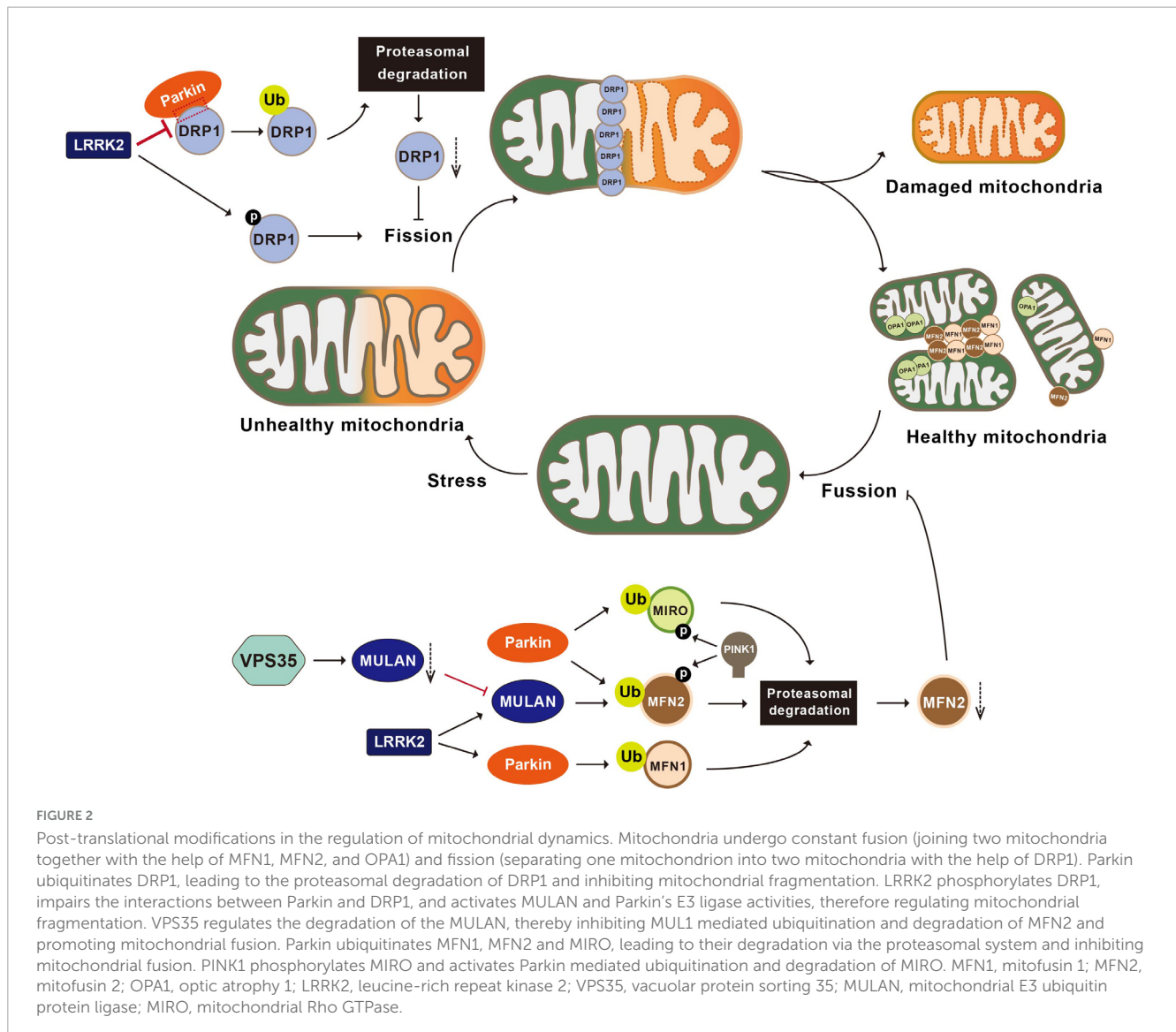
Mitochondria undergo constant fission-and-fusion in reflection of their functional statuses (Lewis and Lewis, 1914; Chen and Chan, 2017; Kraus et al., 2021). Increased mitochondrial fission results in small and round mitochondria to probably facilitate the mitochondrial trafficking within cells, while enhanced mitochondrial fusion leads to elongated mitochondria for efficient ATP production (Martini and Passos, 2023). Certain mitochondrial damages promote fission activity leading to the separation of depolarized mitochondria to facilitate their later removal by mitophagy or other mitochondrial quality control mechanisms (Han et al., 2020; da Silva Rosa et al., 2021; Cai et al., 2022).

Parkin is responsible for the ubiquitination and proteasomal degradation of several bona fide players in mitochondrial fission-and-fusion pathways, including the fission mediator DRP1 (dynamin-related protein 1) and fusion mediators MFN1 and MFN2 (Narendra et al., 2008; Yamada et al., 2018, 2019;

Ham et al., 2020). Parkin interacts with DRP1 through its second RING domain and subsequently ubiquitinates DRP1, leading to its proteasomal degradation. Both the deficiency of Parkin and expression of the PD-associated Parkin mutant C431F inhibit ubiquitination and degradation of DRP1, resulting in mitochondrial fragmentation (Figure 2; Lutz et al., 2009; Wang H. et al., 2011). In *Drosophila*, overexpression of DRP1 rescues muscle degeneration and mitochondrial abnormalities in *PINK1*^{-/-} or *Parkin*^{-/-} mutants (Deng et al., 2008). *In vitro*, Parkin also ubiquitinates MFN-1 and MFN-2. Ubiquitination of MFN-1 and MFN-2 is reduced in either cell lines with Parkin deficiency or fibroblasts derived from PD patients harboring *Parkin* mutations (Gegg et al., 2010; Rakovic et al., 2011). In *Drosophila*, accumulated Marf (*Drosophila* homolog of MFN), along with reduced ubiquitinated Marf and increased non-ubiquitinated Marf, is observed in Parkin mutant flies (Poole et al., 2010; Ziviani et al., 2010). Thus, Parkin participates in regulation of mitochondrial dynamics.

2.3.2 Parkin-mediated ubiquitination and mitochondrial biogenesis

Another mechanism cells employ to cope with mitochondrial damage is to generate new mitochondria, a process known as mitochondrial biogenesis (Ivankovic et al., 2016; Popov, 2020). Mitochondrial biogenesis is governed by the master regulator PGC1- α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha). PGC1- α binds and activates nuclear



transcription factors NRF-1 and 2 (nuclear respiratory factor 1 and 2) to increase transcription and therefore expression of proteins for mitochondrial biogenesis (Scarpulla, 2008; Li et al., 2011, 2021). PARIS (Parkin-interacting substrate) is a zinc finger protein that binds to and represses PGC-1 α . Parkin interacts with PARIS and tags it with Ub chains for proteasomal degradation (Shin et al., 2011; Siddiqui et al., 2015; Stevens et al., 2015; Lee et al., 2017). Parkin deficiency leads to accumulation of PARIS, downregulation of PGC-1 α , and selective loss of SNpc DA neurons. All of these are rescued by PGC-1 α expression (Shin et al., 2011; Stevens et al., 2015; Siddiqui et al., 2016). These observations suggest that Parkin-mediated ubiquitination plays an important regulatory role in the PGC-1 α -mediated mitochondrial biogenesis by ubiquitinating PARIS (Figure 3).

2.3.3 Parkin-mediated ubiquitination and calcium homeostasis

Recent studies suggest that Parkin regulates calcium homeostasis by ubiquitinating a range of tethering proteins involved in mitochondria-endoplasmic reticulum contact

sites (MERCs), such as MFN1, MFN2, MIRO1, and MICU (Figure 4). Parkin in calcium regulation was initially reported by Sandebring et al., 2009. With epidermal growth factor (EGF) stimulation, expression of both PD-associated Parkin mutants (R42P and G328E) or Parkin knockdown results in increased PLC γ 1 (phospholipase C gamma1) and elevated basal cytosolic Ca²⁺ levels. These phenotypes are completely reversed with the treatment of PLC-inhibitor neomycin (Sandebring et al., 2009). A later study demonstrates that glutamate excitotoxicity in neuronal cells triggers Parkin accumulation on the ER and MERCs, suggesting a role of Parkin in the mitochondria-ER crosstalk (Van Laar et al., 2015). In HeLa cells that do not express endogenous Parkin, overexpression of Parkin, but not the Parkin mutant lacking Ubl domain, enhances ER-mitochondrial tethering and increases agonist-induced Ca²⁺ transients (Cali et al., 2013). Conversely, Parkin knockdown impairs mitochondrial Ca²⁺ transfer and reduces mitochondria-ER contacts, suggesting that Parkin may enhance mitochondria-ER Ca²⁺ transfer by maintaining MERCs (Cali et al., 2013). However, confounding evidences are observed in fibroblasts derived from PD patients carrying *Parkin* mutations

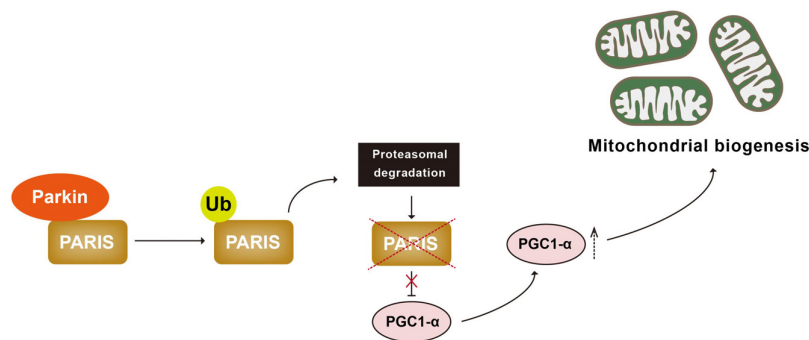


FIGURE 3

Parkin-mediated ubiquitination regulates mitochondrial biogenesis. PARIS binds to and represses PGC 1 α , the master regulator of mitochondrial biogenesis. Parkin interacts with and ubiquitinates PARIS, leading to its proteasomal degradation and promoting mitochondrial biogenesis. PARIS, Parkin-interacting substrate; PGC 1 α , peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

and in *Parkin*^{-/-} mice. Loss of Parkin results in close proximity between ER and mitochondria, leading to increased mitochondria-ER Ca²⁺ transfer, while overexpression of Parkin could restore the cytosolic Ca²⁺ transient to normal (Gautier et al., 2016).

Mitochondria take up Ca²⁺ through the mitochondrial calcium uniporter (MCU) complex that are composed of four core components, including the pore-forming subunit MCU, gatekeeping subunits MICU1 and 2 (mitochondrial calcium uptake 1 and 2), and the auxiliary subunit EMRE (essential mitochondrial regulator) (Sancak et al., 2013; Raffaello et al., 2013). MICU1 and 2, respectively, act as positive and negative regulators of the MCU complex (Plovanich et al., 2013). Under basal conditions, Parkin ubiquitinates MICU1, leading to its rapid degradation via the proteasomal system. Given that MICU2 stability is strictly dependent on MICU1, Parkin-mediated ubiquitination also indirectly regulates the amount of MICU2 (Matteucci et al., 2018). By maintaining appropriate levels of MICUs, Parkin plays a regulatory role in mitochondrial calcium homeostasis. Additionally, Parkin exerts its effects on ER-mitochondrial tethering via ubiquitinating of MFN2. ER located MFN2 forms a homotypic or heterotypic complex with either mitochondria-located MFN2 or mitochondria-located MFN1, thereby bridging mitochondria and ER (de Brito and Scorrano, 2008). Parkin ubiquitinates MFN2 on K416 in the HR1 domain, which in turn positively affects the physical and functional interactions between mitochondria and ER. Parkin-resistant MFN2 mutant K416R loses the ability to restore the decreased mitochondria-ER interactions in Parkin deficient cells and fibroblasts carrying PD-associated Parkin mutants (Basso et al., 2018). MIRO is another substrate of Parkin that regulates mitochondria-ER contacts. In yeast cells, yeast MIRO (Gem1p) deficiency leads to significant decrease of MERCs (Figure 4; Wang X. et al., 2011).

2.4 Ubiquitination of other PD-associated proteins and mitochondrial functions

2.4.1 Ubiquitination of α -synuclein and mitochondrial functions

α -Synuclein, a principal component of LB, is a key protein involved both genetically and pathologically in PD. Mutations

in the *α -synuclein* gene cause familiar forms of PD. The polymorphisms of *α -synuclein* confer a relatively increased risk of developing idiopathic PD. Since 1997, point mutations and duplication of *α -synuclein* gene have been inventoried with autosomal dominant PD, suggesting a gain-of-function mechanism (Polymeropoulos et al., 1997; Fuchs et al., 2007; Elia et al., 2013).

α -Synuclein is predominantly found in the presynaptic terminals of the central nervous system and is implicated in regulating synaptic plasticity and neurotransmitter release (Burre et al., 2010; Venda et al., 2010). Compelling evidence suggests that mitochondrial functions, such as cytochrome c release, calcium homeostasis, ATP production, and mitochondrial fission-and-fusion balance, are also directly regulated by α -synuclein. Remarkably, α -synuclein is found in all mitochondrial compartments and can selectively be localized to mitochondria under stress conditions (Ulmer et al., 2005; Li et al., 2007; Parihar et al., 2008; Zhang et al., 2008; Devi and Anandatheerthavara, 2010; Subramaniam et al., 2014). The N-terminal 32 amino-acid sequence of α -synuclein is critical for its mitochondrial translocation. α -Synuclein undergoes multiple PTMs, including ubiquitination. α -Synuclein is a target of Parkin upon mitochondrial stress. Under basal conditions, no interaction between α -synuclein and Parkin is detected. With the treatment of CCCP or rotenone, Parkin forms a complex with α -synuclein and catalyzes formation of K63-linked Ub chains to recruit Synphilin 1, a negative regulator of α -synuclein toxicity, to the α -synuclein-Parkin complex. Therefore, Parkin-mediated ubiquitination may negatively regulate α -synuclein's response to the mitochondrial stress (Norris et al., 2015). Consistently, α -synuclein is the substrate of RING-type E3 ligase SIAH-1 (seven *in absentia* homolog-1). SIAH-1 facilitates the mono- and poly-ubiquitination of α -synuclein to increase α -synuclein insolubility and exacerbate its aggregation-associated toxicity (Figure 4). Cells overexpressing WT α -synuclein or PD-associated mutant α -synuclein A53T show exacerbated cytochrome c release and apoptosis with increased of SIAH-1 activity (Lee et al., 2008).

Ubiquitinated α -synuclein is predominately found in LBs and has been demonstrated to contribute to the misfolding of α -synuclein, mitochondrial dysfunction, and neuronal death (Spillantini et al., 1997; Devi et al., 2008; Choubey et al., 2011). Despite these associations, efforts to establish α -synuclein as a

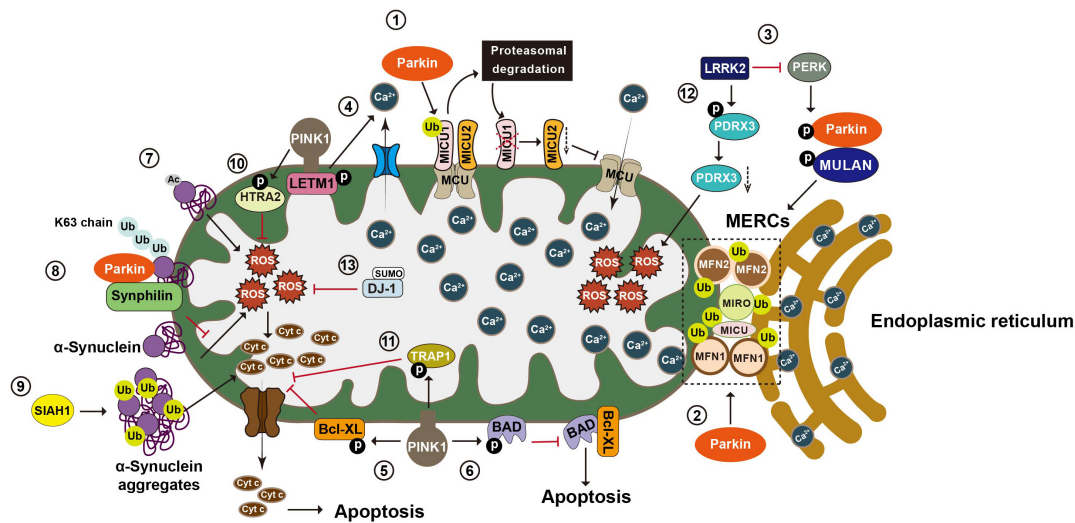


FIGURE 4

Post-translational modifications in the regulation of calcium homeostasis, oxidative stress, and apoptosis. Mitochondria play an essential role in maintaining Ca^{2+} homeostasis, regulating oxidative stress, and integrating apoptosis signals. (1) Mitochondria take up Ca^{2+} through the MCU complex, which is positively and negatively regulated by MICU1 and 2, respectively. Parkin regulates mitochondrial calcium homeostasis by directly ubiquitinating MICU1, leading to its proteasomal degradation, and indirectly affecting MICU2's protein level. (2) Parkin also regulates calcium homeostasis by ubiquitinating tethering proteins involved in mitochondria endoplasmic reticulum contact sites (MERCs), such as MFN1, MFN2, MIRO1, and MICU. (3) LRRK2 blocks PERK mediated phosphorylation and activation of Parkin and MULAN, causing increased degradation of MERCs tethering proteins and reduced ER mitochondrial contacts. (4) PINK1 phosphorylates LETM1, leading to increased calcium release and facilitating calcium transport in mitochondria. (5) PINK1 phosphorylates Bcl XL and prevents its pro apoptotic cleavage. (6) PINK1 also phosphorylates BAD and prevents the formation of pro apoptotic Bcl XL BAD complex. (7) N α acetylation of α synuclein induces mitochondrial dysfunction. (8) Parkin increases K63-linked Ub chains on α synuclein, leading to the recruitment of Synphilin 1 to inhibit α synuclein toxicity. (9) SIAH-1 facilitates ubiquitination of α synuclein, increasing α synuclein's insolubility and exacerbating its aggregation associated toxicity. (10) PINK1 mediated phosphorylation enhances the proteolytic activity of HTRA2 and protects cells against mitochondrial stress. (11) Phosphorylation of TRAP1 by PINK1 inhibits cytochrome c release and reduces cell death during oxidative stress. (12) LRRK2 phosphorylates PRDX3 and decreases its peroxidase activity. (13) SUMOylation of DJ 1 is crucial for of DJ 1's anti-ROS activity. MCU, mitochondrial calcium uniporter; MICU1, mitochondrial calcium uptake 1; MICU2, mitochondrial calcium uptake 2; MFN1, mitofusin 1; MFN2, mitofusin 2; MIRO1, mitochondrial Rho GTPase 1; LRRK2, leucine-rich repeat kinase 2; PERK, protein kinase RNA-like ER kinase; LETM1, leucine zipper-EF-hand-containing transmembrane protein 1; ER, endoplasmic reticulum; Bcl XL, B-cell lymphoma-extra large; BAD, BCL2 associated agonist of cell death; Ub, ubiquitin; SIAH-1, seven *in absentia* homolog-1; HTRA2, high-temperature requirement serine protease A2; TRAP1, TNF receptor-associated protein 1; PRDX3, peroxiredoxin 3; ROS, reactive oxygen species.

biomarker for PD diagnosis or prognosis primarily focus on three species of α -synuclein-total α -synuclein, phosphorylated α -synuclein, and the oligomeric form of α -synuclein-in tissues and fluids like blood components, CSF, saliva, and extracellular vesicle (EVs) (Hong et al., 2010; Tokuda et al., 2010; Mollenhauer et al., 2011, 2013; Foulds et al., 2012; Wang Y. et al., 2012; van Steenoven et al., 2018; Vivacqua et al., 2019; Stuedl et al., 2021). Monoubiquitinated and polyubiquitinated α -synuclein are able to be detected in plasma using a polyclonal anti-ubiquitin antibody (FL-76) (Foulds et al., 2011). It will of interest in studying whether this is useful for PD diagnosis.

2.4.2 FBXO7-regulated ubiquitination and mitochondrial functions

Mutations in *FBXO7* cause autosomal recessive EOPD (Shojaee et al., 2008). Being a F-box domain-containing protein, *FBXO7* (F-box protein 7) acts as an adapter for Skp1-Cullin-F-box (SCF) type E3-ubiquitin ligase (Skowyra et al., 1997). Emerging evidence suggests that *FBXO7* participates in the maintenance of mitochondrial homeostasis through facilitating ubiquitination modification of key proteins in the mitochondrial quality control pathways. Overexpression of *FBXO7* enhances Parkin recruitment onto damaged mitochondria, suggesting a role of *FBXO7* in mitophagy process (Burchell et al., 2013). It seems that

FBXO7 negatively regulates mitophagy activity by enhancing the ubiquitination of PINK1, thereby, suppressing Parkin E3 ligase activity (Figure 1; Liu et al., 2020). Furthermore, ubiquitination of MFN1 was also found to be significantly reduced in both fibroblasts derived from patients harboring homozygous *FBXO7* R378G mutation and in SH-SY5Y cells with *FBXO7* deficiency, which is restored by wild-type *FBXO7*. However, a recent study reports that *FBXO7* is dispensable in the Parkin-mediated mitophagy process. Accumulation of pUb, recruitment of Parkin onto mitochondria, and mitophagy flux are all barely affected in *FBXO7*^{-/-} cells. Moreover, increased pUb foci were detected in *FBXO7*^{-/-} cells than that in control cells after treating with mitochondrial targeted HSP90 (heat shock protein 90) inhibitor Gamitrinib-TPP (Kraus et al., 2023). It is possible that *FBXO7* regulates mitochondrial functions differentially depending on conditions. Nonetheless, the regulation is likely one via ubiquitination modification.

2.4.3 VPS35-regulated ubiquitination and mitochondrial functions

VPS35 (vacuolar protein sorting 35) is a critical component of the retromer complex that is important for the retrograde transport of transmembrane protein-cargo from endosomes to the trans-Golgi network (TGN) (Hierro et al., 2007). Mutations in *VPS35* have recently been identified as the cause of familial PD.

A single missense mutation in *VPS35*, c.1858G > A (p.D620N), has been unambiguously identified to segregate with late-onset PD (LOPD) in an autosomal dominant manner (Zimprich et al., 2011). Studies suggest that *VPS35* can indirectly participate in mitochondrial dynamics via the alteration of ubiquitination events. Using a transgenic mouse model, Tang et al. (2015) revealed that *VPS35* regulates the trafficking and degradation of the MULAN (mitochondrial E3 ubiquitin protein ligase 1), thereby inhibiting MUL1-mediated ubiquitination and degradation of MFN2 and promoting mitochondrial fusion (Figure 2). Consistently, selective deletion of the *VPS35* in DA neuron results in mitochondrial fragmentation and PD-relevant pathologies in *VPS35*[±] mice (Tang et al., 2015).

2.4.4 LRRK2-regulated ubiquitination and mitochondrial functions

Another PD-associated protein that indirectly participate in mitochondrial dynamics through ubiquitination modification is LRRK2 (leucine-rich repeat kinase 2). LRRK2, also known as dardarin (from the Basque word “dardara” that means trembling) and PARK8 (from early identified association with PD), is a large multifunctional kinase. Variants of this gene are associated with increased risk of PD and Crohn’s disease (Funayama et al., 2002). LRRK2, through its N-terminal domain, interacts with mitochondrial membrane-binding E3 ubiquitin ligases MARCH5 (membrane associated Ring-CH-type finger 5), MULAN, and Parkin. The kinase activity of LRRK2 is required for activation of these E3 ligase (Figure 2). No evidence of direct phosphorylation of these E3 ligases by LRRK2 has been found in *in vitro* assays, but screening assay using siRNA library revealed that PERK (protein kinase RNA-like ER kinase) is the kinase that directly phosphorylates and activates these E3 ligases. Via binding to these E3 ligases, LRRK2 WT blocks the PERK-mediated phosphorylation and activation of these E3 ligases. PD-associated LRRK2 mutant G2019S has decreased binding activity to these E3 ligases, resulting in increased phosphorylation and activation of E3 ubiquitin ligases by PERK, which consequently causes increased degradation of MERCS tethering proteins and reduced ER-mitochondrial contacts (Figure 4; Toyofuku et al., 2020).

3 Regulation of mitochondrial functions by phosphorylation in Parkinson’s disease

Protein phosphorylation, a prevalent PTM mediated by kinases, involves the covalent attachment of a phosphate group to an amino acid residue like serine (S), threonine (T), or tyrosine (Y). This dynamic modification offers a swift mechanism to alter protein function, thus playing crucial roles in regulation of various cellular pathways. Emerging evidence indicates that aberrant phosphorylation of proteins impacts mitochondrial functions, such as mitochondrial dynamics, mitophagy, MDV formation, mitochondrial respiratory activity, and calcium homeostasis. Notably, PD-associated kinase proteins, such as PINK1 and LRRK2, have been found to cause mitochondrial dysfunction through their dysregulated phosphorylation activity, ultimately leading to PD pathogenesis. Therefore, we aim to provide an overview elucidating

how PINK1 and LRRK2 modulate a range of mitochondrial functions via their kinase activity, outlining their implications in the pathogenesis of PD through protein phosphorylation (Table 3).

3.1 PINK1-mediated phosphorylation and mitophagy

Mutations in *PINK1* are the second most common cause of EOPD, accounting for 1–9% PD patients. More than 300 *PINK1* variants have been identified from PD patients (Ma et al., 2021; Vizziello et al., 2021). The *PINK1* gene encodes a 581 amino acid protein, which contains an N-terminal mitochondrial targeting sequence (MTS), a transmembrane domain (TMD), and a highly conserved S/T kinase domain (Cardona et al., 2011). Under normal conditions, PINK1 is targeted to mitochondria through its MTS via the TOM (translocase of the outer membrane) and TIM (translocase of the inner membrane) complexes (Lazarou et al., 2012). During the translocation process, PINK1 undergoes consecutive cleavages by MPP (mitochondrial processing peptidase) and PARL (presenilin-associated rhomboid-like protease) (Jin et al., 2010; Deas et al., 2011; Greene et al., 2012), and the cleaved 52-kDa PINK1 is retro-translocated into the cytosol and undergoes rapid turnover by the proteasome via the N-end rule pathway (Whitworth et al., 2008; Greene et al., 2012). Therefore, PINK1 is normally maintained at a very low steady-state level. With damaged mitochondria, PINK1’s mitochondrial import is inhibited by the reduced mitochondrial membrane potential, which leads to the accumulation of full-length PINK1 on the OMM (Jin and Youle, 2013).

The landmark studies suggesting that both Parkin and PINK1 function through a common pathway to regulate mitochondrial function were from a series of *Drosophila* research (Greene et al., 2003; Clark et al., 2006; Park et al., 2006). Not only do *PINK1*^{-/-} and *Parkin*^{-/-} mutant flies exhibit similar degenerative phenotypes in neuron and muscle cells due to mitochondrial abnormalities, but overexpression of Parkin also rescues the *PINK1*^{-/-} phenotype, not vice versa, suggesting PINK1 acts upstream of Parkin in a linear pathway (Yang et al., 2006). Later on, more studies gradually unveil the models of how PINK1 and Parkin work together to regulate various mitochondrial functions (Durcan and Fon, 2015; Mouton-Liger et al., 2017).

PINK1-mediated phosphorylation plays essential roles at multiple steps of the mitophagy process, largely interacting with Parkin-mediated ubiquitination modification (Ordureau et al., 2014). First, autophosphorylation of PINK1 is important for its own activation, coinciding with its accumulation on the OMM (Kondapalli C. et al., 2012). PINK1 activity is determined by autophosphorylation at residues S228, S230, T257, and S402 (Kondapalli C. et al., 2012; Okatsu et al., 2012b; Aerts et al., 2015; Rasool et al., 2022). Although conflicting results regarding the regulatory role of autophosphorylation residues in PINK1 are reported, autophosphorylation at S228 is important for the subsequent phosphorylation of PINK1 substrates in cells (Okatsu et al., 2012a; Aerts et al., 2015; Kumar et al., 2017; Rasool et al., 2018). Furthermore, the equivalent site of human PINK1 S228 is confirmed to be autophosphorylated in multiple PINK1 homologs, including S346 of *Drosophila* PINK1, S205 of

TABLE 3 Phosphorylation of PD-related proteins and mitochondrial dysfunction.

PD-related protein	Enzyme	Substrate	Regulated mitochondrial function	Modification site (human)	References
PINK1	PINK1	PINK1	Activates PINK1	S228, S230, T257, S402	Kondapalli C. et al., 2012; Okatsu et al., 2012b; Aerts et al., 2015
	PINK1	Ub	Activates Parkin	S65	Kazlauskaitė et al., 2014
	PINK1	Parkin	Promotes mitophagy, increases MDVs production	S65	Kazlauskaitė et al., 2014
	PINK1	NDUFA10	Enhances CI activity	S250	Morais et al., 2014
	PINK1	Bcl-XL	Inhibits pro-apoptotic signal	S62	Arena et al., 2013
	PINK1	BAD	Prevents apoptosis	S112, S136	Wan et al., 2018
	PINK1	HTRA2	Reduces mitochondrial stress	S141	Plun-Favreau et al., 2007
	PINK1	TRAP1	Inhibits cytochrome c release	-	Pridgeon et al., 2007
	PINK1	LETM1	Maintains calcium homeostasis	T192	Huang et al., 2017
	MARK2	PINK1	Activates PINK1	T313	Matenia et al., 2012
LRRK2	LRRK2	Parkin	Inhibits mitophagy	-	Bonello et al., 2019
	LRRK2	MIRO	Inhibits mitophagy	-	Hsieh et al., 2016
	LRRK2	Rab10	Inhibits mitophagy	T73	Wauters et al., 2020
	LRRK2	BCL2	Increases mitophagy	T56	Su et al., 2015
	LRRK2	DRP1	Increases mitochondrial fragmentation	T595	Su and Qi, 2013
	LRRK2	4E-BP	Increases oxidative stress	T37, T46	Imai et al., 2008
	LRRK2	PRDX3	Increases oxidative stress	T146	Angeles et al., 2011
	LRRK2	unknown	Exacerbates mtDNA damage	-	Howlett et al., 2017; Gonzalez-Hunt et al., 2020

PINK1, PTEN induced putative kinase 1; Ub, ubiquitin; NDUFA10, NADH: ubiquinone oxidoreductase subunit A10; Bcl-XL, B-cell lymphoma-extra large; BAD, BCL2 associated agonist of cell death; HTRA2, high-temperature requirement serine protease A2; TRAP1, TNF receptor-associated protein 1; LETM1, leucine zipper-EF-hand-containing transmembrane protein 1; MARK2, microtubule affinity-regulating kinase; LRRK2, leucine-rich repeat kinase 2; MIRO, mitochondrial Rho GTPase; BCL2, B-cell lymphoma 2; DRP1, dynamin-related protein 1; 4E-BP, 4E-binding protein; PRDX3, peroxiredoxin 3; MDV, mitochondrial-derived vesicle; CI, mitochondrial respiratory complex I; mtDNA, mitochondrial DNA; T, threonine; S, serine; “-” means no answer.

Tribolium PINK1, and S202 of *Pediculus* PINK1 (Rasool et al., 2018). *Drosophila* carrying the PINK1 S346A mutant displays similar mitochondrial defects to those observed in *PINK1*^{-/-} mutant flies (Clark et al., 2006). Second, PINK1 phosphorylates Parkin at S65 of the ubiquitin domain to induce recruitment of Parkin to mitochondria and the release of Parkin E3 ligase activity. PINK1-mediated phosphorylation is essential for Parkin activation (Xiong et al., 2009; Kondapalli K. C. et al., 2012; Kane et al., 2014; Kazlauskaitė et al., 2014; Koyano et al., 2014; Wauer et al., 2015a). In the absence of an activation signal, Parkin stays in the cytosol in an auto-inhibited structure due to the inhibitory intradomain contacts (Trempe and Gehring, 2023). PINK1 phosphorylates Ub on S65 (Kazlauskaitė et al., 2014; Koyano et al., 2014; Wauer et al., 2015b). pUb serves as a receptor for Parkin to bind. Upon pUb binding, Parkin Ubl domain becomes more accessible by PINK1, leading to the subsequent phosphorylation of Ubl S65 (Durcan and Fon, 2015). Phosphorylation of Parkin by PINK1 further dissociates the inhibitory intradomain-contacting inside Parkin, resulting in the full activation of Parkin's enzymatic activity (Trempe and Gehring, 2023). Third, PINK1-mediated phosphorylation amplifies the Parkin-mediated ubiquitination signal. After activation, Parkin ubiquitinates a large number of mitochondrial proteins and thereby produces increased Ub substrates for PINK1 to generate pUb signals, which successively initiate more Parkin recruitment and greater Parkin activation, creating a feed-forward loop to

reach a maximal of Parkin-mediated ubiquitination (Figure 1; Ordureau et al., 2015; Koyano et al., 2019). On a relevant note, MARK2 (microtubule affinity-regulating kinase) is identified as an activating kinase of PINK1. MARK2 phosphorylates PINK1 at residue T313 that coincidentally is a residue frequently mutated to a non-phosphorylatable form T313M in PD cases (Tang et al., 2006). The expression of PINK1 T313M causes severe toxicity and abnormal mitochondrial accumulation in cells, also suggesting the mitochondrial consequence of the PINK1 activity (Matenia et al., 2012).

PINK1-mediated phosphorylation is a potential biomarker for PD diagnosis (Chin and Li, 2016). An antibody designed for pS65 on Ub (pS65-Ub) reveals that a rapid accumulation of pS65-Ub signal in mitochondria following mitochondrial damage. The presence of pS65-Ub positive granule also increases in cells derived from aging individuals and sporadic PD cases (Fiesel et al., 2015). Furthermore, a patent filed by Geldenhuys et al. (2014) details the use of PINK1 T257 autophosphorylation and PINK1-mediated phosphorylation of Parkin at S56 in serum and CSF as diagnostic measures. Additional efforts will be required to evaluate their clinical applicability.

Of the reported PD-associated *PINK1* mutations, about 30 of them are defined as “pathogenic” or “likely pathogenic,” causing similar clinical symptoms as in the cases caused by *Parkin* mutations (Richards et al., 2015; Ellard et al., 2020). Recently,

Ma et al. (2021) analyzed 50 PINK1 variants and found most these pathogenic variants cause a significant decrease in mitophagy activity. However, these consist of only a small fraction of identified pathogenic PINK1. Further investigation is still needed to understand PINK1-phosphorylation regulated mitophagy in PD pathogenesis (Lin and Kang, 2008).

3.2 PINK1-mediated phosphorylation and mitochondrial-derived vesicles

PINK1, along with Parkin, are identified as key regulators of the MDV pathways that plays important roles in the regulation of mitochondrial turnover and MitAP production (Matheoud et al., 2016). PINK1 was initially found to be required for the formation of MDVs that deliver damaged mitochondrial portion to the lysosome for degradation (Sugiura et al., 2014; Pickrell and Youle, 2015). Ramirez et al. (2022) have recently reported that cannabidiol (CBD) activates PINK1 and Parkin in a dose-dependent manner, leading to elevated production of MDVs. CBD causes PINK1 accumulation on the mitochondrial out membrane to activate Parkin to promote the generation of MDVs (Figure 1). However, detailed mechanism underlying PINK1-regulated MDV formation remains unknown. It is possible that PINK1 participates in recognition of damaged sites of mitochondria and promotes segregation of damaged part of mitochondria. Consistent with this notion, PINK1 is shown to phosphorylate DRP1 at S616 to activate fission, a potential mechanism to separate damaged and health portion of a mitochondrion (Han et al., 2020).

3.3 PINK1-mediated phosphorylation and other mitochondrial functions

3.3.1 PINK1-mediated phosphorylation and mitochondrial dynamics

PINK1 is implicated in the phosphorylation of mitochondrial proteins that are important for the regulation of mitochondrial dynamics. First, PINK1 phosphorylates a group of key players in the mitochondrial dynamic pathways. The dynamin-related GTPase DRP1 is a crucial factor of the mitochondrial fission machinery, and its activity is regulated by phosphorylation (Yu et al., 2019; Han et al., 2020). Around 10 residues of DRP1 are able to be phosphorylated. Phosphorylation of S616 and S637 is extensively studied (Kim et al., 2016; Cha et al., 2021). After recruiting to the OMM, DRP1 is phosphorylated by PKA (protein kinase A) at S637, inhibiting DRP1 GTPase activity and suppressing its translocation to the mitochondria, and thereby impeding mitochondrial fission (Cereghetti et al., 2008). DRP1^{S616} was initially found to be phosphorylated by Cdk1/cyclin B, resulting in mitochondrial fragmentation (Pryde et al., 2016). We recently demonstrate that PINK1 directly phosphorylate DRP1^{S616} site to regulate mitochondrial fission that is independent of Parkin and autophagy activity (Han et al., 2020). MFN2 is also a substrate of PINK1. PINK1 phosphorylates MFN2 at residues T111 and S442, resulting in increased ubiquitination and proteasomal degradation of MFN2, leading to eventual mitochondrial fusion via Parkin

mediated mechanism (Chen and Dorn, 2013; Tsai et al., 2014). Likewise, PINK1 phosphorylates MIRO1 at residue S156, in turn activates Parkin-mediated ubiquitination and degradation of MIRO1, therefore, inhibits axonal transport of mitochondria (Figure 2; Wang X. et al., 2011).

3.3.2 PINK1-mediated phosphorylation and mitochondrial respiratory activity

Both PINK1 deficiency and PD-associated PINK1 mutants impair functions of mitochondrial respiratory complex I (CI) (Morais et al., 2009, 2014). NDUFA10 (NADH: ubiquinone oxidoreductase subunit A10) is an auxiliary subunit of CI. Although it is still unclear whether PINK1 directly phosphorylates NDUFA10, phosphoproteomic analysis reveals abolished phosphorylation of NDUFA10 at residue S250 in PINK1 knockout (KO) mice. Furthermore, both WT NDUFA10 and the phosphomimetic NDUFA10 mutant (S250D) enhance CI activity and rescue PINK1 deficiency-induced mitochondrial damage in mouse and cellular models. In contrast, the phosphorylation deficient mutant NDUFA10 S250A fails to rescue the PINK1 deficiency-related phenotypes (Morais et al., 2014). These results suggest a crucial role of phosphorylated NDUFA10 in the regulation of mitochondrial bioenergetics. Consistently, NDUFA10 improves PINK1 knockdown (KD)-induced mitochondrial hyperfusion in *Drosophila* by increasing CI activity (Pogson et al., 2014).

3.3.3 PINK1-mediated phosphorylation and apoptosis

Mitochondria hold a central position in the apoptosis process. PINK1-mediated phosphorylation is found to prevent mitochondria-mediated cell death in multiple ways. PINK1 phosphorylates Bcl-XL (B-cell lymphoma-extra large) and prevents its pro-apoptotic cleavage. Bcl-XL has an anti-apoptotic activity by protecting the mitochondrial membrane potential ($\Delta\psi$) and preventing cytochrome c release via its binding to and inhibition of VDACs. The N-terminal BH4 domain of the Bcl-XL is essential for this apoptosis inhibition activity (Shimizu et al., 2000). Upon mitochondrial depolarization, PINK1 interacts with Bcl-XL and phosphorylates it at residue S62, leading to the resistance of Bcl-XL to the cleavage of its N-terminal and the reduction of pro-apoptotic signal (Arená et al., 2013). BAD (BCL2 associated agonist of cell death) is a BH3-only protein. Phosphorylation of BAD at residue S112 inhibits its ability to form pro-apoptotic complex with Bcl-XL on the OMM (Hirai and Wang, 2001). Upon CCCP treatment, PINK1 phosphorylates BAD at residues S112 and S136, preventing the formation of pro-apoptotic Bcl-XL-BAD complex, leading to cell survival (Figure 4; Wan et al., 2018).

HTRA2 (high-temperature requirement serine protease A2) is implicated in the pathogenesis of PD and other neurodegenerative conditions. Mutations in *HTRA2* are a risk factor for sporadic PD cases. As a mitochondrial serine protease, HTRA2 functions in mitochondrial quality control and apoptosis. During apoptosis, HTRA2 is released into the cytosol and facilitates apoptosis by antagonizing IAPs (inhibitors of apoptosis). Interestingly, HTRA2 activation is dependent on the direct phosphorylation of its S141 by PINK1. PINK1-mediated S141 phosphorylation enhances the proteolytic activity of HTRA2 and protects cells against

mitochondrial stress (Figure 4; Plun-Favreau et al., 2007). HTRA2 variants, A141S and P143A, identified in sporadic PD patients are in close proximity to the S142, suggesting they may contribute to PD by interfering with PINK1-mediated phosphorylation and HTRA2 activation (Strauss et al., 2005; Lin et al., 2011). Genetic studies in *Drosophila* further demonstrated the functional interaction between PINK1 and HTRA2. These studies collectively suggest that HTRA2, in parallel with Parkin, acts downstream of the PINK1 to maintain mitochondrial integrity (Whitworth et al., 2008; Tain et al., 2009). Consistently, reduced HTRA2 phosphorylation is observed in brains of PD patients carrying *PINK1* mutations (Plun-Favreau et al., 2007).

TRAP1 (TNF receptor-associated protein 1), also known as HSP75 (heat shock protein 75), is a mitochondrial chaperone protein. PINK1 binds to TRAP1 on mitochondria and phosphorylates TRAP1 in the mitochondrial intermembrane space (IMS). Phosphorylation of TRAP1 by PINK1 inhibits cytochrome c release and reduces cell death during oxidative stress. PD-associated PINK1 mutants G309D and L347P, both with reduced kinase activity, diminish the TRAP1 phosphorylation and result in increased apoptosis upon mitochondrial oxidative stress (Pridgeon et al., 2007). In *Drosophila*, TRAP1 deficiency results in mitochondrial dysfunction and vulnerability to various mitochondrial stress. Overexpression of human TRAP1 rescues PINK1-deficiency induced mitochondrial abnormalities (Costa et al., 2013; Zhang et al., 2013).

3.3.4 PINK1-mediated phosphorylation and calcium homeostasis

Mitochondria are both major effectors and essential regulators of intracellular Ca^{2+} levels. The amount of Ca^{2+} retained inside the mitochondrial matrix is regulated by mitochondrial Ca^{2+} transient, which includes Ca^{2+} influx mediated by MCU and mitochondrial Ca^{2+} efflux mediated by $\text{Na}^+/\text{Ca}^{2+}$ and $\text{H}^+/\text{Ca}^{2+}$ antiporters (Szabadkai et al., 2006). PINK1 deficiency leads to dysfunction of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger and causes mitochondrial calcium overload (Gandhi et al., 2009). Studies reveal that LETM1 (leucine zipper-EF-hand-containing transmembrane protein 1) is a mitochondrial $\text{H}^+/\text{Ca}^{2+}$ antiporter situated on the IMM. PINK1 interacts with LETM1 and directly phosphorylates it at residue T192, leading to increased calcium release in liposomes and facilitating calcium transport in mitochondria (Figure 4). Both PINK1 deficiency and PD-associated mutant PINK1 Q456X significantly reduce LETM1 phosphorylation, causing mitochondrial calcium-transport dysfunction and neuronal death (Huang et al., 2017).

3.4 LRRK2-mediated phosphorylation and mitochondrial functions

3.4.1 LRRK2-mediated phosphorylation and mitophagy

Mutations in *LRRK2* are the most common cause of autosomal dominant LOPD (Zimprich et al., 2004). *LRRK2* encodes a 286-kDa protein containing multiple domains, including a leucine-rich repeat (LRR), a Ras of complex protein (ROC) GTPase domain, a mitogen-activated kinase domain, and WD40 domains. Therefore,

LRRK2 is a bienzymatic protein with both GTPase and kinase activities. Six pathogenic mutations have been identified in *LRRK2*, including R1441C/G, N1437H, Y1699C, G2019S, and I2020T (Ross et al., 2011). The most common LRRK2 mutation, G2019S, is located right in the kinase domain. This mutation increases LRRK2 kinase activity toward itself and other substrates (Ross et al., 2011). Thus, the increased kinase activity of LRRK2 is considered important in the pathogenesis of PD.

While majority of LRRK2 is located at cytoplasm, a portion of LRRK2 is associated with the OMM (West et al., 2005; Biskup et al., 2006). iPSC-derived neural cells bearing LRRK2 G2019S and fibroblasts derived from PD patients carrying LRRK2 G2019S show mitochondrial impairment, suggesting that LRRK2 pathogenesis might involve mitochondrial dysfunction (Mortiboys et al., 2010; Sanders et al., 2014). *In vitro*, expression of LRRK2 increases mitochondrial clustering and reduced mitochondrial clearance upon CCCP treatment. In contrast, LRRK2 G2019S further exacerbated the damaging effects (Hsieh et al., 2016). Likewise, reduced mitochondrial autophagy in DA neurons and astrocytes in LRRK2 G2019S mouse brain that is rescued by treatment with LRRK2 kinase inhibitor GSK3357679A (Singh et al., 2021). Several possible mechanisms for the negative regulation of mitophagy by LRRK2 kinase activity are proposed: (1) LRRK2 impairs the interactions between Parkin and DRP1 and their mitochondrial targets in a kinase-dependent manner (Bonello et al., 2019); (2) LRRK2 interacts with MIRO, and the LRRK2 G2019S mutant prevents proteasomal degradation of MIRO, leading to delayed mitophagy (Hsieh et al., 2016); (3) LRRK2 phosphorylates Rab10 on the residue T73, and PD-associated LRRK2 mutants (G2019S and R1441C) impair Rab10 mitochondrial localization and disrupts its interaction with OPTN, resulting in impaired mitochondrial autophagy via a kinase activity related manner (Figures 1, 2; Wauters et al., 2020). In contrast, a study suggests a positive regulation of mitophagy by LRRK2's kinase activity. LRRK2 G2019S phosphorylates BCL2 at residue T56, leading to the loss of $\Delta\psi$ and triggering excessive mitophagy via the recruitment of P62 to the mitochondria, (Su et al., 2015).

Recognizing the crucial role of elevated LRRK2 kinase activity in PD pathogenesis, multiple research groups have undertaken studies to quantitatively assess LRRK2-related phosphorylation across various tissues and biofluids, exploring their potential of being used as a PD diagnosis (Delbroek et al., 2013; Wang et al., 2017; Padmanabhan et al., 2020; Vissers et al., 2023). Collectively, the expressional level of total LRRK2 (tLRRK2), phosphorylation of LRRK2 at S1292 or S935 (pS1292-LRRK2 or pS935-LRRK2), and phosphorylation of the LRRK2 substrate Rab10 at T73 (pT73-Rab10) have been the focus of extensive study. The observed changes of tLRRK2 and LRRK2-associated phosphorylation in PD cases vary among brain regions, tissues, and cell types (Rideout et al., 2020). Increased tLRRK2 in the frontal cortex in sporadic PD cases, conflicting changes of tLRRK2 I in cerebrospinal fluid (CSF) in sporadic PD cases, elevated pS1292-LRRK2 in urinary EVs in but deceased pS935-LRRK2 in PBMCs among LRRK2-G2019S carriers, and increased pT73-Rab10 in neutrophils in idiopathic PD and LRRK2-G2019S carriers have been reported (Cho et al., 2013; Fraser et al., 2016; Fan et al., 2018; Mabrouk et al., 2020; Padmanabhan et al., 2020).

Remarkably, the highest expression of LRRK2 is not observed in neurons but in peripheral blood mononuclear cells (PBMCs) (Thevenet et al., 2011). Particularly, certain cell types in PBMCs show increased LRRK2 expression in PD patients compared to healthy controls, including B cells, T cells, CD16+ monocytes, neutrophils, but not mixed PBMCs (Cook et al., 2017; Atashrazm et al., 2019). An LRRK2 inhibitor MLi2²⁵ significantly reduced pS935-LRRK2 and pT73-Rab10 in both neutrophils and mixed PBMC (Atashrazm et al., 2019). Although pS935-LRRK2 does not directly reflect LRRK2 kinase activity like pS1292-LRRK2, it is sensitive to dephosphorylation caused by LRRK2 kinase inhibitor (Delbroek et al., 2013; Lobbstaël et al., 2013). Therefore, pS935-LRRK2 and pT73-Rab10 are considered potential pharmacodynamics marker in clinical trials of LRRK2 kinase inhibitors.

3.4.2 LRRK2-mediated phosphorylation and other mitochondrial functions

LRRK2 regulates mitochondrial dynamics via DRP1 in a kinase-dependent manner. In BV2 microglia cells and primary cultured microglia cells, treatment of lipopolysaccharide (LPS) activates microglia, resulting in enhanced mitochondrial fragmentation (Ho et al., 2018). Interestingly, LPS-induced mitochondrial fragmentation can be reversed by LRRK2 kinase inhibitor GSK2578215A. Results suggest an important role of LRRK2 kinase activity in regulating mitochondrial dynamics in microglia (Ho et al., 2018). Consistently, overexpression of WT LRRK2 or LRRK2 G2019S in cells results in apparent mitochondrial fragmentation, while overexpression of LRRK2 kinase-dead mutant D1994A does not cause such phenotype (Wang X. et al., 2012; Perez Carrion et al., 2018). LRRK2 directly interacts with and phosphorylates DRP1. PD-associated LRRK2 G2019S and R1441C mutants further enhance this interaction (Su and Qi, 2013; Stafa et al., 2014). LRRK2 G2019S phosphorylates DRP1 at residue T595 (Su and Qi, 2013). In fibroblasts derived from PD patients carrying LRRK2 G2019S, both the selective DRP1-inhibitor P110 or the expression of non-phosphorylatable mutant DRP1 T595A reverse the mitochondrial fragmentation and improve mitochondrial quality, indicating that LRRK2 G2019S-induced mitochondrial fragmentation is possible via a mechanism related to DRP1 T595 phosphorylation (Figure 2; Su and Qi, 2013).

Cells expressing PD associated LRRK2 mutants increase susceptibility to oxidative stress, suggesting that increased LRRK2 kinase activity might interfere antioxidant defense mechanism (Heo et al., 2010; Nguyen et al., 2011; Bahnassawy et al., 2013; Kim et al., 2019). LRRK2 phosphorylates 4E-BP (4E-binding protein) at residues T37/T46, both *in vitro* and *in vivo*. 4E-BP is a eukaryotic translation initiation factor regulating overall protein translation in cells that is crucial for cell survival under stress conditions (Haghighat et al., 1995; Tettweiler et al., 2005). *Drosophila* LRRK2 also phosphorylates 4E-BP, attenuating the resistance to oxidative stress via a 4E-BP phosphorylation-dependent manner (Imai et al., 2008). Therefore, LRRK2 kinase activity regulates cell response to oxidative stress through a 4E-BP mediated pathway. Studies also suggest that LRRK2 affects antioxidant defense mechanism through its phosphorylation of PRDX3 (peroxiredoxin 3). PRDX3 is a mitochondrial antioxidant of the

thioredoxin-peroxidase family, efficiently scavenging peroxides and controlling the level of reactive oxygen species (ROS) in mitochondria (Fujii and Ikeda, 2002). *In vitro*, LRRK2 interacts with PRDX3 and potentially phosphorylates PRDX3 at residue T146. PD-associated mutant LRRK2 G2019S enhances its interaction with and causes decreased peroxidase activity of PRDX3 along with increased cell death (Figure 4; Angeles et al., 2011). Consistently, *Drosophila* expressing LRRK2 G2019S show reduced PRDX3 peroxidase activity and exacerbated oxidative stress (Angeles et al., 2014).

Furthermore, LRRK2 kinase activity is associated with increased mitochondrial DNA (mtDNA) damage. In various cellular models, including iPSC-derived neural cells, immune cells and fibroblasts, PD-associated mutant LRRK2 G2019S increases mtDNA damage that is abrogated by either gene editing to correct the G2019S mutation or by treatment with LRRK2 kinase inhibitors (Howlett et al., 2017; Gonzalez-Hunt et al., 2020).

Together, LRRK2-mediated phosphorylation regulates mitochondrial functions. Elevated LRRK2 kinase activity could contribute PD pathogenesis through impairing mitochondria.

4 Other post-translational modifications: regulating mitochondrial functions in Parkinson's disease

In addition to ubiquitination and phosphorylation, multiple other PTMs regulates mitochondrial functions and is implicated in the PD pathogenesis. In this context, we will provide a summary of recent research findings on how PD-related proteins affect mitochondrial functions through SUMOylation, acetylation, or s-nitrosylation, to elucidate their involvement in the development of PD (Table 4).

4.1 SUMOylation-regulated mitochondrial function and Parkinson's disease

SUMOylation refers to the PTM that covalently attaches small ubiquitin-like modifier (SUMO) to lysine residues on the substrate protein. SUMOylation occurs through multiple steps of enzymatic reactions, very similar to those in the ubiquitination process but with different specific enzymes, causing biochemical and functional changes of the target protein. SUMOylation modifies a broad range of proteins and regulates a diversity of biological processes, such as chromatin remodeling, transcription, and mitochondrial dynamics. SUMOylation regulates mitochondrial dynamics through a number of proteins that are either directly encoded by or in close functional-relationship with PD-associated genes (Guerra de Souza et al., 2016).

Mutations in *DJ-1* cause autosomal recessive forms of PD. Being a peroxiredoxin-like peroxidase, DJ-1 helps maintain mitochondrial function during oxidative stress as a sensor of damage and a regulator of CI activity (Taira et al., 2004; Andres-Mateos et al., 2007). DJ-1 deficiency results in increased

TABLE 4 Other PTMs of PD-related proteins and mitochondrial dysfunction.

Type of PTM	PD-related protein	Enzyme	Substrate	Regulated mitochondrial function	Modification site (human)	References
SUMOylation	DJ-1	/	DJ-1	Inhibits ROS production	K130	Shinbo et al., 2006; Krebiehl et al., 2010
	Parkin	/	Parkin	Increases Parkin's ubiquitination	-	Um and Chung, 2006
Acetylation	PINK1	SIRT3	PINK1	Inhibits PINK1's acetylation	-	Wei et al., 2017
	Parkin	SIRT3	Parkin	Inhibits Parkin's acetylation	-	Wei et al., 2017
S-nitrosylation	Parkin	/	Parkin	Inhibits Parkin	-	Chung et al., 2004
	Parkin	/	Parkin	Activates Parkin	C323	Ozawa et al., 2013
	PINK1	/	PINK1	Inhibits PINK1	C568	Oh et al., 2017

PINK1, PTEN induced putative kinase 1; SIRT3, NAD-dependent protein deacetylase sirtuin-3; ROS, reactive oxygen species; C, cysteine; "-" means no answer.

production of ROS and decreased $\Delta\psi$ in cellular and mouse models (Krebiehl et al., 2010). SUMOylation plays important roles in regulating DJ-1 function. SUMOylation of DJ-1 K130 is crucial for the full activity of DJ-1 (Figure 4). The PD-associated DJ-1 L166P mutant becomes improperly SUMOylated and hence more insoluble, leading to its aggregation in mitochondria, ultimately suppresses its proteasomal degradation (Shinbo et al., 2006). DJ-1 is not only an effector of SUMOylation but also suppresses SUMOylation of other proteins at the global level through its interaction with key proteins of the SUMOylation machinery. For example, DJ-1 inhibits the SUMOylation of PSF (pyrimidine tract-binding protein-associated splicing factor), consequently reducing PSF-mediated apoptosis. The PD-associated pathogenic DJ-1 mutant L166P causes accumulation of high-molecular-weight SUMOylated PSF (Zhong et al., 2006). Together, these findings suggest that SUMOylation is involved in DJ-1's regulation on mitochondria-associated oxidative stress and apoptosis.

Several biomarker studies have aimed to identify and quantify different DJ-1 species levels in PD patients compared to healthy controls. Presently, these studies primarily concentrate on the measurement of total DJ-1 in CSF, DJ-1 isoforms in whole blood, or oxidized DJ-1 in blood or urine (Waragai et al., 2006; Hong et al., 2010; Lin et al., 2012; Gui et al., 2015; Saito, 2017; Jang et al., 2018). Until now, the reliable detection of SUMOylated DJ-1 in various tissues or biofluids, and its potential use as an indicator for PD disease progression, stays unexplored. Similar to the challenge faced in using ubiquitinated proteins as biomarkers, the obstacle here may also be attributed to the lack of specific antibodies targeting SUMOylated DJ-1 (Magalhaes and Lashuel, 2022).

It's noteworthy that not only is proper SUMOylation essential for the solubility and activity of DJ-1 protein, but also is the PKA induced phosphorylation at the T154 residue of DJ-1 (Ko et al., 2019). Currently, there is no evidence showing crosstalk between the T154 phosphorylation and the K130 SUMOylation of DJ-1. However, it is an intriguing question worth investigating.

Parkin has also been reported to selectively interact with SUMO-1 (small ubiquitin like modifier 1), both *in vitro* and *in vivo*, resulting in increased ubiquitination and nuclear translocation of Parkin. Therefore, SUMOylation might play a role in Parkin-mediated ubiquitination and its relevance to PD pathogenesis

(Um and Chung, 2006). In agreement with this, DRP1 is a target of all SUMO isoforms with various functional-consequences. SUMOylation of DRP1 by SUMO-1 enhances its association with mitochondria, promotes mitochondrial fragmentation, and increases apoptosis (Wasiak et al., 2007). In contrast, SUMOylation of DRP1 by SUMO-2/3 decreases its mitochondrial localization and reduces apoptosis under stress conditions (Guo et al., 2013). Collectively, these studies underscore the significance of SUMO-regulated mitochondrial functions in the pathogenesis of PD.

4.2 Acetylation-regulated mitochondrial function and Parkinson's disease

Protein acetylation refers to the transfer of an acetyl group (CH_3CO) from acetyl-CoA to either the ϵ -amino group (NH_3^+) of lysine residues (ϵ -lysine acetylation) or to the N-terminal amino acid of a protein (*N*- α -acetylation). *N*- α -acetylation is an irreversible reaction catalyzed by N-terminal acetyltransferases (NATs), while ϵ -lysine acetylation is a reversible modification tightly regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Drazic et al., 2016). Recent evidence indicates that acetylation of PD-associated proteins might have important functional-consequences in mitochondria, although the detailed mechanism remains largely unknown.

In vitro, *N*- α -acetylation affects the secondary structure of α -synuclein, leading to the oligomeric form with a partial α -helical structure (Kang et al., 2012). *In vivo*, decreased $\Delta\psi$ and increased ROS level are detected in the mouse brain overexpressing predominantly N-terminally acetylated α -synuclein (Sarafian et al., 2013), suggesting that *N*- α -acetylation of α -synuclein cause mitochondrial dysfunction and have pathological implications in PD. Consistently, knockdown of deacetylase SIRT3 (NAD-dependent protein deacetylase sirtuin-3) in SH-SY5Y cells significantly increases rotenone-induced α -synuclein accumulation and reduces the activities of SOD (superoxide dismutase) and GSH (glutathione), leading to increased ROS generation and damaged mitochondria (Zhang et al., 2016). SIRT3 is also reported to be inversely related to the acetylation of Parkin and PINK1—acetylated PINK1 and Parkin are increased with knockdown of SIRT3 but decreased with overexpression of

SIRT3 (Wei et al., 2017). PKAN (pantothenate kinase-associated neurodegeneration) is the enzyme catalyzing the first and rate-limiting step of CoA synthesis (Leonardi et al., 2005). A recently study reported that Fbl (Fumble, *Drosophila* homolog of PANK2), functioning downstream of PINK1, regulates acetylation of Ref(2)P (*Drosophila* homolog of P62) and promotes mitophagy activity (Huang et al., 2022).

4.3 S-nitrosylation-regulated mitochondrial function and Parkinson's disease

S-nitrosylation involves the covalent attachment of a nitro oxide group (-NO) to the thiol side chain of a cysteine residue within a protein (Hess and Stamler, 2012). Like other PTMs, s-nitrosylation has emerged as an important regulator of various classes of proteins. S-nitrosylation plays a role in PD-related mitochondrial pathology through its modification of Parkin and PINK1. The initial two studies showing Parkin could be s-nitrosylated were both published in 2004, yielding contrary conclusions. Chung et al. (2004) reported that s-nitrosylation of Parkin inhibits its E3 ligase activity, resulting in decreased ubiquitination of Parkin substrates, including Parkin itself and Synphilin-1. While Yao et al. (2004) found that s-nitrosylation of Parkin stimulates its E3 ligase activity, leading to increased self-ubiquitination. Later on, Ozawa et al. (2013) reported that Parkin is predominantly s-nitrosylated at residue C323 resulting in activation of Parkin's E3 ligase activity and induces mitochondrial degradation. Interestingly, s-nitrosylation of Parkin is regulated by DJ-1, another PD-associated protein that has been found in the same complex with Parkin and PINK1 (Tang et al., 2006; Xiong et al., 2009). Loss-of-function of DJ-1 results in decreased s-nitrosylation of Parkin, along with increased mitochondrial depolarization and cell death (Ozawa et al., 2020), adding additional evidence for the long-observed functional interaction between Parkin, PINK1, and DJ-1. Intriguingly, s-nitrosylation has also been observed with PINK1 at residue C568 that negatively regulates PINK1 kinase activity, therefore reducing PINK1-dependent phosphorylation and activation of Parkin (Oh et al., 2017). However, the detailed mechanisms of how s-nitrosylation regulates Parkin and PINK1 mediated mitophagy, as well as whether DJ-1 is also required for PINK1's s-nitrosylation, remain unclear and require further study to elucidate.

5 Perspectives and conclusion

Mounting evidence indicates involvement of PTMs-regulated mitochondrial functions in the PD etiology. A major challenge in the field is to distinguish physiological functions from the pathological roles within these pathways implicated in PD. For example, understanding how PINK1/Parkin- and BNIP3-regulated mitophagy contributes to PD pathogenesis is crucial.

It is well known that PINK1 and Parkin can function both collaboratively and independently regulating mitochondrial functions, but which function of PINK1 and Parkin is critical for PD? Moreover, since the deletion of PINK1, Parkin, or both does not result in significant DA neurodegeneration in mouse models, are there other factors important for DA neurodegeneration in patients carrying PINK1 and Parkin mutations?

Phosphorylated tau protein has recently been demonstrated as a valuable biomarker of Alzheimer's disease at a systemic level (Karikari et al., 2020; Teunissen et al., 2022). A deeper understanding of the PD-related, specific alterations of PTMs—especially those with significant consequences on mitochondrial functions—may lead to candidates for the long sought-after biomarkers for PD. However, the development of PD biomarkers based on PTMs is currently in its early stages.

Author contributions

SL: Writing – original draft, Writing – review & editing. DW: Writing – original draft, Writing – review & editing. ZZ: Conceptualization, Writing – review & editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (8171101313, 81842044, 31730036, 81429002, and 31330031), the Discipline Innovative Engineering Plan (111 Program) of China (B13036), the Department of Science and Technology of Hunan Province (2021SK1010, 2016TP1006, 2018SK1030, 2022WZ1027, and 2021SK1014), the Department of Science and Technology of Changsha City (KC1702038), and the Education Department Program of Hunan Province (HNJG-2020-0440).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Aerts, L., Craessaerts, K., De Strooper, B., and Morais, V. A. (2015). PINK1 kinase catalytic activity is regulated by phosphorylation on serines 228 and 402. *J. Biol. Chem.* 290, 2798–2811. doi: 10.1074/jbc.M114.620906
- Akutsu, M., Dikic, I., and Bremm, A. (2016). Ubiquitin chain diversity at a glance. *J. Cell Sci.* 129, 875–880. doi: 10.1242/jcs.183954
- Andres-Mateos, E., Perier, C., Zhang, L., Blanchard-Fillion, B., Greco, T. M., Thomas, B., et al. (2007). DJ-1 gene deletion reveals that DJ-1 is an atypical peroxiredoxin-like peroxidase. *Proc. Natl. Acad. Sci. U.S.A.* 104, 14807–14812. doi: 10.1073/pnas.0703219104
- Angeles, D. C., Gan, B. H., Onstead, L., Zhao, Y., Lim, K. L., Daxsel, J., et al. (2011). Mutations in LRRK2 increase phosphorylation of peroxiredoxin 3 exacerbating oxidative stress-induced neuronal death. *Hum. Mutat.* 32, 1390–1397. doi: 10.1002/humu.21582
- Angeles, D. C., Ho, P., Chua, L. L., Wang, C., Yap, Y. W., Ng, C., et al. (2014). Thiol peroxidases ameliorate LRRK2 mutant-induced mitochondrial and dopaminergic neuronal degeneration in *Drosophila*. *Hum. Mol. Genet.* 23, 3157–3165. doi: 10.1093/hmg/ddu026
- Arena, G., Gelmetti, V., Torosantucci, L., Vignone, D., Lamorte, G., De Rosa, P., et al. (2013). PINK1 protects against cell death induced by mitochondrial depolarization, by phosphorylating Bcl-xL and impairing its pro-apoptotic cleavage. *Cell Death Differ.* 20, 920–930. doi: 10.1038/cdd.2013.19
- Ascherio, A., and Schwarzschild, M. A. (2016). The epidemiology of Parkinson's disease: Risk factors and prevention. *Lancet Neurol.* 15, 1257–1272. doi: 10.1016/S1474-4422(16)30230-7
- Atashrazm, F., Hammond, D., Perera, G., Bolliger, M. F., Matar, E., Halliday, G. M., et al. (2019). LRRK2-mediated Rab10 phosphorylation in immune cells from Parkinson's disease patients. *Mov. Disord.* 34, 406–415. doi: 10.1002/mds.27601
- Bahnassawy, L., Nicklas, S., Palm, T., Menzl, I., Birzele, F., Gillardon, F., et al. (2013). The parkinson's disease-associated LRRK2 mutation R1441G inhibits neuronal differentiation of neural stem cells. *Stem Cells Dev.* 22, 2487–2496. doi: 10.1089/scd.2013.0163
- Basso, V., Marchesan, E., Peggion, C., Chakraborty, J., von Stockum, S., Giacomello, M., et al. (2018). Regulation of ER-mitochondria contacts by Parkin via Mfn2. *Pharmacol. Res.* 138, 43–56. doi: 10.1016/j.phrs.2018.09.006
- Bekris, L. M. I., Mata, F., and Zabetian, C. P. (2010). The genetics of Parkinson disease. *J. Geriatr. Psychiatry Neurol.* 23, 228–242. doi: 10.1177/0891988710383572
- Billingsley, K. J., Barbosa, I. A., Bandres-Ciga, S., Quinn, J. P., Bubbs, V. J., Deshpande, C., et al. (2019). Mitochondria function associated genes contribute to Parkinson's disease risk and later age at onset. *NPJ Park. Dis.* 5:8. doi: 10.1038/s41531-019-0080-x
- Biskup, S., Moore, D. J., Celsi, F., Higashi, S., West, A. B., Andrabi, S. A., et al. (2006). Localization of LRRK2 to membranous and vesicular structures in mammalian brain. *Ann. Neurol.* 60, 557–569. doi: 10.1002/ana.21019
- Blumenreich, S., Barav, O. B., Jenkins, B. J., and Futerman, A. H. (2020). Lysosomal storage disorders shed light on lysosomal dysfunction in Parkinson's disease. *Int. J. Mol. Sci.* 21:4966. doi: 10.3390/ijms21144966
- Bonello, F., Hassoun, S. M., Mouton-Liger, F., Shin, Y. S., Muscat, A., Tesson, C., et al. (2019). LRRK2 impairs PINK1/Parkin-dependent mitophagy via its kinase activity: Pathologic insights into Parkinson's disease. *Hum. Mol. Genet.* 28, 1645–1660. doi: 10.1093/hmg/ddz004
- Bonifati, V., Rizzu, P., van Baren, M. J., Schaap, O., Breedveld, G. J., Krieger, E., et al. (2003). Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science* 299, 256–259. doi: 10.1126/science.1077209
- Broadway, B. J., Boneski, P. K., Bredenberg, J. M., Kolichski, A., Hou, X., Soto-Beasley, A. I., et al. (2022). Systematic functional analysis of PINK1 and PRKN coding variants. *Cells* 11:2426. doi: 10.3390/cells11152426
- Burchell, V. S., Nelson, D. E., Sanchez-Martinez, A., Delgado-Camprubi, M., Ivatt, R. M., Pogson, J. H., et al. (2013). The Parkinson's disease-linked proteins Fbxo7 and Parkin interact to mediate mitophagy. *Nat. Neurosci.* 16, 1257–1265. doi: 10.1038/nn.3489
- Burre, J., Sharma, M., Tsetsenis, T., Buchman, V., Etherton, M. R., and Sudhof, T. C. (2010). Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro. *Science* 329, 1663–1667. doi: 10.1126/science.1195227
- Cadete, V. J., Deschenes, S., Cuillerier, A., Brisebois, F., Sugiura, A., Vincent, A., et al. (2016). Formation of mitochondrial-derived vesicles is an active and physiologically relevant mitochondrial quality control process in the cardiac system. *J. Physiol.* 594, 5343–5362. doi: 10.1113/JP272703
- Cai, C., Wu, F., He, J., Zhang, Y., Shi, N., Peng, X., et al. (2022). Mitochondrial quality control in diabetic cardiomyopathy: From molecular mechanisms to therapeutic strategies. *Int. J. Biol. Sci.* 18, 5276–5290. doi: 10.7150/ijbs.75402
- Cali, T., Ottolini, D., Negro, A., and Brini, M. (2013). Enhanced parkin levels favor ER-mitochondria crosstalk and guarantee Ca(2+) transfer to sustain cell bioenergetics. *Biochim. Biophys. Acta* 1832, 495–508. doi: 10.1016/j.bbadis.2013.01.004
- Cardona, F., Sanchez-Mut, J. V., Dopazo, H., and Perez-Tur, J. (2011). Phylogenetic and in silico structural analysis of the Parkinson disease-related kinase PINK1. *Hum. Mutat.* 32, 369–378. doi: 10.1002/humu.21444
- Cereghetti, G. M., Stangherlin, A., Martins de Brito, O., Chang, C. R., Blackstone, C., Bernardi, P., et al. (2008). Dephosphorylation by calcineurin regulates translocation of Drp1 to mitochondria. *Proc. Natl. Acad. Sci. U.S.A.* 105, 15803–15808. doi: 10.1073/pnas.0808249105
- Cha, Y., Kim, T., Jeon, J., Jang, Y., Kim, P. B., Lopes, C., et al. (2021). SIRT2 regulates mitochondrial dynamics and reprogramming via MEK1-ERK-DRP1 and AKT1-DRP1 axes. *Cell Rep.* 37:110155. doi: 10.1016/j.celrep.2021.110155
- Chan, N. C., Salazar, A. M., Pham, A. H., Sweredoski, M. J., Kolawa, N. J., Graham, R. L., et al. (2011). Broad activation of the ubiquitin-proteasome system by Parkin is critical for mitophagy. *Hum. Mol. Genet.* 20, 1726–1737. doi: 10.1093/hmg/ddr048
- Chen, H., and Chan, D. C. (2017). Mitochondrial dynamics in regulating the unique phenotypes of cancer and stem cells. *Cell Metab.* 26, 39–48. doi: 10.1016/j.cmet.2017.05.016
- Chen, T., Tan, J., Wan, Z., Zou, Y., Afewerky, H. K., Zhang, Z., et al. (2017). Effects of commonly used pesticides in china on the mitochondria and ubiquitin-proteasome system in Parkinson's disease. *Int. J. Mol. Sci.* 18:2507. doi: 10.3390/ijms18122507
- Chen, Y., and Dorn, G. W. II (2013). PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. *Science* 340, 471–475. doi: 10.1126/science.1231031
- Cherian, A., K, P. D., and Vijayaraghavan, A. (2023). Parkinson's disease - genetic cause. *Curr. Opin. Neurol.* 36, 292–301. doi: 10.1097/WCO.0000000000001167
- Chin, L. S., and Li, L. (2016). Ubiquitin phosphorylation in Parkinson's disease: Implications for pathogenesis and treatment. *Transl. Neurodegener.* 5:1. doi: 10.1186/s40035-015-0049-6
- Cho, H. J., Liu, G., Jin, S. M., Parisiadou, L., Xie, C., Yu, J., et al. (2013). MicroRNA-205 regulates the expression of Parkinson's disease-related leucine-rich repeat kinase 2 protein. *Hum. Mol. Genet.* 22, 608–620. doi: 10.1093/hmg/dds470
- Choubey, V., Safulina, D., Vaarmann, A., Cagalinec, M., Wareski, P., Kuum, M., et al. (2011). Mutant A53T alpha-synuclein induces neuronal death by increasing mitochondrial autophagy. *J. Biol. Chem.* 286, 10814–10824. doi: 10.1074/jbc.M110.132514
- Chung, K. K., Thomas, B., Li, X., Pletnikova, O., Troncoso, J. C., Marsh, L., et al. (2004). S-nitrosylation of parkin regulates ubiquitination and compromises Parkin's protective function. *Science* 304, 1328–1331. doi: 10.1126/science.1093891
- Clark, I. E., Dodson, M. W., Jiang, C., Cao, J. H., Huh, J. R., Seol, J. H., et al. (2006). *Drosophila* pink1 is required for mitochondrial function and interacts genetically with parkin. *Nature* 441, 1162–1166. doi: 10.1038/nature04779
- Cook, D. A., Kannarkat, G. T., Cintron, A. F., Butkovich, L. M., Fraser, K. B., Chang, J., et al. (2017). LRRK2 levels in immune cells are increased in Parkinson's disease. *NPJ Park. Dis.* 3:11. doi: 10.1038/s41531-017-0010-8
- Costa, A. C., Loh, S. H., and Martins, L. M. (2013). *Drosophila* Trap1 protects against mitochondrial dysfunction in a PINK1/parkin model of Parkinson's disease. *Cell Death Dis.* 4:e467. doi: 10.1038/cddis.2012.205
- Cunningham, C. N., Baughman, J. M., Phu, L., Tea, J. S., Yu, C., Coons, M., et al. (2015). USP30 and parkin homeostatically regulate atypical ubiquitin chains on mitochondria. *Nat. Cell Biol.* 17, 160–169. doi: 10.1038/ncb3097
- da Silva Rosa, S. C., Martens, M. D., Field, J. T., Nguyen, L., Kereliuk, S. M., Hai, Y., et al. (2021). BNIP3L/Nix-induced mitochondrial fission, mitophagy, and impaired myocyte glucose uptake are abrogated by PRKA/PKA phosphorylation. *Autophagy* 17, 2257–2272. doi: 10.1080/15548627.2020.1821548
- de Brito, O. M., and Scorrano, L. (2008). Mitofusin 2 tethers endoplasmic reticulum to mitochondria. *Nature* 456, 605–610. doi: 10.1038/nature07534
- De Virgilio, A., Greco, A., Fabbri, G., Inghilleri, M., Rizzo, M. I., Gallo, A., et al. (2016). Parkinson's disease: Autoimmunity and neuroinflammation. *Autoimmun. Rev.* 15, 1005–1011. doi: 10.1016/j.autrev.2016.07.022
- Deas, E., Plun-Favreau, H., Gandhi, S., Desmond, H., Kjaer, S., Loh, S. H., et al. (2011). PINK1 cleavage at position A103 by the mitochondrial protease PARL. *Hum. Mol. Genet.* 20, 867–879. doi: 10.1093/hmg/ddq526
- Delbroek, L., Van Kolen, K., Steegmans, L., da Cunha, R., Mandemakers, W., Daneels, G., et al. (2013). Development of an enzyme-linked immunosorbent assay for detection of cellular and in vivo LRRK2 S935 phosphorylation. *J. Pharm. Biomed. Anal.* 76, 49–58. doi: 10.1016/j.jpba.2012.12.002
- Deng, H., Dodson, M. W., Huang, H., and Guo, M. (2008). The Parkinson's disease genes pink1 and parkin promote mitochondrial fission and/or inhibit fusion in *Drosophila*. *Proc. Natl. Acad. Sci. U.S.A.* 105, 14503–14508. doi: 10.1073/pnas.0803998105

- Devi, L., and Anandatheerthavarada, H. K. (2010). Mitochondrial trafficking of APP and alpha synuclein: Relevance to mitochondrial dysfunction in Alzheimer's and Parkinson's diseases. *Biochim. Biophys. Acta* 1802, 11–19. doi: 10.1016/j.bbdis.2009.07.007
- Devi, L., Raghavendran, V., Prabhu, B. M., Avadhani, N. G., and Anandatheerthavarada, H. K. (2008). Mitochondrial import and accumulation of alpha-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain. *J. Biol. Chem.* 283, 9089–9100. doi: 10.1074/jbc.M710012200
- Di Fonzo, A., Dekker, M. C., Montagna, P., Baruzzi, A., Yonova, E. H., Correia Guedes, L., et al. (2009). FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. *Neurology* 72, 240–245. doi: 10.1212/01.wnl.0000338144.10967.2b
- Drazic, A., Myklebust, L. M., Ree, R., and Arnesen, T. (2016). The world of protein acetylation. *Biochim. Biophys. Acta* 1864, 1372–1401. doi: 10.1016/j.bbapap.2016.06.007
- Durcan, T. M., and Fon, E. A. (2015). The three 'P's of mitophagy: PARKIN, PINK1, and post-translational modifications. *Genes Dev.* 29, 989–999. doi: 10.1101/gad.262758.115
- Durcan, T. M., Kontogianna, M., Bedard, N., Wing, S. S., and Fon, E. A. (2012). Ataxin-3 deubiquitination is coupled to Parkin ubiquitination via E2 ubiquitin-conjugating enzyme. *J. Biol. Chem.* 287, 531–541. doi: 10.1074/jbc.M111.288449
- Durcan, T. M., Tang, M. Y., Perusse, J. R., Dashti, E. A., Aguilera, M. A., McLelland, G. L., et al. (2014). USP8 regulates mitophagy by removing K6-linked ubiquitin conjugates from parkin. *EMBO J.* 33, 2473–2491. doi: 10.15252/embj.201489729
- Ebrahimi-Fakhari, D., Wahlster, L., and McLean, P. J. (2012). Protein degradation pathways in Parkinson's disease: Curse or blessing. *Acta Neuropathol.* 124, 153–172. doi: 10.1007/s00401-012-1004-6
- Eiyama, A., and Okamoto, K. (2015). PINK1/Parkin-mediated mitophagy in mammalian cells. *Curr. Opin. Cell Biol.* 33, 95–101. doi: 10.1016/j.ccb.2015.01.002
- Elia, A. E., Petrucci, S., Fasano, A., Guidi, M., Valbonesi, S., Bernardini, L., et al. (2013). Alpha-synuclein gene duplication: Marked intrafamilial variability in two novel pedigrees. *Mov. Disord.* 28, 813–817. doi: 10.1002/mds.25518
- Ellard, S., Colclough, K., Patel, K. A., and Hattersley, A. T. (2020). Prediction algorithms: Pitfalls in interpreting genetic variants of autosomal dominant monogenic diabetes. *J. Clin. Invest.* 130, 14–16. doi: 10.1172/JCI133516
- Fan, Y., Howden, A. J. M., Sarhan, A. R., Lis, P., Ito, G., Martinez, T. N., et al. (2018). Interrogating Parkinson's disease LRRK2 kinase pathway activity by assessing Rab10 phosphorylation in human neutrophils. *Biochem. J.* 475, 23–44. doi: 10.1042/BCJ20170803
- Fiesel, F. C., Ando, M., Hudec, R., Hill, A. R., Castanedes-Casey, M., Caulfield, T. R., et al. (2015). (Patho-)physiological relevance of PINK1-dependent ubiquitin phosphorylation. *EMBO Rep.* 16, 1114–1130. doi: 10.15252/embr.201540514
- Foulds, P. G., Mitchell, J. D., Parker, A., Turner, R., Green, G., Diggie, P., et al. (2011). Phosphorylated alpha-synuclein can be detected in blood plasma and is potentially a useful biomarker for Parkinson's disease. *FASEB J.* 25, 4127–4137. doi: 10.1096/fj.10-179192
- Foulds, P. G., Yokota, O., Thurston, A., Davidson, Y., Ahmed, Z., Holton, J., et al. (2012). Post mortem cerebrospinal fluid alpha-synuclein levels are raised in multiple system atrophy and distinguish this from the other alpha-synucleinopathies, Parkinson's disease and Dementia with Lewy bodies. *Neurobiol. Dis.* 45, 188–195. doi: 10.1016/j.nbd.2011.08.003
- Frank-Cannon, T. C., Tran, T., Ruhn, K. A., Martinez, T. N., Hong, J., Marvin, M., et al. (2008). Parkin deficiency increases vulnerability to inflammation-related nigral degeneration. *J. Neurosci.* 28, 10825–10834. doi: 10.1523/JNEUROSCI.3001-08.2008
- Fraser, K. B., Rawlins, A. B., Clark, R. G., Alcalay, R. N., Standaert, D. G., Liu, N., et al. (2016). Ser(P)-1292 LRRK2 in urinary exosomes is elevated in idiopathic Parkinson's disease. *Mov. Disord.* 31, 1543–1550. doi: 10.1002/mds.26686
- Fuchs, J., Nilsson, C., Kachergus, J., Munz, M., Larsson, E. M., Schule, B., et al. (2007). Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. *Neurology* 68, 916–922. doi: 10.1212/01.wnl.0000254458.17630.c5
- Fujii, J., and Ikeda, Y. (2002). Advances in our understanding of peroxiredoxin, a multifunctional, mammalian redox protein. *Redox Rep.* 7, 123–130. doi: 10.1179/135100002125000352
- Funayama, M., Hasegawa, K., Kowa, H., Saito, M., Tsuji, S., and Obata, F. (2002). A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. *Ann. Neurol.* 51, 296–301. doi: 10.1002/ana.10113
- Funayama, M., Ohe, K., Amo, T., Furuya, N., Yamaguchi, J., Saiki, S., et al. (2015). CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: A genome-wide linkage and sequencing study. *Lancet Neurol.* 14, 274–282. doi: 10.1016/S1474-4422(14)70266-2
- Futter, C. E., Pearce, A., Hewlett, L. J., and Hopkins, C. R. (1996). Multivesicular endosomes containing internalized EGF-EGF receptor complexes mature and then fuse directly with lysosomes. *J. Cell Biol.* 132, 1011–1023. doi: 10.1083/jcb.132.6.1011
- Gandhi, S., Wood-Kaczmar, A., Yao, Z., Plun-Favreau, H., Deas, E., Klupsch, K., et al. (2009). PINK1-associated Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. *Mol. Cell* 33, 627–638. doi: 10.1016/j.molcel.2009.02.013
- Gautier, E. F., Ducamp, S., Leduc, M., Salnot, V., Guillonnet, F., Dussiot, M., et al. (2016). Comprehensive proteomic analysis of human erythropoiesis. *Cell Rep.* 16, 1470–1484. doi: 10.1016/j.celrep.2016.06.085
- Ge, P., Dawson, V. L., and Dawson, T. M. (2020). PINK1 and Parkin mitochondrial quality control: A source of regional vulnerability in Parkinson's disease. *Mol. Neurodegener.* 15:20. doi: 10.1186/s13024-020-00367-7
- Gegg, M. E., Cooper, J. M., Chau, K. Y., Rojo, M., Schapira, A. H., and Taanman, J. W. (2010). Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. *Hum. Mol. Genet.* 19, 4861–4870. doi: 10.1093/hmg/ddq419
- Geldenhuys, W. J., Abdelmagid, S. M., Gallegos, P. J., and Safadi, F. F. (2014). Parkinson's disease biomarker: A patent evaluation of WO2013153386. *Expert Opin. Ther. Pat.* 24, 947–951. doi: 10.1517/13543776.2014.931375
- Gilks, W. P., Abou-Sleiman, P. M., Gandhi, S., Jain, S., Singleton, A., Lees, A. J., et al. (2005). A common LRRK2 mutation in idiopathic Parkinson's disease. *Lancet* 365, 415–416. doi: 10.1016/S0140-6736(05)17830-1
- Goldman, S. M. (2014). Environmental toxins and Parkinson's disease. *Annu. Rev. Pharmacol. Toxicol.* 54, 141–164. doi: 10.1146/annurev-pharmtox-011613-135937
- Gonzalez-Hunt, C. P., Thacker, E. A., Toste, C. M., Boularand, S., Deprets, S., Dubois, L., et al. (2020). Mitochondrial DNA damage as a potential biomarker of LRRK2 kinase activity in LRRK2 Parkinson's disease. *Sci. Rep.* 10:17293. doi: 10.1038/s41598-020-74195-6
- Greene, A. W., Grenier, K., Aguilera, M. A., Muise, S., Farazifard, R., Haque, M. E., et al. (2012). Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment. *EMBO Rep.* 13, 378–385. doi: 10.1038/embor.2012.14
- Greene, J. C., Whitworth, A. J., Kuo, I., Andrews, L. A., Feany, M. B., and Pallanck, L. J. (2003). Mitochondrial pathology and apoptotic muscle degeneration in Drosophila parkin mutants. *Proc. Natl. Acad. Sci. U.S.A.* 100, 4078–4083. doi: 10.1073/pnas.0737556100
- Guerra de Souza, A. C., Prediger, R. D., and Cimarosti, H. (2016). SUMO-regulated mitochondrial function in Parkinson's disease. *J. Neurochem.* 137, 673–686. doi: 10.1111/jnc.13599
- Gui, Y., Liu, H., Zhang, L., Lv, W., and Hu, X. (2015). Altered microRNA profiles in cerebrospinal fluid exosome in Parkinson disease and Alzheimer disease. *Oncotarget* 6, 37043–37053. doi: 10.18632/oncotarget.6158
- Guo, C., Hildick, K. L., Luo, J., Dearden, L., Wilkinson, K. A., and Henley, J. M. (2013). SENP3-mediated deSUMOylation of dynamin-related protein 1 promotes cell death following ischaemia. *EMBO J.* 32, 1514–1528. doi: 10.1038/emboj.2013.65
- Haghighat, A., Mader, S., Pause, A., and Sonenberg, N. (1995). Repression of cap-dependent translation by 4E-binding protein 1: Competition with p220 for binding to eukaryotic initiation factor-4E. *EMBO J.* 14, 5701–5709. doi: 10.1002/j.1460-2075.1995.tb00257.x
- Ham, S. J., Lee, D., Yoo, H., Jun, K., Shin, H., and Chung, J. (2020). Decision between mitophagy and apoptosis by Parkin via VDAC1 ubiquitination. *Proc. Natl. Acad. Sci. U.S.A.* 117, 4281–4291. doi: 10.1073/pnas.1909814117
- Han, H., Tan, J., Wang, R., Wan, H., He, Y., Yan, X., et al. (2020). PINK1 phosphorylates Drp1(S616) to regulate mitophagy-independent mitochondrial dynamics. *EMBO Rep.* 21:e48686. doi: 10.15252/embr.201948686
- Henchcliffe, C., and Beal, M. F. (2008). Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. *Nat. Clin. Pract. Neurol.* 4, 600–609. doi: 10.1038/ncpneu0924
- Heo, H. Y., Park, J. M., Kim, C. H., Han, B. S., Kim, K. S., and Seol, W. (2010). LRRK2 enhances oxidative stress-induced neurotoxicity via its kinase activity. *Exp. Cell Res.* 316, 649–656. doi: 10.1016/j.yexcr.2009.09.014
- Heo, J. M., Ordureau, A., Paulo, J. A., Rinehart, J., and Harper, J. W. (2015). The PINK1-PARKIN mitochondrial ubiquitylation pathway drives a program of OPTN/NDP52 recruitment and TBK1 activation to promote mitophagy. *Mol. Cell* 60, 7–20. doi: 10.1016/j.molcel.2015.08.016
- Hernandez, D. G., Reed, X., and Singleton, A. B. (2016). Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. *J. Neurochem.* 139 Suppl 1(Suppl. 1), 59–74. doi: 10.1111/jnc.13593
- Hess, D. T., and Stamler, J. S. (2012). Regulation by S-nitrosylation of protein post-translational modification. *J. Biol. Chem.* 287, 4411–4418. doi: 10.1074/jbc.R111.285742
- Heyn, J., Heuschkel, M. A., and Goettsch, C. (2023). Mitochondrial-derived vesicles link to extracellular vesicles and implications in cardiovascular disease. *Int. J. Mol. Sci.* 24:2637. doi: 10.3390/ijms24032637
- Hierro, A., Rojas, A. L., Rojas, R., Murthy, N., Effantin, G., Kajava, A. V., et al. (2007). Functional architecture of the retromer cargo-recognition complex. *Nature* 449, 1063–1067. doi: 10.1038/nature06216
- Hirai, I., and Wang, H. G. (2001). Survival-factor-induced phosphorylation of Bad results in its dissociation from Bcl-x(L) but not Bcl-2. *Biochem J* 359(Pt. 2), 345–352. doi: 10.1042/0264-6021:3590345

- Ho, D. H., Je, A. R., Lee, H., Son, I., Kweon, H. S., Kim, H. G., et al. (2018). LRRK2 kinase activity induces mitochondrial fission in microglia via Drp1 and modulates neuroinflammation. *Exp. Neurobiol.* 27, 171–180. doi: 10.5607/en.2018.27.3.171
- Hong, Z., Shi, M., Chung, K. A., Quinn, J. F., Peskind, E. R., Galasko, D., et al. (2010). DJ-1 and alpha-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. *Brain* 133(Pt. 3), 713–726. doi: 10.1093/brain/awq008
- Howlett, E. H., Jensen, N., Belmonte, F., Zafar, F., Hu, X., Kluss, J., et al. (2017). LRRK2 G2019S-induced mitochondrial DNA damage is LRRK2 kinase dependent and inhibition restores mtDNA integrity in Parkinson's disease. *Hum. Mol. Genet.* 26, 4340–4351. doi: 10.1093/hmg/ddx320
- Hsieh, C. H., Shaltouki, A., Gonzalez, A. E., Bettencourt da Cruz, A., Burbulla, L. F., St Lawrence, E., et al. (2016). Functional impairment in miro degradation and mitophagy is a shared feature in familial and sporadic Parkinson's disease. *Cell Stem Cell* 19, 709–724. doi: 10.1016/j.stem.2016.08.002
- Huang, E., Qu, D., Huang, T., Rizzi, N., Boonying, W., Krolak, D., et al. (2017). PINK1-mediated phosphorylation of LETM1 regulates mitochondrial calcium transport and protects neurons against mitochondrial stress. *Nat. Commun.* 8:1399. doi: 10.1038/s41467-017-01435-1
- Huang, Y., Wan, Z., Tang, Y., Xu, J., Laboret, B., Nallamothu, S., et al. (2022). Pantothenate kinase 2 interacts with PINK1 to regulate mitochondrial quality control via acetyl-CoA metabolism. *Nat. Commun.* 13:2412. doi: 10.1038/s41467-022-30178-x
- Hunn, B. H., Cragg, S. J., Bolam, J. P., Spillantini, M. G., and Wade-Martins, R. (2015). Impaired intracellular trafficking defines early Parkinson's disease. *Trends Neurosci.* 38, 178–188. doi: 10.1016/j.tins.2014.12.009
- Imai, Y., Gehrke, S., Wang, H. Q., Takahashi, R., Hasegawa, K., Oota, E., et al. (2008). Phosphorylation of 4E-BP by LRRK2 affects the maintenance of dopaminergic neurons in *Drosophila*. *EMBO J.* 27, 2432–2443. doi: 10.1038/emboj.2008.163
- Imai, Y., Soda, M., and Takahashi, R. (2000). Parkin suppresses unfolded protein stress-induced cell death through its E3 ubiquitin-protein ligase activity. *J. Biol. Chem.* 275, 35661–35664. doi: 10.1074/jbc.C000447200
- Ivankovic, D., Chau, K. Y., Schapira, A. H., and Gegg, M. E. (2016). Mitochondrial and lysosomal biogenesis are activated following PINK1/parkin-mediated mitophagy. *J. Neurochem.* 136, 388–402. doi: 10.1111/jnc.13412
- Jang, J., Jeong, S., Lee, S. I., Seol, W., Seo, H., Son, I., et al. (2018). Oxidized DJ-1 levels in urine samples as a putative biomarker for Parkinson's disease. *Park. Dis.* 2018:1241757. doi: 10.1155/2018/1241757
- Jin, S. M., and Youle, R. J. (2013). The accumulation of misfolded proteins in the mitochondrial matrix is sensed by PINK1 to induce PARK2/Parkin-mediated mitophagy of polarized mitochondria. *Autophagy* 9, 1750–1757. doi: 10.4161/autophagy.26122
- Jin, S. M., Lazarou, M., Wang, C., Kane, L. A., Narendra, D. P., and Youle, R. J. (2010). Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. *J. Cell Biol.* 191, 933–942. doi: 10.1083/jcb.201008084
- Juhasz, G. (2016). A mitochondrial-derived vesicle HOPS to endolysosomes using Syntaxin-17. *J. Cell Biol.* 214, 241–243. doi: 10.1083/jcb.201607024
- Kalia, L. V., and Lang, A. E. (2015). Parkinson's disease. *Lancet* 386, 896–912. doi: 10.1016/S0140-6736(14)61393-3
- Kane, L. A., Lazarou, M., Fogel, A. I., Li, Y., Yamano, K., Sarraf, S. A., et al. (2014). PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. *J. Cell Biol.* 205, 143–153. doi: 10.1083/jcb.201402104
- Kang, L., Moriarty, G. M., Woods, L. A., Ashcroft, A. E., Radford, S. E., and Baum, J. (2012). N-terminal acetylation of alpha-synuclein induces increased transient helical propensity and decreased aggregation rates in the intrinsically disordered monomer. *Protein Sci.* 21, 911–917. doi: 10.1002/pro.2088
- Karbowsky, M., and Youle, R. J. (2011). Regulating mitochondrial outer membrane proteins by ubiquitination and proteasomal degradation. *Curr. Opin. Cell Biol.* 23, 476–482. doi: 10.1016/j.ccb.2011.05.007
- Karikari, T. K., Pascoal, T. A., Ashton, N. J., Janelidze, S., Benedet, A. L., Rodriguez, J. L., et al. (2020). Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: A diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol.* 19, 422–433. doi: 10.1016/S1474-4422(20)30071-5
- Karve, T. M., and Cheema, A. K. (2011). Small changes huge impact: The role of protein posttranslational modifications in cellular homeostasis and disease. *J. Amino Acids* 2011:207691. doi: 10.4061/2011/207691
- Kazlauskaitė, A., Kondapalli, C., Gourlay, R., Campbell, D. G., Ritorto, M. S., Hofmann, K., et al. (2014). Parkin is activated by PINK1-dependent phosphorylation of ubiquitin at Ser65. *Biochem. J.* 460, 127–139. doi: 10.1042/BJ20140334
- Khoury, G. A., Baliban, R. C., and Floudas, C. A. (2011). Proteome-wide post-translational modification statistics: Frequency analysis and curation of the swiss-prot database. *Sci. Rep.* 1:190. doi: 10.1038/srep00090
- Kim, D. I., Lee, K. H., Gabr, A. A., Choi, G. E., Kim, J. S., Ko, S. H., et al. (2016). Abeta-Induced Drp1 phosphorylation through Akt activation promotes excessive mitochondrial fission leading to neuronal apoptosis. *Biochim. Biophys. Acta* 1863, 2820–2834. doi: 10.1016/j.bbamer.2016.09.003
- Kim, J., Pajarillo, E., Rizor, A., Son, D. S., Lee, J., Aschner, M., et al. (2019). LRRK2 kinase plays a critical role in manganese-induced inflammation and apoptosis in microglia. *PLoS One* 14:e0210248. doi: 10.1371/journal.pone.0210248
- Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., et al. (1998). Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 392, 605–608. doi: 10.1038/33416
- Ko, Y. U., Kim, S. J., Lee, J., Song, M. Y., Park, K. S., Park, J. B., et al. (2019). Protein kinase A-induced phosphorylation at the Thr154 affects stability of DJ-1. *Park. Relat. Disord.* 66, 143–150. doi: 10.1016/j.parkrelidis.2019.07.029
- Kondapalli, C., Kazlauskaitė, A., Zhang, N., Woodroof, H. I., Campbell, D. G., Gourlay, R., et al. (2012). PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating Serine 65. *Open Biol.* 2:120080. doi: 10.1098/rsob.120080
- Kondapalli, K. C., Kallay, L. M., Muszelik, M., and Rao, R. (2012). Unconventional chemiosmotic coupling of NHA2, a mammalian Na⁺/H⁺ antiporter, to a plasma membrane H⁺ gradient. *J. Biol. Chem.* 287, 36239–36250. doi: 10.1074/jbc.M112.403550
- König, T., Nolte, H., Aaltonen, M. J., Tatsuta, T., Krols, M., Stroth, T., et al. (2021). MIROs and DRP1 drive mitochondrial-derived vesicle biogenesis and promote quality control. *Nat. Cell Biol.* 23, 1271–1286. doi: 10.1038/s41556-021-00798-4
- Koyano, F., Okatsu, K., Kosako, H., Tamura, Y., Go, E., Kimura, M., et al. (2014). Ubiquitin is phosphorylated by PINK1 to activate parkin. *Nature* 510, 162–166. doi: 10.1038/nature13392
- Koyano, F., Yamano, K., Kosako, H., Tanaka, K., and Matsuda, N. (2019). Parkin recruitment to impaired mitochondria for nonselective ubiquitylation is facilitated by MITOL. *J. Biol. Chem.* 294, 10300–10314. doi: 10.1074/jbc.RA118.006302
- Kraus, F., Goodall, E. A. I., Smith, R., Jiang, Y., Paoli, J. C., Adolf, F., et al. (2023). PARK15/FBXO7 is dispensable for PINK1/Parkin mitophagy in iNeurons and HeLa cell systems. *EMBO Rep.* 24:e56399. doi: 10.15252/embr.202256399
- Kraus, F., Roy, K., Pucadyil, T. J., and Ryan, M. T. (2021). Function and regulation of the divisome for mitochondrial fission. *Nature* 590, 57–66. doi: 10.1038/s41586-021-03214-x
- Krebiehl, G., Ruckerbauer, S., Burbulla, L. F., Kieper, N., Maurer, B., Waak, J., et al. (2010). Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson's disease-associated protein DJ-1. *PLoS One* 5:e9367. doi: 10.1371/journal.pone.0009367
- Kulathu, Y., and Komander, D. (2012). Atypical ubiquitylation - the unexplored world of polyubiquitin beyond Lys48 and Lys63 linkages. *Nat. Rev. Mol. Cell Biol.* 13, 508–523. doi: 10.1038/nrm3394
- Kumar, A., Tamjar, J., Waddell, A. D., Woodroof, H. I., Raimi, O. G., Shaw, A. M., et al. (2017). Structure of PINK1 and mechanisms of Parkinson's disease-associated mutations. *Elife* 6:e29985. doi: 10.7554/eLife.29985
- Lajoie, A. C., Lafontaine, A. L., and Kaminska, M. (2021). The spectrum of sleep disorders in Parkinson disease: A review. *Chest* 159, 818–827. doi: 10.1016/j.chest.2020.09.099
- Langston, J. W., Ballard, P., Tetrud, J. W., and Irwin, I. (1983). Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 219, 979–980. doi: 10.1126/science.6823561
- Lazarou, M., Jin, S. M., Kane, L. A., and Youle, R. J. (2012). Role of PINK1 binding to the TOM complex and alternate intracellular membranes in recruitment and activation of the E3 ligase Parkin. *Dev. Cell* 22, 320–333. doi: 10.1016/j.devcel.2011.12.014
- Lee, J. T., Wheeler, T. C., Li, L., and Chin, L. S. (2008). Ubiquitination of alpha-synuclein by Siah-1 promotes alpha-synuclein aggregation and apoptotic cell death. *Hum. Mol. Genet.* 17, 906–917. doi: 10.1093/hmg/ddm363
- Lee, Y., Stevens, D. A., Kang, S. U., Jiang, H., Lee, Y. I., Ko, H. S., et al. (2017). PINK1 primes parkin-mediated ubiquitination of PARIS in dopaminergic neuronal survival. *Cell Rep.* 18, 918–932. doi: 10.1016/j.celrep.2016.12.090
- Leonardi, R., Zhang, Y. M., Rock, C. O., and Jackowski, S. (2005). Coenzyme A: Back in action. *Prog. Lipid Res.* 44, 125–153. doi: 10.1016/j.plipres.2005.04.001
- Lewis, M. R., and Lewis, W. H. (1914). Mitochondria in tissue culture. *Science* 39, 330–333. doi: 10.1126/science.39.1000.330
- Li, L., Muhlfeld, C., Niemann, B., Pan, R., Li, R., Hilfiker-Kleiner, D., et al. (2011). Mitochondrial biogenesis and PGC-1alpha deacetylation by chronic treadmill exercise: Differential response in cardiac and skeletal muscle. *Basic Res. Cardiol.* 106, 1221–1234. doi: 10.1007/s00395-011-0213-9
- Li, W. W., Yang, R., Guo, J. C., Ren, H. M., Zha, X. L., Cheng, J. S., et al. (2007). Localization of alpha-synuclein to mitochondria within midbrain of mice. *Neuroreport* 18, 1543–1546. doi: 10.1097/WNR.0b013e3282f03db4
- Li, Y., Feng, Y. F., Liu, X. T., Li, Y. C., Zhu, H. M., Sun, M. R., et al. (2021). Songorine promotes cardiac mitochondrial biogenesis via Nrf2 induction during sepsis. *Redox Biol.* 38:101771. doi: 10.1016/j.redox.2020.101771

- Lin, C. H., Chen, M. L., Chen, G. S., Tai, C. H., and Wu, R. M. (2011). Novel variant Pro143Ala in HTRA2 contributes to Parkinson's disease by inducing hyperphosphorylation of HTRA2 protein in mitochondria. *Hum. Genet.* 130, 817–827. doi: 10.1007/s00439-011-1041-6
- Lin, W., and Kang, U. J. (2008). Characterization of PINK1 processing, stability, and subcellular localization. *J. Neurochem.* 106, 464–474. doi: 10.1111/j.1471-4159.2008.05398.x
- Lin, X., Cook, T. J., Zabetian, C. P., Leverenz, J. B., Peskind, E. R., Hu, S. C., et al. (2012). DJ-1 isoforms in whole blood as potential biomarkers of Parkinson disease. *Sci. Rep.* 2:954. doi: 10.1038/srep00954
- Liu, W., Duan, X., Fang, X., Shang, W., and Tong, C. (2018). Mitochondrial protein import regulates cytosolic protein homeostasis and neuronal integrity. *Autophagy* 14, 1293–1309. doi: 10.1080/15548627.2018.1474991
- Liu, Y., Lear, T. B., Verma, M., Wang, K. Z., Otero, P. A., McKelvey, A. C., et al. (2020). Chemical inhibition of FBXO7 reduces inflammation and confers neuroprotection by stabilizing the mitochondrial kinase PINK1. *JCI Insight* 5:e131834. doi: 10.1172/jci.insight.131834
- Lobbstaël, E., Zhao, J. I., Rudenko, N., Beylina, A., Gao, F., Wetter, J., et al. (2013). Identification of protein phosphatase 1 as a regulator of the LRRK2 phosphorylation cycle. *Biochem. J.* 456, 119–128. doi: 10.1042/BJ20121772
- Lopez-Domenech, G., Covill-Cooke, C., Ivankovic, D., Halff, E. F., Sheehan, D. F., Norkett, R., et al. (2018). Miro proteins coordinate microtubule- and actin-dependent mitochondrial transport and distribution. *EMBO J.* 37, 321–336. doi: 10.15252/embj.201696380
- Lutz, A. K., Exner, N., Fett, M. E., Schlehe, J. S., Kloos, K., Lammernann, K., et al. (2009). Loss of parkin or PINK1 function increases Drp1-dependent mitochondrial fragmentation. *J. Biol. Chem.* 284, 22938–22951. doi: 10.1074/jbc.M109.035774
- Lwin, A., Orvisky, E., Goker-Alpan, O., LaMarca, M. E., and Sidransky, E. (2004). Glucocerebrosidase mutations in subjects with parkinsonism. *Mol. Genet. Metab.* 81, 70–73. doi: 10.1016/j.ymgme.2003.11.004
- Ma, K. Y., Fokkens, M. R., van Laar, T., and Verbeek, D. S. (2021). Systematic analysis of PINK1 variants of unknown significance shows intact mitophagy function for most variants. *NPJ Park. Dis.* 7:113. doi: 10.1038/s41531-021-00258-8
- Mabrouk, O. S., Chen, S., Edwards, A. L., Yang, M., Hirst, W. D., and Graham, D. L. (2020). Quantitative measurements of LRRK2 in human cerebrospinal fluid demonstrates increased levels in G2019S patients. *Front. Neurosci.* 14:526. doi: 10.3389/fnins.2020.00526
- Magalhaes, P., and Lashuel, H. A. (2022). Opportunities and challenges of alpha-synuclein as a potential biomarker for Parkinson's disease and other synucleinopathies. *NPJ Park. Dis.* 8:93. doi: 10.1038/s41531-022-00357-0
- Manohar, S., Jacob, S., Wang, J., Wiechecki, K. A., Koh, H. W. L., Simoes, V., et al. (2019). polyubiquitin chains linked by lysine residue 48 (K48) selectively target oxidized proteins in vivo. *Antioxid. Redox Signal.* 31, 1133–1149. doi: 10.1089/ars.2019.7826
- Martinez, A., Lectez, B., Ramirez, J., Popp, O., Sutherland, J. D., Urbe, S., et al. (2017). Quantitative proteomic analysis of Parkin substrates in Drosophila neurons. *Mol. Neurodegener.* 12:29. doi: 10.1186/s13024-017-0170-3
- Martinez-Martin, P., Schapira, A. H., Stocchi, F., Sethi, K., Odin, P., MacPhee, G., et al. (2007). Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. *Mov. Disord.* 22, 1623–1629. doi: 10.1002/mds.21586
- Martini, H., and Passos, J. F. (2023). Cellular senescence: All roads lead to mitochondria. *FEBS J.* 290, 1186–1202. doi: 10.1111/febs.16361
- Matenia, D., Hempp, C., Timm, T., Eikhof, A., and Mandelkow, E. M. (2012). Microtubule affinity-regulating kinase 2 (MARK2) turns on phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) at Thr-313, a mutation site in Parkinson disease: Effects on mitochondrial transport. *J. Biol. Chem.* 287, 8174–8186. doi: 10.1074/jbc.M111.262287
- Matheoud, D., Sugiura, A., Bellemare-Pelletier, A., Laplante, A., Rondeau, C., Chemali, M., et al. (2016). Parkinson's disease-related proteins PINK1 and parkin repress mitochondrial antigen presentation. *Cell* 166, 314–327. doi: 10.1016/j.cell.2016.05.039
- Matsuda, N., Sato, S., Shiba, K., Okatsu, K., Saisho, K., Gautier, C. A., et al. (2010). PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. *J. Cell Biol.* 189, 211–221. doi: 10.1083/jcb.200910140
- Matteucci, A., Patron, M., Vecellio Reane, D., Gastaldello, S., Amoroso, S., Rizzuto, R., et al. (2018). Parkin-dependent regulation of the MCU complex component MICU1. *Sci. Rep.* 8:14199. doi: 10.1038/s41598-018-32551-7
- McLelland, G. L., Lee, S. A., McBride, H. M., and Fon, E. A. (2016). Syntaxin-17 delivers PINK1/parkin-dependent mitochondrial vesicles to the endolysosomal system. *J. Cell Biol.* 214, 275–291. doi: 10.1083/jcb.201603105
- McLelland, G. L., Soubannier, V., Chen, C. X., McBride, H. M., and Fon, E. A. (2014). Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. *EMBO J.* 33, 282–295. doi: 10.1002/embj.201385902
- Meng, H., Yamashita, C., Shiba-Fukushima, K., Inoshita, T., Funayama, M., Sato, S., et al. (2017). Loss of Parkinson's disease-associated protein CHCHD2 affects mitochondrial cristae structure and destabilizes cytochrome c. *Nat. Commun.* 8:15500. doi: 10.1038/ncomms15500
- Meredith, G. E., Totterdell, S., Beales, M., and Meshul, C. K. (2009). Impaired glutamate homeostasis and programmed cell death in a chronic MPTP mouse model of Parkinson's disease. *Exp. Neurol.* 219, 334–340. doi: 10.1016/j.expneurol.2009.06.005
- Mitsumoto, A., Nakagawa, Y., Takeuchi, A., Okawa, K., Iwamatsu, A., and Takanezawa, Y. (2001). Oxidized forms of peroxiredoxins and DJ-1 on two-dimensional gels increased in response to sublethal levels of paraquat. *Free Radic. Res.* 35, 301–310. doi: 10.1080/10715760100300831
- Mollenhauer, B., Locascio, J. J., Schulz-Schaeffer, W., Sixel-Doring, F., Trenkwalder, C., and Schlossmacher, M. G. (2011). alpha-Synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: A cohort study. *Lancet Neurol.* 10, 230–240. doi: 10.1016/S1474-4422(11)70014-X
- Mollenhauer, B., Trautmann, E., Taylor, P., Manninger, P., Sixel-Doring, F., Ebentheuer, J., et al. (2013). Total CSF alpha-synuclein is lower in de novo Parkinson patients than in healthy subjects. *Neurosci. Lett.* 532, 44–48. doi: 10.1016/j.neulet.2012.11.004
- Morais, V. A., Haddad, D., Craessaerts, K., De Bock, P. J., Swerts, J., Vilain, S., et al. (2014). PINK1 loss-of-function mutations affect mitochondrial complex I activity via Ndufa10 ubiquinone uncoupling. *Science* 344, 203–207. doi: 10.1126/science.1249161
- Morais, V. A., Verstreken, P., Roethig, A., Smet, J., Snellinx, A., Vanbrabant, M., et al. (2009). Parkinson's disease mutations in PINK1 result in decreased Complex I activity and deficient synaptic function. *EMBO Mol. Med.* 1, 99–111. doi: 10.1002/emmm.200900006
- Mortiboys, H., Johansen, K. K., Aasly, J. O., and Bandmann, O. (2010). Mitochondrial impairment in patients with Parkinson disease with the G2019S mutation in LRRK2. *Neurology* 75, 2017–2020. doi: 10.1212/WNL.0b013e3181ff9685
- Mouton-Liger, F., Jacoupy, M., Corvol, J. C., and Corti, O. (2017). PINK1/parkin-dependent mitochondrial surveillance: From pleiotropy to Parkinson's disease. *Front. Mol. Neurosci.* 10:120. doi: 10.3389/fnmol.2017.00120
- Nalls, M. A., Blauwendraat, C., Vallerga, C. L., Heilbron, K., Bandres-Ciga, S., Chang, D., et al. (2019). Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: A meta-analysis of genome-wide association studies. *Lancet Neurol.* 18, 1091–1102. doi: 10.1016/S1474-4422(19)30320-5
- Narendra, D., Tanaka, A., Suen, D. F., and Youle, R. J. (2008). Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J. Cell Biol.* 183, 795–803. doi: 10.1083/jcb.200809125
- Nguyen, H. N., Byers, B., Cord, B., Shcheglovitov, A., Byrne, J., Gujar, P., et al. (2011). LRRK2 mutant iPSC-derived DA neurons demonstrate increased susceptibility to oxidative stress. *Cell Stem Cell* 8, 267–280. doi: 10.1016/j.stem.2011.01.013
- Nicoletti, V., Palermo, G., Del Prete, E., Mancuso, M., and Ceravolo, R. (2021). Understanding the multiple role of mitochondria in Parkinson's disease and related disorders: Lesson from genetics and protein-interaction network. *Front. Cell Dev. Biol.* 9:636506. doi: 10.3389/fcell.2021.636506
- Norris, K. L., Hao, R., Chen, L. F., Lai, C. H., Kapur, M., Shaughnessy, P. J., et al. (2015). Convergence of Parkin, PINK1, and alpha-Synuclein on Stress-induced Mitochondrial Morphological Remodeling. *J. Biol. Chem.* 290, 13862–13874. doi: 10.1074/jbc.M114.634063
- Oh, C. K., Sultan, A., Platzer, J., Dolatabadi, N., Soldner, F., McClatchy, D. B., et al. (2017). S-Nitrosylation of PINK1 Attenuates PINK1/Parkin-Dependent Mitophagy in hiPSC-Based Parkinson's Disease Models. *Cell Rep.* 21, 2171–2182. doi: 10.1016/j.celrep.2017.10.068
- Okatsu, K., Iemura, S., Koyano, F., Go, E., Kimura, M., Natsume, T., et al. (2012a). Mitochondrial hexokinase HKI is a novel substrate of the Parkin ubiquitin ligase. *Biochem. Biophys. Res. Commun.* 428, 197–202. doi: 10.1016/j.bbrc.2012.10.041
- Okatsu, K., Oka, T., Iguchi, M., Imamura, K., Kosako, H., Tani, N., et al. (2012b). PINK1 autophosphorylation upon membrane potential dissipation is essential for Parkin recruitment to damaged mitochondria. *Nat. Commun.* 3:1016. doi: 10.1038/ncomms2016
- Olzmann, J. A., Li, L., Chudav, M. V., Chen, J., Perez, F. A., Palmiter, R. D., et al. (2007). Parkin-mediated K63-linked polyubiquitination targets misfolded DJ-1 to aggregates via binding to HDAC6. *J. Cell Biol.* 178, 1025–1038. doi: 10.1083/jcb.200611128
- Ordureau, A., Heo, J. M., Duda, D. M., Paulo, J. A., Olszewski, J. L., Yanishevski, D., et al. (2015). Defining roles of PARKIN and ubiquitin phosphorylation by PINK1 in mitochondrial quality control using a ubiquitin replacement strategy. *Proc. Natl. Acad. Sci. U.S.A.* 112, 6637–6642. doi: 10.1073/pnas.1506593112
- Ordureau, A., Paulo, J. A., Zhang, W., Ahfeldt, T., Zhang, J., Cohn, E. F., et al. (2018). Dynamics of PARKIN-dependent mitochondrial ubiquitylation in induced neurons and model systems revealed by digital snapshot proteomics. *Mol. Cell* 70, 211–227e8. doi: 10.1016/j.molcel.2018.03.012
- Ordureau, A., Sarraf, S. A., Duda, D. M., Heo, J. M., Jedrychowski, M. P., Sviderskiy, V. O., et al. (2014). Quantitative proteomics reveal a feedforward mechanism for

- mitochondrial PARKIN translocation and ubiquitin chain synthesis. *Mol. Cell* 56, 360–375. doi: 10.1016/j.molcel.2014.09.007
- Ozawa, K., Komatsubara, A. T., Nishimura, Y., Sawada, T., Kawafune, H., Tsumoto, H., et al. (2013). S-nitrosylation regulates mitochondrial quality control via activation of parkin. *Sci. Rep.* 3:2202. doi: 10.1038/srep02202
- Ozawa, K., Tsumoto, H., Miura, Y., Yamaguchi, J., Iguchi-Ariga, S. M. M., Sakuma, T., et al. (2020). DJ-1 is indispensable for the S-nitrosylation of Parkin, which maintains function of mitochondria. *Sci. Rep.* 10:4377. doi: 10.1038/s41598-020-61287-6
- Padman, B. S., Nguyen, T. N., Uoselis, L., Skulsupaisarn, M., Nguyen, L. K., and Lazarou, M. (2019). LC3/GABARAPs drive ubiquitin-independent recruitment of Optineurin and NDP52 to amplify mitophagy. *Nat. Commun.* 10:408. doi: 10.1038/s41467-019-08335-6
- Padmanabhan, S., Lanz, T. A., Gorman, D., Wolfe, M., Joyce, A., Cabrera, C., et al. (2020). An assessment of LRRK2 serine 935 phosphorylation in human peripheral blood mononuclear cells in idiopathic Parkinson's disease and G2019S LRRK2 cohorts. *J. Park. Dis.* 10, 623–629. doi: 10.3233/JPD-191786
- Palacino, J. J., Sagi, D., Goldberg, M. S., Krauss, S., Motz, C., Wacker, M., et al. (2004). Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J. Biol. Chem.* 279, 18614–18622. doi: 10.1074/jbc.M401135200
- Parihar, M. S., Parihar, A., Fujita, M., Hashimoto, M., and Ghafourifar, P. (2008). Mitochondrial association of alpha-synuclein causes oxidative stress. *Cell Mol. Life Sci.* 65, 1272–1284. doi: 10.1007/s00018-008-7589-1
- Park, J., Lee, S. B., Lee, S., Kim, Y., Song, S., Kim, S., et al. (2006). Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin. *Nature* 441, 1157–1161. doi: 10.1038/nature04788
- Perez Carrion, M., Pischedda, F., Biosa, A., Russo, I., Straniero, L., Civiero, L., et al. (2018). The LRRK2 variant E193K prevents mitochondrial fission upon MPP+ treatment by altering LRRK2 binding to DRP1. *Front. Mol. Neurosci.* 11:64. doi: 10.3389/fnmol.2018.00064
- Pickrell, A. M., and Youle, R. J. (2015). The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron* 85, 257–273. doi: 10.1016/j.neuron.2014.12.007
- Plovanich, M., Bogorad, R. L., Sancak, Y., Kamer, K. J., Strittmatter, L., Li, A. A., et al. (2013). MICU2, a paralog of MICU1, resides within the mitochondrial uniporter complex to regulate calcium handling. *PLoS One* 8:e55785. doi: 10.1371/journal.pone.0055785
- Plun-Favreau, H., Klupsch, K., Moiso, N., Gandhi, S., Kjaer, S., Frith, D., et al. (2007). The mitochondrial protease HtrA2 is regulated by Parkinson's disease-associated kinase PINK1. *Nat. Cell Biol.* 9, 1243–1252. doi: 10.1038/ncb1644
- Pogson, J. H., Ivatt, R. M., Sanchez-Martinez, A., Tufi, R., Wilson, E., Mortiboys, H., et al. (2014). The complex I subunit NDUFA10 selectively rescues Drosophila pink1 mutants through a mechanism independent of mitophagy. *PLoS Genet.* 10:e1004815. doi: 10.1371/journal.pgen.1004815
- Polymeroopoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., et al. (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 276, 2045–2047. doi: 10.1126/science.276.5321.2045
- Poole, A. C., Thomas, R. E., Yu, S., Vincow, E. S., and Pallanck, L. (2010). The mitochondrial fusion-promoting factor mitofusin is a substrate of the PINK1/parkin pathway. *PLoS One* 5:e10054. doi: 10.1371/journal.pone.0010054
- Popov, L. D. (2020). Mitochondrial biogenesis: An update. *J. Cell Mol. Med.* 24, 4892–4899. doi: 10.1111/jcmm.15194
- Popov, L. D. (2022). Mitochondrial-derived vesicles: Recent insights. *J. Cell Mol. Med.* 26, 3323–3328. doi: 10.1111/jcmm.17391
- Pridgeon, J. W., Olzmann, J. A., Chin, L. S., and Li, L. (2007). PINK1 protects against oxidative stress by phosphorylating mitochondrial chaperone TRAP1. *PLoS Biol.* 5:e172. doi: 10.1371/journal.pbio.0050172
- Pryde, K. R., Smith, H. L., Chau, K. Y., and Schapira, A. H. (2016). PINK1 disables the anti-fission machinery to segregate damaged mitochondria for mitophagy. *J. Cell Biol.* 213, 163–171. doi: 10.1083/jcb.201509003
- Raffaello, A., De Stefani, D., Sabbadin, D., Teardo, E., Merli, G., Picard, A., et al. (2013). The mitochondrial calcium uniporter is a multimer that can include a dominant-negative pore-forming subunit. *EMBO J.* 32, 2362–2376. doi: 10.1038/emboj.2013.157
- Rakovic, A., Grunewald, A., Kottwitz, J., Bruggemann, N., Pramstaller, P. P., Lohmann, K., et al. (2011). Mutations in PINK1 and Parkin impair ubiquitination of Mitofusins in human fibroblasts. *PLoS One* 6:e16746. doi: 10.1371/journal.pone.0016746
- Ramirez, A., Heimbach, A., Grundemann, J., Stiller, B., Hampshire, D., Cid, L. P., et al. (2006). Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. *Nat. Genet.* 38, 1184–1191. doi: 10.1038/ng1884
- Ramirez, A., Old, W., Selwood, D. L., and Liu, X. (2022). Cannabidiol activates PINK1-Parkin-dependent mitophagy and mitochondrial-derived vesicles. *Eur. J. Cell Biol.* 101:151185. doi: 10.1016/j.ejcb.2021.151185
- Rasool, S., Soya, N., Truong, L., Croteau, N., Lukacs, G. L., and Trempe, J. F. (2018). PINK1 autophosphorylation is required for ubiquitin recognition. *EMBO Rep.* 19:e44981. doi: 10.15252/embr.201744981
- Rasool, S., Veyron, S., Soya, N., Eldeeb, M. A., Lukacs, G. L., Fon, E. A., et al. (2022). Mechanism of PINK1 activation by autophosphorylation and insights into assembly on the TOM complex. *Mol. Cell* 82, 44–59.e6. doi: 10.1016/j.molcel.2021.11.012
- Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., et al. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* 17, 405–424. doi: 10.1038/gim.2015.30
- Rideout, H. J., Chartier-Harlin, M. C., Fell, M. J., Hirst, W. D., Huntwork-Rodriguez, S., Lyons, C. E. G., et al. (2020). The current state-of-the-art of LRRK2-based biomarker assay development in Parkinson's disease. *Front. Neurosci.* 14:865. doi: 10.3389/fnins.2020.00865
- Rose, C. M., Isasa, M., Ordureau, A., Prado, M. A., Beausoleil, S. A., Jedrychowski, M. P., et al. (2016). Highly multiplexed quantitative mass spectrometry analysis of ubiquitylomes. *Cell Syst.* 3, 395–403.e4. doi: 10.1016/j.cels.2016.08.009
- Rosina, M., Ceci, V., Turchi, R., Chuan, L., Borcherding, N., Sciarretta, F., et al. (2022). Ejection of damaged mitochondria and their removal by macrophages ensure efficient thermogenesis in brown adipose tissue. *Cell Metab.* 34, 533–548.e12. doi: 10.1016/j.cmet.2022.02.016
- Ross, O. A., Soto-Ortolaza, A. I., Heckman, M. G., Aasly, J. O., Abahuni, N., Annesi, G., et al. (2011). Association of LRRK2 exonic variants with susceptibility to Parkinson's disease: A case-control study. *Lancet Neurol.* 10, 898–908. doi: 10.1016/S1474-4422(11)70175-2
- Ryan, T. A., Phillips, E. O., Collier, C. L., Jb Robinson, A., Routledge, D., Wood, R. E., et al. (2020). Tollip coordinates Parkin-dependent trafficking of mitochondrial-derived vesicles. *EMBO J.* 39:e102539. doi: 10.15252/embj.2019102539
- Saito, Y. (2017). DJ-1 as a biomarker of Parkinson's disease. *Adv. Exp. Med. Biol.* 1037, 149–171. doi: 10.1007/978-981-10-6583-5_10
- Sancak, Y., Markhard, A. L., Kitami, T., Kovacs-Bogdan, E., Kamer, K. J., Udeshi, N. D., et al. (2013). EMRE is an essential component of the mitochondrial calcium uniporter complex. *Science* 342, 1379–1382. doi: 10.1126/science.1242993
- Sandebring, A., Dehvari, N., Perez-Manso, M., Thomas, K. J., Karpilovski, E., Cookson, M. R., et al. (2009). Parkin deficiency disrupts calcium homeostasis by modulating phospholipase C signalling. *FEBS J.* 276, 5041–5052. doi: 10.1111/j.1742-4658.2009.07201.x
- Sanders, L. H., Laganieri, J., Cooper, O., Mak, S. K., Vu, B. J., Huang, Y. A., et al. (2014). LRRK2 mutations cause mitochondrial DNA damage in iPSC-derived neural cells from Parkinson's disease patients: Reversal by gene correction. *Neurobiol. Dis.* 62, 381–386. doi: 10.1016/j.nbd.2013.10.013
- Sarafian, T. A., Ryan, C. M., Souda, P., Maslah, E., Kar, U. K., Vinters, H. V., et al. (2013). Impairment of mitochondria in adult mouse brain overexpressing predominantly full-length, N-terminally acetylated human alpha-synuclein. *PLoS One* 8:e63557. doi: 10.1371/journal.pone.0063557
- Sarraf, S. A., Raman, M., Guarani-Pereira, V., Sowa, M. E., Huttlin, E. L., Gygi, S. P., et al. (2013). Landscape of the PARKIN-dependent ubiquitylome in response to mitochondrial depolarization. *Nature* 496, 372–376. doi: 10.1038/nature12043
- Sauve, V., Lilov, A., Seirafi, M., Vranas, M., Rasool, S., Kozlov, G., et al. (2015). A Ubl/ubiquitin switch in the activation of Parkin. *EMBO J.* 34, 2492–2505. doi: 10.15252/embj.201592237
- Scarpulla, R. C. (2008). Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiol. Rev.* 88, 611–638. doi: 10.1152/physrev.00025.2007
- Seibenhener, M. L., Babu, J. R., Geetha, T., Wong, H. C., Krishna, N. R., and Wooten, M. W. (2004). Sequestosome 1/p62 is a polyubiquitin chain binding protein involved in ubiquitin proteasome degradation. *Mol. Cell Biol.* 24, 8055–8068. doi: 10.1128/MCB.24.18.8055-8068.2004
- Shimizu, S., Konishi, A., Kodama, T., and Tsujimoto, Y. (2000). BH4 domain of antiapoptotic Bcl-2 family members closes voltage-dependent anion channel and inhibits apoptotic mitochondrial changes and cell death. *Proc. Natl. Acad. Sci. U.S.A.* 97, 3100–3105. doi: 10.1073/pnas.97.7.3100
- Shimura, H., Hattori, N., Kubo, S., Mizuno, Y., Asakawa, S., Minoshima, S., et al. (2000). Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. *Nat. Genet.* 25, 302–305. doi: 10.1038/77060
- Shin, J. H., Ko, H. S., Kang, H., Lee, Y., Lee, Y. I., Pletinkova, O., et al. (2011). PARS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. *Cell* 144, 689–702. doi: 10.1016/j.cell.2011.02.010
- Shinbo, Y., Niki, T., Taira, T., Ooe, H., Takahashi-Niki, K., Maita, C., et al. (2006). Proper SUMO-1 conjugation is essential to DJ-1 to exert its full activities. *Cell Death Differ.* 13, 96–108. doi: 10.1038/sj.cdd.4401704
- Shojaee, S., Sina, F., Banihosseini, S. S., Kazemi, M. H., Kalhor, R., Shahidi, G. A., et al. (2008). Genome-wide linkage analysis of a Parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. *Am. J. Hum. Genet.* 82, 1375–1384. doi: 10.1016/j.ajhg.2008.05.005

- Siddiqui, A., Bhaumik, D., Chinta, S. J., Rane, A., Rajagopalan, S., Lieu, C. A., et al. (2015). Mitochondrial quality control via the PGC1alpha-TFEB signaling pathway is compromised by Parkin Q311X mutation but independently restored by rapamycin. *J. Neurosci.* 35, 12833–12844. doi: 10.1523/JNEUROSCI.0109-15.2015
- Siddiqui, A., Rane, A., Rajagopalan, S., Chinta, S. J., and Andersen, J. K. (2016). Detrimental effects of oxidative losses in parkin activity in a model of sporadic Parkinson's disease are attenuated by restoration of PGC1alpha. *Neurobiol. Dis.* 93, 115–120. doi: 10.1016/j.nbd.2016.05.009
- Singh, F., Prescott, A. R., Rosewell, P., Ball, G., Reith, A. D., and Ganley, I. G. (2021). Pharmacological rescue of impaired mitophagy in Parkinson's disease-related LRRK2 G2019S knock-in mice. *Elife* 10:e67604. doi: 10.7554/eLife.67604
- Skowrya, D., Craig, K. L., Tyers, M., Elledge, S. J., and Harper, J. W. (1997). F-box proteins are receptors that recruit phosphorylated substrates to the SCF ubiquitin-ligase complex. *Cell* 91, 209–219. doi: 10.1016/s0092-8674(00)80403-1
- Sliter, D. A., Martinez, J., Hao, L., Chen, X., Sun, N., Fischer, T. D., et al. (2018). Parkin and PINK1 mitigate STING-induced inflammation. *Nature* 561, 258–262. doi: 10.1038/s41586-018-0448-9
- Soubannier, V., McLelland, G. L., Zunino, R., Braschi, E., Rippstein, P., Fon, E. A., et al. (2012a). A vesicular transport pathway shuttles cargo from mitochondria to lysosomes. *Curr. Biol.* 22, 135–141. doi: 10.1016/j.cub.2011.11.057
- Soubannier, V., Rippstein, P., Kaufman, B. A., Shoubridge, E. A., and McBride, H. M. (2012b). Reconstitution of mitochondrial derived vesicle formation demonstrates selective enrichment of oxidized cargo. *PLoS One* 7:e52830. doi: 10.1371/journal.pone.0052830
- Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R., and Goedert, M. (1997). Alpha-synuclein in Lewy bodies. *Nature* 388, 839–840. doi: 10.1038/42166
- Stafa, K., Tsika, E., Moser, R., Musso, A., Glauser, L., Jones, A., et al. (2014). Functional interaction of Parkinson's disease-associated LRRK2 with members of the dynamin GTPase superfamily. *Hum. Mol. Genet.* 23, 2055–2077. doi: 10.1093/hmg/ddt600
- Stevens, D. A., Lee, Y., Kang, H. C., Lee, B. D., Lee, Y. I., Bower, A., et al. (2015). Parkin loss leads to PARIS-dependent declines in mitochondrial mass and respiration. *Proc. Natl. Acad. Sci. U.S.A.* 112, 11696–11701. doi: 10.1073/pnas.1500624112
- Stram, A. R., and Payne, R. M. (2016). Post-translational modifications in mitochondria: Protein signaling in the powerhouse. *Cell Mol. Life Sci.* 73, 4063–4073. doi: 10.1007/s00018-016-2280-4
- Strauss, K. M., Martins, L. M., Plun-Favreau, H., Marx, F. P., Kautzmann, S., Berg, D., et al. (2005). Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. *Hum. Mol. Genet.* 14, 2099–2111. doi: 10.1093/hmg/ddi215
- Stuendl, A., Kraus, T., Chatterjee, M., Zapke, B., Sadowski, B., Moebius, W., et al. (2021). alpha-Synuclein in plasma-derived extracellular vesicles is a potential biomarker of Parkinson's disease. *Mov. Disord.* 36, 2508–2518. doi: 10.1002/mds.28639
- Su, Y. C., and Qi, X. (2013). Inhibition of excessive mitochondrial fission reduced aberrant autophagy and neuronal damage caused by LRRK2 G2019S mutation. *Hum. Mol. Genet.* 22, 4545–4561. doi: 10.1093/hmg/ddt301
- Su, Y. C., Guo, X., and Qi, X. (2015). Threonine 56 phosphorylation of Bcl-2 is required for LRRK2 G2019S-induced mitochondrial depolarization and autophagy. *Biochim. Biophys. Acta* 1852, 12–21. doi: 10.1016/j.bbdis.2014.11.009
- Subramaniam, S. R., Vergnes, L., Franich, N. R., Reue, K., and Chesselet, M. F. (2014). Region specific mitochondrial impairment in mice with widespread overexpression of alpha-synuclein. *Neurobiol. Dis.* 70, 204–213. doi: 10.1016/j.nbd.2014.06.017
- Sugiura, A., McLelland, G. L., Fon, E. A., and McBride, H. M. (2014). A new pathway for mitochondrial quality control: Mitochondrial-derived vesicles. *EMBO J.* 33, 2142–2156. doi: 10.15252/embj.201488104
- Sun, Y., Vashisht, A. A., Tchiew, J., Wohlschlegel, J. A., and Dreier, L. (2012). Voltage-dependent anion channels (VDACs) recruit Parkin to defective mitochondria to promote mitochondrial autophagy. *J. Biol. Chem.* 287, 40652–40660. doi: 10.1074/jbc.M112.419721
- Szabadkai, G., Simoni, A. M., Bianchi, K., De Stefani, D., Leo, S., Wiekowski, M. R., et al. (2006). Mitochondrial dynamics and Ca²⁺ signaling. *Biochim. Biophys. Acta* 1763, 442–449. doi: 10.1016/j.bbamcr.2006.04.002
- Tain, L. S., Chowdhury, R. B., Tao, R. N., Plun-Favreau, H., Moiso, N., Martins, L. M., et al. (2009). Drosophila HtrA2 is dispensable for apoptosis but acts downstream of PINK1 independently from Parkin. *Cell Death Differ.* 16, 1118–1125. doi: 10.1038/cdd.2009.23
- Taira, T., Saito, Y., Niki, T., Iguchi-Ariga, S. M., Takahashi, K., and Ariga, H. (2004). DJ-1 has a role in antioxidant stress to prevent cell death. *EMBO Rep.* 5, 213–218. doi: 10.1038/sj.embor.7400074
- Tanaka, A., Cleland, M. M., Xu, S., Narendra, D. P., Suen, D. F., Karbowski, M., et al. (2010). Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin. *J. Cell Biol.* 191, 1367–1380. doi: 10.1083/jcb.201007013
- Tang, B., Xiong, H., Sun, P., Zhang, Y., Wang, D., Hu, Z., et al. (2006). Association of PINK1 and DJ-1 confers digenic inheritance of early-onset Parkinson's disease. *Hum. Mol. Genet.* 15, 1816–1825. doi: 10.1093/hmg/ddl104
- Tang, F. L., Liu, W., Hu, J. X., Erion, J. R., Ye, J., Mei, L., et al. (2015). VPS35 deficiency or mutation causes dopaminergic neuronal loss by impairing mitochondrial fusion and function. *Cell Rep.* 12, 1631–1643. doi: 10.1016/j.celrep.2015.08.001
- Tanner, C. M. (1992). Occupational and environmental causes of parkinsonism. *Occup. Med.* 7, 503–513.
- Taylor, M., and Alessi, D. R. (2020). Advances in elucidating the function of leucine-rich repeat protein kinase-2 in normal cells and Parkinson's disease. *Curr. Opin. Cell Biol.* 63, 102–113. doi: 10.1016/j.celb.2020.01.001
- Tettweiler, G., Miron, M., Jenkins, M., Sonenberg, N., and Lasko, P. F. (2005). Starvation and oxidative stress resistance in Drosophila are mediated through the eIF4E-binding protein, d4E-BP. *Genes Dev.* 19, 1840–1843. doi: 10.1101/gad.1311805
- Teunissen, C. E. I., Verberk, M. W., Thijssen, E. H., Vermunt, L., Hansson, O., Zetterberg, H., et al. (2022). Blood-based biomarkers for Alzheimer's disease: Towards clinical implementation. *Lancet Neurol.* 21, 66–77. doi: 10.1016/S1474-4422(21)00361-6
- Thevenet, J., Pescini Gobert, R., Hooft van Huijsduijnen, R., Wiessner, C., and Sagot, Y. J. (2011). Regulation of LRRK2 expression points to a functional role in human monocyte maturation. *PLoS One* 6:e21519. doi: 10.1371/journal.pone.0021519
- Tokuda, T., Qureshi, M. M., Ardah, M. T., Varghese, S., Shehab, S. A., Kasai, T., et al. (2010). Detection of elevated levels of alpha-synuclein oligomers in CSF from patients with Parkinson disease. *Neurology* 75, 1766–1772. doi: 10.1212/WNL.0b013e3181fd613b
- Toyofuku, T., Okamoto, Y., Ishikawa, T., Sasawatari, S., and Kumanogoh, A. (2020). LRRK2 regulates endoplasmic reticulum-mitochondrial tethering through the PERK-mediated ubiquitination pathway. *EMBO J.* 39:e100875. doi: 10.15252/embj.2018100875
- Trempe, J. F., and Gehring, K. (2023). Structural mechanisms of mitochondrial quality control mediated by PINK1 and Parkin. *J. Mol. Biol.* 435:168090. doi: 10.1016/j.jmb.2023.168090
- Trempe, J. F., Sauve, V., Grenier, K., Seirafi, M., Tang, M. Y., Menade, M., et al. (2013). Structure of parkin reveals mechanisms for ubiquitin ligase activation. *Science* 340, 1451–1455. doi: 10.1126/science.1237908
- Tsai, P. I., Course, M. M., Lovas, J. R., Hsieh, C. H., Babic, M., Zinsmaier, K. E., et al. (2014). PINK1-mediated phosphorylation of Miro inhibits synaptic growth and protects dopaminergic neurons in Drosophila. *Sci. Rep.* 4:6962. doi: 10.1038/srep06962
- Ulmer, T. S., Bax, A., Cole, N. B., and Nussbaum, R. L. (2005). Structure and dynamics of micelle-bound human alpha-synuclein. *J. Biol. Chem.* 280, 9595–9603. doi: 10.1074/jbc.M411805200
- Um, J. W., and Chung, K. C. (2006). Functional modulation of parkin through physical interaction with SUMO-1. *J. Neurosci. Res.* 84, 1543–1554. doi: 10.1002/jnr.21041
- Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M., Harvey, K., Gispert, S., et al. (2004). Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* 304, 1158–1160. doi: 10.1126/science.1096284
- Van Laar, V. S., Roy, N., Liu, A., Rajprohat, S., Arnold, B., Dukes, A. A., et al. (2015). Glutamate excitotoxicity in neurons triggers mitochondrial and endoplasmic reticulum accumulation of Parkin, and, in the presence of N-acetyl cysteine, mitophagy. *Neurobiol. Dis.* 74, 180–193. doi: 10.1016/j.nbd.2014.11.015
- van Steenoven, I., Majbour, N. K., Vaikath, N. N., Berendse, H. W., van der Flier, W. M., van de Berg, W. D. J., et al. (2018). alpha-Synuclein species as potential cerebrospinal fluid biomarkers for dementia with lewy bodies. *Mov. Disord.* 33, 1724–1733. doi: 10.1002/mds.111
- Vasam, G., Nadeau, R., Cadete, V. J. J., Lavallee-Adam, M., Menzies, K. J., and Burrelle, Y. (2021). Proteomics characterization of mitochondrial-derived vesicles under oxidative stress. *FASEB J.* 35:e21278. doi: 10.1096/fj.202002151R
- Venda, L. L., Cragg, S. J., Buchman, V. L., and Wade-Martins, R. (2010). Alpha-Synuclein and dopamine at the crossroads of Parkinson's disease. *Trends Neurosci.* 33, 559–568. doi: 10.1016/j.tins.2010.09.004
- Vilarino-Guell, C., Wider, C., Ross, O. A., Dachsel, J. C., Kachergus, J. M., Lincoln, S. J., et al. (2011). VPS35 mutations in Parkinson disease. *Am. J. Hum. Genet.* 89, 162–167. doi: 10.1016/j.ajhg.2011.06.001
- Vissers, M., Troyer, M. D., Thijssen, E., Pereira, D. R., Heuberger, J. A., Groeneveld, G. J., et al. (2023). A leucine-rich repeat kinase 2 (LRRK2) pathway biomarker characterization study in patients with Parkinson's disease with and without LRRK2 mutations and healthy controls. *Clin. Transl. Sci.* 16, 1408–1420. doi: 10.1111/cts.13541
- Vivacqua, G., Suppa, A., Mancinelli, R., Belvisi, D., Fabbrini, A., Costanzo, M., et al. (2019). Salivary alpha-synuclein in the diagnosis of Parkinson's disease and Progressive Supranuclear Palsy. *Park. Relat. Disord.* 63, 143–148. doi: 10.1016/j.parkrel.2019.02.014
- Vizziello, M., Borellini, L., Franco, G., and Ardolino, G. (2021). Disruption of mitochondrial homeostasis: The role of PINK1 in Parkinson's disease. *Cells* 10:3022. doi: 10.3390/cells10113022

- Wan, H., Tang, B., Liao, X., Zeng, Q., Zhang, Z., and Liao, L. (2018). Analysis of neuronal phosphoproteome reveals PINK1 regulation of BAD function and cell death. *Cell Death Differ.* 25, 904–917. doi: 10.1038/s41418-017-0027-x
- Wang, H., Song, P., Du, L., Tian, W., Yue, W., Liu, M., et al. (2011). Parkin ubiquitinates Drp1 for proteasome-dependent degradation: Implication of dysregulated mitochondrial dynamics in Parkinson disease. *J. Biol. Chem.* 286, 11649–11658. doi: 10.1074/jbc.M110.144238
- Wang, S., Liu, Z., Ye, T., Mabrouk, O. S., Maltbie, T., Aasly, J., et al. (2017). Elevated LRRK2 autophosphorylation in brain-derived and peripheral exosomes in LRRK2 mutation carriers. *Acta Neuropathol. Commun.* 5:86. doi: 10.1186/s40478-017-0492-y
- Wang, X., Winter, D., Ashrafi, G., Schlehe, J., Wong, Y. L., Selkoe, D., et al. (2011). PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. *Cell* 147, 893–906. doi: 10.1016/j.cell.2011.10.018
- Wang, X., Yan, M. H., Fujioka, H., Liu, J., Wilson-Delfosse, A., Chen, S. G., et al. (2012). LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLP1. *Hum. Mol. Genet.* 21, 1931–1944. doi: 10.1093/hmg/dds003
- Wang, Y., Shi, M., Chung, K. A., Zabetian, C. P., Leverenz, J. B., Berg, D., et al. (2012). Phosphorylated alpha-synuclein in Parkinson's disease. *Sci. Transl. Med.* 4:121ra20. doi: 10.1126/scitranslmed.3002566
- Waragai, M., Wei, J., Fujita, M., Nakai, M., Ho, G. J., Masliah, E., et al. (2006). Increased level of DJ-1 in the cerebrospinal fluids of sporadic Parkinson's disease. *Biochem. Biophys. Res. Commun.* 345, 967–972. doi: 10.1016/j.bbrc.2006.05.011
- Wasiak, S., Zunino, R., and McBride, H. M. (2007). Bax/Bak promote sumoylation of DRP1 and its stable association with mitochondria during apoptotic cell death. *J. Cell Biol.* 177, 439–450. doi: 10.1083/jcb.200610042
- Wauer, T., Simicek, M., Schubert, A., and Komander, D. (2015a). Mechanism of phospho-ubiquitin-induced PARKIN activation. *Nature* 524, 370–374. doi: 10.1038/nature14879
- Wauer, T., Swatek, K. N., Wagstaff, J. L., Gladkova, C., Pruneda, J. N., Michel, M. A., et al. (2015b). Ubiquitin Ser65 phosphorylation affects ubiquitin structure, chain assembly and hydrolysis. *EMBO J.* 34, 307–325. doi: 10.15252/embj.2014.89847
- Wauters, F., Cornelissen, T., Imberechts, D., Martin, S., Koentjoro, B., Sue, C., et al. (2020). LRRK2 mutations impair depolarization-induced mitophagy through inhibition of mitochondrial accumulation of RAB10. *Autophagy* 16, 203–222. doi: 10.1080/15548627.2019.1603548
- Wei, T., Huang, G., Gao, J., Huang, C., Sun, M., Wu, J., et al. (2017). Sirtuin 3 deficiency accelerates hypertensive cardiac remodeling by impairing angiogenesis. *J. Am. Heart Assoc.* 6:e006114. doi: 10.1161/JAHA.117.006114
- West, A. B., Moore, D. J., Biskup, S., Bugayenko, A., Smith, W. W., Ross, C. A., et al. (2005). Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity. *Proc. Natl. Acad. Sci. U.S.A.* 102, 16842–16847. doi: 10.1073/pnas.0507360102
- Whitworth, A. J., Lee, J. R., Ho, V. M., Flick, R., Chowdhury, R., and McQuibban, G. A. (2008). Rhomboid-7 and HtrA2/Omi act in a common pathway with the Parkinson's disease factors Pink1 and Parkin. *Dis. Model. Mech.* 1, 168–74; discussion 173. doi: 10.1242/dmm.000109
- Xiong, H., Wang, D., Chen, L., Choo, Y. S., Ma, H., Tang, C., et al. (2009). Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation. *J. Clin. Invest.* 119, 650–660. doi: 10.1172/JCI37617
- Yamada, T., Dawson, T. M., Yanagawa, T., Iijima, M., and Sesaki, H. (2019). SQSTM1/p62 promotes mitochondrial ubiquitination independently of PINK1 and PRKN/parkin in mitophagy. *Autophagy* 15, 2012–2018. doi: 10.1080/15548627.2019.1643185
- Yamada, T., Murata, D., Adachi, Y., Itoh, K., Kameoka, S., Igarashi, A., et al. (2018). Mitochondrial stasis reveals p62-mediated ubiquitination in parkin-independent mitophagy and mitigates nonalcoholic fatty liver disease. *Cell Metab.* 28, 588–604.e5. doi: 10.1016/j.cmet.2018.06.014
- Yang, Y., Kovacs, M., Sakamoto, T., Zhang, F., Kiehart, D. P., and Sellers, J. R. (2006). Dimerized Drosophila myosin VIIA: A processive motor. *Proc. Natl. Acad. Sci. U.S.A.* 103, 5746–5751. doi: 10.1073/pnas.0509935103
- Yao, D., Gu, Z., Nakamura, T., Shi, Z. Q., Ma, Y., Gaston, B., et al. (2004). Nitrosative stress linked to sporadic Parkinson's disease: S-nitrosylation of parkin regulates its E3 ubiquitin ligase activity. *Proc. Natl. Acad. Sci. U.S.A.* 101, 10810–10814. doi: 10.1073/pnas.0404161101
- Yi, W., MacDougall, E. J., Tang, M. Y., Krahn, A. I., Gan-Or, Z., Trempe, J. F., et al. (2019). The landscape of Parkin variants reveals pathogenic mechanisms and therapeutic targets in Parkinson's disease. *Hum. Mol. Genet.* 28, 2811–2825. doi: 10.1093/hmg/ddz080
- Yu, R., Liu, T., Ning, C., Tan, F., Jin, S. B., Lendahl, U., et al. (2019). The phosphorylation status of Ser-637 in dynamin-related protein 1 (Drp1) does not determine Drp1 recruitment to mitochondria. *J. Biol. Chem.* 294, 17262–17277. doi: 10.1074/jbc.RA119.008202
- Zhang, J. Y., Deng, Y. N., Zhang, M., Su, H., and Qu, Q. M. (2016). SIRT3 acts as a neuroprotective agent in rotenone-induced parkinson cell model. *Neurochem. Res.* 41, 1761–1773. doi: 10.1007/s11064-016-1892-2
- Zhang, L., Karsten, P., Hamm, S., Pogson, J. H., Muller-Rischart, A. K., Exner, N., et al. (2013). TRAP1 rescues PINK1 loss-of-function phenotypes. *Hum. Mol. Genet.* 22, 2829–2841. doi: 10.1093/hmg/ddt132
- Zhang, L., Zhang, C., Zhu, Y., Cai, Q., Chan, P., Ueda, K., et al. (2008). Semi-quantitative analysis of alpha-synuclein in subcellular pools of rat brain neurons: An immunogold electron microscopic study using a C-terminal specific monoclonal antibody. *Brain Res.* 1244, 40–52. doi: 10.1016/j.brainres.2008.08.067
- Zhang, Y., Gao, J., Chung, K. K., Huang, H., Dawson, V. L., and Dawson, T. M. (2000). Parkin functions as an E2-dependent ubiquitin-protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1. *Proc. Natl. Acad. Sci. U.S.A.* 97, 13354–13359. doi: 10.1073/pnas.240347797
- Zhong, N., Kim, C. Y., Rizzu, P., Geula, C., Porter, D. R., Pothos, E. N., et al. (2006). DJ-1 transcriptionally up-regulates the human tyrosine hydroxylase by inhibiting the sumoylation of pyrimidine tract-binding protein-associated splicing factor. *J. Biol. Chem.* 281, 20940–20948. doi: 10.1074/jbc.M601935200
- Zimprich, A., Benet-Pages, A., Struhal, W., Graf, E., Eck, S. H., Offman, M. N., et al. (2011). A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. *Am. J. Hum. Genet.* 89, 168–175. doi: 10.1016/j.ajhg.2011.06.008
- Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., et al. (2004). Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* 44, 601–607. doi: 10.1016/j.neuron.2004.11.005
- Ziviani, E., Tao, R. N., and Whitworth, A. J. (2010). Drosophila parkin requires PINK1 for mitochondrial translocation and ubiquitinates mitofusin. *Proc. Natl. Acad. Sci. U.S.A.* 107, 5018–5023. doi: 10.1073/pnas.0913485107