# The interplay between parkin and alpha-synuclein; possible implications for the pathogenesis of Parkinson's disease

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Parkin and alpha-synuclein (α-syn) are two key proteins involved in the pathophysiology of Parkinson's disease (PD). Oligomerization/aggregation and excessive secretion of α-syn contributes to PD through free radical stress, mitochondrial impairment, and synaptic dysfunction. Parkin, an E3 ubiquitin ligase, is considered to be a pleiotropic, neuroprotective protein that modulates metabolic turnover and the accumulation of α-syn. This is in addition to parkin's role in counteracting the more distant effects of α-syn on cellular survival by altering proteasomal, autophagic, and calpain-mediated protein degradation pathways that can reduce α-syn levels. Moreover, parkin regulates mitochondrial turnover, cell survival, and immune phenomena – processes that are all known to be disturbed in PD. In addition, parkin might have an impact on the spreading and propagation of α-syn by controlling its post-translational modifications. On the other hand, recent research has shown that α-syn oligomers affect the expression, post-translational modification, and activity of parkin. This review focuses on the molecular mechanisms of cross-talk between parkin and α-syn in PD. The physical and functional interactions between α-syn and parkin, which have been incompletely characterized to-date, may present a new therapeutic avenue in PD and related synucleinopathies. The development of effective, clinically feasible modulators may offer great hopes for the therapy of PD.

Key words: protein aggregation, cross-talk, neurodegeneration, cell death

## INTRODUCTION

Parkinson's disease (PD) is one of the most common age-related neurodegenerative disorders. Despite years of intense research and testing of candidate treatments, all available therapies are symptomatic. The long period of stealthy, relatively symptom-free development is shared with other neurodegenerative disorders (notably, with Alzheimer's disease – AD), and hampers diagnosis, elucidation of disease mechanisms, and possible therapy (reviewed in Jęśko et al., 2017). The main neuropathological hallmarks of PD are 1) intraneuronal cytoplasmic inclusions, termed Lewy bodies (LB), that contain α-synuclein (α-syn) as a major component and multiple other proteins including the E3-ubiquitin ligase parkin, and 2) the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta which leads to reduced dopamine (DA) levels in the striatum – a brain region that controls locomotor activity. The majority of PD cases are characterized as spontaneous. Only about 20% of patients show a family history of the disease and, of those with a family history, only a minority follow Mendelian patterns of inheritance. α-syn and parkin are two of the genes with mutations that have been associated with typical forms of PD (Coppedè, 2012). Beyond PD, other relatively common

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synucleinopathies include the PD spectrum diseases PD dementia (PDD) and dementia with Lewy bodies (DLB), and the relatively more distant multiple system atrophy (MSA).

α-syn is a soluble, 140-amino acid protein with predominantly presynaptic localization, but is also found in lower quantities in other cell regions (e.g., nuclear envelope, perikaryon). α-syn is abundantly expressed in the brain, particularly in the cerebral cortex, hippocampus, substantia nigra, striatum, and olfactory bulb, and is also present outside the central nervous system (CNS) (Adamczyk et al., 2005b; Taguchi et al., 2016: Jęśko et al., 2017). The proposed physiological functions of α-syn are numerous and complex. Indeed, α-syn is implicated in synaptic signaling (i.e., neurotransmitter release, functioning of the synaptic vesicle pool), $Ca^{2+}$ homeostasis, and the regulation of gene expression. Importantly, α-syn plays a significant role in dopaminergic neurotransmission, which is selectively deregulated in PD. A wealth of data indicate that loss or perturbation of physiological activity of α-syn contributes to the development and progression of PD. However, results obtained to-date focus primarily on α-syn's gain-of-function mechanism, i.e., the acquisition of neurotoxic properties by α-syn. Misfolded α-syn oligomerizes and then forms fibrils, and is sometimes suggested to have prion-like properties (the capability of initiating aggregation of further, 'native' α-syn molecules). Cell-to-cell transfer of α-syn, whether leading to spread of misfolding or simply to α-syn presence in recipient cells, is a novel mode of pathology propagation, previously underestimated but potentially crucial, leading to the characteristic spatial sequence of pathological events in PD development (Jęśko et al., 2017). The gain-of-function neurotoxic alterations in α-syn may be evoked by mutations in the α-syn gene, *SNCA*, via post-translational modifications of the α-syn protein and/or by its oligomerization or aggregation. PD-linked dominant *SNCA* mutations range from missense changes that cause single amino acid substitutions to gene dosage changes (i.e., duplication or triplication; Farrer et al., 1998, 2004). Deregulated post-translational α-syn modifications, including phosphorylation, oxidation, or nitration, may also alter the metabolism and function of α-syn (Jęśko et al., 2017). Hypotheses describing potential mechanisms of α-syn toxicity include (for review, see Wong and Krainc, 2017):

- Disruption of numerous vesicular pathways, including deregulation of the DA release mechanism which may lead to intracellular accumulation and cytotoxic oxidation of the neurotransmitter. In addition, disruption of autophagy, which governs the removal of dysfunctional proteins and organelles.

- Damage to the endoplasmic reticulum (ER) and Golgi apparatus, leading to deregulated transport of macromolecules and induction of ER stress.
- Impaired mitochondrial fission and fusion.
- Deregulation of transcription factors.
- Disrupted inter-organellar contacts, such as mitochondria-associated ER membranes (MAM).

Parkin is a 52kDa, 465aa E3 ubiquitin-protein ligase with broad-spectrum neuroprotective activities and is found in LB along with α-syn. Parkin substrates include *O*-glycosylated α-syn, $Aβ_{1-42}$, and cytoskeletal proteins (reviewed in Shimura et al., 2012). Parkin is involved in the maintenance of mitochondrial metabolism, which is particularly critical in the richly arborized DAergic neurons of the substantia nigra (Giguère et al., 2018). As a component of the ubiquitin-proteasome system (UPS), parkin plays a key role in the degradation of damaged or misfolded proteins, and in the removal of defective mitochondria via mitophagy (Geisler et al., 2010). Parkin is engaged in 1) the classical K48-G76 ubiquitination which leads to proteasomal degradation, but also in 2) monoubiquitination and 3) K63-linked polyubiquitination that targets proteins – or whole organelles – for autophagic degradation (Olzmann et al., 2007; Zheng and Hunter, 2013; Zhu et al., 2017). K63-linked polyubiquitination additionally serves distinct signaling purposes in the regulation of protein synthesis-dependent response to oxidative stress (Silva et al., 2015).

Parkin can bind to promoter DNA and behave as a transcriptional activator or repressor, thereby regulating the gene expression of p53 or presenillin-1 and -2 (da Costa et al., 2009; Duplan et al., 2013). Moreover, parkin is translocated to the nucleus in response to DNA damage. In the nucleus, parkin binds to Nijmegen breakage syndrome 1 (NBS1), a protein engaged in DNA double strand break signaling and repair, and ensures its efficient recruitment to UV-induced DNA lesions (Zhu et al., 2017). Parkin also monoubiquitinates proliferating cell nuclear antigen (PCNA), which is an essential co-factor for DNA polymerase δ that is engaged in repair-linked and general DNA replication (Zhu et al., 2017). Taken together, the resulting effects of parkin on DNA repair may underlie the observed increased risk of skin tumors in PD (Zhu et al., 2017).

Various rearrangements of the parkin gene (*PARK*), including exon deletion, multiplication, and point mutations, have been implicated in the pathogenesis of familial PD (Pankratz et al., 2009). Analysis of the variations of *PARK* as well as plasma levels of parkin protein may yield a useful diagnostic factor for PD (Geldenhuys et al., 2014). Indeed, disturbances in post-translational modifications of parkin protein, such as phosphorylation, S-nitrosylation, or oxidative damage, might be linked to the development of PD (also in the sporadic

disease forms) (reviewed by Dawson and Dawson, 2014). Stimulation of parkin phosphorylation at Ser65 (by PINK1) has been shown to facilitate parkin recruitment to the mitochondria (Hertz et al., 2013). Thus, activation of PINK1 with, for e.g., kinetin triphosphate, an ATP analog (Hertz et al., 2013), might promote parkin recruitment to the impaired mitochondria.

## THE POSSIBLE INVOLVEMENT OF PARKIN IN THE MODULATION OF A-SYNUCLEIN METABOLISM AND AGGREGATION

Excessive α-syn accumulation, oligomerization, and the resulting toxicity appear to be critical for the pathogenesis of PD and other synucleinopathies (Jęśko et al., 2017). Indeed, oligomers, fibrils, and/or large aggregates of α-syn form following overexpression of α-syn, exposure to oxidative or nitrosative stress, apoptotic stimuli, or interactions with DA or histones (Gentile et al., 2008; Giasson et al., 2000; Goers et al.,2003; Mor et al., 2017; Ponzini et al., 2019; Singleton et al, 2004).

### Parkin and α-syn secretion

Recent studies indicate that α-syn is secreted into the extracellular space, and secretion appears to be a precisely regulated, physiological process (Jęśko et al., 2017). However, in PD, abnormal excess release of monomeric and/or aggregated α-syn might lead to free radical stress (Wilkaniec et al., 2019) and trigger immunological response of surrounding astrocytes and microglia, thereby accelerating the neurotoxic insult (Allen Reish and Standaert, 2015). Moreover, the internalization of secreted α-syn by neurons and glia spreads the neurodegenerative pathology and involves other cell types, including cells that do not typically express significant levels of α-syn (Jęśko et al., 2017). Transport of α-syn to neighboring cells has been reported to propagate neurodegeneration (Desplats et al., 2009). α-syn is sometimes likened to the prion protein due to its ability to transfer between different types of cells, and refold from the physiological α-helix-rich conformation into an oligomerization-prone β-sheet structure, (Jęśko et al., 2017).

The role of parkin in secretion of α-syn into the extracellular space has not been studied extensively to-date. Previous research demonstrates that normal function of parkin is essential for LB formation, given that mutations in the parkin gene result in the absence of LB (Chung et al., 2001). This has led to suggestion that the formation of intracellular inclusions might be a tissue protective mechanism reducing α-syn release into ex-

tracellular space and the propagation of the pathology to neighboring cells, effectively at the expense of single cell survival (Chung et al., 2001). Despite these data, it remains unclear whether parkin's participation in inclusion formation is actually neuroprotective or not.

### Parkin and post-translational modifications of α-syn

There is much evidence that the elusive physiological functions of α-syn undergo tight regulation via covalent modifications. Moreover, many of these modifications, such as Ser129 phosphorylation, nitration, mono-/diubiquitination, and cleavage (e.g., C-terminal proteolysis), have been shown to enhance α-syn oligomerization and may therefore influence α-syn toxicity (Fig. 1).

α-syn is phosphorylated at serine residues Ser 87 and Ser 129. Parkin overexpression leads to activation of protein phosphatase 2A (PP2A), which subsequently results in de-phosphorylation of α-syn at Ser 87 and Ser 129. Dephosphorylation of α-syn results in attenuation of α-syn-induced cell death and inflammation (Khandelwal et al., 2010) (Fig. 1).

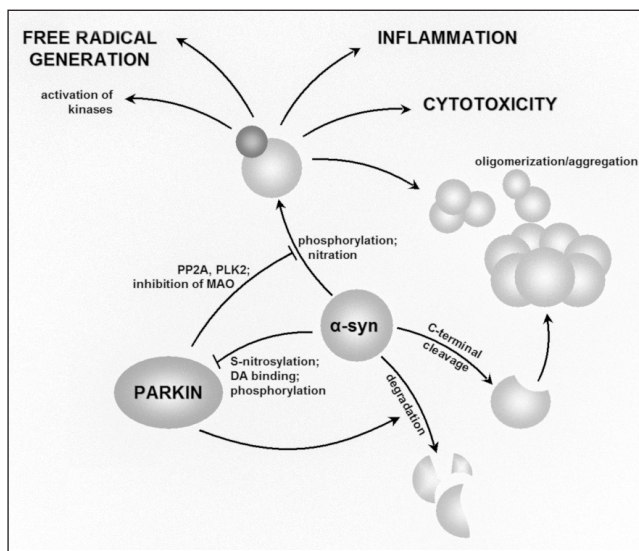Free radicals can cause oxidation of all four α-syn methionine residues. Oxidation of methionine resi-



Fig. 1. Parkin and α-syn mutually regulate their post-translational modifications. Numerous cytotoxic actions of α-syn require post-translational modifications of its molecule, such as phosphorylation, nitration, or partial cleavage. Parkin-dependent inhibition of monoamine oxidase (MAO) may decrease oxidation and nitration of α-syn. Parkin, through increased protein phosphatase 2A (PP2A) activity and the resulting inhibition of polo-like kinase 2 (PLK2), can also reduce α-syn phosphorylation. In turn α-Syn, through its influence on dopamine metabolism and signaling pathways can lead to decreased parkin E3 ubiquitin-ligase activity.

dues can subsequently promote the formation of α-syn oligomers and inhibit α-syn fibrillization, thus increasing α-syn toxicity (Leong et al., 2009). Previous research has also documented tyrosine-nitrated residues in α-syn (Uversky et al., 2005). Although some results suggest that nitration of α-syn has neuroprotective effects (Yamin et al., 2003), other research shows that nitration results in decreased solubility of α-syn, which subsequently impairs its proteolytic degradation and enhances formation of intracellular inclusions (Giasson et al., 2000). Moreover, nitration of α-syn has been shown to increase toxicity towards DAergic neurons (Yu et al., 2010). Consistent with this, high levels of nitrated α-syn have been found in LB from post-mortem PD brains (Giasson et al., 2000). In addition, increased α-syn nitration at Tyr39 can result from stress evoked by monoamine oxidase B (MAO-B) (Danielson et al., 2009), whereas parkin can reduce MAO-B expression (Jiang et al., 2006). Loss of parkin, in turn, led to increased MAO expression and free radical stress in human midbrain DAergic neurons (Jiang et al., 2012) (Fig. 2A).

Proteolytic cleavage of α-syn may not only lead to its degradation, but also to its pathological aggrega-tion. Indeed, previous research shows that C-terminally truncated α-syn has a stronger tendency towards aggregation and is observed in pathologically altered neurites (intriguingly, also in AD without conventional LB) (Lewis et al., 2010).

Importantly, post-translational modifications of parkin may change its activity and role in the modulation of α-syn metabolism (Fig. 1). Indeed, parkin undergoes an α-syn-induced S-nitrosylation (Wilkaniec et al., 2019), which can lead to parkin autoubiquitination and degradation in PC12 cells (Wilkaniec et al., 2019). Other research has shown that covalent binding of DA reduces parkin solubility and inhibits its activity as an E3 ubiquitin ligase (LaVoie et al., 2005). Numerous kinases may be involved in the regulation of parkin phosphorylation on serines 101, 127, 131, 378 and Tyr 143. One potential kinase is cdk5, which regulates parkin solubility together with casein kinase-1 (Chakraborty et al., 2017). Previous research in PC12 cells shows activation of cdk5 in response to α-syn-induced $Ca^{2+}$ rise sensed by calpain. In addition, inhibition of cdk5 reduces α-syn cytotoxicity (Czapski et al.,2013). It remains to be seen if parkin aggregation occurs in response to α-syn-evoked activation of cdk5 *in vivo*, and if the po-
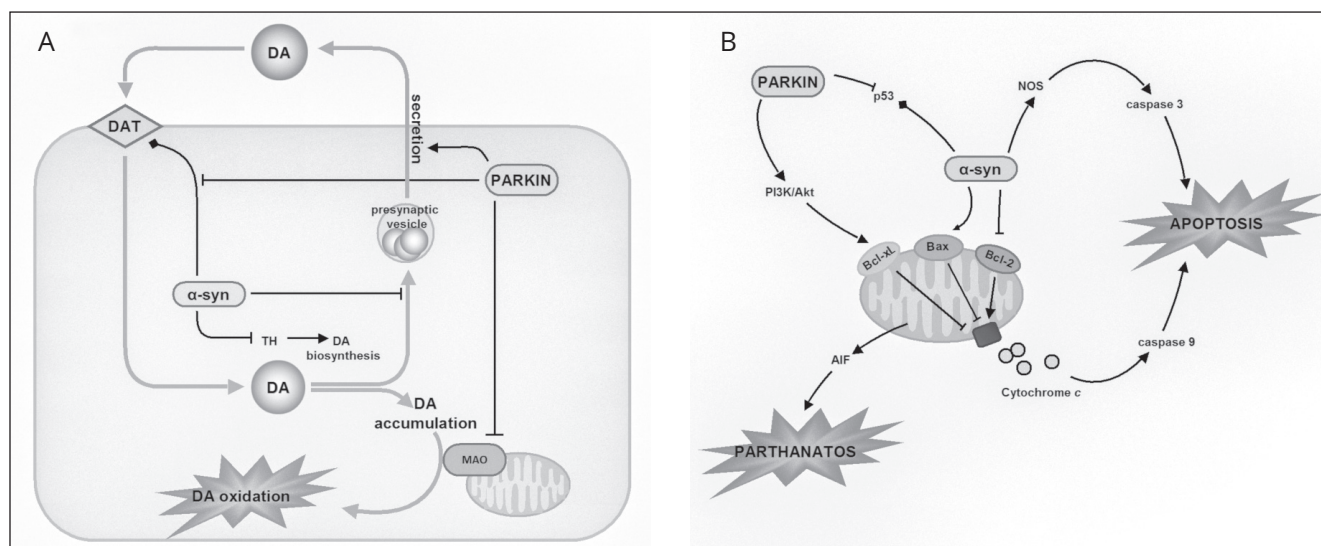


Fig. 2. Parkin and α-syn can affect dopamine neurotoxicity and selected pathways of programmed cell death signaling. (A) Both α-syn and parkin affect dopaminergic neurotransmission, although especially parkin's significance is poorly characterized. Parkin can prevent cytosolic DA accumulation, partially through inhibition of the complex influence of α-syn on dopamine transport. Parkin may also reduce dopamine oxidation by inhibiting monoamine oxidase (MAO). (B) Parkin's neuroprotective influence (largely exerted through PI3K/Akt signaling and through negative regulation of p53 expression) is disturbed in PD, underlying some of the neuronal susceptibility to death. In turn, α-syn has a more ambiguous influence on p53, and – depending on concentration – can inhibit anti-apoptotic Bcl-2 family proteins. α-syn accumulation may lead to the release of cytochrome c from mitochondria and activation of caspases, and/or to the release of AIF which can signal parthanatos, a cell death mode engaging chromatin-binding proteins normally associated with DNA repair. However, although links between parkin, α-syn, and the AIF release/parthanatos have been observed, their exact mechanism is unclear.

➡ stimulation of the expression or activity;

⊢ reduction of expression/inhibition of activity;

➡◆ ambiguous or changing interactions (positive or inhibitory influence depending on the concentration of the protein in question, cellular metabolic status, or biological model used).

tential loss of parkin activity contributes to α-syn neurotoxicity in the Parkinsonian brain.

## Parkin and α-syn degradation

The extensive network of redundant pathways that are capable of degrading α-syn highlights the importance of continuous control of α-syn concentration. Strikingly, parkin has been found to modulate the degradation of α-syn by multiple mechanisms.

α-syn is a substrate for parkin-mediated ubiquitination, and the UPS appears to be a major pathway of α-syn degradation (Jęśko et al., 2017). Whereas loss of parkin activity leads to accumulation of non-ubiquitinated forms of α-syn (Shimura et al., 2001), compounds that augment proteasomal α-syn degradation have beneficial neuroprotective effects and are considered to have a potential therapeutic application in PD (Jęśko et al., 2017; Li et al., 2018). However, accumulation and aggregation of α-syn can negatively affect UPS function, potentially leading to a runaway failure (Snyder et al., 2003). The mechanism and significance of α-syn level control by UPS still raise questions. For example, not all α-syn cleaved by proteasomes is ubiquitinated. In addition, the aforementioned incomplete cleavage of α-syn by a pathologically overloaded proteasome system may lead to the generation of α-syn fragments that are prone to aggregation (Liu et al., 2005).

α-syn is also degraded via the autophagic pathway. Indeed, PD-linked alterations in parkin lead to the accumulation of unprocessed α-syn in autophagosomes (Lonskaya et al., 2013). Similar to UPS, the potential of autophagy as a backup degradation pathway for α-syn is limited by its sensitivity to inhibition by accumulated or aggregated α-syn (Jęśko et al., 2017).

Parkin-activated cysteine protease calpain is also involved in degradation of α-syn (Kim et al., 2003). However, the ability of this cleavage mechanism to limit neurotoxic α-syn accumulation and/or aggregation is unclear (Beyer and Ariza, 2013).

## THE ROLE OF PARKIN IN THE MODULATION OF PATHWAYS MEDIATING A-SYNUCLEIN TOXICITY

Parkin's protective role against α-syn toxicity might involve multiple mechanisms besides direct interactions. Parkin can modify α-syn's influence on the DAergic system, potentially affecting the DA-mediated toxicity in PD; parkin also has a plethora of neuroprotective activities that might counteract more distant effects of α-syn-related pathology (Table I).

## Parkin and the α-syn – affected dopamine metabolism, transport, and secretion

α-syn has been shown to affect various aspects of DAergic signaling (Fig. 2A), including DA biosynthesis, release, and re-uptake. Parkin has also been shown to affect multiple α-syn-modulated steps of DA metabolism and transport, although the results are somewhat contradictory. For example, research shows that α-syn binds to and inhibits tyrosine hydroxylase (TH), the rate-limiting DA biosynthesis enzyme (Perez et al., 2002). In pathological conditions, α-syn alters DA synaptic homeostasis, including dopamine transporter (DAT) modification (Adamczyk et al., 2006, Moszczynska et al., 2007) and impairment of DA packaging into synaptic vesicles, which leads to cytosolic DA accumulation, DA oxidation, and cellular stress (Guo et al., 2008). Parkin appears to have an opposite influence on DA, as disruption of parkin function leads to cytosolic DA accumulation at the cost of packaging into vesicles (Itier et al., 2003). The role of parkin in DAT regulation is less characterized, although it is known that parkin can bind to DAT and prevent DAT's interaction with α-syn (Moszczynska et al., 2007). Consistent with this, reduced DAT levels have been detected in parkin-deficient mice (Itier et al., 2003) (see Fig. 2A and Table I).

## Parkin and the α-syn-induced oxidative and nitrosative stress

Although α-syn has been widely associated with the induction of oxidative stress, some results suggest that its physiological role might instead be linked to antioxidative defense (Deas et al., 2016; Jęśko et al., 2017). Interestingly, aggregation of α-syn appears to generate and be driven by free radicals. Indeed, previous research shows that hydroxyl radical (•OH) is produced in the course of *in vitro* α-syn aggregation in the presence of iron (II) (Turnbull et al., 2001), and that iron-induced α-syn aggregation can be blocked by the reactive oxygen species (ROS) scavenger vitamin E (Li et al., 2011). Reactive nitrogen species (RNS) and nitrosative stress have also been shown to contribute to Parkinsonian pathology (Gatto et al., 2000). Indeed, extracellular α-syn can open N-methyl-D-aspartate receptor (NMDAR) ion channels, which leads to $Ca^{2+}$ influx and activation of neuronal nitric oxide synthase (nNOS) in the rat brain (Adamczyk et al., 2009). Nitric oxide (NO) can react with superoxide to form the highly harmful peroxynitrite ($ONOO^-$), which damages proteins, lipids, and DNA. α-syn also contributes to the oxidative imbalance by depleting cellular glutathione levels and can also induce aggregation of superoxide dismutase protein. However, results

Table I. Mechanisms of α-syn neurotoxicity and their modulation by parkin.

| | Parkin | References | α-Syn | References |
|---|---|---|---|---|
| **Neurotransmission** | ↑ dopamine packaging into synaptic vesicles (VMAT) | Itier et al., 2003 | ↓ tyrosine hydroxylase activity | Perez et al., 2002 |
| | ↑ dopamine transporter level | Itier et al., 2003 | [?] dopamine re-uptake | Adamczyk et al., 2006; Moszczynska et al., 2007; |
| | ↓ dopamine transporter interaction with α-syn | Moszczynska et al., 2007 | ↓ vesicular monoamine transporter-2 activity | Guo et al., 2008 |
| **Oxidative / nitrosative and ER stress** | | | ↑ free radical generation during aggregation process | Turnbull et al., 2001 Li et al., 2011 |
| | ↓ oxidative stress ↓ MAO-A, MAO-B expression and activity | Itier et al., 2003 Jiang et al., 2006 Palacino et al., 2004 | ↑ NMDA receptor-dependent nitric oxide synthesis | Adamczyk et al., 2009 |
| | | | ↑ expression of inducible nitric oxide synthase in microglia | Su et al., 2008 |
| | ↓ ER stress signaling (Pael-R) | Imai et al., 2001 | ↑ ER stress | Xu et al., 2014 |
| | ↑ autophagic turnover of damaged macromolecules and organelles | Lonskaya et al., 2013 | ↓ proteasomal and autophagic protein degradation (especially mutated α-syn) | reviewed in Jęśko et al., 2017 |
| **Cytoskeleton, cellular transport** | ↓ α-syn – dependent (hyper)phosphorylation of microtubule associated proteins by GSK-3β, JNK, ERK, and p38 | Khandelwal et al., 2010; McLelland et al., 2018; Moussa, 2009; Ren et al., 2009 | ↑ GSK-3β activity, cytoskeleton destabilizagtion | Duka et al., 2009 Gąssowska et al., 2014 Khandelwal et al., 2010 |
| | | | ↓ cellular transport of organellae (overexpressed or mutant α-syn) | Xie and Chung, 2012 |
| **Mitochondria** | [?] mitochondrial fusion and fission depending on stress levels ↓ α-syn – induced mitochondrial fragmentation | Kamp et al., 2010 | ↑ mitochondrial fission, ↓ mitochondrial fusion and elongation | Kamp et al., 2010 Norris et al., 2015 |
| | ↑ neuronal respiration ↑ transcription of mitochondrial genes | Damiano et al., 2014 Palacino et al., 2004 Kuroda et al., 2006 Shin et al., 2011 | ↓ activity of transcription factors engaged in the expression of genes coding for mitochondrial proteins | Ryan et al., 2013 |
| | ↑ mitophagy, targeting damaged mitochondria for elimination | Ashrafi and Schwarz, 2015 Chan and Chan, 2011 Jin and Youle, 2013 Norris et al., 2015 | [?] mitophagy (overexpressed, mutant, or aggregated α-syn) | Choubey et al., 2011 Grassi et al., 2018 Martinez et al., 2018 Shaltouki et al., 2018 |
| **Cell death** | ↓ cell death *via* apoptosis and autophagy ↓ parthanatos? | Hwang et al., 2017; Lee et al., 2013; Lonskaya et al., 2013; Vercammen et al., 2006 | ↑ apoptosis ↑ autophagic cell death? ↑ parthanatos | Adamczyk et al., 2010 Desplats et al., 2009; Gómez-Santos et al., 2003; Kam et al., 2018; Venderova, Park 2012 |
| **Inflammation** | ↓ α-syn – dependent microglia activation | Khandelwal et al., 2010 | ↑ production of pro-inflammatory cytokines in microglia | Khandelwal et al., 2010; Su et al., 2008 |
| | ↓ nigral sensitivity to inflammation-related degeneration | Frank-Cannon et al., 2008 | | |

on these effects are inconsistent (Deas et al., 2016; Koo et al., 2013; Koch et al., 2016). Moreover, oxidized gluta-thione produced in the course of ROS detoxication can itself contribute to α-syn aggregation (Paik et al., 2003). In turn, oxidative or nitrosative stress may influence in-tracellular α-syn localization, function, and release into the extracellular space (Jang et al., 2010; Sangchot et al., 2002). Oxidative or nitrosative stress may also mediate cytotoxic outcomes of DA metabolism deregulation by α-syn (Riobó et al., 2002).

It has been suggested that parkin plays a neuropro-tective role against oxidative stress. Indeed, parkin-null mice have been shown to display increased vulnerabili-ty to oxidative stress (Palacino et al., 2004),  and parkin can suppress the expression and activity of MAO-A and -B, which generate ROS during DA oxidation (Itier et al., 2003; Jiang et al., 2006) (see Fig. 2A and Table I). Howev-er, parkin protein itself has been shown to be extremely sensitive to biochemical stressors. Indeed, oxidative con-ditions and DA toxicity can inhibit parkin, and induce its assembly into multimers that may be degraded via mac-roautophagy or the roteasome (Wang et al., 2005).

## Parkin, α-syn, endoplasmic reticulum (ER) stress, and the unfolded protein response

Parkin and α-syn have also been shown to have roughly opposite functions in the mechanism of ER stress and the unfolded protein response (see Table I). Whereas α-syn is considered to be necessary for ER stress-induced signaling via 78, 94-kDa glucose-regu-lated protein (GRP78/94), C/EBP homologous protein (CHOP), and caspase-12 (Xu et al., 2014), parkin pro-tects the cells against the unfolded protein-induced cell death by promoting degradation of parkin asso-ciated endothelin-like receptor (Pael-R) (Imai et al., 2001). Moreover, parkin has been shown to suppress degeneration of DA neurons induced by Pael-R toxicity (Yang et al., 2003).

## The protective role of parkin against α-syn-evoked microtubule destabilization

Microtubules are involved in the axonal transport of proteins and organelles. Microtubule disruption has been shown to inhibit neuronal activity, and may also lead to axonal accumulation of cargo normally trans-ported along the cytoskeleton, such as aggregated pro-teins (thereby boosting α-syn aggregation) or damaged mitochondria-containing autophagosomes (thus fur-ther deepening auto- or mitophagic dysfunction and mitochondrial deregulation) (Esteves et al., 2014).

Mitochondrial abnormalities observed in PD may lead to a lack of energy, which detrimentally affects the functioning of the microtubular cytoskeleton, for e.g., the molecular motors that transport the cargo (Esteves et al., 2014).

The role of α-syn in microtubule depolymerization and polymerization in nigral DAergic neurons has been studied by several groups. These studies have shown that α-syn binds to and is necessary for the activity of glycogen synthase kinase 3β (GSK-3β), a serine/thre-onine kinase that phosphorylates microtubule-associ-ated protein (MAP) Tau (Duka et al., 2009; Khandelwal et al., 2010). α-syn-dependent Tau hyperphosphorylation by GSK-3β results in destabilization of the cytoskeleton and impairment of cellular survival (Duka et al., 2009; Khandelwal et al., 2010; Gąssowska et al., 2014).

Research on a mutation in the parkin gene that re-sults in Tau hyperphosphorylation suggests that func-tional parkin deficits can trigger Tau pathology (Sán-chez et al., 2002). Indeed, parkin can decrease GSK-3β protein levels and attenuate the α-syn-evoked GSK-3β activation, Tau hyperphosphorylation, inflammation, and cell death (Moussa, 2009; Khandelwal et al., 2010) (see Table I). Parkin might also play a neuroprotective role by attenuating the activation of the MAP kinases c-Jun N-terminal kinase (JNK), extracellular signal-re-lated kinase (ERK), and p38 (Ren et al., 2009). Moreover, parkin has been shown to have a stabilizing effect on microtubules (Ren et al., 2009).

## Potential anti-inflammatory role of parkin

Inflammation has been shown to play an import-ant role in the progression of PD. Indeed, α-syn has been shown to act as an inflammatory stimulator that modulates microglial expression of proinflammato-ry cytokines, such as tumor necrosis factor α (TNF-α) and inducible NOS (iNOS) (Khandelwal et al., 2010; Su et al., 2008). Nitrosative and oxidative stress has been observed in cells overexpressing or treated with α-syn (Wilkaniec et al., 2019). α-syn may exert its effects in part through the NF-κB pathway, which is crucially en-gaged in inflammatory signaling (Yuan et al., 2008).

It has been suggested that parkin plays a protective role against inflammatory responses evoked by α-syn (Table I). Indeed, research shows enhanced inflamma-tory damage in parkin knock-out mice (Frank-Cannon et al., 2008), whereas virally expressed parkin signifi-cantly reversed the effect of α-syn on glial number and morphology, and reduced the up-regulation of TNF-α and iNOS (Khandelwal et al., 2010). It has been pro-posed that the neuroprotective effects of parkin de-pend on the NF-κB pathway (Henn et al., 2007). Howev-

er, α-syn-induced stress can lead to S-nitrosylation and degradation of parkin (Wilkaniec et al., 2019).

## Parkin and α-syn in the regulation of apoptosis, autophagy, and parthanatos

Neuronal death in PD involves elevated apoptotic effectors, including caspase-1, -3, -8, and -9 (Hartmann et al., 2000; 2001; Mogi et al., 2000). α-syn has been shown to trigger down-regulation of the anti-apoptotic protein Bcl-2, which leads to cytochrome *c* release and apoptotic cell death via caspases 3 and 9 (Adamczyk et al.,2010; Yuan et al., 2008; Liu et al., 2011) (Fig. 2B). α-syn also has complex impact on the expression and activity of p53 (Martin et al., 2006; da Costa et al., 2009). However, in some circumstances, α-syn might protect against cell death, for e.g., through the aforementioned prevention of DA accumulation and oxidation following parkin knockdown (Machida et al., 2005).

The role of both α-syn and parkin on the PI3K-Akt/PKB pathway has been incompletely characterized to-date. The PI3K-Akt/PKB pathway is a highly interconnected modulator of cellular metabolism and survival and death through, for e.g., NF-κB, GSK-3β, Forkhead family transcription factors, Bad, or caspase-9. Parkin supports pro-survival PI3K-Akt signaling (Fallon et al., 2006) whereas α-syn has a more complex role. Nanomolar α-syn activates PI3K-Akt whereas micromolar α-syn has been shown to exert opposite effects, including reduction of Bcl-xL expression, up-regulation of Bax, and inducing the release of cytochrome *c* from mitochondria (Seo et al., 2002). Based on these data, it is highly probable that the fine-tuned activities of α-syn in this context may be successfully modified by the documented interactions with parkin.

Autophagy as a cell death mechanism also appears to be involved in PD (Venderova and Park, 2012). Indeed, α-syn has been shown to be involved in autophagosome regulation by negatively affecting early stages of autophagosome formation. These data suggest that a *loss-of-function* mechanism might be involved in PD pathogenesis (Winslow and Rubinsztein, 2011).

Parthanatos is a relatively recently characterized mode of cell death that was named after PAR, poly(ADP-ribose) and Thanatos. Parthanatos involves proteins that are typically engaged in DNA repair, including poly(ADP-ribose) polymerase (PARP1) or 8-oxoG glycosylase1 (OGG1), These proteins lead to PAR-mediated signaling from the nucleus to the mitochondria, triggering release of apoptosis-inducing factor (AIF), chromatin condensation and large scale fragmentation, and ultimately, cell death. Parthanatos seems to be significantly involved in PD and MPTP-induced models of PD (Lee et al., 2014). α-syn is known to interact with AIF signaling (Zhu et al., 2011) and has been shown to interact bi-directionally with PARP-1 signaling, although the topic requires further research (Adamczyk et al., 2005a; Adamczyk and Kaźmierczak, 2009; Chiba-Falek et al., 2005; Outeiro et al., 2007).

Several reports indicate that parkin protects against autophagic and apoptotic cell death in DA neurons (Hwang et al., 2017; Vercammen et al., 2006). In addition, loss of parkin due to decreased solubility in PD or genetic ablation in animal models leads to increased susceptibility of neurons to apoptosis (Vercammen et al., 2006; Lonskaya et al., 2013) (see Table I). However, parkin has also been shown to support neuroprotective autophagy of proteins and damaged organelles (Khan et al., 2017; Lonskaya et al., 2013). This neuroprotective has been shown to involve parkin's physical interaction with the p53 promoter, which leads to down-regulation of p53 mRNA and p53-dependent signaling. PD-linked parkin mutations abolish this interaction (da Costa et al., 2009). Parkin may also exert its anti-apoptotic functions through the aforementioned regulation of pro-survival Akt signaling (Fallon et al., 2006; Hasegawa et al., 2008).

## Defining roles of parkin and α-syn in mitochondrial remodeling and dynamics

To uphold the pool of bioenergetically competent mitochondria, the 'life cycle' of mitochondria must pass through the stages of biogenesis, remodeling via repeated cycles of fusion/fission, and mitophagy (see Fig. 3). Although the mechanistic details of the neuroprotective mechanism behind fusion/fission remain obscure, it has been hypothesized that fission could improve mitochondrial quality through asymmetric segregation of faulty proteins into one daughter organelle. Fusion, in contrast might allow for complementation of the best components from the two original mitochondria (Scarffe et al., 2014).

Overexpression of wildtype (wt) or mutant α-syn has been shown to promote neuronal cell death via mitochondrial dysfunction and fragmentation (Kamp et al., 2010; Zhu et al., 2011). α-syn is an inhibitor of membrane fusion and knockdown of α-syn has been shown to promote mitochondrial elongation (Norris et al., 2015). Interestingly, mitochondrial fragmentation evoked by α-syn overexpression can be rescued by co-expression of parkin, PINK1, or DJ-1, suggesting that α-syn and parkin may take part in the same pathway (as described below) (Kamp et al., 2010). Recently, it was also indicated that α-syn accumulation or the α-syn A53T mutation leads to inhibition of mitochondrial motility (Xie and Chung, 2012).

Parkin also appears to be an essential component of the quality control system in the mitochondria (Venderova and Park, 2012), and inactivation of parkin leads to reduced striatal neuron respiration and oxidative damage (Damiano et al., 2014; Palacino et al., 2004). Parkin has been shown to regulate multiple aspects of the mitochondrial life cycle, from biogenesis to mitophagy (Lim et al., 2012) (see also Table I). These regulatory effects are described below:

- Parkin enhances transcription of mitochondrial DNA (mtDNA) via its negative influence on the transcription modulator, parkin interacting substrate (PARIS). Loss of parkin activity in PD leads to the accumulation of PARIS and inhibition of its target peroxisome, proliferator-activated receptor gamma-coactivator 1α (PGC1-α) (Kuroda et al., 2006; Shin et al., 2011). Down-regulation of PGC1-α has been shown to increase risk of PD (Zheng et al., 2010) whereas parkin appears to prevent against the drop of PGC1-α level, thus augmenting mitochondrial biosynthesis. α-syn can also signal through PGC1-α; indeed, α-syn has been shown to reduce mitochondrial biogenesis through increased transcription factor oxidation and S-nitrosylation (Ryan et al., 2013). Preservation of PGC-1α levels through maintenance of parkin activity or reduction of PARIS neurotoxicity have been proposed as therapeutic strategies in PD (Dawson and Dawson, 2014).

- Parkin regulates mitochondrial fusion, fission, and mitophagy in a manner that depends on cellular condition. In physiological conditions, parkin can inhibit fusion-promoting Mfn family proteins and the fission-related Drp1. Under moderate mitochondrial stress, parkin may play a fusion-promoting role that allows the repair of damaged organelles while counteracting fission. Of note, fission occurs intensely in parkin-deficient cells in response to mitochondrial toxins (Norris et al., 2015). In contrast, heavily damaged mitochondria trigger its mitophagy-promoting activity (Norris et al., 2015).

- Parkin may also play an essential role in intracellular transport of mitochondria through regulation of proteins of the axonal and dendritic trafficking machinery, including Miro1 (McLelland et al., 2018).

Impaired clearance of damaged mitochondria may be one of the triggers causing demise of DAergic neurons in PD brain. Post-mitotic neurons have fewer opportunities to remove defective mitochondria than cycling cells, and at the same time, post-mitotic neurons have extreme energy demands, making them more vulnerable to disturbances. Previous studies confirm accumulation of defective mitochondria PD patients (de Vries and Przedborski, 2013).

Mitophagy is a subtype of lysosome-mediated autophagy that is required to clear damaged mitochondria. Research shows that many genes linked to PD are engaged in the regulation of mitophagy (Ryan et al., 2015). Disturbed or delayed mitophagy in the presence of accumulated α-syn may be an essential mediator of α-syn toxicity and thus represent a pathological mechanism leading to PD (Shaltouki et al.,2018). Other research demonstrates enhanced mitophagy in a cell line that overexpresses α-syn (Martinez et al., 2018); in particular, in midbrain DAergic neurons transfected with A53T α-syn (which, in that case, leads to cell death) (Choubey et al., 2011). Mitophagy was also found to be stimulated by nonfibrillar, phosphorylated α-syn aggregates found in the neurons of PD patient brains (Grassi et al.,2018). The role of α-syn in autophagy of mitochondria is therefore unclear, and its disease-associated molecular alterations appear to autophagy profoundly.

Interestingly, under exposure to the mitochondrial toxin, parkin, together with E2 conjugating enzyme Ubc13 has been shown to stimulate K63-linked α-syn
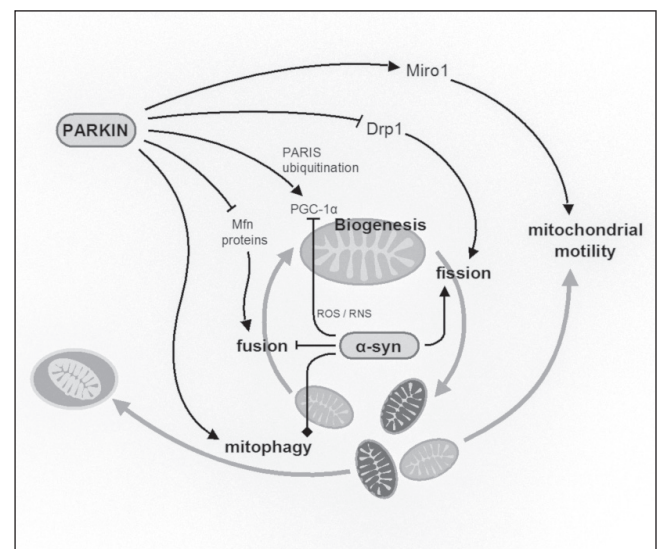


Fig. 3. Involvement of parkin and α-syn in the mitochondrial 'life cycle'. Mitochondrial 'life cycle' involves their biogenesis, remodeling through repeated rounds of fusion/fission, and mitophagy. It is suggested that parkin causes ubiquitination and degradation of the PARIS protein, removing its negative influence on the levels of PGC-1α; thus, parkin leads to elevated PGC-1α, increased replication of mtDNA, and intensified mitochondrial biogenesis. Moreover, depending on the state of cellular metabolism parkin may upregulate mitochondrial motility and mitophagy through interaction with Miro-1 and autophagolysosomal proteins, respectively. α-syn – evoked oxidative/nitrosative stress downregulates de novo mitochondrial biogenesis. α-syn also supports mitochondrial fission, inhibits fusion, and can influence mitophagy leading to accumulation of damaged mitochondria and cell death.

→  stimulation of the expression or activity;

⊣  reduction of expression/inhibition of activity;

⇒  ambiguous or changing influence.

ubiquitination. The observed effect of parkin on mitochondrial turnover can be phenocopied by α-syn-targeting siRNA (Norris et al., 2015). Parkin itself has been shown to play an essential role in removing damaged mitochondria from the cell via mitophagy, including local liquidation of mitochondria in the axon, which has direct relevance for neuronal activity (Ashrafi and Schwarz, 2015; Chan and Chan, 2011). Mitochondria that accumulate misfolded proteins in the matrix can trigger the translocation of parkin, which activates subsequent removal (Jin and Youle, 2013) (Fig. 3).

## THE RECIPROCAL INFLUENCE OF A-SYN ON PARKIN, AND A-SYN-PARKIN CO-REGULATION

α-syn appears to modify parkin's ubiquitination activity and function by binding to parkin and shifts parkin's activity towards K63-linked ubiquitination. α-syn's modification of parkin stimulates mitochondrial fusion, and this interaction occurs in response to mild mitochondrial stress (Norris et al., 2015). α-syn can also modify the phosphorylation state of parkin, given that overexpression of A53T α-syn has been shown to leads to parkin modification by p38MAPK. Modification of parkin, in turn, reduces its cytoprotective influence on mitochondrial turnover (Chen et al., 2018).

A recent study by Liu et al. (2019) described another mechanism linking deregulation of parkin with α-syn in PD. In this work, Liu et al. (2019) found an upregulation of ubiquitin-specific protease USP13 in Parkinsonian brains. USP13 removes ubiquitin from proteins, and thus, USP13 is able to reduce α-syn-induced parkin ubiquitination. Likewise, USP13 de-ubiquitinated α-syn, and a USP13 knockdown has been shown to facilitate the ubiquitination and removal of α-syn. However, the observed effect on α-syn ubiquitination was shown to be independent of parkin (Liu et al., 2019).

## CONCLUSIONS

Parkin is extensively engaged in protein degradation pathways, and as such may offer significant therapeutic potential. α-syn levels may be controlled by parkin-dependent proteasomal degradation. Parkin also appears to modulate autophagic degradation of α-syn, as well as, control calpain, an α-syn-degrading enzyme. All of these pathways are shown to be disturbed in PD, at least partially due to parkin's sensitivity to α-syn-induced stress. In-depth understanding of this mechanism is a necessary aspect of PD characterization and may lead to identification of new therapeutic opportunities. Parkin and α-syn mutually regulate their own post-translational modifications. This relatively easy to manipulate mechanism influences the neuroprotective activity of parkin and the tendency of α-syn to aggregate, thus offering important insights into pathophysiological mechanisms leading to PD and potential therapeutic value. Importantly, α-syn also alters parkin levels and activity (Wilkaniec et al., 2019), potentially creating a cycle of self-fueling pathology.

The multiple neuroprotective functions of parkin raise hopes that, in addition to modulating α-syn behavior, parkin may also alter the downstream effects of α-syn neurotoxicity. Effects on α-syn neurotoxicity may allow for a more established and/or easier to implement avenue for therapeutic intervention. A promising aspect of parkin's role in the cell is linked to its engagement in mitochondrial turnover and/or quality maintenance, and in cytoskeletal functions. These functions are particularly important in neuronal cells, which are extremely dependent on efficient oxidative metabolism, and efficient maintenance of intracellular transport. In line with this, mitochondrial metabolism is known to be compromised in neurodegenerative disorders. Moreover, parkin may influence multiple steps of DA turnover, preventing its intracellular accumulation, oxidation-mediated toxicity, and moderating other mechanisms of cellular stress. Parkin can also modulate cell survival signaling and inhibit apoptotic and autophagic cell death, and parthanatos. Neuronal death is a relatively distant effect of the partially obscure processes that lead to the development of PD. However, as only symptomatic treatments are currently available for neurodegenerative disorders, interventions that are capable of preserving neuronal populations in affected brain regions would be of extreme value in the struggle against PD.

Recent progress in the understanding of parkin and α-syn dysfunction provide hope for the discovery of new therapeutic approaches for synucleinopathies. Research addressing practical aspects of the restoration of parkin activity primarily concentrate on:

• Compounds that stimulate parkin activity and/or its recruitment to impaired mitochondria or small molecules that mimic phospho-ubiquitin action or mimic the effects of PINK1-dependent parkin phosphorylation (Kazlauskaite et al., 2014). Hydrogen sulfide donors may be another therapeutic approach, as sulfhydration enhances parkin E3 ligase activity (Vandiver et al., 2013).

• Anti-oxidative compounds such as creatine, coenzyme Q10, resveratrol, and uric acid have been tested in PD (Chaturvedi and Beal, 2013; Ferretta et al., 2014; Jin et al., 2014), given that oxidative and nitrosative stress has been shown to decrease parkin solubility, thus impairing its function (Wang et al., 2005).

# ACKNOWLEDGMENTS

# REFERENCES

Adamczyk A, Czapski GA, Jeśko H, Stroszmajder RP (2005a) Non A beta component of Alzheimer's disease amyloid and amyloid beta peptides evoked poly(ADP-ribose) polymerase-dependent release of apoptosis-inducing factor from rat brain mitochondria. J Physiol Pharmacol 56: 5–13.

Adamczyk A, Czapski GA, Kaźmierczak A, Stroszmajder JB (2009) Effect of N-methyl-D-aspartate (NMDA) receptor antagonists on alpha-synuclein-evoked neuronal nitric oxide synthase activation in the rat brain. Pharmacol Rep 61: 1078–1085.

Adamczyk A, Kaźmierczak A (2009) Alpha-synuclein inhibits poly (ADP-ribose) polymerase-1 (PARP-1) activity via NO-dependent pathway. Folia Neuropathol 47: 247–251.

Adamczyk A, Kaźmierczak A, Czapski GA, Stroszmajder JB (2010) Alpha-synuclein induced cell death in mouse hippocampal (HT22) cells is mediated by nitric oxide-dependent activation of caspase-3. FEBS Lett 584: 3504–3508.

Adamczyk A, Kaźmierczak A, Stroszmajder JB (2006) Alpha-synuclein and its neurotoxic fragment inhibit dopamine uptake into rat striatal synaptosomes. Relationship to nitric oxide. Neurochem Int 49: 407–412.

Adamczyk A, Solecka J, Stroszmajder JB (2005b) Expression of alpha-synuclein in different brain parts of adult and aged rats. J Physiol Pharmacol 56: 29–37.

Allen Reish HE, Standaert DG (2015) Role of α-synuclein in inducing innate and adaptive immunity in Parkinson disease. J Parkinsons Dis 5: 1–19.

Ashrafi G, Schwarz TL (2015) PINK1- and PARK2-mediated local mitophagy in distal neuronal axons. Autophagy 11: 187–189.

Beyer K, Ariza A (2013) α-Synuclein posttranslational modification and alternative splicing as a trigger for neurodegeneration. Mol Neurobiol 47: 509–524.

Chakraborty J, Basso V, Ziviani E (2017) Post translational modification of Parkin. Biol Direct 12: 6.

Chan NC, Chan DC (2011) Parkin uses the UPS to ship off dysfunctional mitochondria. Autophagy 7: 771–772.

Chaturvedi RK, Beal MF (2013) Mitochondria targeted therapeutic approaches in Parkinson's and Huntington's diseases. Mol Cell Neurosci 55: 101–14.

Chen J, Ren Y, Gui C, Zhao M, Wu X, Mao K, Li W, Zou F (2018) Phosphorylation of Parkin at serine 131 by p38 MAPK promotes mitochondrial dysfunction and neuronal death in mutant A53T α-synuclein model of Parkinson's disease. Cell Death Dis 9: 700.

Chiba-Falek O, Kowalak JA, Smulson ME, Nussbaum RL (2005) Regulation of alpha-synuclein expression by poly (ADP ribose) polymerase-1 (PARP-1) binding to the NACP-Rep1 polymorphic site upstream of the SNCA gene. Am J Hum Genet 76: 478–92.

Choubey V, Safiulina D, Vaarmann A, Cagalinec M, Wareski P, Kuum M, Zharkovsky A, Kaasik A (2011) Mutant A53T alpha-synuclein induces neuronal death by increasing mitochondrial autophagy. J Biol Chem 286: 10814–10824.

Chung KK, Zhang Y, Lim KL, Tanaka Y, Huang H, Gao J, Ross CA, Dawson VL, Dawson TM (2001) Parkin ubiquitinates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. Nat Med 7: 1144–1150.

Coppedè F (2012) Genetics and epigenetics of Parkinson's disease. ScientificWorldJournal 2012: 489830.

Costa CA da, Sunyach C, Giaime E, West A, Corti O, Brice A, Safe S, Abou-Sleiman PM, Wood NW, Takahashi H, Goldberg MS, Shen J, et al. (2009) Transcriptional repression of p53 by parkin and impairment by mutations associated with autosomal recessive juvenile Parkinson's disease. Nat Cell Biol 11: 1370–3175.

Czapski GA, Gąssowska M, Wilkaniec A, Cieślik M, Adamczyk A (2013) Extracellular alpha-synuclein induces calpain-dependent overactivation of cyclin-dependent kinase 5 in vitro. FEBS Lett 587: 3135–3141.

Damiano M, Gautier CA, Bulteau A-L, Ferrando-Miguel R, Gouarne C, Paoli MG, Pruss R, Auchère F, L'Hermitte-Stead C, Bouillaud F, Brice A, Corti O, Lombès A (2014) Tissue- and cell-specific mitochondrial defect in Parkin-deficient mice. PLoS One 9: e99898.

Danielson SR, Held JM, Schilling B, Oo M, Gibson BW, Andersen JK (2009) Preferentially increased nitration of alpha-synuclein at tyrosine-39 in a cellular oxidative model of Parkinson's disease. Anal Chem 81: 7823–7828.

Dawson TM, Dawson VL (2014) Parkin plays a role in sporadic Parkinson's disease. Neurodegener Dis 13: 69–71.

Deas E, Cremades N, Angelova PR, Ludtmann MHR, Yao Z, Chen S, Horrocks MH, Banushi B, Little D, Devine MJ, Gissen P, Klenerman D, Dobson CM, Wood NW, Gandhi S, Abramov AY (2016) Alpha-synuclein oligomers interact with metal ions to induce oxidative stress and neuronal death in Parkinson's disease. Antioxid Redox Signal 24: 376–391.

Desplats P, Lee HJ, Bae EJ, Patrick C, Rockenstein E, Crews L, Spencer B, Masliah E, Lee SJ (2009) Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. Proc Natl Acad Sci 106: 13010–13015.

de Vries RLA, Przedborski S (2013) Mitophagy and Parkinson's disease: Be eaten to stay healthy. Mol Cell Neurosci 55: 37–43.

Duka T, Duka V, Joyce JN, Sidhu A (2009) Alpha-Synuclein contributes to GSK-3beta-catalyzed Tau phosphorylation in Parkinson's disease models. FASEB J 23: 2820–2830.

Duplan E, Sevalle J, Viotti J, Goiran T, Bauer C, Renbaum P, Levy-Lahad E, Gautier CA, Corti O, Leroudier N, Checler F, Costa CA da (2013) Parkin differently regulates presenilin-1 and presenilin-2 functions by direct control of their promoter transcription. J Mol Cell Biol 5: 132–142.

Esteves AR, Gozes I, Cardoso SM (2014) The rescue of microtubule-dependent traffic recovers mitochondrial function in Parkinson's disease. Biochim Biophys Acta 1842: 7–21.

Fallon L, Bélanger CML, Corera AT, Kontogiannea M, Regan-Klapisz E, Moreau F, Voortman J, Haber M, Rouleau G, Thorarinsdottir T, Brice A, van Bergen En Henegouwen PMP, Fon EA (2006) A regulated interaction with the UIM protein Eps15 implicates parkin in EGF receptor trafficking and PI(3)K-Akt signalling. Nat Cell Biol 8: 834–842.

Farrer M, Kachergus J, Forno L, Lincoln S, Wang D-S, Hulihan M, Maraganore D, Gwinn-Hardy K, Wszolek Z, Dickson D, Langston JW (2004) Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. Ann Neurol 55: 174–179.

Farrer M, Wavrant-De Vrieze F, Crook R, Boles L, Perez-Tur J, Hardy J, Johnson WG, Steele J, Maraganore D, Gwinn K, Lynch T (1998) Low frequency of α-synuclein mutations in familial Parkinson's disease. Ann Neurol 43: 394–397.

Ferretta A, Gaballo A, Tanzarella P, Piccoli C, Capitanio N, Nico B, Annese T, Paola M Di, Dell'aquila C, Mari M De, Ferranini E, Bonifati V, et al. (2014) Effect of resveratrol on mitochondrial function: implications in parkin-associated familiar Parkinson's disease. Biochim Biophys Acta 1842: 902–915.

Frank-Cannon TC, Tran T, Ruhn KA, Martinez TN, Hong J, Marvin M, Hartley M, Treviño I, O'Brien DE, Casey B, Goldberg MS, Tansey MG (2008) Parkin deficiency increases vulnerability to inflammation-related nigral degeneration. J Neurosci 28: 10825–10834.

Gąssowska M, Czapski GA, Pająk B, Cieślik M, Lenkiewicz AM, Adamczyk A (2014) Extracellular α-synuclein leads to microtubule destabilization via GSK-3β-dependent Tau phosphorylation in PC12 cells. PLoS One 9: e94259.

Gatto EM, Riobó NA, Carreras MC, Cherñavsky A, Rubio A, Satz ML, Poderoso JJ (2000) Overexpression of neutrophil neuronal nitric oxide synthase in Parkinson's disease. Nitric oxide 4: 534–539.

Geisler S, Holmström KM, Treis A, Skujat D, Weber SS, Fiesel FC, Kahle PJ, Springer W (2010) The PINK1/Parkin-mediated mitophagy is compromised by PD-associated mutations. Autophagy 6: 871–878.

Geldenhuys WJ, Abdelmagid SM, Gallegos PJ, Safadi FF (2014) Parkinson's disease biomarker: a patent evaluation of WO2013153386. Expert Opin Ther Pat 24: 947–951.

Gentile A, Amadoro G, Corsetti V, Ciotti MT, Serafino A, Calissano P (2008) Spontaneous aggregation and altered intracellular distribution of endogenous alpha-synuclein during neuronal apoptosis. J Alzheimers Dis 13: 151–160.

Giasson BI, Duda JE, Murray I V, Chen Q, Souza JM, Hurtig HI, Ischiropoulos H, Trojanowski JQ, Lee VM (2000) Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. Science 290: 985–989.

Giguère N, Pacelli C, Saumure C, Bourque M-J, Matheoud D, Levesque D, Slack RS, Park DS, Trudeau LÉ (2018) Comparative analysis of Parkinson's disease–associated genes in mice reveals altered survival and bioenergetics of Parkin-deficient dopamine neurons. J Biol Chem 293: 9580–9593.

Goers J, Manning-Bog AB, McCormack AL, Millett IS, Doniach S, Di Monte DA, Uversky VN, Fink AL (2003) Nuclear localization of alpha-synuclein and its interaction with histones. Biochemistry. 42: 8465–8471.

Gómez-Santos C, Ferrer I, Santidrián AF, Barrachina M, Gil J, Ambrosio S (2003) Dopamine induces autophagic cell death and alpha-synuclein increase in human neuroblastoma SH-SY5Y cells. J Neurosci Res. 73: 341–350.

Grassi D, Howard S, Zhou M, Diaz-Perez N, Urban NT, Guerrero-Given D, Kamasawa N, Volpicelli-Daley LA, LoGrasso P, Lasmézas CI (2018) Identification of a highly neurotoxic α-synuclein species inducing mitochondrial damage and mitophagy in Parkinson's disease. Proc Natl Acad Sci 115: E2634–2643.

Guo JT, Chen AQ, Kong Q, Zhu H, Ma CM, Qin C (2008) Inhibition of vesicular monoamine transporter-2 activity in alpha-synuclein stably transfected SH-SY5Y cells. Cell Mol Neurobiol 28: 35–47.

Hartmann A, Hunot S, Michel PP, Muriel MP, Vyas S, Faucheux BA, Mouatt-Prigent A, Turmel H, Srinivasan A, Ruberg M, Evan GI, Agid Y, et al. (2000) Caspase-3: A vulnerability factor and final effector in apoptotic death of dopaminergic neurons in Parkinson's disease. Proc Natl Acad Sci 97: 2875–2880.

Hartmann A, Troadec JD, Hunot S, Kikly K, Faucheux BA, Mouatt-Prigent A, Ruberg M, Agid Y, Hirsch EC (2001) Caspase-8 is an effector in apoptotic death of dopaminergic neurons in Parkinson's disease, but pathway inhibition results in neuronal necrosis. J Neurosci 21: 2247–2255.

Hasegawa T, Treis A, Patenge N, Fiesel FC, Springer W, Kahle PJ (2008) Parkin protects against tyrosinase-mediated dopamine neurotoxicity by suppressing stress-activated protein kinase pathways. J Neurochem 105: 1700–1715.

Henn IH, Bouman L, Schlehe JS, Schlierf A, Schramm JE, Wegener E, Nakaso K, Culmsee C, Berninger B, Krappmann D, Tatzelt J, Winklhofer KF (2007) Parkin mediates neuroprotection through activation of IkappaB kinase/nuclear factor-kappaB signaling. J Neurosci 27: 1868–1878.

Hertz NT, Berthet A, Sos ML, Thorn KS, Burlingame AL, Nakamura K, Shokat KM (2013) A neo-substrate that amplifies catalytic activity of parkinson's-disease-related kinase PINK1. Cell 154: 737–747.

Hwang CJ, Kim YE, Son DJ, Park MH, Choi D-Y, Park P-H, Hellström M, Han SB, Oh KW, Park EK, Hong JT (2017) Parkin deficiency exacerbate ethanol-induced dopaminergic neurodegeneration by P38 pathway dependent inhibition of autophagy and mitochondrial function. Redox Biol 11: 456–468.

Imai Y, Soda M, Inoue H, Hattori N, Mizuno Y, Takahashi R (2001) An unfolded putative transmembrane polypeptide, which can lead to endoplasmic reticulum stress, is a substrate of Parkin. Cell 105: 891–902.

Itier J-M, Ibanez P, Mena MA, Abbas N, Cohen-Salmon C, Bohme GA, Laville M, Pratt J, Corti O, Pradier L, Ret G, Joubert C, et al. (2003) Parkin gene inactivation alters behaviour and dopamine neurotransmission in the mouse. Hum Mol Genet 12: 2277–2291.

Jang A, Lee HJ, Suk JE, Jung JW, Kim KP, Lee SJ (2010) Non-classical exocytosis of alpha-synuclein is sensitive to folding states and promoted under stress conditions. J Neurochem 113: 1263–1274.

Jęśko H, Lenkiewicz AM, Adamczyk A (2017) Treatments and compositions targeting α-synuclein: a patent review (2010–2016). Expert Opin Ther Pat 27: 427–438.

Jiang H, Jiang Q, Liu W, Feng J (2006) Parkin Suppresses the Expression of Monoamine Oxidases. J Biol Chem 281: 8591–8599.

Jiang H, Ren Y, Yuen EY, Zhong P, Ghaedi M, Hu Z, Azabdaftari G, Nakaso K, Yan Z, Feng J (2012) Parkin controls dopamine utilization in human midbrain dopaminergic neurons derived from induced pluripotent stem cells. Nat Commun 3: 668.

Jin H, Kanthasamy A, Ghosh A, Anantharam V, Kalyanaraman B, Kanthasamy AG (2014) Mitochondria-targeted antioxidants for treatment of Parkinson's disease: preclinical and clinical outcomes. Biochim Biophys Acta 1842: 1282–1294.

Jin SM, Youle RJ (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.

Kam TI, Mao X, Park H, Chou SC, Karuppagounder SS, Umanah GE, Yun SP, Brahmachari S, Panicker N, Chen R, Andrabi SA, Qi C, Poirier GG, Pletnikova O, Troncoso JC, Bekris LM, Leverenz JB, Pantelyat A, Ko HS, Rosenthal LS, Dawson TM, Dawson VL (2018) Poly(ADP-ribose) drives pathologic α-synuclein neurodegeneration in Parkinson's disease. Science 362: pii: eaat8407.

Kamp F, Exner N, Lutz AK, Wender N, Hegermann J, Brunner B, Nuscher B, Bartels T, Giese A, Beyer K, Eimer S, Winklhofer KF, et al. (2010) Inhibition of mitochondrial fusion by α-synuclein is rescued by PINK1, Parkin and DJ-1. EMBO J 29: 3571–3589.

Kazlauskaite A, Kondapalli C, Gourlay R, Campbell DG, Ritorto MS, Hofmann K, Alessi DR, Knebel A, Trost M, Muqit MMK (2014) Parkin is activated by PINK1-dependent phosphorylation of ubiquitin at Ser[65]. Biochem J 460: 127–141.

Khan SH, Zhao D, Shah SZA, Hassan MF, Zhu T, Song Z, Zhou X, Yang L (2017) Parkin overexpression ameliorates PrP106–126-induced neurotoxicity via enhanced autophagy in N2a cells. Cell Mol Neurobiol 37: 717–728.

Khandelwal PJ, Dumanis SB, Feng LR, Maguire-Zeiss K, Rebeck G, Lashuel HA, Moussa CE (2010) Parkinson-related parkin reduces α-Synuclein phosphorylation in a gene transfer model. Mol Neurodegen 5: 47.

Kim SJ, Sung JY, Um JW, Hattori N, Mizuno Y, Tanaka K, Paik SR, Kim J, Chung KC (2003) Parkin cleaves intracellular alpha-synuclein inclusions via the activation of calpain. J Biol Chem 278: 41890–41899.

Koch Y, Helferich AM, Steinacker P, Oeckl P, Walther P, Weishaupt JH, Danzer KM, Otto M (2016) Aggregated α-Synuclein Increases SOD1 Oligomerization in a Mouse Model of Amyotrophic Lateral Sclerosis. Am J Pathol 186: 2152–2161.

Koo HJ, Yang JE, Park JH, Paik SR (2013) α-Synuclein-mediated defense against oxidative stress via modulation of glutathione peroxidase. Biochim Biophys Acta 1834: 972–976.

Kuroda Y, Mitsui T, Kunishige M, Shono M, Akaike M, Azuma H, Matsumoto T (2006) Parkin enhances mitochondrial biogenesis in proliferating cells. Hum Mol Genet 15: 883–895.

LaVoie MJ, Ostaszewski BL, Weihofen A, Schlossmacher MG, Selkoe DJ (2005) Dopamine covalently modifies and functionally inactivates parkin. Nat Med 11: 1214–1221.

Lee Y, Karuppagounder SS, Shin JH, Lee YI, Ko HS, Swing D, Jiang H, Kang SU, Lee BD, Kang HC, Kim D, Tessarollo L, Dawson VL, Dawson TM (2013) Parthanatos mediates AIMP2-activated age-dependent dopaminergic neuronal loss. Nat Neurosci 16: 1392–1400.

Lee Y, Kang HC, Lee BD, Lee Y-I, Kim YP, Shin J-H (2014) Poly (ADP-ribose) in the pathogenesis of Parkinson's disease. BMB Rep 47: 424–432.

Leong SL, Pham CLL, Galatis D, Fodero-Tavoletti MT, Perez K, Hill AF, Masters CL, Ali FE, Barnham KJ, Cappai R (2009) Formation of dopa-

mine-mediated alpha-synuclein-soluble oligomers requires methionine oxidation. Free Radic Biol Med 46: 1328–1337.

Lewis KA, Su Y, Jou O, Ritchie C, Foong C, Hynan LS, White CL, Thomas PJ, Hatanpaa KJ (2010) Abnormal neurites containing C-terminally truncated alpha-synuclein are present in Alzheimer's disease without conventional Lewy body pathology. Am J Pathol 177: 3037–3050.

Li T, Feng Y, Yang R, Wu L, Li R, Huang L, Yang Q, Chen J (2018) Salidroside Promotes the Pathological α-Synuclein Clearance Through Ubiquitin-Proteasome System in SH-SY5Y Cells. Front Pharmacol 9: 377.

Li W, Jiang H, Song N, Xie J (2011) Oxidative stress partially contributes to iron-induced α-synuclein aggregation in SK-N-SH cells. Neurotox Res 19: 435–442.

Lim KL, Ng XH, Grace LGY, Yao TP (2012) Mitochondrial dynamics and Parkinson's disease: focus on parkin. Antioxid Redox Signal 16: 935–949.

Liu CW, Giasson BI, Lewis KA, Lee VM, Demartino GN, Thomas PJ (2005) A precipitating role for truncated alpha-synuclein and the proteasome in alpha-synuclein aggregation: implications for pathogenesis of Parkinson disease. J Biol Chem 280: 22670–22678.

Liu S, Sawada T, Lee S, Yu W, Silverio G, Alapat P, Millan I, Shen A, Saxton W, Kanao T, Takahashi R, Hattori N, Imai Y, Lu B 2012) Parkinson's disease-associated kinase PINK1 regulates Miro protein level and axonal transport of mitochondria. PLoS Genet 8: e1002537.

Liu X, Hebron M, Shi W, Lonskaya I, Moussa CE-H (2019) Ubiquitin specific protease-13 independently regulates parkin ubiquitination and alpha-synuclein clearance in alpha-synucleinopathies. Hum Mol Genet 28: 548–560.

Liu Z, Yu Y, Li X, Ross CA, Smith WW (2011) Curcumin protects against A53T alpha-synuclein-induced toxicity in a PC12 inducible cell model for Parkinsonism. Pharmacol Res 63: 439–444.

Lonskaya I, Hebron ML, Algarzae NK, Desforges N, Moussa CE-H (2013) Decreased parkin solubility is associated with impairment of autophagy in the nigrostriatum of sporadic Parkinson's disease. Neuroscience 232: 90–105.

Machida Y, Chiba T, Takayanagi A, Tanaka Y, Asanuma M, Ogawa N, Koyama A, Iwatsubo T, Ito S, Jansen PH, Shimizu N, Tanaka K, et al. (2005) Common anti-apoptotic roles of parkin and alpha-synuclein in human dopaminergic cells. Biochem Biophys Res Commun 332: 233–240.

Martin LJ, Pan Y, Price AC, Sterling W, Copeland NG, Jenkins NA, Price DL, Lee MK (2006) Parkinson's disease α-synuclein transgenic mice develop neuronal mitochondrial degeneration and cell death. J Neurosci 26: 41–50.

Martinez JH, Alaimo A, Gorojod RM, Porte Alcon S, Fuentes F, Coluccio Leskow F, Kotler ML (2018) Drp-1 dependent mitochondrial fragmentation and protective autophagy in dopaminergic SH-SY5Y cells overexpressing alpha-synuclein. Mol Cell Neurosci. 88: 107–117.

McLelland G-L, Goiran T, Yi W, Dorval G, Chen CX, Lauinger ND, Krahn AI, Valimehr S, Rakovic A, Rouiller I, Durcan TM, Trempe J-F, et al. (2018) Mfn2 ubiquitination by PINK1/parkin gates the p97-dependent release of ER from mitochondria to drive mitophagy. Elife 7: pii: e32866.

Mogi M, Togari A, Kondo T, Mizuno Y, Komure O, Kuno S, Ichinose H, Nagatsu T (2000) Caspase activities and tumor necrosis factor receptor R1 (p55) level are elevated in the substantia nigra from Parkinsonian brain. J Neural Transm 107: 335–341.

Mor DE, Tsika E, Mazzulli JR, Gould NS, Kim H, Daniels MJ, Doshi S, Gupta P, Grossman JL, Tan VX, Kalb RG, Caldwell KA, Caldwell GA, Wolfe JH, Ischiropoulos H (2017) Dopamine induces soluble α-synuclein oligomers and nigrostriatal degeneration. Nat Neurosci 20: 1560–1568.

Moszczynska A, Saleh J, Zhang H, Vukusic B, Lee FJS, Liu F (2007) Parkin disrupts the alpha-synuclein/dopamine transporter interaction: consequences toward dopamine-induced toxicity. J Mol Neurosci 32: 217–227.

Moussa CE-H (2009) Parkin attenuates wild-type tau modification in the presence of beta-amyloid and alpha-synuclein. J Mol Neurosci 37: 25–36.

Norris KL, Hao R, Chen L-F, Lai C-H, Kapur M, Shaughnessy PJ, Chou D, Yan J, Taylor JP, Engelender S, West AE, Lim K-L, et al. (2015) Conver-

gence of Parkin, PINK1, and α-Synuclein on Stress-induced Mitochondrial Morphological Remodeling. J Biol Chem 290: 13862–13274.

Olzmann JA, Li L, Chudaev M V, Chen J, Perez FA, Palmiter RD, Chin L-S (2007) Parkin-mediated K63-linked polyubiquitination targets misfolded DJ-1 to aggresomes via binding to HDAC6. J Cell Biol 178: 1025–1038.

Outeiro TF, Grammatopoulos TN, Altmann S, Amore A, Standaert DG, Hyman BT, Kazantsev AG (2007) Pharmacological inhibition of PARP-1 reduces alpha-synuclein- and MPP+-induced cytotoxicity in Parkinson's disease in vitro models. Biochem Biophys Res Commun 357: 596–602.

Paik SR, Lee D, Cho H-J, Lee E-N, Chang C-S (2003) Oxidized glutathione stimulated the amyloid formation of alpha-synuclein. FEBS Lett 537: 63–67.

Palacino JJ, Sagi D, Goldberg MS, Krauss S, Motz C, Wacker M, Klose J, Shen J (2004) Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. J Biol Chem 279: 18614–18622.

Pankratz N, Kissell DK, Pauciulo MW, Halter CA, Rudolph A, Pfeiffer RF, Marder KS, Foroud T, Nichols WC, Parkin Study Group-PROGENI Investigators (2009) Parkin dosage mutations have greater pathogenicity in familial PD than simple sequence mutations. Neurology 73: 279–286.

Perez RG, Waymire JC, Lin E, Liu JJ, Guo F, Zigmond MJ (2002) A role for alpha-synuclein in the regulation of dopamine biosynthesis. J Neurosci 22: 3090–3099.

Ponzini E, De Palma A, Cerboni L, Natalello A, Rossi R, Moons R, Konijnenberg A, Narkiewicz J, Legname GA, Sobott F, Mauri P, Santambrogio C, Grandori R (2019) Methionine oxidation in α-synuclein inhibits its propensity for ordered secondary structure. J Biol Chem., *in press* pii: jbc.RA118.001907.

Ren Y, Jiang H, Yang F, Nakaso K, Feng J (2009) Parkin protects dopaminergic neurons against microtubule-depolymerizing toxins by attenuating microtubule-associated protein kinase activation. J Biol Chem 284: 4009–4017.

Riobó NA, Schöpfer FJ, Boveris AD, Cadenas E, Poderoso JJ (2002) The reaction of nitric oxide with 6-hydroxydopamine: implications for Parkinson's disease. Free Radic Biol Med 32: 115–121.

Ryan SD, Dolatabadi N, Chan SF, Zhang X, Akhtar MW, Parker J, Soldner F, Sunico CR, Nagar S, Talantova M, Lee B, Lopez K, et al. (2013) Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1α transcription. Cell 155: 1351–1364.

Ryan BJ, Hoek S, Fon EA, Wade-Martins R (2015) Mitochondrial dysfunction and mitophagy in Parkinson's: from familial to sporadic disease. Trends Biochem Sci 40: 200–210.

Sánchez MP, Gonzalo I, Avila J, Yébenes JG De (2002) Progressive supranuclear palsy and tau hyperphosphorylation in a patient with a C212Y parkin mutation. J Alzheimers Dis 4: 399–404.

Sangchot P, Sharma S, Chetsawang B, Porter J, Govitrapong P, Ebadi M (2002) Deferoxamine attenuates iron-induced oxidative stress and prevents mitochondrial aggregation and alpha-synuclein translocation in SK-N-SH cells in culture. Dev Neurosci 24: 143–153.

Scarffe LA, Stevens DA, Dawson VL, Dawson TM (2014) Parkin and PINK1: much more than mitophagy. Trends Neurosci 37: 315–324.

Seo J-H, Rah J-C, Choi SH, Shin JK, Min K, Kim H-S, Park CH, Kim S, Kim E-M, Lee S-H, Lee S, Suh SW, et al. (2002) Alpha-synuclein regulates neuronal survival via Bcl-2 family expression and PI3/Akt kinase pathway. FASEB J 16: 1826–1828.

Shaltouki A, Hsieh CH, Kim MJ, Wang X (2018) Alpha-synuclein delays mitophagy and targeting Miro rescues neuron loss in Parkinson's models. Acta Neuropathol. 136: 607–620.

Shimura H, Mizuno Y, Hattori N (2012) Parkin and Parkinson Disease. Clin Chem 58: 1260–1261.

Shimura H, Schlossmacher MG, Hattori N, Frosch MP, Trockenbacher A, Schneider R, Mizuno Y, Kosik KS, Selkoe DJ (2001) Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. Science 293: 263–269.

Shin J-H, Ko HS, Kang H, Lee Y, Lee Y-I, Pletinkova O, Troconso JC, Dawson VL, Dawson TM (2011) PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. Cell 144: 689–702.

Silva GM, Finley D, Vogel C (2015) K63 polyubiquitination is a new modulator of the oxidative stress response. Nat Struct Mol Biol 22: 116–123.

Singleton A, Gwinn-Hardy K, Sharabi Y, Li ST, Holmes C, Dendi R, Hardy J, Singleton A, Crawley A, Goldstein DS (2004) Association between cardiac denervation and parkinsonism caused by alpha-synuclein gene triplication. Brain 127: 768–772.

Snyder H, Mensah K, Theisler C, Lee J, Matouschek A, Wolozin B (2003) Aggregated and monomeric alpha-synuclein bind to the S6′ proteasomal protein and inhibit proteasomal function. J Biol Chem 278: 11753–11759.

Su X, Maguire-Zeiss KA, Giuliano R, Prifti L, Venkatesh K, Federoff HJ (2008) Synuclein activates microglia in a model of Parkinson's disease. Neurobiol Aging 29: 1690–1701.

Taguchi K, Watanabe Y, Tsujimura A, Tanaka M (2016) Brain region-dependent differential expression of alpha-synuclein. J Comp Neurol. 524: 1236–1258.

Turnbull S, Tabner BJ, El-Agnaf OM, Moore S, Davies Y, Allsop D (2001) alpha-Synuclein implicated in Parkinson's disease catalyses the formation of hydrogen peroxide in vitro. Free Radic Biol Med 30: 1163–1170.

Uversky VN, Yamin G, Munishkina LA, Karymov MA, Millett IS, Doniach S, Lyubchenko YL, Fink AL (2005) Effects of nitration on the structure and aggregation of α-synuclein. Mol Brain Res 134: 84–102.

Vandiver MS, Paul BD, Xu R, Karuppagounder S, Rao F, Snowman AM, Ko HS, Lee Y Il, Dawson VL, Dawson TM, Sen N, Snyder SH (2013) Sulfhydration mediates neuroprotective actions of parkin. Nat Commun 4: 1626.

Venderova K, Park DS (2012) Programmed Cell Death in Parkinson's Disease. Cold Spring Harb Perspect Med 2: a009365.

Vercammen L, Perren A Van der, Vaudano E, Gijsbers R, Debyser Z, Haute C Van den, Baekelandt V (2006) Parkin Protects against Neurotoxicity in the 6-Hydroxydopamine Rat Model for Parkinson's Disease. Mol Ther 14: 716–723.

Vries RLA de, Przedborski S (2013) Mitophagy and Parkinson's disease: be eaten to stay healthy. Mol Cell Neurosci 55: 37–43.

Wang C, Ko HS, Thomas B, Tsang F, Chew KCM, Tay S-P, Ho MWL, Lim T-M, Soong T-W, Pletnikova O, Troncoso J, Dawson VL, et al. (2005) Stress-induced alterations in parkin solubility promote parkin aggregation and compromise parkin's protective function. Hum Mol Genet 14: 3885–3897.

Wilkaniec A, Lenkiewicz AM, Czapski GA, Jęśko HM, Hilgier W, Brodzik R, Gąssowska-Dobrowolska M, Culmsee C, Adamczyk A (2019) Extracellular Alpha-Synuclein Oligomers Induce Parkin S-Nitrosylation: Relevance to Sporadic Parkinson's Disease Etiopathology. Mol Neurobiol 56: 125–140.

Winslow AR, Rubinsztein DC (2011) The Parkinson disease protein α-synuclein inhibits autophagy. Autophagy 7: 429–431.

Wong YC, Krainc D (2017) α-synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies. Nat Med 23: 1–13.

Xie W, Chung KKK (2012) Alpha-synuclein impairs normal dynamics of mitochondria in cell and animal models of Parkinson's disease. J Neurochem 122: 404–414.

Xu B, Wang F, Wu S-W, Deng Y, Liu W, Feng S, Yang T-Y, Xu Z-F (2014) α-Synuclein is involved in manganese-induced ER stress via PERK signal pathway in organotypic brain slice cultures. Mol Neurobiol 49: 399–412.

Yamin G, Uversky VN, Fink AL (2003) Nitration inhibits fibrillation of human alpha-synuclein in vitro by formation of soluble oligomers. FEBS Lett 542: 147–152.

Yang Y, Nishimura I, Imai Y, Takahashi R, Lu B (2003) Parkin suppresses dopaminergic neuron-selective neurotoxicity induced by Pael-R in Drosophila. Neuron 37: 911–924.

Yu Z, Xu X, Xiang Z, Zhou J, Zhang Z, Hu C, He C (2010) Nitrated alpha-synuclein induces the loss of dopaminergic neurons in the substantia nigra of rats. PLoS One 5: e9956.

Yuan Y, Jin J, Yang B, Zhang W, Hu J, Zhang Y, Chen NH (2008) Overexpressed alpha-synuclein regulated the nuclear factor-kappaB signal pathway. Cell Mol Neurobiol 28: 21–33.

Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, Watt ML, Eklund AC, Zhang-James Y, Kim PD, Hauser MA, Grunblatt E, Moran LB, et al. (2010) PGC-1α, A Potential Therapeutic Target for Early Intervention in Parkinson's Disease. Sci Transl Med 2: 52ra73.

Zheng X, Hunter T (2013) Parkin mitochondrial translocation is achieved through a novel catalytic activity coupled mechanism. Cell Res 23: 886–897.

Zhu X, Ma X, Tu Y, Huang M, Liu H, Wang F, Gong J, Wang J, Li X, Chen Q, Shen H, Zhu S, et al., (2017) Parkin regulates translesion DNA synthesis in response to UV radiation. Oncotarget 8: 36423–36437.

Zhu Y, Duan C, Lü L, Gao H, Zhao C, Yu S, Uéda K, Chan P, Yang H (2011) α-Synuclein overexpression impairs mitochondrial function by associating with adenylate translocator. Int J Biochem Cell Biol 43: 732–741.