PINK1 and Parkin mitochondrial quality control: a source of regional vulnerability in Parkinson’s disease

Preston Ge 1,2,3,4,5,6, Valina L. Dawson 1,2,3* and Ted M. Dawson 1,2,3*

Abstract

That certain cell types in the central nervous system are more likely to undergo neurodegeneration in Parkinson’s disease is a widely appreciated but poorly understood phenomenon. Many vulnerable subpopulations, including dopamine neurons in the substantia nigra pars compacta, have a shared phenotype of large, widely distributed axonal networks, dense synaptic connections, and high basal levels of neural activity. These features come at substantial bioenergetic cost, suggesting that these neurons experience a high degree of mitochondrial stress. In such a context, mechanisms of mitochondrial quality control play an especially important role in maintaining neuronal survival. In this review, we focus on understanding the unique challenges faced by the mitochondria in neurons vulnerable to neurodegeneration in Parkinson’s and summarize evidence that mitochondrial dysfunction contributes to disease pathogenesis and to cell death in these subpopulations. We then review mechanisms of mitochondrial quality control mediated by activation of PINK1 and Parkin, two genes that carry mutations associated with autosomal recessive Parkinson’s disease. We conclude by pinpointing critical gaps in our knowledge of PINK1 and Parkin function, and propose that understanding the connection between the mechanisms of sporadic Parkinson’s and defects in mitochondrial quality control will lead us to greater insights into the question of selective vulnerability.

Keywords: Parkinson disease, Parkin, PINK1, Mitochondria, Mitophagy, Selective vulnerability, Substantia nigra

Background

Parkinson’s disease (PD) is a late-onset neurodegenerative disease characterized by a core triad of symptoms; resting tremor, bradykinesia, and elevated resting tone [1]. While 10% of patients carry single gene mutations that cause PD (monogenic PD), over 90% of patients have no known family history or known genetic cause of their disease (sporadic PD, or sPD) [1]. PD has traditionally been viewed as a disease caused by the selective degeneration of dopamine (DA) neurons found in the substantia nigra pars compacta (SNpc) due to early findings that SNpc degeneration is the most consistent postmortem finding in patient brains, that dopamine replacement through L-DOPA is an effective management strategy for the motor symptoms, and that the selective SNpc DA neuron toxin MPTP recapitulates the clinical phenotype of PD [2]. However, systematic, large-scale characterization of postmortem PD brains has provided a contrasting image of disease progression based on the presence of Lewy bodies (LB), large aggregates of misfolded α-synuclein protein, which has served as a canonical marker of disease pathogenesis for decades [2, 3]. Pathologic staging of α-synuclein-positive LBs has revealed widespread involvement of most major subdivisions of the central nervous system (CNS), ranging from brainstem nuclei to cortex [3, 4]. A growing body of evidence in both human patients and preclinical animal models suggests that LBs may initially appear in the brainstem or enteric nervous system and spread across the brain in a prion-like manner [5–12].

The realization that PD pathology is not solely confined to the SNpc and can spread across the CNS has profoundly altered our understanding of PD pathogenesis and disease progression. However, despite evidence of widespread pathology, not all cell populations are

* Correspondence: vdawson@jhmi.edu; tdawson@jhmi.edu

1Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Department of Neurology, Department of Physiology, Solomon H. Snyder Department of Neuroscience, Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, 733 North Broadway, Suite 731, Baltimore, MD 21205, USA

Full list of author information is available at the end of the article

© The Author(s). 2020 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
equally resilient. Certain populations of neurons remain more vulnerable to developing LB pathology and to neurodegeneration in PD, suggesting that cell-intrinsic factors can gate selective vulnerability. The most vulnerable neuronal subpopulations include SNpc DA neurons; cholinergic neurons in the pedunculopontine nucleus, nucleus basalis of Meynert, and dorsal motor nucleus of vagus; noradrenergic neurons in the locus coeruleus; and serotonergic neurons in the raphe nucleus [4, 13]. While the factors regulating regional heterogeneity in disease susceptibility are not fully known, mitochondrial stress and failure of mitochondrial quality control pathways are thought to contribute to regional differences in pathology and neurodegeneration [4]. Here, we review the contribution of mitochondrial dysfunction to selective neuronal vulnerability in PD and summarize the current understanding of neuronal mitochondria maintenance through PINK1/Parkin-mediated mitochondrial quality control.

**Main text**

**Importance of mitochondria in PD**

**The many facets of mitochondrial function**

Mitochondria are membrane-bound organelles that perform a diverse range of critical cellular functions. They are double-membranated structures, with outer and inner mitochondrial membranes (OMM and IMM respectively) separated by an intermembrane space and a central matrix enclosed by the IMM. Reflecting their evolutionary origins as endosymbiotic bacteria, mitochondria carry their own unique circular genome (mtDNA) at copy numbers upwards of 10–100 per mitochondrion [14]. Their genome encodes two unique rRNAs, 22 tRNAs, and 13 polypeptides required to assemble the mitochondrial ribosome and parts of the electron transport chain (ETC), while the nuclear genome encodes 1000+ mitochondrial genes [14, 15]. While traditional textbook pictures show mitochondria as static, bean-shaped structures, in reality they exist as dynamic networks shifting from innumerable punctate organelles to cell-wide tubular networks governed by a complex fission/fusion machinery [16]. Mitochondria are highly multifunctional. They not only generate the bulk of ATP in most cell types through oxidative phosphorylation, but also metabolize and synthesize complex macromolecules (e.g. lipids, amino acids, and nucleotides); buffer reactive oxygen species (ROS) and cytoplasmic Ca^{2+}; regulate cellular redox balances; control apoptosis; and serve as key anchoring scaffolds for intracellular signaling networks [14, 17, 18].

Though critical for cell survival, these energetically demanding processes generate reactive intermediates and oxidizing agents that damage nucleic acids, proteins, and lipids, necessitating various waste removal and damage control mechanisms such as the urea cycle, glutathione antioxidants, and H_{2}S detoxification [16–18]. While these mechanisms perform detoxification of reactive metabolic intermediaries and end products, mitochondria also possess several sophisticated systems for maintaining structural integrity and proper protein function. These systems, collectively known as mitochondrial quality control (MQC), include AAA proteases that degrade proteins in the matrix and intermembrane space, the ubiquitin-proteasome system for removing OMM proteins, the removal of larger portions of mitochondria through mitochondrial derived vesicles (MDVs) and mitophagy, and regulation of fission/fusion dynamics [15, 19].

**Neuron subpopulation-specific bioenergetic vulnerabilities in PD**

Mitochondria within the CNS exist in a unique metabolic environment due to the sheer energetic demand of neural activity and the structural polarization of CNS cells. The brain comprises roughly 2 % of total body mass yet consumes 20% of the body’s oxygen intake and 25% of glucose supply, of which the bulk goes towards sustaining membrane potentials and facilitating neurotransmission [19, 20]. Neuronal mitochondria must meet the immense energetic demands of neuronal signaling while also buffering waves of Ca^{2+} entry, which leads to the generation of excitotoxic ROS if left unchecked [20]. Furthermore, neuronal architecture is complex and exquisitely polarized, with some neurons carrying the vast majority of their cytoplasm and mitochondria in long dendrites and axons that can be as far as a meter away from the soma [15, 21]. Given the functional specialization of these cellular subcompartments, it is likely that such structural polarization leads to local metabolic needs that may require sub-specialization of mitochondrial function, such as increased Ca^{2+} buffering at the pre- and postsynaptic termini and increased biosynthetic functions at the soma. While other somatic cells can oftentimes rely on cell division to generate fresh mitochondria, neurons are postmitotic cells that must overcome the aforementioned challenges for an entire lifetime.

These bioenergetic demands are particularly evident in the neuronal populations selectively vulnerable in PD, including most of the nuclei described in the introduction. Many of these neurons send extensive, branching axons throughout the brain and influence large, diffuse brain areas [4]. The axons of SNpc DA neurons, for example, form vast branching nets that have been estimated to form up to 100–400 thousand synapses within the striatum and extend on average around 30–46 cm in length in rats [22–24]. In humans, they have been estimated to form up to 1–2 million synapses [15]. When compared to the less vulnerable neighboring DA
neurons in the ventral tegmental area, SNpc DA neurons have more complex axons, a higher density of axonal mitochondria, higher rates of oxidative phosphorylation, and increased superoxide production [25]. Genetic perturbation of MQC in cultured SNpc DA neurons led to a reduction in the size of axonal arbors, while neurons with smaller axonal arbors tended to be more resilient to MPP+, providing further evidence that the morphological architecture of SNpc DA neuron axons imposes significant strain on mitochondrial function [26]. Furthermore, many of these vulnerable populations extend unmyelinated axons [21], which likely demand even more energy than myelinated neurons due to the need to regenerate the membrane potential along the entire axon rather than just at nodes of Ranvier. Thus, the extreme cytoarchitectural specialization of these neuronal subpopulations places a large bioenergetic burden on their mitochondria and may contribute to their selective vulnerability in PD.

**Evidence of mitochondrial dysfunction in human PD**

The idea that mitochondria may be involved in the pathogenesis of PD was first suggested by observing the effects of MPTP, a byproduct of illicit synthesis of the opioid drug desmethylprodine. MPTP is metabolized to the mitochondrial complex I inhibitor MPP+, which in turn causes acute-onset Parkinsonism with selective destruction of SNpc neurons [2, 27]. Since the discovery of MPTP, three major lines of evidence – epidemiological, pathological, and genetic – have pointed to mitochondrial dysfunction as a central driver of disease. First, mitochondrial toxins have either been shown to cause or correlate with increased risk of PD. In addition to MPTP, exposure to the pesticide rotenone, a complex I inhibitor, has been associated with increased risk of PD in epidemiological studies [28–30]. Second, postmortem studies of human PD patients have found widespread evidence of mitochondrial dysfunction. Complex I dysfunction has been consistently identified in the SNpc of deceased patients, with some reports of more generalized complex dysfunction that may affect other tissues as well [31–34]. In addition to these bioenergetic defects, mitochondria in postmortem tissue also show evidence of genetic defects, with greater age-dependent accumulation of mtDNA deletions and somatic mosaicism than control subjects [33–36]. Numerous other studies have identified dysregulation in the expression of various mitochondrial proteins, such as the molecular chaperone prohibitin, OMM protein VDAC1, mitochondrial import protein Tom40, and serine protease HtrA2 [37], as well as increased oxidative damage to mitochondrial proteins [38]. Third, mutations in genes that cause monogenic PD have been linked to mitochondrial function. For example, the PD-associated gene VPS35, which encodes a key subunit of the retromer complex responsible for sorting proteins between membranous organelles [39], contributes to the formation of MDVs and regulates fission/fusion dynamics [40–42]. The mutant proteins encoded by other genes that cause monogenic PD, such as LRRK2, SNCA, ATP13A2, have likewise been found to cause mitochondrial pathologies ranging from increased fragmentation, disruption of ER-mitochondrial interactions, impaired Ca2+ buffering, elevated numbers of mtDNA mutations, and increased ROS production [43–47].

Most prominent of the monogenic PD-associated genes involved in mitochondrial function are PINK1, encoding the PTEN-induced serine/threonine kinase 1, and PRKN, encoding an E3 ubiquitin ligase Parkin [18, 33, 48, 49]. Following these findings, genetic studies in Drosophila implicated a shared biological pathway for Parkin and PINK1 function [50–52], with further mechanistic work establishing their function in detecting mitochondrial damage and recruiting mechanisms to remove and replace dysfunctional mitochondrial components. The activation and functions of the PINK1/Parkin system of MQC are arguably some of the most well-studied pathways of PD pathogenesis and will be reviewed in detail below (Fig. 1). Collectively, these findings firmly establish mitochondrial dysfunction as a core pathologic feature of PD. The contribution of mitochondrial dysfunction to neurodegeneration relative to other mechanisms is not fully known, though it likely differs between monogenic versus familial PD and is dependent on the brain region in question.

**PINK1/Parkin as core organizers of mitochondrial quality control**

**Mutations in PINK1 or PRKN (Parkin) cause selective loss of SNpc DA neurons**

Loss of function mutations in PINK1 and PRKN are the most common known causes of autosomal recessive and early onset PD (before the age of 45) [48, 49, 53]. Despite an earlier age of onset, PD associated with PINK1 or PRKN mutations is usually more benign with slower progression, high L-DOPA responsiveness, and normal cognition, but with high likelihood of dyskinesias, dystonia, hyperreflexia, and psychiatric symptoms [53–55]. The clinical presentation of PINK1/PRKN PD is intriguing in its relatively pure motor phenotype compared to other cases of PD and the robust and long-lasting (sometimes in the range of decades) responsiveness to dopamine replacement therapy, suggesting that these patients may experience a disease process that is largely confined to the SNpc DA system. This hypothesis is consistent with postmortem pathology in seventeen cases of PRKN and one case of PINK1 PD, which is striking for the highly specific loss of SNpc neurons with relative sparing of the locus coeruleus (LC) and other brain regions [53, 56]. Whereas LB pathology is found in virtually all cases of sPD, it was found only inconsistently in PINK1/
Fig. 1 (See legend on next page)
**PRKN PD (6/17 genetically confirmed PRKN PD, and trace amounts in 1/1 PINK1),** suggesting that α-synuclein may be a minor player in these cases [53, 56]. In contrast, the clinical-pathologic features of sporadic PD and other monogenic causes of PD tend to exhibit significantly greater variation and wider involvement of other cell populations [54–56]. While it is important to note that the limited availability of autopsy cases may cause an underestimation of the pathological heterogeneity of PRKN and PINK1 PD, the combined clinical-pathological evidence of highly selective SNpc DA neuron loss suggests that these genes may represent an Achilles heel of SNpc DA neurons and that studying downstream pathological pathways may be critical for yielding insights into the vulnerability of the population in PD.

**Mechanism of PINK1/Parkin activation**

PINK1 and Parkin function as the first steps of a signaling pathway that activates mitochondrial quality control pathways in response to mitochondrial damage [57]. Under basal conditions, PINK1’s N-terminus is transferred across the OMM to the IMM, with the kinase domain located closer to the C-terminus protruding out into the cytosol. PINK1 is then cleaved by IMM-bound proteases and subsequently degraded by the proteasome, leading to undetectable basal levels of PINK1 [58, 59]. Stressors such as membrane depolarization, mitochondrial complex dysfunction, mutagenic stress, and proteotoxicity lead to accumulation of PINK1 on the OMM by impairing intermembrane transport of the N-terminus domain to the IMM. Subsequent homodimerization of PINK1 on the OMM leads to autophosphorylation, which promotes kinase activation and facilitates binding to substrates Parkin and ubiquitin [58–61]. Thus, PINK1’s ability to rapidly accumulate and activate in response to mitochondrial stressors allows it to function as a sensor of mitochondrial damage.

Parkin is an E3 ubiquitin ligase that contains a ubiquitin-like domain and four RING domains: RING0, RING1, IBR, and RING2 [62]. Its basal activity is minimal due to intramolecular interactions that block the active site and compete with E2 ligase binding [57]. Upon mitochondrial injury, PINK1 activates Parkin through two mechanisms. First, it phosphorylates ubiquitin on S65, which competes with an autoinhibitory domain within Parkin and stabilizes it in an active conformation. Second, PINK1 directly phosphorylates Parkin on S65 in Parkin’s ubiquitin-like domain, which induces conformational changes that allow for binding of the charged E2 ligase [57–59, 63–70]. These mechanisms increase Parkin’s E3 ubiquitin ligase activity, with both required for full activation, though it is unclear whether either mechanism contributes differentially to activation [63, 66, 71]. Thus, Parkin amplifies a damage detection signal from PINK1 by facilitating the formation of ubiquitin chains, which recruit more Parkin to the mitochondria [57].

Once recruited to the mitochondria, Parkin exhibits two waves of ubiquitination: the first wave targets many outer OMM and mitochondrial matrix proteins within the first 2 h of activation, whereas the second wave targets IMM proteins [58, 72, 73]. Parkin has also been found to ubiquitinate many cytosolic targets [73], though it is unclear whether these targets are phosphorylated by mitochondrial bound Parkin or whether there may be cytosolic activation of Parkin. Among these cytosolic targets are AIMP2, whose accumulation leads to PARP1 and MIF-dependent cell death of nigral DA neurons; and Parkin Interacting Substrate (PARIS, ZNF746), which causes neurotoxicity by suppressing mitochondrial biogenesis [74–82]. The diversity of Parkin substrates and the formation of multiple types of ubiquitin linkages (K6, K11, K48, and K63), poses the question of whether Parkin ubiquitination may have diverse effects on cellular signaling beyond targeting proteins for degradation [18, 73, 83]. Substrate specificity and chain formation may show some cell-type dependence. For example, a recent proteomic profile of Parkin substrates in HeLa cells and human neurons suggests differences in which substrates are targeted, which residues are
ubiquitinated on the same substrate, and which ubiquitin chains are generated [84]. Thus, it is possible that differences in Parkin substrate recognition and targeting may lead to divergent Parkin function in a cell-type specific manner.

**PINK1/Parkin regulate tiers of mitochondrial quality control pathways**

**Parkin/PINK1-mediated mitophagy** A prevailing model for PINK1/Parkin function in recent years has suggested that their accumulation on the outer mitochondrial membrane can trigger the macroautophagy of mitochondria (mitophagy) (Fig. 1a). In numerous cell lines including HeLa cells and mouse embryonic fibroblasts, exposure to numerous mitochondrial toxins such as CCCP, antimycin A, valinomycin, and rotenone reproducibly triggers the accumulation of PINK1 on the mitochondrial membrane and the subsequent recruitment of Parkin [59, 85–89]. Formation of ubiquitin chains on mitochondrial proteins leads to the binding of autophagy receptors, such as optineurin and NDP52, as well as Rab signaling proteins RABGEF1, RAB5, and RAB7A to the mitochondrial surface [90–93]. These mediators of mitophagy assemble autophagosomal membranes to eliminate damaged mitochondria [94]. While these findings have been robustly demonstrated in immortalized cell lines exposed to mitotoxic and mutagenic stress, compelling evidence of PINK1/Parkin-mediated mitophagy occurring in neurons in a disease-relevant context remains scarce.

Both in cultured neurons and in the mouse brain, mitochondrial translocation of PINK1/Parkin onto mitochondria is far less consistently observed or dramatic than that observed in cell lines. In comparison to cell lines, cultured primary neurons show much weaker recruitment of Parkin to mitochondrial surfaces, slower temporal kinetics on the order of ~ 6–18 h of exposure to CCCP, and oftentimes require a combination of exogenous Parkin overexpression and apoptosis inhibitors to maintain neuronal survival under these conditions [16, 18, 95–98]. Even in cases where neuronal parkin translocation was observed, most studies do not assay mitophagy directly, instead using proxy measures such as mitochondrial membrane potential or mtDNA levels that cannot rule contribution from other PINK1/Parkin functions (see below) [98, 99]. One important factor that may complicate the study of PINK1/Parkin mitophagy in neurons is subcellular localization and local factors may gate activation of this system. A recent study suggests that damage to axonal mitochondria in cultured neurons can induce rapid (within ~1 h) Parkin translocation followed by recruitment of autophagosomes and removal via lysosomes [100]. Thus, in contrast to cell lines, variability in the intracellular environment and mitochondrial stresses of different neuronal compartments may impose additional limitations to PINK1/Parkin mitophagy.

A few recent studies using mitochondria-targeted pH-sensitive fluorescent indicators suggest that low levels of basal mitophagy occur throughout both wild-type mouse and *Drosophila* brains, including in DA neurons [101–106]. The rate of basal mitophagy appears to increase with the metabolic demands of the tissue and in response to stressors such as hypoxia and mtDNA mutagenic stress [102, 104, 106]. Though age also appears to affect the rate of basal mitophagy, the directionality of the effect is unclear, as it has been reported to increase with age in *Drosophila* but decrease in mice [102, 106]. Despite evidence of mitophagy occurring in vivo, it remains unclear whether PINK1/Parkin activation plays the same role in basal mitophagy in vivo as it does in artificially induced mitophagy in vitro. A proteomics study quantifying rates of protein turnover in *Drosophila* via stable isotope labeling found that Parkin or autophagy-deficient Atg7 mutants showing increased half-lives in mitochondrial proteins [107]. However, the effects on mitochondrial protein half-lives were only weakly correlated between the two mutants, suggesting either that mitophagy may be influenced by Parkin-independent regulatory pathways or that Parkin may regulate mitochondrial protein turnover through autophagy-independent mechanisms [107]. Moreover, three of the previously mentioned studies found that PINK1 and Parkin knockouts had no effect on basal mitophagy in mouse and *Drosophila* [103–105], whereas one study found that PINK1 or Parkin deficiency in *Drosophila* abrogated an age-dependent increase in basal mitophagy [106]. Furthermore, if driving mitophagy is a primary role of endogenous Parkin/PINK1, then one might expect that loss of either gene would lead to accumulation of mitochondria. However, numerous reports have found that PINK1-KO or Parkin-KO lead to reductions in mitochondrial content in neurons in vitro and in vivo [80, 95, 108]. Thus, there is yet to be a convincing demonstration that PINK1/Parkin play a major role in driving mitophagy in the mature CNS. This does not rule out the possibility that PINK1/Parkin-independent mitophagy pathways play a role in the CNS (reviewed in [109]), as many of these pathways showing cell type and context-dependent activation. Because most of these potential alternative mitophagy pathways were studied in non-neuronal cell lines and tissues [109], further experimentation is required to establish their role in the nervous system.

A central question that remains is why PINK1/Parkin mitophagy is readily inducible in cell culture yet difficult to observe in neurons. One possibility is that PINK1/Parkin mitophagy may be gated by insult-specific or localization-specific factors. For example, it is possible
that only certain sources of mitochondrial stress may
trigger PINK1/Parkin activation, such as accumulation of
mtDNA mutations by knocking out a mtDNA repair
gene [96]. Though mtDNA mutations do accumulate in
human PD cases, it is unclear how accurately mutant
mice recapitulate the stress experienced in the human
disease and whether mtDNA mutations cause or simply correlate with disease. In addition, some findings have
suggested that PINK1/Parkin mitophagy occurs prefer-
entially in the distal axons [100, 110], where turnover of
defective mitochondria may be more frequent due to the
difficulty of maintaining mitochondria so far from the
soma. Presynaptic mitochondria can sometimes take
time to be trafficked from the soma to their destination
[15], during which time mitochondrial proteins are dam-
aged by ROS produced through oxidative phosphoryl-
ation and undergo normal turnover. Compared to
mitochondria at the soma, synaptic mitochondria tend
to undergo increased oxidation during aging, show
higher vulnerability to Ca\(^{2+}\)-induced damage, and exhibit
lower spare respiratory capacity [19, 111–113]. Given
the damage dependence of mitophagy, it is possible that
synaptic/axonal mitochondria may rely more on this
process for ensuring MQC. These possibilities require
careful exploration of physiologically relevant mitochon-
drial insults and more precise subcellular localization of
PINK1/Parkin in order to establish their true role in
mitophagy.

It is also possible that the bioenergetic demands of
neurons are incompatible with significant upregulation
of mitophagy. Immortalized cell lines are highly glyco-
lytic due to their origin as cancer cells and thus can
likely afford to degrade many of their mitochondria.
However, neurons rely primarily on oxidative phosphor-
ylation to survive, generating nearly 95% of their ATP
through oxidative phosphorylation [16, 18–20]. Even
under acute mitochondrial injury, neurons cannot switch
a substantial portion of ATP generation from oxidative
phosphorylation to glycolysis [97]. Indeed, forcing HeLa
or RPE1 cells to rely on oxidative phosphorylation
through the use of galactose as the main carbohydrate
source greatly inhibits stress-induced Parkin transloca-
tion and blocks mitophagy [97, 114]. Thus, while it is
possible neurons undergo a low level of basal mitophagy,
their dependence on oxidative phosphorylation and the
sparsity of mitochondria in distal neuronal processes
may prevent neurons from undergoing extreme injury-
induced PINK1/Parkin-mediated mitophagy as observed in
cell culture.

**Mitochondrial QC through fission/fusion regulation**

Mitochondrial networks undergo constant remodeling and
depend on the balance between fission and fusion to meet
the changing metabolic needs of their host cell. For
example, increased mitochondria fission leads to the gener-
ation of smaller mitochondria, which facilitates intracellular
transport (such as distribution of mitochondria into the
dendrites of Purkinje neurons), heat generation in brown
adipose tissue, mitophagy, and apoptosis [115–117]. Con-
versely, enhanced fusion increases mitochondrial length,
which may increase the efficiency of oxidative phos-
phorylation and allow cells to meet higher energy demands
[115, 116]. In mammals, the primary mediators of fission
and fusion are dynamin family proteins. Fission requires a
single protein, Drp1, which assembles into multimeric spi-
rais around mitochondrial tubules and constricts them in a
GTP-dependent fashion [115, 116]. Fusion is more mech-
anismically complex and requires mediators on the OMM
(Mitofusins 1 and 2) and IMM (Opa1) [115, 116]. In
response to different stressors, fission/fusion dynamics
undergo one of two responses. Mild stress such as nutrient
deprivation and mild toxin exposure leads to stress-induced
mitochondrial hyperfusion, possibly facilitating the combi-
nation of mildly damaged mitochondrial components with
healthy ones to dilute the effects of damage. More severe
damage such as mitochondrial depolarization promotes fission,
leading to the formation of smaller fragments that can
undergo mitophagy or other forms of removal [115]. How-
ever, it is unclear how this stress response varies across cell
types, how cells decide to undergo hyperfusion or fragmen-
tation, and what mechanism(s) lead(s) to the two different
responses.

Early studies characterizing Parkin- or PINK1-null
*Drosophila* mutants found evidence of swollen mito-
chondria in numerous tissue [50–52, 118, 119], suggest-
ing that PINK1 and Parkin may either drive fission or
inhibit fusion. These pathological features could be ame-
liorated by increasing expression of Drp1 or reducing
Opa1 or Mitofusin [120–123], suggesting a genetic inter-
action between PINK1/Parkin and canonical fission/fu-
ison regulatory pathways. Both PINK1 and Parkin
promote degradation of critical mitochondrial fusion
proteins Mitofusin 1 and 2 [72, 124–131], while PINK1
is sufficient to promote mitochondrial fission by recruit-
ing Drp1 to mitochondria [132, 133]. Thus, Parkin/
PINK1 activation seems to drive mitochondrial dynamics
towards fission by activating pro-fission and inactivating
pro-fusion pathways (Fig. 1b). PINK1/Parkin-induced
mitochondrial fission potentially contributes to MQC
through two parallel mechanisms. First, it could act to
segregate areas of focal damage. For example, a recent
study in HeLa cells used mutant, aggregation-prone orn-
ithine transcarbamylase (OTC) to induce misfolded
protein foci in mitochondria [134]. These foci led to
local accumulation of PINK1/Parkin and subsequent
OTC clearance by mitochondrial fission [134]. Ablating
mitochondrial fission through Drp1-KO did not affect the
rate of OTC clearance; instead, it lead to generalized
recruitment of PINK1/Parkin and substantial upregulation of mitophagy [134]. Thus, in the case of focal damage, mitochondrial fission appears to be an initial defense which enables selective removal of dysfunctional components, thereby preventing mitophagy from destroying healthy mitochondria. However, this process relies on focal concentrations of mitochondrial damage. It is unclear if and how mitochondrial fission could contribute to the management of more diffuse damage or to baseline MQC in the absence of an insult.

A second potential mechanism for fission-regulated MQC relies on the ability of fission/fusion cycles to locally enrich for degradation targets. A proteomic profile of stationary phase yeast found heterogeneity in the turnover rates of different mitochondrial matrix proteins, and that deleting Dnm1 (yeast Drp1) suppresses some of these differences [135]. These findings suggest that during baseline MQC, mitochondrial fission may engage a selectivity filter that enriches for certain degradation targets and segregates them for replacement. While the nature of this selectivity filter is still largely unknown, a recent study has suggested that differential phosphorylation on substrates may contribute to target selection [136].

**Removal of focal damage through mitochondrial derived vesicles** While mitochondrial fission may be well-suited for the segregation of relatively large domains of damaged mitochondrial components, it may lead to unwanted elimination of healthy regions when damage is confined to smaller domains. A potential mechanism allowing for more selective isolation of damaged components is the formation of MDVs, which have a diameter of 70–150 nm and can be either single or double membraned [137]. The formation of MDVs is Drp1-independent, indicating that it is mechanistically distinct from mitochondrial fission [138, 139]. A number of subtypes of MDVs have been identified, including those that traffic to lysosomes, multivesicular bodies, macrophage phagosomes, and peroxisomes [137, 140–142]. Numerous markers have been found to mark MDVs including Tom20, MAPL, Stx17, Pex3, Rab7/9, and Sod2 [137, 140–143]. The presence of specific proteins on different MDV subpopulations seems to contribute to differential end targets. For example, MAPL+ or Pex3/Pex14+ MDVs target peroxisomes, Sod2+ MDVs target bacteria-containing phagolysosomes, and Stx17+ or Tom20+ MDVs are trafficked to the endolysosomes [137–139, 141–144]. However, the overlap in marker expression between MDV subtypes and the precise correlation between markers and MDV functions or targeting properties are not yet fully elucidated. While molecular and functional profiling of different MDV subtypes is still in its early stages, MDVs are emerging as potential facilitators of mitochondrial quality control [137], peroxisome biogenesis [142], and immune function [140, 141, 145]. While it has been demonstrated that PINK1/Parkin are involved in the generation of some MDVs, such as those destined for endolysosomes and those involved in destruction of endocytosed bacteria in macrophages [137, 141], it is not clear whether all MDVs are generated via PINK1/Parkin activation. MDVs containing only OMM proteins such as Tom20 may not require PINK1/Parkin [144], suggesting that certain subpopulations of MDVs may be PINK1/Parkin independent.

One important subgroup of PINK1/Parkin-dependent MDVs may preserve mitochondrial integrity by removing localized patches of mitochondrial damage (Fig. 1c). Production of these MDVs is stimulated by the presence of oxidative and mutagenic stress and their contents tend to be enriched with oxidized proteins [138, 144, 146]. Incorporation of protein cargo into these MDVs is dependent on PINK1/Parkin and shows a degree of cargo selectivity dependent on the nature of the insult. For example, cytosolic ROS generated from xanthine oxidase leads to the incorporation of OMM-localized VDAC, whereas mitochondrial ROS resulting from antimycin A lead to incorporation of IMM-localized complex III [139, 144]. Ultimately, the subpopulation of MDVs enriched for oxidized protein cargo are targeted to the lysosome for degradation [138, 144]. Furthermore, Parkin-null or PINK1-null *Drosophila* mutants show increased half-lives of mitochondrial proteins, with a selective overrepresentation of ETC components [107]. Given that ETC components are exposed to a highly oxidative environment, one intriguing possibility – as pointed out by the authors – is that PINK1/Parkin-associated MDVs may provide a vehicle by which oxidatively damaged ETC components are selected for turnover. Overall, it is likely that MDV formation is an earlier and milder response to stress compared to mitophagy. The temporal progression of MDV formation supports this hypothesis, as antimycin A, oligomycin, or CCCP causes MDV formation in HeLa cells with the peak rate occurring on the order of 1–4 h, whereas mitophagy occurs on the scale of 4–24 h [139].

Whereas mitophagy is a more severe response to stress resulting in the destruction of entire mitochondria, MDVs may play an intermediate role contributing to mitochondrial homeostasis. MDV formation has also been shown to occur under baseline conditions in cell lines and cardiomyocytes [138, 139, 146], with varying percentages of mitochondrial proteins (roughly 1–4%) being ejected via MDVs in a cell-free mitochondrial budding assay [144]. These findings suggest that PINK1/Parkin-mediated MDV formation may serve as a mechanism for selectively isolating and eliminating pockets of damaged mitochondria while preserving the integrity of the remaining mitochondrial network, and thus may be preferable to mitophagy for neurons. In support of this hypothesis, mitochondria in
cardiomyocytes, which likewise depend on oxidative phosphorylation, have been shown to form MDVs both at a basal rate under resting conditions and at a heightened rate when under mutagenic stress from the chemotherapeutic doxorubicin [146]. While this study also found evidence of highly limited mitophagy when cardiomyocytes were exposed to doxorubicin, the number of MDV budding events outnumbered mitophagosome formation by an order of magnitude. These findings in heart tissue provide evidence for a mechanism by which cells reliant on oxidative phosphorylation can use MDVs as a physiological system for MQC. However, further validation is needed to confirm that MDVs serve the same function in the nervous system.

**PINK1/Parkin facilitate the generation of new mitochondrial components**

**Stimulation of mitochondrial biogenesis through PGC-1α** While removal of damaged mitochondria is crucial in order to limit the consequences of injury, it is equally important to generate new mitochondria as replacement. Mitochondrial biogenesis is governed in large part by the PGC-1 family of transcription factors, including PGC-1α, PGC-1β, and PRC. PGC-1 family proteins regulate numerous downstream targets, including transcription factors Nrf-1 and Nrf-2, which subsequently increase cellular respiration rates, energy utilization, and mitochondrial biogenesis (see review [147]). PINK1/Parkin regulate PGC-1α activation through degradation of PARIS. PARIS is a KRAB and zinc finger protein that binds to an insulin responsive sequence of PGC-1α and induces its transcriptional repression [79]. PINK1 directly phosphorylates PARIS at S322 and S613, priming it for ubiquitination by Parkin, which interacts with the C-terminus zinc finger of PARIS and tags it for destruction [79–81, 148]. Loss or inactivation of Parkin leads to accumulation of PARIS, which downregulates PGC-1α, leading to selective degeneration of SNpc DA neurons that can be rescued by overexpressing PGC-1α and restoring mitochondrial biogenesis [79, 80, 82]. Conversely, overexpressing Parkin in WT cortical neurons increases PGC-1α levels, mtDNA copy number, and mitochondrial density [149]. Thus, by tagging PARIS for destruction, PINK1/Parkin drive the generation of new mitochondria by increasing PGC-1α levels (Fig. 1d).

These findings suggest that the role of the PINK1/Parkin system in mitochondrial turnover is intrinsically linked to its role in biogenesis. This raises an important question: why is a single system responsible for coordinating both biogenesis and mitophagy? One explanation is that the simultaneous activation of mitochondrial removal and biogenesis moderates changes in overall mitochondrial function; runaway activation of one process would have deleterious effects on cellular health. In support of this, while PGC-1α overexpression protects against insults such as Parkin loss, PARIS overexpression, α-synuclein overexpression, and rotenone [79, 80, 150, 151], its overexpression in the SNpc of WT mice leads to loss of DA neurons and increased sensitivity to MPTP [149, 152, 153]. Conversely, knocking out PGC-1α in mice potentiates sensitivity to MPTP toxicity, triggers formation of α-synuclein aggregates, induces gene expression changes consistent with those found in preclinical and early stage PD patient brains, and causes vacuolization in different brain regions during development [150, 154–157]. Conditional adult and cell type specific PGC-1α-KO likewise indicate that PGC-1α is necessary for the survival of SNpc DA neurons and basal ganglia medium spiny neurons, which are involved in Huntington’s disease [158, 159]. These findings indicate that mitochondrial density and energy production are highly dosage-sensitive. Thus, it may be advantageous for neurons to use PINK1/Parkin to as a central coordinator of both MQC and biogenesis rather than engaging two independent systems that may become unsynchronized in disease.

**Local mitochondrial repair mechanisms through localized translation and protein import** PINK1/Parkin-mediated mitochondrial biogenesis acts primarily on the transcriptional level and acts to generate new, whole mitochondria. However, in cases of mild damage or basal MQC, it may be sufficient to replace individual proteins or protein complexes rather than entire mitochondria. Moreover, due to the dependence on transcription as a key regulatory step, biogenesis may not act quickly enough to sustain mitochondrial function in the event of acute damage, especially in distal processes far removed from the nucleus. One mechanism by which PINK1/Parkin may compensate for the limitations of PGC-1α-dependent biogenesis is by promoting localized translation of nuclear-encoded mitochondrial RNAs (nc-mtRNAs) on the mitochondrial surface. Organelle-localized translation has been most classically studied at the surface of the rough endoplasmic reticulum (RER), where secreted, plasma membrane, and other membrane-organellar proteins are synthesized. Nuclear-encoded mitochondrial proteins are traditionally believed to be translated in the cytosol and then carried in an unfolded state by chaperones to the mitochondria, due to the presence of a mitochondrial targeting sequence (MTS) at the N-terminus of the preprotein [160, 161]. However, extensive differential centrifugation, IF colocalization, ultrastructure, and cross-linking experiments have established that a significant complement of nc-mtRNAs, up to 70% in yeast, are localized to and translated near the mitochondria [160–163]. Cytosolic ribosomes initiate translation of nc-mtRNA and bind to the mitochondrial translocase of the outer mitochondrial membrane (TOM) complex,
which imports proteins into the mitochondria, via the nascent peptide chain in a mechanism reminiscent of the canonical synthesis of secreted and membrane proteins at the RER [160, 161]. Mitochondria-localized translation has been mostly studied in yeast and the extent to which this system is preserved in humans has not been thoroughly characterized yet. However, there are reports of specific genes encoding Oxa1, F1B-ATPase, TMEM126A that are translated at the mitochondria in human cell lines [160].

Recent studies have suggested that PINK1 and Parkin may play a role in facilitating localized translation of nc-mtRNAs. Loss of PINK1 in Drosophila neuromuscular tissue, human cell lines, and human DA neurons derived from patient iPSCs impairs localization of nc-mtRNAs to mitochondria, including several key ETC components, without affecting total RNA levels of these nc-mtRNAs [164]. Further genetic and biochemical studies described several potential mechanisms by which PINK1/Parkin could affect translation of mitochondria-localized nc-mtRNAs, including PINK1 serving as a binding scaffold for bringing together import receptor Tom20 and mRNA 5’ caps, PINK1/Parkin recruiting the translation initiation complex, and Parkin ubiquitinating and triggering degradation of translational repressor hnRNP-F [164]. These findings suggest that local recruitment of PINK1/Parkin on to mitochondria may induce the synthesis of new mitochondrial proteins, perhaps to replace damaged components removed through mitophagy or MDVs (Fig. 1e). Such a system of localized translation may be particularly advantageous in neurons as it reduces the costs of transport and potential protein misfolding errors from synthesizing proteins exclusively at the soma. For example, a recent study in cultured superior cervical ganglion axons found evidence of transcripts from at least 100 unique nuclear mtRNA genes localized to the axon [165], while an in vivo experiment pulling down ribosome-associated mRNA from retinal ganglion cell axons found enrichment of nuclear genes involved in mitochondrial function such as ETC components in the axonal compartment [166]. Given the unique architecture and bioenergetic demands of SNpc DA neurons, where the time needed to transport mitochondria to the presynapse may exceed the half-lives of many mitochondrial proteins [15], localized translation of nc-mtRNA is likely necessary to maintain mitochondrial function in a temporally and energetically efficient manner.

Furthermore, these nuclear encoded mitochondrial proteins rely on the TOM complex to enter the mitochondria, a process that recent findings suggest may be regulated by PINK1/Parkin (Fig. 1f). Several proteomics profiling and biochemical studies in Drosophila and human cells have found that PINK1-activated Parkin can induce ubiquitylation of TOM receptor proteins Tom70 and Tom20 [63, 72, 167, 168]. This ubiquitylation may increase the import of the endogenous mitochondrial protein HSD17B10 or a reporter peptide carrying a MTS, with cells carrying PD-associated PINK1 or PRKN showing impaired import [168, 169]. If these findings generalize to other imported proteins, it would suggest that PINK1/Parkin may also directly drive protein influx into the mitochondria through posttranslational regulation of the TOM complex. While exciting, these preliminary findings require further validation in more complex, in vivo mammalian systems. Moreover, further studies into whether ubiquitylation always leads to increased import (vs. degradation), and whether this mechanism leads to global increases in protein import or may have target-specific effects (eg. on ETC components) may yield important insights into the contribution of PINK1/Parkin to mitochondrial protein import. Given that PINK1 stabilization serves as a sentinel signal for import defects [58, 59], the ability of PINK1/Parkin to subsequently promote mitochondrial import may act as a direct negative feedback mechanism to preserve function by ensuring a steady supply of fresh, undamaged protein components.

These exciting recent findings point to a novel role of PINK1/Parkin in driving the local supply and replacement of mitochondrial proteins without the need to rely on slow transcriptional processes in a distant nucleus. While much work lies ahead to establish the role of PINK1/Parkin in driving localized translation and protein import in both healthy and disease contexts in the mammalian CNS, these mechanisms hint at a degree of temporal and spatial flexibility in the PINK1/Parkin system in mitochondrial regeneration that has previously been underappreciated.

Open questions for MQC in PD

Contribution of PINK1/Parkin MQC dysfunction to sporadic PD

While it is clear that genetic loss of PINK1/Parkin contribute to selective loss of SNpc neurons, these genetic cases represent only a small fraction of PD, which remains by and large a sporadic disease with no clear genetic etiology [1, 53]. Though plenty of evidence indicate that mitochondria dysfunction is widespread in sporadic PD cases (summarized above), these alterations are not necessarily specific to dysfunction of PINK1/Parkin MQC. Thus, the question of whether the mechanisms of MQC failure delineated in genetic models of PINK1/Parkin loss translate to the sporadic disease carries major implications for how we understand neuronal vulnerability in sPD.

Our understanding of MQC dysfunction in sPD has arisen largely from surveys of pathological changes in postmortem patient brains and mechanistic studies
linking α-synuclein aggregation to deficits in the PINK1/Parkin pathway. The two broad classes of potential responses that PINK1/Parkin MQC may exhibit in sPD are either protective activation in response to mitochondrial damage, or inactivation leading to an additional pathway of neurodegeneration. While there is evidence that PINK1 levels are stabilized and increased in PD patient brains [170], Parkin is S-nitrosylated and sequestered into LBs, leading to reduced availability of soluble Parkin to perform its native functions [171–175]. Because Parkin acts downstream of PINK1 activation, its inactivation in sPD likely blocks the effects of PINK1 accumulation. This is supported by the accumulation of proteins normally targeted for degradation by the PINK1/Parkin system. Consistent with findings of Parkin inactivation in PD brains, protein levels of multiple Parkin substrates – AIMP2, FBP1, PARIS, PDCD2, STEP61 – have been found to be elevated in patient midbrain tissue [74–76, 79, 176, 177]. PGC-1α, whose levels would be expected to drop with inactivation of the PINK1/Parkin pathway, has likewise been found to be downregulated in PD brains [150, 155].

Evidence that the PINK1/Parkin pathway is inactivated in PD raises two important questions: how does the pathway become inactivated in sPD, and to what degree does inactivation contribute to neurodegeneration? Current literature suggests that Parkin inactivation may derive from chemical inactivation [172, 174, 175, 178–180], or may occur downstream of α-synuclein aggregation (Fig. 2) [181, 182]. Initial findings that Parkin and α-synuclein do not directly interact with one another and that Parkin-KO failed to aggravate mutant α-synuclein toxicity in mice suggested that these proteins acted along independent pathways [183–185], though Parkin overexpression was able to rescue α-synuclein toxicity in multiple model systems [186–189]. However, these apparently contradictory results are consistent with a model in which Parkin inactivation occurs downstream of α-synuclein toxicity. A number of recent studies have suggested that α-synuclein pathology drives the activation of nonreceptor tyrosine kinase c-Abl, which phosphorylates Parkin at Y143 and inactivates it, leading to accumulation of Parkin substrates such as PARIS [75, 76, 181, 182, 190, 191]. Other potential mechanisms could involve direct sequestration of Parkin into α-synuclein aggregates [192] or the activation of other pathways that add inactivating post-translational modifications on Parkin [193]. Thus, a possible explanation for why genetic Parkin-KO does not

![Fig. 2](image-url)
exacerbate α-synuclein toxicity is because it phenocopies the Parkin inactivation induced by α-synuclein.

An important caveat to many of these studies is the use of transgenic mice that overexpress mutant α-synuclein, indicating that these mechanisms must be validated in a disease model more representative of the human disease. One recent study from our lab attempted to bridge this gap in knowledge by using the preformed fibrils (PFF) model, a more physiologically accurate model system of induced α-synuclein pathology in WT mice. We found that blocking the accumulation of Parkin substrate PARIS rescued behavioral, molecular, and lifespan deficits as effectively as in transgenic α-synuclein mouse models [181]. Though these findings suggest that these mechanisms of α-synuclein-induced inactivation of Parkin are conserved from transgenic mouse models to human PD, more systematic efforts in non-transgenic model systems are needed. Furthermore, while these studies heavily emphasize the role of α-synuclein aggregation in inactivating Parkin (Fig. 2), whether α-synuclein-independent pathways of MQC inactivation such as oxidative damage may also be at play requires future study. Regardless, these findings implicate PINK1/Parkin inactivation not just as a cause of selective SNpc degeneration in the small percentage of PD cases associated with monogenic PRKN or PINK1 mutations, but also in the sporadic disease driven by α-synuclein aggregation as well.

Mitochondrial dysfunction and neuroinflammation

While significant work has gone into understanding mitochondrial dysfunction within SNpc neurons in PD, it is less well understood how mitochondrial defects may contribute to neurodegeneration through non-cell autonomous mechanisms. While it is becoming increasingly clear that glial dysfunction and neuroinflammation play an important role in neurodegeneration in PD [194], the degree to which defects in MQC function contribute to neuroinflammation is relatively understudied. A few studies suggest that loss of PINK1 or Parkin may alter glial proliferation, leading to hypersensitized astrocytes and microglia that have greater levels of basal and triggered inflammatory cytokine release, nitric oxide (NO) production, and NLRP3 inflammasome activation [26, 195–198]. Co-culturing WT glia with Parkin-KO SNpc DA neurons has been shown to rescue neuron death and sensitivity to MPP+ observed in pure Parkin-KO co-cultures, suggesting that Parkin deficient glia contributes to cell death [26].

In addition to alterations in the glial inflammatory profile, compromised PINK1/Parkin MQC may also lead to pathological alterations to the interaction between the CNS and peripheral immune system. For example, PINK1/Parkin may play a role in suppressing mitochondrial antigen presentation (mitAP) on MHC-I in macrophages and dendritic cells [140, 145]. Postmortem human catecholaminergic neurons as well as cultured mouse SNpc neurons can express MHC-I receptors, which can be up-regulated over a PINK1-KO background or in response to infection, inflammatory mediators, oxidative stress, and α-synuclein [145, 199]. MitAP caused by loss of PINK1 can lead to brain infiltration of mitochondrial antigen-specific CD8+ cytotoxic T cells, which then attack SNpc DA neurons [145]. Thus, loss of PINK1/Parkin activity could trigger an adaptive immune response against mitochondrial proteins and engage the peripheral immune system in an improper assault against the CNS. Furthermore, these mechanisms may be occurring in a broader milieu of peripheral immune dysfunction. In macrophages, PINK1/Parkin generate MDVs containing mitochondrial ROS that are delivered to bacteria-containing phagosomes [141]. Loss of Parkin impairs bactericidal activity and leads to defective infection clearance, prolonged infection course, and elevated cytokine production [141]. Furthermore, human subjects with biallelic loss of Parkin show elevated systemic cytokine levels, with milder increases observed in heterozygous subjects [200]. These findings suggest that defects in MQC lead to three interesting effects on immune function that could contribute to PD neurodegeneration: an aggravated glia inflammatory phenotype, loss of immune tolerance and possible autoimmunity against neurons vulnerable in PD, and peripheral immune dysfunction. However, these mechanisms have largely been studied independently of one another. We lack an integrated model of how MQC defects produce (neuro)immune dysfunction and subsequent neurodegeneration. Furthermore, these mechanisms have been demonstrated in the context of global PINK1/Parkin ablation, whereas MQC defects in sPD may lead to more CNS-specific and milder immune dysfunction. Findings in sporadic PD patients of elevated systemic cytokines, CNS immune cell infiltration, and T cells recognizing α-synuclein peptide do suggest a certain degree of concurrent CNS and peripheral immune activation [194, 200, 201], but these studies are inherently correlated and give limited insight into the mechanisms by which these phenotypes arise. The degree to which diverse inflammatory mechanisms converge to cause neurodegeneration, and the importance of MQC defects to these mechanisms in sPD, are important areas of future research.

Conclusions

Cell-intrinsic and non-cell autonomous mechanisms

Early studies have long implicated selective vulnerability of SNpc DA neurons and mitochondrial dysfunction as core features of PD. While we now understand that PD
processes are far more distributed across the CNS and may be driven primarily by prion-like mechanisms spreading α-synuclein aggregates, these non-cell autonomous mechanisms likely act in concert with cell- and region-specific factors that lead to selective vulnerability to neurodegeneration. Though these cell-intrinsic factors are likely complex and varied across the different vulnerable subpopulations, in SNpc DA neurons findings over the last few decades point to the unique mitochondrial challenges and stresses due to complex cytoarchitecture as a potential major cause. Probing the function of PINK1/Parkin has led to critical insights into their role in maintaining mitochondrial integrity and proteostasis in the face of the stressors faced by mitochondria. These protective mechanisms comprise multiple tiers of MQC, such as facilitating mitophagy, regulating fission/fusion dynamics, triggering removal of damaged mitochondrial components through MDV generation, promoting mitochondrial biogenesis by increasing PGC-1α, and regulating the local translation of mitochondrial genes (Fig. 1), though many of these proposed mechanisms require convincing validation in the mammalian CNS. Newer areas of research have begun to establish mechanisms by which α-synuclein aggregation causes inactivation of MQC (Fig. 2), which have clear implications for sPD, as well as how MQC defects in neurons and non-neuronal cells may contribute to neuroimmune mechanisms of neurodegeneration.

Critical gaps in understanding
Despite the immense progress we have made, critical gaps in our understanding of PINK1/Parkin MQC remain. Our understanding of PINK1/Parkin pathways has been built up across a staggering variety of model systems ranging from *Drosophila, C. elegans*, mice, immortalized human cell lines, human iPSCs; whether all these pathways or a specific subset of these pathways is critical to the survival of human SNpc DA neurons requires further disambiguation. We have only just begun to elucidate the organizational principles of these diverse mechanisms, and it is likely that subcellular localization, cell-type specific factors, degree of damage, and nature of the damage are important factors governing which MQC processes become activated and when. For example, it is likely that MDVs activated in response to focal damage whereas mitophagy may be required for more severe, global mitochondrial damage. An additional possibility is that subcellular localization may shape dependence on PGC-1α-mediated biogenesis, a nucleus-dependent process, versus more spatially restricted mechanisms such as localized translation, which can operate in compartments far from the nucleus. Establishing the driving principles underlying how PINK1/Parkin juggle these various processes may answer many of the fundamental questions about cell-type vulnerability and disease mechanism in sPD.

Furthermore, how defects in MQC may interact with other sources of neuronal vulnerability in PD is another major gap in knowledge. Other populations of neurons that selectively degenerate in PD, such as the LC, are relatively spared in patients with PINK1/PRKN mutations [53, 56], indicating that deficiencies in PINK1/Parkin-mediated MQC are not the sole determinant of selective vulnerability. Other proposed causes include oxidative stress (eg. loss of iron homeostasis), dopamine toxicity, autonomous pacemaking driving rhythmic Ca^{2+}-dependent action potentials, and other vulnerabilities in mitochondrial function arising from the size of axonal arbors (Reviewed in [4] and [13]). Many of these mechanisms are clearly interlinked – such as intracellular Ca^{2+} influx driving mitochondrial Ca^{2+} uptake leading to increased ATP and ROS production [202, 203] – but where MQC deficits sits in the intertwined network of vulnerability factors is unclear. Further exploring the relationships within these networks may reveal key hubs that may prove to be more amenable to disease modifying therapeutics.

Beyond a neuron-centric view of PD pathogenesis, recent and ongoing studies of non-neuronal MQC defects and neuroinflammation will bolster our understanding of non-cell autonomous mechanisms of neurodegeneration. Finally, further elucidating the mechanistic interaction of α-synuclein aggregation and PINK1/Parkin MQC inactivation will be critical for establishing the role of MQC in sPD and synthesizing a more unified understanding of PD pathogenesis.

**Abbreviations**

(nc)-mtRNA: (nuclear encoded) mitochondrial RNA; CCCP: Carbonyl cyanide m-chlorophenyl hydrazone; CNS: Central nervous system; DA: Dopamine; ETC: Electron transport chain; IMM: Inner mitochondrial membrane; LB: Lewy bodies; MDV: Mitochondria-derived vesicle; mitAP: mitochondrial antigen presentation; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MQC: Mitochondrial quality control; mtDNA: mitochondrial DNA; OMM: Outer mitochondrial membrane; OTC: Ornithine transcarbamylase; PARS: Parkin Interacting Substrate; PD: PARKINSON’S disease; PFF: Preformed fibrils; RER: Rough endoplasmic reticulum; ROS: Reactive oxygen species; SNpc: Substantia nigra pars compacta; sPD: sporadic Parkinson’s disease; TOM: Translocase of the outer mitochondrial membrane

**Acknowledgements**

We thank Audrey H. Effenberger at MIT for discussions and editorial comments during the preparation of the manuscript. We thank I-Hsun Wu for designing the figures. TMD is the Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases.

**Authors’ contributions**

PG conducted the literature review, wrote initial draft, and conceived the figures. All authors contributed to conceiving the outline, reviewing, and editing the manuscript and figures. VLD and TMD approved the manuscript for submission. The authors read and approved the final manuscript.

**Funding**

All authors were supported by grants from the National Institute of Neurological Disorders and Stroke (NS38377, NS097049, and NS082205) and
the National Institute of Aging (AG059686) JPB Foundation. The authors were also supported by the Adrienne Helli Malvin Medical Research Foundation and the Diana Helli Henny Medical Research Foundation through their Parkinson’s Disease Programs (H-1 and M-2016). PG was further supported by a National Institutes of Health Medical Scientist Training Program grant (T32GM007753).

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
TMD is a consultant for Mitokinin and owns stock options as well as equity in, Neuraly, Inc. These arrangements have been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

Author details
1Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Department of Neurology, Department of Physiology, Solomon H. Snyder Department of Neuroscience, Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, 733 North Broadway, Suite 731, Baltimore, MD 21205, USA. *Adrienne Helli Malvin Medical Research Foundation, New Orleans, LA 70130, USA. 2Present address: Harvard-MIT MD/PhD Program, Harvard Medical School, Boston, MA 02115, USA. 3Adrienne Helli Henny Medical Research Foundation, New Orleans, LA 70130, USA. 4Present address: Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. 5Present address: Picower Institute for Learning and Memory, Cambridge, MA 02139, USA. 6Present address: Harvard-MIT MD/PhD Program, Harvard Medical School, Boston, MA 02115, USA.

Received: 27 November 2019 Accepted: 13 February 2020

Published online: 13 March 2020

References
1. Klein C, Westenberger A. Genetics of Parkinson’s disease. Cold Spring Harb Perspect Med. 2012;2(10):a008888.
2. Obeso JA, Stamelou M, Goetz CG, Poeewe W, Lang AE, Weintaub D, et al. Past, present, and future of Parkinson’s disease: a special essay on the 200th anniversary of the shaking palsy. Mov Disord. 2017;32(9):294–310.
3. Bhak G, Hofeldt T, Najvar R, de la Paz RS, Erbrink T, Stank. E. Staging of brain pathology related to sporadic Parkinson’s disease. Neurobiol Aging. 2003;24(2):191–211.
4. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson’s disease. Nat Rev Neurosci. 2017;18(2):101–13.
5. Li JY, Englund E, Holton JL, Soulet D, Hulc R, Lees AJ, et al. Lewy bodies in grafted neurons in subjects with Parkinson’s disease suggest host-to-graft disease propagation. Nat Med. 2008;14(5):501–3.
6. Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson’s disease. Nat Med. 2008;14(5):504–6.
7. Volpocelli-Daly LA, Luk KC, Patel TP, Tanik SA, Riddle DM, Stieber A, et al. Exogenous alpha-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. Neuron. 2011;72(1):57–71.
8. Luk KC, Kehm V, Carroll J, Zhang B, O’Brien P, Trojanowsky JQ, et al. Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science. 2012;338(6090):949–53.
9. Mao X, Ou MT, Karuppagounder SS, Kam TJ, Yin X, Xiong Y, et al. Pathological alpha-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science. 2016;353(6306):3374.
10. Kim S, Kwon SH, Kam TJ, Panicker N, Karuppagounder SS, Lee S, et al. Transeurotransmission of pathologic alpha-Synuclein from the gut to the brain models Parkinson’s disease. Neuron. 2019;103(4):627–41.e7.
11. Uemura N, Yagi H, Uemura MT, Hatanaka Y, Yamakado H, Takahashi R. Induction of alpha-synuclein preformed fibrils into the mouse gastrointestinal tract induces Lewy body-like aggregates in the brainstem via the vagus nerve. Mol Neurodegener. 2018;13(1):21.
12. Brundin P, Melki R. Prying into the prion hypothesis for Parkinson’s disease. J Neurosci. 2017;37(14):9808–18.
13. Giguere N, Burke Sanni S, Trudeau LE. On cell loss and selective vulnerability of neuronal populations in Parkinson’s disease. Front Neurol. 2018;9:455.
14. Bose A, Beal MF. Mitochondrial dysfunction in Parkinson’s disease. J Neurochem. 2016;139(Suppl 1):12–31.
15. Misgeld T, Schwarz TL. Mitostasis in neurons: maintaining mitochondria in an extended cellular architecture. Neuron. 2017;96(3):651–66.
16. Grenier K, McLellan GL, Fon EA. Parkin- and PINK1-dependent Mitophagy in neurons: will the real pathway please stand up? Front Neurol. 2013;4:180.
17. Spinnell JB, Hagis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018;20(7):745–54.
18. Scarfe LA, Stevens DA, Dawson VL, Dawson TM, Parkin and PINK1: much more than mitophagy. Trends Neurosci. 2014;37(6):215–24.
19. Amadore H, Esseri V, Florenza F, Atlante A, Bobba A, Nicolin V, et al. Morphological and bioenergetic demands underlying the mitophagy in post-mitotic neurons: the pink-parkin pathway. Front Aging Neurosci. 2014;6:181.
20. Kann O, Kovacs R. Mitochondria and neuronal activity. An J Phys Cell Phys. 2007;29(2):C641–57.
21. Bolam JP, Pissadaki EK. Living on the edge with too many mouths to feed: why dopamine neurons die. Mov Disord. 2012;27(7):2147–83.
22. Moss J, Bolam JP. A dopaminergic axon lattice in the striatum and its relationship with cortical and thalamic terminals. J Neurosci. 2008;28(4):11221–30.
23. Matsuda W, Furuta T, Nakamura KC, Hoki H, Fujiyama F, Ari A, et al. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. J Neurosci. 2009;29(4):444–53.
24. Anden NE, Hfuxe K, Hambrecht B, Holkett T. A quantitative study on the nigro-neostriatal dopamine neuron system in the rat. Acta Physiol Scand. 1966;67(3):306–12.
25. Pacelli C, Giguere N, Bourque MJ, Levesque M, Slack RS, Trudeau LE. Elevated mitochondrial bioenergetics and axonal Arborization size are key contributors to the vulnerability of dopamine neurons. Curr Biol. 2015;25(18):2349–60.
26. Giguere N, Pacelli C, Saumure C, Bourque MJ, Mathoud O, Levesque D, et al. Comparative analysis of Parkinson’s disease-associated genes in mice reveals altered survival and bioenergetics of Parkin-deficient dopamine neurons. J Biol Chem. 2018;293(25):9580–93.
27. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science. 1983;219(4587):797–80.
28. Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, et al. Rotenone, paraquat, and Parkinson’s disease. Environ Health Perspect. 2011;119(6):866–72.
29. Dhillon AS, Tarbutt GL, Levin JL, Plotkin GM, Lowry LX, Nalbone JT, et al. Pesticide/environmental exposures and Parkinson’s disease in East Texas. J Agromedicine. 2008;13(1):37–48.
30. Dawson TM, Dawson VL. Molecular pathways of neurodegeneration in Parkinson’s disease. Science. 2003;302(5646):819–22.
31. Schapira AH, Cooper JM, Dexter D, Jenner P, Clark JB, Marsden CD. Mitochondrial complex I deficiency in Parkinson’s disease. Lancet. 1989;186(4949):1269.
32. Bindoff LA, Birch-Machin M, Cartlidge NE, Parker WD Jr, Turnbull DM. Mitochondrial function in Parkinson’s disease. Lancet. 1989;28(6533):49.
33. Giaccocarco MP, La Morgia C, Rizzo G, Carelli V. Mitochondrial DNA and primary mitochondrial dysfunction in Parkinson’s disease. Mov Disord. 2017;32(3):346–53.
34. Grunevald A, Rygier KA, Hepplewhite PD, Morris CM, Picard M, Turnbull DM. Mitochondrial DNA depletion in respiratory chain-deficient Parkinson disease neurons. Ann Neurol. 2016;79(3):366–78.
35. Cokhead J, Kuzrava-Akanbi M, Hussain R, Pyle A, Chinnery P, Hudson G. Somatic mtDNA variation is an important component of Parkinson’s disease. Neurobiol Aging. 2016;38(2):41–6.
36. Dolle C, Florin I, Nido GS, Miletic H, Osaguyu N, Kristofferson S, et al. Defective mitochondrial DNA homeostasis in the substantia nigra in Parkinson disease. Nat Commun. 2016;7:13548.
37. Toulorge D, Schapira AH, Hajj R. Molecular changes in the postmortem parkinsonian brain. J Neurochem. 2016;139(Suppl 1):27–58.
38. Navarro A, Boveris A, Bandeaz MJ, Sanchez-Pino MJ, Gomez C, Muntane G, et al. Human brain cortex: mitochondrial oxidative damage and adaptive response in Parkinson disease and in dementia with Lewy bodies. Free Radic Biol Med. 2009;46(12):1574–80.

39. Deng H, Gao K, Jankovic J. The VPS35 gene and Parkinson’s disease. Mov Disord. 2013;28(5):569–75.

40. Trischl E, Goyon V, Zunino R, Mohanty A, Xu L, McBride HM. Vps35 mediates vesicle transport between the mitochondria and peroxisomes. Curr Biol. 2010;20(10):1310–5.

41. Wang W, Wang X, Fujioka H, Hoppel C, Whone AL, Caldwell MA, et al. Mitochondrial dysfunction by recycling DLP1 complexes. Nat Med. 2016;22(1):54–63.

42. Yang Y, Gehrke S, Imai Y, Huang Z, Ouyang Y, Wang JW, et al. Mitochondrial quality control via the PGC1alpha-TFEB signaling pathway is compromised by Parkin Q311X mutation but independently restored by PARIS-dependent declines in mitochondrial mass and respiration. Proc Natl Acad Sci U S A. 2015;112(2):667–8.

43. Walinda E, Morimoto D, Sugase K, Shirakawa M. Dual function of Phosphohubiquitin in E3 activation of Parkin. J Biol Chem. 2016;291(32):16879–91.

44. Pao KC, Stanley M, Han C, Lai YC, Murphy P, Balk K, et al. Probes of ubiquitin E3 ligases enable systematic dissection of parkin activation. Nat Chem Biol. 2012;8(3):324–31.

45. Park JS, Davis RL, Sue CM. Mitochondrial dysfunction in Parkinson’s disease: new mechanistic insights and therapeutic perspectives. Curr Neurol Neurosci Rep. 2018;18(5):21.

46. Aguirre JD, Dunkley KM, Mercer P, Shaw GS. Structure of phosphorylated ubiquitin domain and insights into PINK1-orchestrated parkin activation. Proc Natl Acad Sci U S A. 2017;114(2):298–303.

47. Park JS, Koentjoro B, Veivers D, Mackay-Sim A, Sue CM. Parkinson’s disease-associated human ATP13A2 (PARK9) deficiency causes zinc dyshomeostasis and mitochondrial dysfunction. Nat Rev Mol Cell Biol. 2018;19(2):93–107.

48. Koyano F, Okatsu K, Kosako H, Tamura Y, Go E, Kimura M, et al. Ubiquitin is phosphorylated by PINK1 to activate parkin. Nature. 2014;510(7503):162–6.

49. Okatsu K, Koyano F, Kimura M, Kosako H, Sae K, Tanaka K, et al. Phosphorylated ubiquitin chain is the genuine Parkin receptor. J Cell Biol. 2015;209(1):111–28.

50. Rose CM, Isasa M, Ordureau A, Prado MA, Beausoleil SA, Jedrychowski MP, et al. Highly multiplexed quantitative mass spectrometry analysis of Ubiquitylomes. Cell Biol. 2016;3(4):395–403.

51. Park JS, Davis RL, Sue CM. Mitochondrial dysfunction in Parkinson’s disease: new mechanistic insights and therapeutic perspectives. Curr Neurol Neurosci Rep. 2018;18(5):21.

52. Walinda E, Morimoto D, Sugase K, Shirakawa M. Dual function of Phosphohubiquitin in E3 activation of Parkin. J Biol Chem. 2016;291(32):16879–91.

53. Oruduea A, Saraf SA, Duda DM, Heo JM, Jедрычковский MP, Svidersky VO, et al. Quantitative proteomics reveals a feedforward mechanism for mitochondrial PARKIN translocation and ubiquitin chain synthesis. Mol Cell. 2014;56(3):360–73.

54. Shiba-Fukushima K, Arano T, Matsumoto G, Inoshita T, Yoshida S, Ishihara Y, et al. Phosphorylation of mitochondrial polyubiquitin by PINK1 promotes Parkin mitochondrial tethering. PLoS Genet. 2014;10(12):e1004861.

55. Oruduea A, Heo JM, Duda DM, Paulu JA, Olzewski JI, Yanishievski D, et al. 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. 2015;112(21):6673–82.

56. Oruduea A, Park JS, Davis RL, Sue CM. Mitochondrial dysfunction in Parkinson’s disease: new mechanistic insights and therapeutic perspectives. Curr Neurol Neurosci Rep. 2018;18(5):21.

57. Park JS, Davis RL, Sue CM. Mitochondrial dysfunction in Parkinson’s disease: new mechanistic insights and therapeutic perspectives. Curr Neurol Neurosci Rep. 2018;18(5):21.

58. Park JS, Koentjoro B, Veivers D, Mackay-Sim A, Sue CM. Parkinson’s disease-associated human ATP13A2 (PARK9) deficiency causes zinc dyshomeostasis and mitochondrial dysfunction. Nat Rev Mol Cell Biol. 2018;19(2):93–107.

59. Koyano F, Okatsu K, Kosako H, Tamura Y, Go E, Kimura M, et al. Ubiquitin is phosphorylated by PINK1 to activate parkin. Nature. 2014;510(7503):162–6.

60. Okatsu K, Koyano F, Kimura M, Kosako H, Sae K, Tanaka K, et al. Phosphorylated ubiquitin chain is the genuine Parkin receptor. J Cell Biol. 2015;209(1):111–28.

61. Park JS, Davis RL, Sue CM. Mitochondrial dysfunction in Parkinson’s disease: new mechanistic insights and therapeutic perspectives. Curr Neurol Neurosci Rep. 2018;18(5):21.
neurons and model systems revealed by digital snapshot proteomics. Mol Cell. 2018;70(2):211–27.

85. Vives-Bauza C, Zhou C, Huang Y, Cui M, De Vries RL, Kim J, et al. PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. Proc Natl Acad Sci U S A. 2010;107(1):378–83.

86. Narenda D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol. 2008;183(5):795–803.

87. Matsuda N, Sato S, Shiba K, Okatsu K, Saisho K, Gautier CA, et al. PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. J Cell Biol. 2010;189(2):21–21.

88. Geisler S, Holstom KM, Skjut D, Fiesel FC, Rothfuss OC, Kahle PJ, et al. PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/ SQSTM1. Nat Cell Biol. 2010;12(2):119–31.

89. Narenda DF, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, et al. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol. 2010;8(1):e1000298.

90. Lazarenko M, Sitter DA, Kane LA, Sarraf SA, Wang C, Burman JL, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature. 2015;524(7565):309–14.

91. Wong YC, Holzbaur EL. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. Proc Natl Acad Sci U S A. 2014;111(42):E4349–48.

92. Heo JM, Ordureau A, Paulo JA, Rinehart J, Harper JW. The PINK1–Parkin mitochondrial ubiquilatory pathway drives a program of OPTN/NDP52 recruitment and TBK1 activation to promote mitophagy. Mol Cell. 2015;60(4):685–95.

93. Yamano K, Wang C, Sarraf SA, Munch C, Kikuchi R, Noda NN, et al. Endosomal Rab cycles regulate Parkin-mediated mitophagy. Elife. 2018;7:e31326.

94. Palikaris K, Liora E, Tavaranakis N. Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. Nat Cell Biol. 2018;20(20):913–22.

95. Sun H, Tandarich LC, Nguyen K, Hollenbeck PJ. Compartmentalized regulation of Parkin-mediated mitochondrial quality control in the Drosophila nervous system in vivo. J Neurosci. 2016;36(28):7375–91.

96. Pickrell AM, Huang CH, Kennedy SR, Ordoneau A, Siders DP, Hoekstra JG, et al. Endogenous Parkin preserves dopaminergic substantia nigral neurons following mitochondrial DNA mutagenic stress. Neuron. 2015;87(2):271–81.

97. Van Laar VS, Arnold B, Casady SJ, Chu CT, Burton EA, Berman SB. Bioenergetics of neurons inhibit the translocation response of Parkin following rapid mitochondrial depolarization. Hum Mol Genet. 2011;20(5):1027–40.

98. Cai Q, Zakata HM, Simone A, Sheng ZH. Spatial parkin translocation and degradation of damaged mitochondria via mitophagy in live cortical neurons. Curr Biol. 2012;22(6):546–52.

99. Siebler P, Graziotto J, Jeong H, Simunovic F, Klein C, Krainc D. Mitochondrial Parkin recruitment is impaired in neurons derived from mutant PINK1 induced pluripotent stem cells. J Neurosci. 2011;31(16):5970–6.

100. Ashraf G, Schlehe JS, LaVoie MJ, Schwarz TL. Mitophagy of damaged mitochondrial morphology is dependent on mitochondrial axonal neurons and requires PINK1 and Parkin. J Cell Biol. 2014;206(5):655–70.

101. McWilliams TG, Prescott AR, Allen GF, Tamjor J, Munson JM, Thomson C, et al. Mitoc-QC illuminates mitophagy and mitochondrial architecture in vivo. J Cell Biol. 2016;214(1):333–45.

102. Sun N, Yun J, Liu J, Maldie D, Liu C, Rovira J, et al. Measuring in vivo Parkinsonian motor dysfunction: a comparison of 6-OHDA and MPTP models. Brain. 2016;139(1):258–74.

103. Lee JJ, Sanchez-Martinez A, Zarate AM, Benincia C, Mayor U, Clague MJ, et al. Basal mitophagy is widespread in Drosophila but minimally affected by loss of Park1 or parkin. J Cell Biol. 2018;217(5):1613–22.

104. McWilliams TG, Prescott AR, Montava-Garriga L, Ball G, Singh F, Barinov E, et al. Basal Mitophagy occurs independently of PINK1 in mouse tissues of high metabolic demand. Cell Metab. 2018;27(2):439–49.e5.

105. Kim YY, Um JH, Yoon JH, Kim H, Lee DY, Lee YJ, et al. Assessment of mitophagy in mt-Kema Drosophila revealed an essential role of the PINK1–Parkin pathway in mitophagy induction in vivo. FASEB J. 2019;33(9):9742–51.

106. Corneren T, Vliet S, Vints K, Gauron N, Verstreken P, Vandenbergh W, et al. Deficiency of parkin and PINK1 impairs age-dependent mitophagy in Drosophila. Elife. 2018;7:e35878.

107. Vincow ES, Menihew G, Thomas RE, Shulman NJ, Beyer RP, MacCoss MJ, et al. The PINK1–Parkin pathway promotes both mitophagy and selective respiratory chain turnover in vivo. Proc Natl Acad Sci U S A. 2013;110(16):6400–5.
132. Buhlmam L, Damiano M, Bertolin G, Fernando-Miguez R, Lombes A, Bric A, et al. Functional interplay between Parkin and Drp1 in mitochondrial fission and clearance. Biochim Biophys Acta. 2014;1843(9):2012–26.

133. Pryde KR, Smith HL, Chau KY, Schapira AH. PARK1 functions in the anti-fission machinery to secrete damaged mitochondria for mitophagy. J Cell Biol. 2016;213(2):163–71.

134. Rumjan JL, Pickles S, Wang C, Sekine S, Vargas JNS, Zhang Z, et al. Mitochondrial fission facilitates the selective mitophagy of protein aggregates. J Cell Biol. 2017;216(10):3231–47.

135. Abellovich H, Zarei M, Rlobgolt KT, Youle RJ, Dengel J. Involvement of mitochondrial dynamics in the segregation of mitochondrial matrix proteins during stationary phase mitophagy. Nat Commun. 2013;4:2789.

136. Koltsida P, Zhou J, Rackiewicz M, Nolic V, Dengel J, Abellovich H. Phosphorylation of mitochondrial matrix proteins regulates their selective mitophagic degradation. Proc Natl Acad Sci U S A. 2019;116(4):2051–7.

137. Sugiuira M, McClelland GL, Fon EA, McBride HM. A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. EMBO J. 2014;33(19):2412–56.

138. Soubannier V, McClelland GL, Zunino R, Braschi E, Rippstein P, Fon EA, et al. A vesicular transport pathway shuttles cargo from mitochondria to lysosomes. Curr Biol. 2012;22(2):135–41.

139. McClelland GL, Soubannier V, Chen CX, McBride HM, Fon EA. Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. EMBO J. 2014;33(4):2822–95.

140. Matheoud D, Sugiuira A, Bellermare-Pelletier A, Laplante A, Rondou C, Chemali M, et al. Parkinson’s disease-related proteins PINK1 and Parkin repress mitochondrial antigen presentation. Cell. 2016;165(2):314–27.

141. Abutaia BH, Schultz TL, O’Riordan MX. Mitochondrion-derived vesicles deliver antimicrobial reactive oxygen species to control phagosome-localized Staphylococcus aureus. Cell Host Microbe. 2018;24(5):625–36.e5.

142. Sugiuira A, Mattei S, Prudent J, McBride HM. Newly born peroxisomes are a hybrid of mitochondrial and ER-derived pre-peroxisomes. Nature. 2017;540(7640):201–4.

143. McClelland GL, Lee SA, McBride HM, Fon EA. Syntaxin-17 delivers PARK1-parkin-dependent mitochondrial vesicles to the endolysosomal system. J Cell Biol. 2016;214(3):275–91.

144. Soubannier V, Rippstein P, Kaufman BA, Shoubridge EA, McBride HM. Reconstitution of mitochondrial derived vesicle formation demonstrates selective enrichment of oxidized cargo. PLoS One. 2012;7(12):e52800.

145. Matheoud D, Cannon T, Voisin A, Penttinen AM, Ramet L, Fahmy AM, et al. Intestinal infection triggers Parkinson’s disease-like symptoms in Pink1−/− mice. Nature. 2015;521(7507):565–9.

146. Cadete VJ, Denisches S, Cuillerier A, Brisebois F, Sugiura A, Vincent A, et al. Formation of mitochondrial-derived vesicles is an active and physiologically relevant mitochondrial quality control process in the cardiac system. J Physiol. 2016;594(18):5434–62.

147. Finck BN, Kelly DP. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. J Clin Invest. 2006;116(3):615–23.

148. Lee Y, Stevens DA, Kang SU, Jiang H, Lee YI, Ko HS, et al. PARK1 primes Parkin-mediated ubiquitination of PARLS in dopaminergic neuronal survival. Cell Rep. 2017;17(8):1918–28.

149. Zheng L, Bernard-Marissal N, Moullan N, D’Amico D, Auverge J, Moore DJ, et al. Parkin functionally interacts with PGC-1alpha to preserve mitochondria and protect dopaminergic neurons. Hum Mol Genet. 2017;26(3):582–98.

150. Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, Watt ML, et al. PGC-1alpha, a potential therapeutic target for early intervention in Parkinson’s disease. Sci Transl Med. 2010;2(52):52ra73.

151. Ciron C, Zheng L, Bobela W, Knott GW, Leone TC, Kelly DP, et al. PGC-1alpha activity in nigral dopamine neurons determines vulnerability to alpha-synuclein. Acta Neuropathol Commun. 2015;3:16.

152. Clark J, Silvaggi JM, Kiselak T, Zheng K, Clore EL, Dai Y, et al. PGC1alpha overexpression downregulates Ptx3 and increases susceptibility to MMP toxicity associated with decreased Bdnf. PLoS One. 2012;7(11):e48925.

153. Ciron C, Lengacher S, Dusonchet J, Aebischer P, Schneider BL. Stained expression of PGC-1alpha in the rat nigrostriatal system selectively impairs dopaminergic function. Hum Mol Genet. 2012;21(22):4861–76.

154. St-Pierre J, Droit S, Uldry M, Silvaggi JM, Rhe J, Jager S, et al. Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. Cell. 2006;127(2):397–408.

155. Eschbach J, von Einem B, Muller K, Bayer H, Scheffold A, Morrison BE, et al. Mutual exacerbation of peroxisome proliferator-activated receptor gamma coactivator 1alpha deregulation and alpha-synuclein oligomerization. Ann Neurol. 2015;77(1):15–32.

156. Lin J, Wu PH, Tarr PT, Lindenberg KS, St-Pierre J, Zhang CY, et al. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. Cell. 2004;119(1):121–35.

157. Leone TC, Lehman JJ, Finck BN, Schaeffer PJ, Wende AR, Boudina S, et al. PGC-1alpha deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. PLoS Biol. 2005;3(4):e101.

158. Jiang H, Kang SU, Zhang S, Kaurapagounder S, Xu J, Lee YK, et al. Adult Conditional Knockout of PGC-1alpha Leads to Loss of Dopamine Neurons. eNeuro. 2016;3:e0183–16.2016.

159. McMeelkin LJ, Li Y, Fox SN, Rowe GC, Crossman DK, Day II, et al. Cell-specific deletion of PGC-1alpha from medium spiny neurons causes transcriptional alterations and age-related motor impairment. J Neurosci. 2018;38(3):5273–86.

160. Lesnik C, Golani-Amron A, Araya Y. Localized translation near the mitochondrial outer membrane: An update. RNA Biol. 2015;12(8):801–9.

161. Chacinska A, Koehler CM, Milenkovic D, Lithgow T, Pfanner N. Importing mitochondrial proteins: machineries and mechanisms. Cell. 2009;138(6):528–44.

162. Williams CC, Jan CH, Weissman JS. Targeting and plasticity of mitochondrial proteins revealed by proximity-specific ribosome profiling. Science. 2014;346(6210):748–51.

163. Zhang L, Shimoji M, Thomas B, Moore DJ, Yu SW, Marupudi NL, et al. Mitochondrial localization of the Parkinson’s disease related protein DJ-1: implications for pathogenesis. Hum Mol Genet. 2005;14(18):2063–73.

164. Gehl M, Sun W, Wu Z, Kinkenberg M, Sun Y, Auburger G, Guo S, et al. PARK1 and Parkin control mitochondrial translation in respiratory chain component mRNAs on mitochondrial outer membrane. Cell Metab. 2015;21(1):958–1008.

165. Asnafha A, Kar AN, Gale JR, Elkhalfoun AG, Vargas JN, Sales N, et al. A heterogeneous population of nuclear-encoded mitochondrial mRNAs is present in the axons of primary sympathetic neurons. Mitochondrion. 2016;30:18–23.

166. Sugaoka T, Jung H, Jung J, Turner-Bridger B, Okk, J, Lin JQ, et al. Dynamic axonal translation in developing and mature visual circuits. Cell. 2016;166(1):181–92.

167. Martinez A, Lectez B, Ramiez J, Popo O, Sutherland JD, Urbe S, et al. Quantitative proteomic analysis of Parkin substrates in Drosophila neurons. Mol Neurodegener. 2017;12(1):29.

168. Jacoupy M, Hamon-Keromen E, Oudrea E, Erpapazoglou Z, Coge F, Corvol JC, et al. The PINK1 kinase-driven ubiquitin ligase Parkin promotes mitochondrial protein import through the presequence pathway in living cells. Sci Rep. 2019;9(1):11829.

169. Gerolino G, Girlando F, Tarr PT, Lindenberg KS, St-Pierre J, Zhang CY, et al. Mitochondria-derived vesicle formation demonstrates mutual exacerbation of peroxisome proliferator-activated receptor gamma and mitochondrial dysfunction in patients with autosomal recessive Parkinson’s disease. FEBS Lett. 2009;583(3):521–5.
178. Yao D, Gu Z, Nakamura T, Shi QZ, Ma Y, Gastro B, et al. 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. 2004;101(19):10810–4.

179. Wong ES, Tan JM, Wang C, Zhang Z, Tay SP, Zaiden N, et al. Relative sensitivity of parkin and other cytokine-containing enzymes to stress-induced solubility alterations. J Biol Chem. 2007;282(16):12310–8.

180. Wang C, Ko HS, Thomas B, Tsang F, Chiew KC, Tay SP, et al. Stress-induced alterations in parkin solubility promote parkin aggregation and compromise parkin's protective function. Hum Mol Genet. 2005;14(24):3885–97.

181. Brahmachari S, Lee S, Kim S, Yuan C, Karuppagounder SS, Ge P, et al. Parkin interacting substrate zinc finger protein 746 is a pathologidal mediator in Parkinson's disease. Brain. 2019;142(8):2380–401.

182. Brahmachari S, Karuppagounder SS, Ge P, Lee S, Dawson VL, Dawson TM, et al. C-Abl and Parkinson's disease: mechanisms and therapeutic potential. J Park Dis. 2017;4(7):589–601.

183. Chung KK, Zhang Y, Lim KL, Tanaka Y, Huang H, Gao J, et al. Parkin ubiquititates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. Nat Med. 2001;7(10):1144–50.

184. Liani E, Eyal A, Avraham E, Shemer R, Sargel R, Berg D, et al. Ubiquitylation of synphilin-1 and alpha-synuclein by SAHF and its presence in cellular inclusions and Lewy bodies imply a role in Parkinson's disease. Proc Natl Acad Sci U S A. 2004;101(15):5500–5.

185. von Coelln R, Thomas B, Andrali SA, Lim KL, Savitt JM, Saffary R, et al. Inclusion body formation and neurodegeneration are parkin independent in a mouse model of alpha-synucleinopathy. J Neurosci. 2006;26(14):3685–96.

186. Lo Banco C, Schneider BL, Bauer M, Sajadi A, Iwatsubo T, et al. Lentrival vector delivery of parkin prevents dopaminergic degeneration in an alpha-synuclein rat model of Parkinson's disease. Proc Natl Acad Sci U S A. 2004;101(50):17510–5.

187. Petrucelli L, O'Farrell C, Lockhart PJ, Baptista M, Kehoe K, Vink L, et al. Parkin deficiency modulates NLRP3 inflammasome activation by attenuating an A20-dependent negative feedback loop. Glia. 2018;66(11):2427–39.

188. Kawahara K, Hashimoto M, Bar-On P, Ho GJ, Crews L, Mizuno H, et al. Alpha-synuclein aggregates interfere with Parkin solubility and distribution: role in the pathogenesis of Parkinson's disease. J Biol Chem. 2008;283(11):7388–97.

189. Yang Y, Nishimura I, Imai Y, Takahashi R, Lu B. Parkin suppresses neuronal death in mutant A53T alpha-synuclein model of Parkinson's disease. Cell Death Dis. 2018;9(6):700.

190. Haywood AF, Staveley BE. Parkin counteracts symptoms in a Drosophila model of Parkinson’s disease. BMC Neurosci. 2004;5:14.

191. Lang Y, Nishimura I, Imai Y, Takahashi R, Lu B. Parkin suppresses dopaminergic neuron-selective toxicity induced by Pacl-R in a Drosophila model. Neurobiol. 2003;376(9):911–24.

192. Mahul-Mellier AL, Fauvet B, Gysbers A, Dikiy I, Oueslati A, Georgeon S, et al. C-Abl phosphorylates alpha-synuclein and regulates its degradation; implication for alpha-synuclein clearance and contribution to the pathogenesis of Parkinson's disease. Hum Mol Genet. 2014;23(11):2858–79.

193. Brahmachari S, Ge P, Lee SH, Kim D, Karuppagounder SS, Ge P, et al. Activation of tyrosine kinase c-Abl contributes to alpha-synuclein-induced neurodegeneration. J Clin Invest. 2016;126(8):2970–88.

194. Kawahara K, Hashimoto M, Bar-On P, Ho GJ, Crews L, Mizuno H, et al. Alpha-Synuclein aggregates interfere with Parkin solubility and distribution: role in the pathogenesis of Parkinson's disease. J Biol Chem. 2008;283(11):6979–87.

195. Chen J, Ren Y, Gui C, Zhao M, Wu X, Mao K, et al. Phosphorylation of Parkin at serine 131 by p38 MAPK promotes mitochondrial dysfunction and neuronal death in mutant A53T alpha-synuclein model of Parkinson's disease. Cell Death Dis. 2018;9(6):700.

196. Fuzzati-Armentero MT, Cerri S, Blandini F. Peripheral-central Neuroimmune crosstalk in Parkinson's disease: what do patients and animal models tell us? Front Neurol. 2019;10:232.

197. Singh K, Han K, Tilve S, Wu K, Geller HM, Sack MN. Parkin targets NOD2 to regulate astrocyte endoplasmic reticulum stress and inflammation. Glia. 2018;66(11):2427–39.

198. Mouton-Liger F, Rosazza T, Sepulveda-Diaz J, Jeang A, Hassoun SM, Claire E, et al. Parkin deficiency modulates NLRP3 inflammasome activation by attenuating an A20-dependent negative feedback loop. Glia. 2018;66(8):1736–51.

199. Guzman JN, Sanchez-Padilla J, Wokosin D, Kondapalli J, Illici E, Schumacker PT, et al. Oxidant stress evoked by pacing in dopaminergic neurons is attenuated by DJ-1. Nature. 2010;468(7324):696–700.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.