Mitochondrial dysfunction and Parkinson disease: a Parkin–AMPK alliance in neuroprotection

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Although a subject of intense research, the etiology of Parkinson disease (PD) remains poorly understood. However, a wide range of studies conducted over the past few decades have collectively implicated aberrant mitochondrial homeostasis as a key contributor to the development of PD. Particularly strong support for this came from the recent demonstration that parkin, a familial PD-linked gene, is a critical regulator of mitochondrial quality control. Indeed, Parkin appears to be involved in all stages of the mitochondrial life cycle (i.e., from biogenesis to its exit from the cell (via mitophagy). Interestingly, the role of Parkin in the biogenesis and clearance of mitochondria is akin to that performed by the energy sensor AMP-activated protein kinase (AMPK), suggesting that the two proteins might act in a functionally converging manner to maintain the quality of cellular mitochondria. In this review, we discuss the contribution of mitochondrial dysfunction to PD pathogenesis and the role of Parkin and AMPK in preserving neuronal mitochondrial homeostasis. Alongside this, we will also articulate our thoughts on the potential alliance between Parkin and AMPK in offering neuroprotection through their ability to maintain energy balance in the brain.

Keywords: mitophagy; neurodegeneration; PINK1; LRRK2; PGC-1α; dopamine

Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer’s disease (AD). Currently, PD affects approximately 5–6 million predominantly elderly individuals worldwide, a number that is expected to escalate to 10 million or more by the year 2030 as the world’s population rapidly ages.1 Clinically, the disease is characterized by a constellation of motoric deficits including bradykinesia (slowness in movements), postural instability, rigidity, and tremor that arises as a result of striatal dopamine depletion owing to the progressive loss of midbrain dopaminergic neurons in the substantia nigra pars compacta (SNpc) that innervate the striatum. Accordingly, pharmacological replacement of dopamine represents an effective symptomatic recourse for the PD patient, although this mainstay treatment after a prolonged period is associated with wearing-off effects and problematic drug-induced dyskinesia, emphasizing the need to develop more effective PD therapeutics. The specific pattern of dopaminergic neurodegeneration is often accompanied by the presence of eosinophilic intracytoplasmic inclusions, known as Lewy bodies (LBs), in surviving neurons in the SN. Notably, α-synuclein, a presynaptic protein whose mutations are causative of familial PD, is a major component of LBs. However, it is now recognized that PD pathology is not just confined to the SN but is also observed in several extranigral structures, such as the dorsal motor nucleus of the vagus, locus coeruleus, and olfactory nuclei.2 Moreover, in advanced stages of the disease, limbic structures and the neocortex could be affected as well.2 Notably, nonmotor features arising from these extranigral pathologies, including autonomic, sensory, and cognitive dysfunctions, present additional sources of considerable consternation and disability for affected individuals that could be as debilitating as the movement-related problems.3

doi: 10.1111/nyas.12820

Notwithstanding this, many would still consider the loss of SN dopaminergic neurons as the principal, and arguably most important, lesion that defines PD. Accordingly, why and how nigral dopaminergic neurons undergo degeneration in the PD brain is a topic that has been intensely researched over the past several decades by the global PD research community, with the view that the insights gained from these studies would facilitate the development of novel PD therapeutics and biomarkers. Collectively, these studies consistently implicate aberrant mitochondrial and protein homeostasis as key contributors to the development of PD, with oxidative stress likely acting as an important nexus. Here, we focus our discussion on the important relationship between mitochondrial dysfunction and PD, and why the Parkin–AMPK axis may be a relevant pathway to explore in this context.

Mitochondrial dysfunction and PD

The idea that mitochondrial dysfunction could contribute to the development of PD originally surfaced in the early 1980s when Dr. William Langston and colleagues noticed that a group of young drug abusers exposed to 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) display motoric features that bear uncanny resemblance to those exhibited by sporadic PD patients. It turned out that the active metabolite of MPTP (i.e., MPP\textsuperscript{+}) mediates marked dopaminergic neurotoxicity by virtue of its selectivity for the dopamine transporter and its ability to inhibit mitochondrial complex I once it enters the neurons, highlighting for the first time that mitochondrial dysfunction may be a possible culprit responsible for neurodegeneration in PD. Soon after this discovery, several laboratories reported a significant reduction in the activity of mitochondrial complex I as well as ubiquinone (coenzyme Q10) in the SN of diseased samples. Similar observations were made with platelet mitochondria purified from PD patients but not those from age-matched control subjects, suggesting that the observed complex I deficiency is not a nonspecific effect of aging. These early studies have given rise to the mitochondria theory of PD, which remains a favored theory to date. Further support for the theory came from studies in animal models (including nonhuman primates) subjected to mitochondrial poisoning through the administration of toxins such as MPTP and rotenone, all of which faithfully recapitulate the salient features of the disease. Indeed, toxin-induced dopaminergic neurodegeneration represents a popular strategy to model the disease. Interestingly, whereas dopaminergic neurodegeneration induced by MPTP can be explained by the selectivity of MPP\textsuperscript{+} for dopaminergic neurons, it is intriguing to note that rotenone can produce the same outcomes even though the compound is more broadly distributed in the brain following its administration in animals. Despite this, the toxicity of rotenone is mostly confined to dopaminergic neurons, suggesting that dopaminergic neurons are uniquely susceptible to complex I inhibition. More recently, a genetic mouse model of mitochondrial dysfunction, known as MitoPark, was generated by conditional ablation of mitochondrial transcription factor A (TFAM), which plays a critical role in maintaining mitochondrial DNA, in dopaminergic neurons. Similar to toxin-induced models, mitochondrial dysfunction induced by TFAM deficiency results in energy crises and progressive dopaminergic neuronal loss that is accompanied by the presence of intraneuronal cytoplasmic inclusions (albeit not α-synuclein positive). Supporting the relevance of these findings to the general human population, epidemiological studies revealed that chronic exposure to rotenone (which is popularly used as a pesticide in farming) renders individuals susceptible to PD. Similarly, regular consumption of fruit and tea from annonaceous plants, such as soursop, that contain annonacin, a complex I inhibitor, is linked to the development of atypical Parkinsonism in the French West Indies (Guadeloupe). Taken together, a role for mitochondrial dysfunction in PD pathogenesis appears compelling. In recent years, the mitochondria theory of PD has gained further attention especially following the discovery that a pair of familial PD-linked gene products (i.e., Parkin and PINK1) function as key regulators of mitochondrial quality control (QC).

Parkin/PINK1 model of mitochondrial QC

Far from being solitary and static structures, mitochondria are now recognized to be dynamic organelles that constantly undergo membrane remodeling through repeated cycles of fusion and fission as well as regulated turnover via a specialized form of the lysosome-mediated degradation pathway known as mitophagy. Collectively, these
processes help to maintain the quality, and thereby optimal function, of mitochondria and allow the organelle to respond rapidly to changes in cellular energy status. Such a rapid response system is especially vital for neurons, which are strictly dependent on mitochondrial ATP production to meet their high energy demands. It is therefore not surprising to also note that mitochondrial dysfunction underlies several neurodegenerative diseases. For example, genetic mutations that disrupt the function of mitochondrial fusion/fission regulators lead to Charcot–Marie–Tooth disease type 2A, a classic axonal peripheral sensorimotor neuropathy characterized by degeneration of long peripheral nerves, and autosomal dominant optic atrophy—the most common form of inherited childhood blindness (for a recent review, see Ref. 13).

Recent studies have revealed that two genes whose mutations are linked to familial recessive Parkinsonism (i.e., PARK2 (Parkin; encoding a ubiquitin ligase) and PINK1 (encoding a serine/threonine kinase)) play a pivotal role in regulating mitochondrial QC. Interestingly, one of the first hints linking the function of these two genes to mitochondrial homeostasis came from studies in fruit flies. Indeed, it was documented more than a decade ago that Drosophila adult parkin null mutants exhibit their most prominent pathology not in the brain but in the flight musculature, which is plagued by muscle degeneration and pronounced mitochondrial lesions. Subsequent to this discovery, pink1 null flies were found to phenocopy their parkin-deficient counterparts, and, importantly, parkin overexpression in pink1−/− flies was able to rescue all the mutant phenotypes tested, although the reverse did not happen, suggesting that parkin acts in the same pathway but downstream of pink1. It is now known from several follow-up studies in flies and other model systems that the Parkin/PINK1 pathway is an important regulator of mitochondrial fission/fusion dynamics, although it is currently controversial whether the pathway promotes mitochondrial fission or fusion (for a recent review, see Ref. 15). More recently, both these PD-linked genes have also been linked to mitophagy. According to the proposed model as depicted in Figure 1, a key initial event that occurs upon mitochondrial depolarization is the selective accumulation of PINK1 on the outer mitochondrial membrane (OMM) of the damaged organelle. This does not usually occur in healthy mitochondria as the PINK1 protein is normally rapidly degraded through an elaborate process. The accumulation of PINK1 on the OMM allows it to phosphorylate Parkin and ubiquitin. Parkin, whose latent ubiquitin ligase activity becomes unmasked along the way owing to its phosphorylation by PINK1 and its interaction with phospho-ubiquitin, is recruited to the mitochondria through association with the phosphorylated ubiquitin chain. Activated Parkin then promotes the ubiquitination and subsequent degradation of many OMM proteins. During the process, Parkin-decorated mitochondria progressively cluster toward the perinuclear region to form mito-aggresomes, which by virtue of their association with lysosomal components are removed with time in an autophagy-dependent manner. In the case of neurons, where mitochondria may reside at the distal ends of neuronal projections, damage to mitochondria apparently triggers an arrest in their motility along the axon. This occurs through the degradation of the mitochondrial motor adaptor protein Miro in a pathway that is also mediated by PINK1 and Parkin, leading to arrested motility, which suggests that the PINK1/Parkin pathway may quarantine damaged mitochondria before their clearance. Indeed, a follow-up study demonstrated that Parkin/PINK1–mediated mitophagy of damaged mitochondria occurs locally in distal neuronal axons instead of at the soma.

Aside from its role in mitochondrial dynamics and removal, Parkin apparently also participates in the biogenesis of the organelle. A recent study revealed that Parkin can potentially regulate mitochondrial biogenesis by regulating the expression of PGC-1α (a key regulator of mitochondrial biogenesis) indirectly through its ability to downregulate PARIS, a major transcriptional repressor of PGC-1α. PGC-1α is a transcriptional coactivator that normally promotes mitochondrial biogenesis by activating a group of transcription factors, including nuclear respiratory factor 1 and 2 (NRF1/2), that in turn switch on biogenesis factors such as TFAM. The repression of PGC-1α by PARIS is expected to result in reduced mitochondrial mass, which, if unregulated, could compromise the ability of the cell to adapt to energy crises. Importantly, PARIS accumulates in postmortem PD brain tissue as well as in the ventral midbrain region of mice that is conditionally ablated of Parkin expression.
Figure 1. Parkin/PINK1 model of mitophagy. Illustration depicting the sequence of mitophagy events: (1) Upon mitochondrial depolarization, PINK1 stabilization on the outer mitochondrial membrane (OMM) leads to its (2) dual autophosphorylation. Activated PINK1 then phosphorylates Parkin and ubiquitin, which triggers Parkin recruitment and catalytic activation. (3) Parkin ubiquitinates several proteins on the OMM that results in their degradation by the proteasome recruited on the mitochondrial surface. (4) Mitophagy induction then occurs, presumably assisted by the autophagy adaptor proteins p62 and HDAC6 that bind to K63 polyubiquitinated proteins that are enriched on the damaged organelle.

which may help explain the significant reduction of PGC-1α levels seen in diseased brains.29 Taken together, Parkin appears to be involved in the entire spectrum of mitochondrial dynamics (i.e., from biogenesis, fusion/fission, and intracellular movements to its exit from the cell). It is therefore surprising to note the lack of overt phenotype in parkin null mice,31 which suggests that its loss-of-function may be compensated by other factors. This is particularly intriguing considering that Parkin is also a key regulator of protein homeostasis by virtue of its physiological function as a multifunctional ubiquitin ligase.32 Accordingly, the envisaged compensatory mechanism is likely to be complex and
possibly involves multiple redundant factors. Pertaining to the role of Parkin in mitochondrial homeostasis, it is attractive to propose that AMP-activated protein kinase (AMPK), which operates in many ways in a functionally equivalent manner to Parkin, may be a key compensatory factor for Parkin.

**AMPK and mitochondrial homeostasis**

AMPK is a key cellular nutrient and energy sensor that is activated in response to falling energy supply (e.g., ATP depletion or glucose starvation). It exists as a heterotrimer comprised of a catalytic α subunit (α1 or α2) and two regulatory subunits: β (β1 or β2) and γ (γ1, γ2, or γ3) and becomes activated upon phosphorylation of the α subunit on threonine (Thr)172 (Fig. 2). The upstream kinases identified to be responsible for AMPK Thr172 phosphorylation are liver kinase B1 (LKB1) and calcium/calmodulin–dependent kinase β (CaMKKβ), although the transforming growth factor-β–activated kinase 1 (Tak1) has also been reported as a putative kinase for AMPK phosphorylation. The major phosphatase involved in returning the activated AMPK to its basal state is protein phosphatase 2A (PP2A). In neurons, CaMKKβ seems to be the major kinase involved in AMPK activation, the trigger for which is an increase in cellular calcium without necessarily involving a change in the AMP/ADP ratio. Notably, AMPK can also be activated by hormones such as adiponectin and leptin, as well as through pharmacological means that include compounds such as 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) and the widely used antidiabetic drug metformin. Resveratrol and epigallocatechin-3-gallate (EGCG) are examples of natural compounds derived from plant products that are known to activate AMPK. When activated, AMPK switches on catabolic processes, such as glycolysis and amino acid oxidation, that favor energy conservation and restoration, while simultaneously switching off energy-consuming processes, such as gluconeogenesis and fatty acid synthesis.

Given the critical role of AMPK in regulating intracellular energy metabolism as an adaptive response to energy depletion, it is perhaps not surprising to note that AMPK has profound influence on mitochondrial homeostasis amid a plethora of metabolic events that it controls. Like Parkin, AMPK can regulate mitochondrial biogenesis as well as its clearance. It is well documented that AMPK works through PGC-1α to promote biogenesis of mitochondria. Although the mechanism by which AMPK upregulates PGC-1α activity remains unclear, studies have suggested that it could phosphorylate PGC-1α directly or activate the transcriptional coactivator indirectly by promoting its deacetylation by the NAD+-dependent deacetylase SIRT1. Interestingly, a recently identified target of AMPK is UNC-51–like kinase 1 (ULK1), a mammalian ortholog of the yeast Atg1 kinase that functions as a key initiator of the autophagy cascade. By activating ULK1, AMPK promotes autophagy, including mitophagy. Accordingly, in the absence of functional ULK1, nutrient

Figure 2. AMPK and its regulators. AMPK consists of three subunits: α, β, and γ. There are various isoforms for each subunit (α1, α2, β1, β2, γ1, γ2, and γ3). LKB1 and CaMKKβ are upstream kinases that directly activate AMPK via phosphorylation of Thr172 residue in the activation loop of α subunit. TAK1 has also been identified as a putative upstream kinase of AMPK. PP2A is an upstream phosphatase that dephosphorylates AMPK at Thr172, leading to the inhibition of its activity. When activated, AMPK inhibits the activity of its direct substrate ACC and activates downstream PGC1α, leading to fatty acid beta oxidation and mitochondrial biogenesis, respectively. AMPK can also activate autophagy through the coordinated phosphorylation of the mammalian autophagy-initiating kinase ULK1, among many other events that it controls.
starvation-induced autophagy is impaired, resulting in the accumulation of abnormal mitochondria with reduced potential. The same is observed when the known AMPK-mediated phosphorylation sites on ULK1 are abolished, suggesting that the clearance of damaged mitochondria is dependent on the AMPK–ULK1 pathway. That the regulatory role played by AMPK in both the biogenesis and clearance of mitochondria bears an uncanny resemblance to the function performed by Parkin is an interesting feature that one could readily appreciate from the discussion thus far. However, we believe the two proteins most likely exert their functionally converging influence on the organelle via parallel pathways rather than being upstream/downstream components of a linear pathway. Supporting this, Kwon et al. demonstrated that carbonyl cyanide-m-chlorophenylhydrazone (CCCP)-induced Parkin/PINK1–mediated mitophagy occurs in an AMPK-independent manner, although the study did not reveal whether AMPK activation might rescue mitophagy defects in Parkin-deficient cells.

**Parkin, AMPK, and neuroprotection**

Given the central role that mitochondria play in cellular survival and death, it is logical to expect that key mitochondrial regulators, such as Parkin and AMPK, that could preserve the function of the organelle would be cytoprotective in function. Not surprisingly, Parkin is widely accepted to be a potent neuroprotectant, capable of protecting neurons against a wide variety of insults, including those that compromise mitochondrial function. In the absence of functional Parkin, it is intuitive to think that the quality of mitochondria will progressively decline with time and will finally reach a state where it would become untenable for neurons to survive. Supporting this, we and other researchers have demonstrated that disease-associated Parkin mutations indeed compromise mitochondrial function in a chronic fashion and lead to progressive neurodegeneration (for a recent review on this topic, see Ref. 48).

Compared to Parkin, the role of AMPK in neuroprotection is more controversial, notwithstanding earlier discussion that AMPK activation helps to maintain mitochondrial QC and should in theory promote cellular survival. Interestingly, AMPK expression varies throughout development and in different neuronal subtypes. The level of expression of α2, β1, and γ1 subunits appears to be highest in areas of the brain that have been reported to have the highest glucose utilization, including the pyramidal cells in the hippocampus and the Purkinje cells in the cerebellum. The high levels of these subunits in the same defined population of high glucose-utilizing cells may suggest a more specialized role for these subunits in glucose metabolism. Furthermore, the α2 and β2 subunits are also differentially expressed throughout development. Notably, the expression of α2 and β2 increases during the time of neuronal differentiation. The upregulation of the expression of these subunits during neurogenesis indicates a specific role that they may play in neuronal cell function. Several studies have, however, demonstrated that AMPK activation could be detrimental to neuronal survival. For example, McCullough et al. showed that AMPK is hyperactivated in the brain following cerebral ischemia and that pharmacological activation or genetic ablation of its catalytic α2 (but curiously not α1) subunit provides marked protection against stroke-induced neuronal death. Similarly, in Huntington disease (HD) models, AMPK activation enhances neuronal loss and brain atrophy. Notably, the expression of the α1 subunit is elevated in the brains of HD patients. Curiously, a separate study showed that treatment of transgenic HD mice with metformin, a known activator of AMPK, increases brain AMPK activity and promotes the survival of these mice, suggesting that AMPK activation may not necessarily be negative. Indeed, a recent study demonstrated that prolonged treatment of mice with metformin significantly improves both their lifespan and healthspan, although the brain AMPK profile was not examined. In favor of a neuroprotective role of AMPK, its activation is associated with reduced neuronal death during glucose starvation. Moreover, others have found that pharmacological activation of AMPK via AICAR or resveratrol treatment produces beneficial effects in a mouse model of AD, the positive effects of which may be blunted by the AMPK inhibitor compound C. In Drosophila, genetic ablation of AMPK subunits generally results in progressive neurodegeneration, whether from knocking out the γ-subunit (lochrig mutant) or β-subunit (alicorn mutant), suggesting again that AMPK activity is important for neuronal survival.
Figure 3. Functional convergence of Parkin and AMPK at the level of mitochondrial biogenesis and clearance. AMPK promotes mitochondrial biogenesis by phosphorylating PGC-1α directly or indirectly by promoting its deacetylation by the NAD⁺-dependent deacetylase SIRT1. By phosphorylating ULK1, it enhances mitophagy. Similarly, Parkin promotes the biogenesis of mitochondria by ubiquitin-mediated degradation of PARIS, a transcriptional repressor of PGC-1α, and enhances mitophagy through its partnership with PINK1.

In the case of PD, AMPK activation is similarly a double-edged sword, promoting or aggravating neurodegeneration under different circumstances. Supporting a neuroprotective role of AMPK in PD, a recent report demonstrated that AMPK is activated in mice treated with MPTP and that inhibition of AMPK function by compound C enhances MPP⁺-induced cell death. Similar findings were made in another recent study, albeit in cultured cells exposed to rotenone. Given that MPP⁺ and rotenone are both complex I inhibitors, the rescue of these PD models by AMPK activation is consistent with its role in the maintenance of mitochondrial homeostasis. Contradicting these findings, Kim et al. found that AMPK mediates the atrophy of dopaminergic neurons in mice exposed to 6-hydroxydopamine (6-OHDA) and that metformin-induced AMPK activation accelerates, rather than retards, 6-OHDA–induced neurodegeneration in treated mice. In a related study, Xu et al. observed similar detrimental effects of AMPK activation in primary neurons treated with 6-OHDA, MPP⁺, or rotenone, and further suggest that neuronal death occurs via the cooperative activation of AMPK and inactivation of Akt following the suppression by these PD toxins. Notably, AMPK and Akt are known negative and positive regulators of the mTOR pathway, a central controller of cell growth and survival. Thus, whether AMPK activation is neuroprotective or a neuronal killer in PD remains unknown. However, it is noteworthy to mention that a recent cohort-based study involving 800,000 individuals revealed that metformin-inclusive sulfonylurea therapy significantly reduces the risk for PD occurring with type 2 diabetes in a Taiwanese population, suggesting that AMPK activation is
beneficial for PD. Our own data, as discussed in the next section, concur with this and other studies, suggesting a neuroprotective role of AMPK activation. In essence, we found that AMPK activation can compensate for the loss of Parkin function, thereby suggesting a Parkin–AMPK axis in neuroprotection.

A Parkin–AMPK alliance in neuroprotection

Using *Drosophila* as a model, we found that genetic ablation of the fly *parkin* gene results in prominent mitochondrial abnormalities and progressive loss of selected clusters of dopaminergic neurons accompanied by an age-dependent decline in locomotion ability. Features that bear striking resemblance to human PD that were originally reported by Pallanck’s group. Accordingly, we hypothesized that compounds that could rescue the phenotypes of *parkin* null flies would, in theory, be able to compensate for the loss of parkin function. In an attempt to identify such a compound, we conducted a pilot screen and found that EGCG, a green tea–derived catechin, could ameliorate all the PD-associated features of parkin-deficient flies. Notably, besides possessing antioxidant properties, EGCG has been reported to be an activator of AMPK. We speculated that AMPK activation may be involved in EGCG-mediated protective effects, as treatment of the mutant flies with baicalein, an established antioxidant, failed to ameliorate their pathologic phenotypes (unpublished observations). Indeed, we could demonstrate by pharmacological approaches (by means of metformin and AICAR treatment) or by genetic means that the activation of AMPK replicates EGCG-mediated protective effects in *parkin* null mutant *Drosophila*. Importantly, the positive effects of EGCG are abolished when AMPK expression is silenced or when a dominant negative AMPK mutant is overexpressed in the *parkin* mutant flies, indicating that AMPK is indeed the target. Before making this discovery, we had shown that Parkin overexpression could rescue the Parkinsonian phenotypes of transgenic *Drosophila* overexpressing human LRRK2 G2019S, a mutation responsible for familial and sporadic PD that is particularly prevalent in Western populations. Although LRRK2 may elicit its neurotoxicity in a variety of ways, we and other researchers have provided evidence that it could also promote mitochondrial pathology. Indeed, we found that the dopaminergic neurons of mutant LRRK2 flies are plagued with abnormal mitochondria, which may underlie their progressive degeneration. Given our demonstration that Parkin protects against LRRK2-mediated toxicity and that AMPK activation could mimic Parkin’s function, we reasoned that the same approach would be beneficial to mitigate LRRK2-induced neurotoxicity. Supporting this, we found that *Drosophila* LRRK2 mutants had reduced pathologic phenotypes after treatment with EGCG, metformin, or AICAR, or through the coexpression of a constitutively active AMPK mutant. Together, our results strongly suggest that Parkin and AMPK act in a parallel pathway to maintain dopaminergic neuronal homeostasis and that their activation is neuroprotective (at least in flies), although we cannot completely rule out at this stage the possibility that AMPK acts downstream of Parkin. Further support of an intimate relationship between Parkin and AMPK came from a recent study by Ferretta *et al.* who demonstrated that resveratrol, a natural polyphenolic compound found in the skin of fruits such as grapes and berries and, importantly, a relatively strong activator of AMPK in neurons, increased mitochondrial biogenesis and improved oxidative phosphorylation in patients’ fibroblasts harboring Parkin mutations.

Precisely how AMPK activation compensates for the loss of Parkin function to bring about a virtually complete rescue of its pathological phenotypes in flies is a question that we are currently actively pursuing. As mentioned earlier, AMPK and Parkin perform functionally equivalent roles at the level of mitochondrial biogenesis and clearance. Both are capable of positively regulating the activity of PGC-1α and also the mitophagy pathway, albeit through different strategies (Fig. 3). It is therefore likely that enhanced mitochondrial biogenesis and/or mitophagy could help maintain a viable pool of bioenergetically competent mitochondria necessary for dopaminergic neuronal survival. Notably, the resveratrol-based study by Ferretta *et al.* also revealed its ability to enhance autophagy flux in Parkin mutant fibroblasts. Accordingly, approaches toward promoting these processes may be of therapeutic value for PD. Notwithstanding this, one has to be cautious in exploiting the Parkin–AMPK axis in neuroprotection. Indeed, a few recent studies have indicated that prolonged activation of Parkin may not necessarily
be positive. For example, Van Rompuy et al. showed that long-term expression of wild-type Parkin in rat substantia nigra induces, rather than retards, dopaminergic neurodegeneration. 70 Another study by Carroll et al. demonstrated that Parkin sensitizes toward apoptosis in response to mitochondrial impairment through lowering the threshold for opening of the mitochondrial Bax/Bak channel, at least in part through degradation of the pro-survival Bcl-2 family member Mcl-1,71 suggesting again that Parkin may be cytotoxic, depending on the extent of the mitochondrial damage. Similarly, as discussed in earlier sections, AMPK activation can be neuroprotective or neurotoxic. For future therapies targeting the Parkin–AMPK axis, the dose and duration of their activation would have to be fine tuned.

Concluding remarks

The mitochondrial theory of PD is attractive and is presently enjoying a renaissance of support following a period when much attention was diverted toward the proteasome theory of PD and, subsequently, the autophagy theory of PD. Notwithstanding the periodic bias in favor of a particular disease-associated pathway, our opinion is that PD pathogenesis is unlikely a result of a singular pathway but rather a combination of interconnected events contributing to pathogenicity.72 Obviously, designing a silver bullet for PD pathogenesis seems unrealistic at this stage. However, what we have learned from the different lines of studies supporting the mitochondrial theory of PD is that bioenergetic failure is a key denominator of neurodegeneration and may very well be a common factor that connects the myriad events in PD. Certainly, bioenergetics and aging can be regarded as two peas in the same pod. Aging is by far the only unequivocal risk factor for PD. Accordingly, any modulators that can affect aging should influence an individual’s risk for PD. AMPK functions at the nexus of bioenergetics and aging and is widely accepted to be an important modulator of longevity. It is thus not surprising to note its neuroprotective effects. Along the same vein, a recent study also demonstrated the prolongevity effects of Parkin. 73 An alliance between Parkin and AMPK in neuroprotection therefore seems logical given their similar roles as key regulators of cellular bioenergetics and in life span extension. Importantly, the proposed alliance also forces one to think about the need to audit the brain with respect to its energy balance sheet, as any irregularities that occur (especially a debit in its reserves) is likely to take a significant toll on energy-sensitive neurons, potentially affecting their survival.

Acknowledgments

This work was supported by grants from the National Medical Research Council–Translational Clinical Research Program in Parkinson disease and Collaborative Basic Research Grant (LKL). Ms. Hang is supported by a graduate scholarship from the National University of Singapore Graduate School for Integrative Sciences and Engineering.

Conflicts of interest

The authors declare no conflicts of interest.

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