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THINK AGAIN

Insights & Perspectives

The PINK1 repertoire: Not just a one trick pony

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Abstract

PTEN-induced kinase 1 (PINK1) is a Parkinson's disease gene that acts as a sensor for mitochondrial damage. Its best understood role involves phosphorylating ubiquitin and the E3 ligase Parkin (PRKN) to trigger a ubiquitylation cascade that results in selective clearance of damaged mitochondria through mitophagy. Here we focus on other physiological roles of PINK1. Some of these also lie upstream of Parkin but others represent autonomous functions, for which alternative substrates have been identified. We argue that PINK1 orchestrates a multi-arm response to mitochondrial damage that impacts on mitochondrial architecture and biogenesis, calcium handling, transcription and translation. We further discuss a role for PINK1 in immune signalling co-ordinated at mitochondria and consider the significance of a freely diffusible cleavage product, that is constitutively generated and degraded under basal conditions.

KEYWORDS
ISR, mitochondria, mitochondrial quality control, mitophagy, Parkin, Parkinson's disease, PINK1, stress response

INTRODUCTION

The protein PTEN-induced kinase 1 (PINK1) was associated with early onset Parkinson's disease (PD) around the turn of the millennium.[1,2] It was shortly thereafter linked to a second PD associated gene, the ubiquitin E3 ligase PRKN (Parkin), using *Drosophila* models.[3–5] Whilst a genetic association was established, the cellular pathway governed by these two genes remained unknown, until the pioneering work of Richard Youle and co-workers demonstrated PINK1 accumulation and activation at damaged or depolarised mitochondria.[6] This leads to the recruitment and activation of Parkin, resulting in wide scale ubiquitylation of mitochondrial proteins followed by selective autophagy of the damaged mitochondria, otherwise known as mitophagy.[7] The explanatory power of these findings and the dazzling array of subsequent studies, which have filled in many of the details, have taken the limelight. After briefly describing this pathway, here we will focus on other aspects of PINK1 function, linked to mitochondrial quality control and beyond.

PINK1 is constitutively imported into mitochondria. Upon passage through the outer mitochondrial membrane (OMM) via the TOMM complex, PINK1 is cleaved by the inner mitochondrial membrane protease PARL.[8,9] Cleaved PINK1 is either released from mitochondria, or retained in part, and degraded via the N-end rule and ERAD pathways respectively.[10,11] If mitochondrial membrane potential is disrupted, experimentally through ionophores or OXPHOS inhibitors, PINK1 is stabilised on mitochondria in association with the TOMM complex.[12,13] Homo-dimerisation and trans-autophosphorylation then promotes the kinase activity of PINK1.[14] Activated PINK1 phosphorylates ubiquitin on mitochondria, and the E3 ligase Parkin at its ubiquitin-like domain.[15–18] Phosphorylated ubiquitin acts as a receptor for Parkin, recruiting it to mitochondria and Parkin phosphorylation by PINK1 fully activates its E3 ligase activity.[19] The combined activity of PINK1 and Parkin result in a feed-forward loop: Parkin introduces more ubiquitin substrates for PINK1 phosphorylation, which in turn recruits more Parkin.[20] Accumulated ubiquitin and phospho-ubiquitin on mitochondria recruits

Abbreviations: ETC, electron transport chain; ISR, integrated stress response; MDV, mitochondrial derived vesicle; MERC, mitochondria—endoplasmic reticulum contact; mitAP, mitochondrial antigen presentation; nRCC, nuclear-encoded respiratory chain complex; OMM, outer mitochondrial membrane; PD, Parkinson's disease

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autophagy receptors triggering engulfment of mitochondria in an autophagosome.[21–24]

Defects in mitophagy, owing to PINK1 or Parkin loss of function mutations, provide a compelling link to PD. A popular idea is that this leads to increased oxidative stress, whose effects may accumulate over time. Dopaminergic neurons are thought to be particularly vulnerable to mitochondrial dysfunction due to their large number of synapses and high energy demand.[25,26] Accordingly, depletion of PINK1 sensitises neurons to the mitochondrial poison MPTP. Viability can be rescued by re-expression of wild-type PINK1, but not by PD associated mutant forms. However, a soluble form of PINK1 lacking the mitochondrial targeting motif also restores neurotoxic protection.[27,28] Thus, a major pathophysiological consequence of PINK1 function can be uncoupled from its role in mitophagy. One may take this as a first indication that there are other strings to PINK1, at mitochondria and elsewhere. A second point for consideration is that the bulk of basal mitophagy occurring in animals is actually independent of PINK1 and Parkin.[29,30] The PINK1 mitophagy pathway is most prominent under artificial conditions of acute mitochondrial depolarisation, often accompanied by over-expression of Parkin in tissue culture cell lines. Neurons are dependent on OXPHOS for ATP production and cannot tolerate a switch to glycolysis.[31] For this reason, they may be prohibited from large scale sacrifice of their mitochondrial network. Studies in neurons have suggested that their particular bioenergetics inhibit Parkin translocation following acute mitochondrial depolarisation.[32] In one report visualisation of mitophagy in human fibroblasts could be achieved by over-expression of Parkin, but not in IPS-derived neurons over-expressing similar levels of Parkin.[33] Nevertheless, there are now multiple studies that have been able to directly visualise PINK1 and Parkin dependent mitophagy in a neuronal context.[34]

The PINK1 mitochondrial damage sensor signals earlier distress calls, before a commitment to mitophagy is made, enlisting other arms of mitochondrial quality control. PINK1 phosphorylation of ubiquitin and activation of Parkin also proves key to several of these other pathways, but there are other outlets for PINK1 kinase activity. Proteomic screens have identified other candidate PINK1 substrates. In one major study, a sub-set of RAB family proteins were shown to be phosphorylated in a PINK1 dependent manner, although they are not believed to be direct substrates.[35] This is especially interesting as some RAB family members are also phosphorylated by another PD associated gene LRRK2,[36] albeit at an adjacent site.[37] Further examples from more directed studies will be discussed below.

PINK1 linkage to mitochondrial biogenesis and dynamics

The cell responds to mitochondrial damage and associated mitophagy through active replenishment of mitochondrial mass and function. Peroxisome proliferator-activated receptor gamma (PPARγ) co-activator 1α (PGC-1α) is a master regulator of mitochondrial biogenesis. It functions as a transcriptional co-factor for numerous mitochondrial proteins. Expression of PGC-1α is itself repressed by a KRAB and Zinc Finger protein, Parkin interacting substrate (PARIS/ZNF746), that accumulates in PD brains and in models of Parkin inactivation.[38] Knock-down of PARIS has been shown to correct defects in respiration and restore mitochondrial mass in the ventral brain of adult knock-out Parkin mice.[39] In *Drosophila*, the accumulation of PARIS in dopaminergic neurons recapitulates the neuronal survival and motor deficits associated with PINK1 or Parkin loss and can be reversed by their over-expression.[40] PARIS is a direct ubiquitylation substrate of Parkin, which thereby governs its turnover. Thus, PINK1 activation of Parkin will impact on PARIS. However, recent data indicate that PARIS is also a direct phosphorylation substrate of PINK1 at Ser322 and Ser613 and that mutation of these sites abrogates Parkin-dependent ubiquitylation.[41] Therefore, PINK1 has a dual function in control of PARIS turnover, as both a 'priming kinase' and more canonically as an activator of Parkin (Figure 1).

Mitochondria are double membrane bounded organelles that form a reticular network. The connectivity within this network is governed by a balance of fusion and fission events that are mediated by specific GTPases.[42] The mitochondrial fusion protein, mitofusin 2 (MFN2), is co-ordinately extracted from mitochondrial membranes and degraded in a PINK1 and Parkin dependent manner.[43–45] PINK1 directly phosphorylates MFN2 and this in turn dictates Parkin binding, representing a similar priming mechanism to that described above for PARIS.[44]

Fission provides a means to isolate defective areas of the network and to provide discrete structures for autophagic engulfment. In PINK1 and Parkin mutant *Drosophila*, mitochondria appear swollen, consistent with a defect in fission or with an up-regulation of fusion.[46,47] However, this is not always faithfully reproduced in human cell studies.[48–50] Over-expression of dynamin-related protein 1 (DRP1) promotes fission in both *Drosophila* and human cell lines, rescuing the morphological effects of PINK1 depletion. DRP1 can be efficiently phosphorylated by PINK1 at Ser616 and mutating this residue to alanine but not to a phosphomimetic glutamic acid, impairs its ability to recover fission in PINK1 defective cells. The ability of wild-type DRP1 to rescue in the face of PINK knock-out suggests that other kinases may have some level of redundancy with PINK1. Parkin is dispensable for the PINK1/DRP1 axis regulation of fission, providing us with our first clear example of autonomous PINK1 function.[51] Recently DRP1 has been shown to rupture a fraction of OMM under specific conditions of compromised mitochondrial translation.[52] Any role for PINK1 is yet to be established, but we highlight it here as one means by which the inner mitochondrial proteins can be rendered prone to post-translational modification by exposure to cytosolic enzymes.

Mitochondria are transported to distant sites via microtubules. The mitochondrial GTPase MIRO recruits motor proteins, such as kinesin-1, which mediates axonal transport. Both PINK1 and Parkin suppress mitochondrial motility and MIRO is specifically degraded in a PINK1 and Parkin dependent manner.[53] Following acute mitochondrial depolarisation, MIRO is degraded prior to the onset of mitophagy. There are competing claims as to whether MIRO is a direct substrate of PINK1.[54–56] In one study, in vitro phosphorylation is observed and mutation of Ser156 to alanine prevents its degradation in response

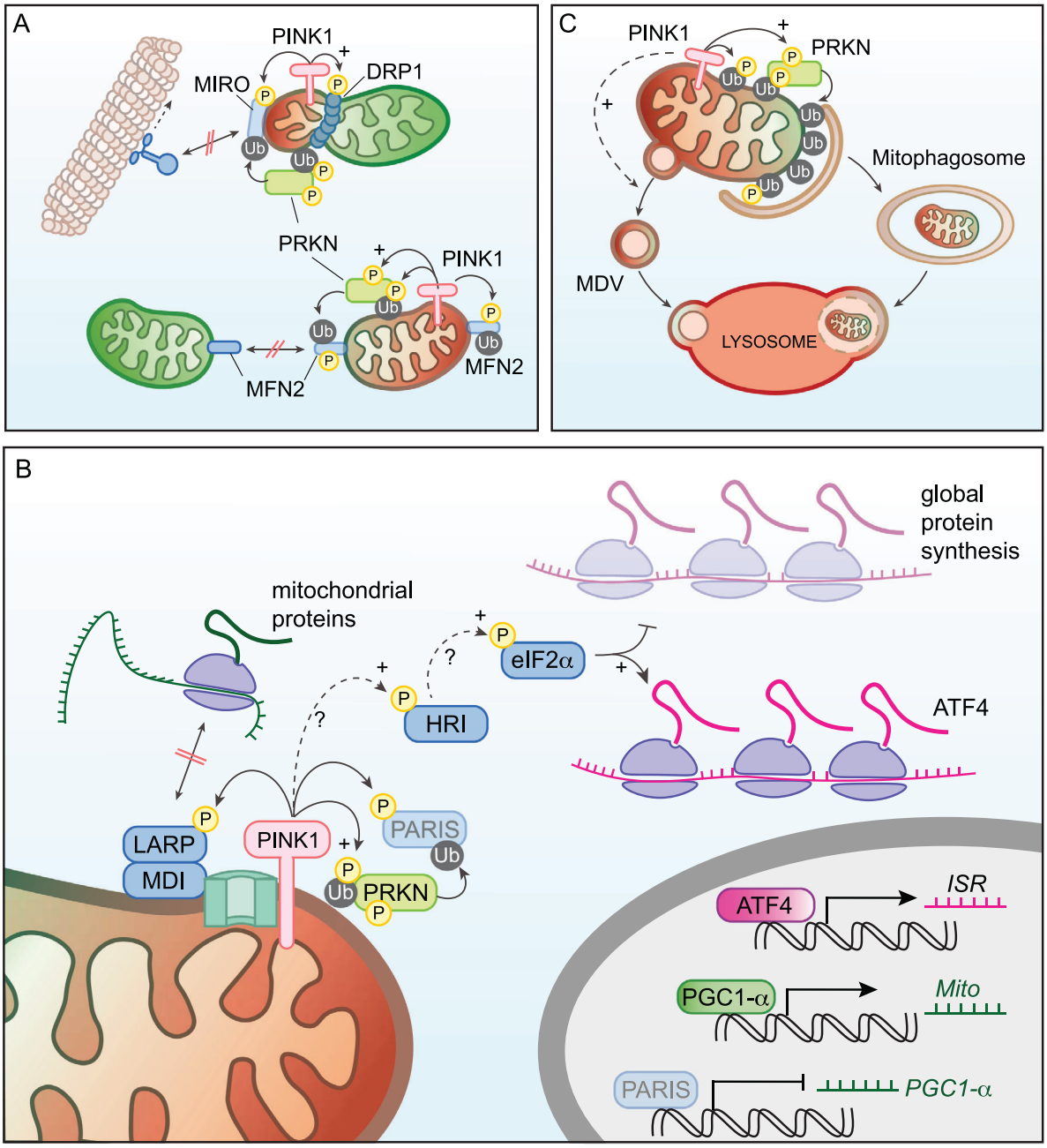

FIGURE 1 Activated PINK1 accumulates on damaged mitochondria and co-ordinates a multilayered response. (A) *Quarantine*. PINK1 phosphorylation (P) of three mitochondrial GTPases ensures the isolation of damaged mitochondria. Mitochondrial fission is promoted in a Parkin (PRKN) independent manner through PINK1 phosphorylation of DRP1. Mitochondrial fusion and microtubule mediated transport are inhibited through PINK1 and Parkin dependent ubiquitylation (Ub) and degradation of MFN2 and MIRO respectively.
(B) *Shutdown*. At defective mitochondria in *Drosophila* oocytes, PINK1 can repress localized translation of mitochondrial proteins (Mito; green) through inhibitory phosphorylation of LARP, a translational activator that is recruited to mitochondria by the AKAP protein MDI. Under depolarising conditions, PINK1 also phosphorylates the stress sensor kinase HRI. We speculate (indicated by dashed line) that this may enhance its activation of eIF2α. EIF2α inhibits global protein synthesis while promoting translation of ATF4, a master transcription factor of the integrated stress response (ISR) that can reconfigure cellular metabolism. The coupled activities of PINK1 and Parkin promote mitochondrial biogenesis by destabilising the transcriptional repressor PARIS, thereby enhancing expression of PGC1-α, the central transcriptional co-activator for mitochondrial biogenesis. Dashed-lines indicate speculative function.
(C) *Removal*. Sustained damage of mitochondria leads to accumulation of PINK1 beyond a threshold sufficient to initiate mitophagy. PINK1 phosphorylates both ubiquitin and the E3 ligase Parkin (PRKN). Once fully activated, Parkin ubiquitylates a wide range of OMM proteins providing more ubiquitin substrate for PINK1, thereby amplifying the ubiquitin signal. The 'ubiquitin coat' recruits autophagy receptors promoting the safe engulfment of damaged mitochondrial fragments in a mitophagosome which subsequently fuses with, a lysosome. PINK1 and Parkin also promote the generation of a subset of mitochondrial derived vesicles (MDVs) that traffic oxidised mitochondrial cargo to the lysosome independently of the autophagy machinery

to Parkin over-expression.[54] Mimicking phosphorylation with S156E mutation enhanced Parkin binding to MIRO, promoting its recruitment to mitochondria.[57] This results in a trafficking arrest, but is insufficient to induce mitophagy. Thus, PINK1 kinase activity controls three means to quarantine damaged mitochondria: promotion of fission via DRP1, inhibition of fusion via MFN2/Parkin and immobilisation via MIRO/Parkin.

PINK1 controls inner mitochondrial membrane architecture and function

The inner mitochondrial membrane invaginates into the matrix to form cristae. These tubular structures are open towards the inter-membrane space at so called crista junctions. The specific topology of cristae is critical to mitochondrial function.[58] Tsai *et al*. identified a fraction of PINK1 within the inter-membrane space in *Drosophila* and discovered that the inner mitochondrial membrane protein and major component of the mitochondrial contact site and cristae organising system (MICOS), dMICC60, is a PINK1 substrate. Phosphorylation of MICC60 is proposed to stabilise its oligomerisation, which is crucial for the formation of cristae junctions. Rare mis-sense mutations in the mitochondrial targeting sequence of MICC60 were identified in people with sporadic PD. When these are expressed in *Drosophila*, mitochondrial cristae junction formation is impaired in a dominant negative manner.[59]

The mitochondrial cristae harbour the components of the electron transport chain (ETC) and the ATP synthase. A robust phenotype of PINK1 loss, across humans, mice and flies, is an enzymatic defect in mitochondrial complex I and reduced membrane potential ($\Delta\psi_m$) and ATP levels.[60] Phosphoproteomic analysis of mouse complex I revealed a single PINK1-sensitive phosphorylation site at Ser250 in NDufA10. Stable transfection of a phosphomimetic form of NDufA10, but not wild type could rescue $\Delta\psi_m$, ATP levels and PINK1$^{-/-}$ synaptic phenotypes in *Drosophila*, without improving mitochondrial morphology, muscle degeneration or flight defects.[61] The phosphorylation of NDufA10 is required for reduction of ubiquinone. Intriguingly, an alternative electron carrier, Vitamin K_2, can rescue mitochondrial and systemic defects in a PINK1 defective *Drosophila* line.[62] Definitive evidence for direct phosphorylation of NDufA10 by PINK1 is lacking, but mitochondrial targeting of PINK1 is required. Furthermore, in common with the work of Tsai *et al*. discussed above,[59] the authors note that a fraction of PINK1 at mitochondria is protected from proteinase K, implying that it is not directly accessible from the cytosol. Other studies have not clearly identified a proteinase K insensitive fraction of PINK1.[63] We believe this is an important issue which needs further clarification.

One provocative mass spectrometry study of mitochondrial protein turnover in *Drosophila* indicates that in both PINK1 and Parkin defective animals, there is a selective deficiency in turnover of ETC components.[64] The PINK1 and Parkin dependent turnover of these proteins was also independent of the canonical autophagy (and hence mitophagy) machinery. How can this be? One explanation may lie in the budding of small double membrane entities from mitochondria which have been named mitochondrial derived vesicles (MDVs).[65] Several types of MDVs have been proposed with differing cargoes and destinations.[66] At least some MDVs require PINK1 expression and Parkin function and are delivered directly to the lysosome. Little is known about cargo selection for these vesicles, but it appears that oxidation may be a key factor. Addition of a complex III inhibitor, antimycin A, to mitochondria in vitro led to the generation of MDVs carrying the complex III subunit core2, without any enrichment in the OMM protein, VDAC.[67]

PINK1 regulation of protein translation

Mitochondrial dysfunction activates the integrated stress response (ISR), which controls phosphorylation of eukaryotic translation initiation factor 2 Alpha (eIF2α) by virtue of four known kinase sensors (PERK, PKR, GCN2, HRI).[68] Phosphorylation of eIF2α reduces global protein synthesis,[69] whilst promoting the translation of specific mRNAs which act to generate the ISR.[70] This strikes us as interesting, not least because the mitochondrial surface itself is an active site of protein translation. Many ribosomes can be seen directly interacting with the TOMM complex and strong evidence for co-translational import has been provided.[71,72] ATF4, the key transcription factor controlling the ISR, is elevated in PINK1 and Parkin mutant *Drosophila*.[73] Moreover, a pathway has recently been elucidated that links stress-induced release of the inner mitochondrial membrane protein DELE1 to activation of HRI and consequent induction of ATF4.[74] Thus, under basal conditions, PINK1 most likely suppresses the ISR by virtue of maintaining healthy mitochondria. The phosphoproteomic screen that discovered the PINK1-dependent, but indirect, phosphorylation of RAB proteins, also uncovered PINK1-dependent phosphorylation of the ISR sensor, HRI at Ser41, under conditions of acute depolarisation.[35] The functional relevance of this needs further investigation, but it is intriguing given that the conditions which lead to PINK1 accumulation correlate with ISR activation.

As well as global control of protein synthesis, there are contexts when it may be advantageous to regulate local protein production. This is in fact exemplified by PINK1 itself. Its short half-life is incompatible with mitophagy in neurons at sites distant from the soma. PINK1 mRNA hitches a ride on mitochondria and is transported to distant sites by association with synaptojanin 2 in complex with SYNJ2BP.[75]

The nuclear encoded mRNAs for respiratory chain proteins (nRCCs) are specifically repressed in the cytosol. These mRNAs can be recruited to the mitochondrial surface in a manner dependent on TOM20. This is facilitated by PINK1 binding of the nRCC mRNAs, which competes with their binding to translational repressors.[76] The same study finds that PINK1 physically associates with the mRNA 5′ cap structure in a RNA-independent manner and that this interaction is impaired by the PD mutation, G309D. Some aspects of this derepression are also associated with Parkin ubiquitylation, such as the mono-ubiquitylation of mRNA repressor protein hnRNP-Glo. Thus, the PINK1 pathway may be linked to a further line of mitochondrial quality control by boosting local translation of ETC components, which may precede both the

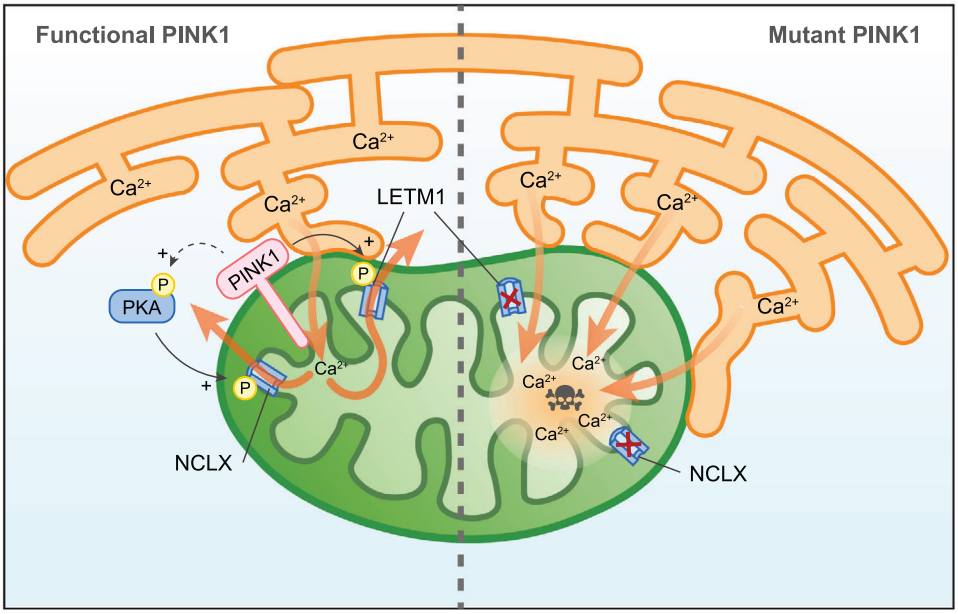

FIGURE 2 PINK1 safeguards against calcium overload.
Mitochondria buffer calcium released from the endoplasmic reticulum (ER). ER to mitochondria calcium flow occurs at distinct mitochondria—endoplasmic reticulum contacts (MERCs). In the absence of functional PINK1, enhanced MERCS and reduced calcium efflux work together to cause intra-mitochondrial calcium overload and ultimately cell death. PINK1 is proposed to prevent calcium overload in a Parkin independent manner by phosphorylating and thereby activating the LETM1 H^+/Ca^{2+} exchanger. In addition, PINK1 may also positively regulate the NCLX Na^+/Ca^{2+} exchanger indirectly by activating PKA. The topology suggests a functional pool of PINK1 may be accessible to the inner mitochondrial membrane. Dashed-line arrows indicate suggested function

transcriptional effects following PARIS degradation and mitophagy. Mildly damaged mitochondria may benefit from a local increase in production of respiratory chain proteins to reinvigorate oxidative phosphorylation.

During oogenesis in *Drosophila* there is a strong selection against defective mitochondria, amidst a high degree of mitochondrial proliferation. In distinction to observations in somatic tissues and cultured cells,[77,78] Parkin is not required for selective inheritance of mtDNA in the *Drosophila* female germ line.[79] However, PINK1 is required and preferentially accumulates on germ cell mitochondria, which carry a deleterious mtDNA mutation. Zhang *et al*. suggest that PINK1 thereby selects for healthy mitochondria, through the inhibitory phosphorylation of the mitochondrial translational activator La Ribonucleoprotein 1 (LARP1).[80] How might these findings fit together? Perhaps they indicate a graded response. Under basal conditions or contained damage, PINK1 localizes and activates transcription of specific mRNAs maintaining mitochondrial homeostasis. Once a certain threshold is crossed, PINK1 activity switches off local translation through LARP1 and activates the ISR pathway (Figure 1B).

The impact of PINK1 upon cellular calcium signalling

Mitochondria can influence Ca^{2+} signalling indirectly through the production of metabolites. A more direct mechanism involves the import of Ca^{2+} via a Calcium uniporter and its release by means of Na^+/Ca^{2+} and H^+/Ca^{2+} exchangers. Mitochondria buffer Ca^{2+} released by the endoplasmic reticulum and this can be made highly efficient by the interaction between the two organelles. siRNA screening in Parkin over-expressing RPE1 cells uncovered a role for IP3-receptor mediated transfer of Ca^{2+} from the ER to mitochondria, in the mitophagy pathway downstream of Parkin.[81]

Substantia nigra pars compacta (SNc) dopaminergic (Da) neurons are particularly reliant upon Ca^{2+} fluxes for their pace making activity.[82,83] Defective Ca^{2+} signalling has been implicated in PD,[82,83] but to what extent can this be linked to PINK1? Loss of PINK1 in mouse neurons leads to higher levels of Ca^{2+} in mitochondria. In the face of repetitive increases in cytosolic Ca^{2+}, mitochondrial Ca^{2+} overload occurs. This leads to opening of the permeability transition pore, causing cell death.[84] This pathway has been linked to defects in the Na^+/Ca^{2+} exchanger (NCLX) and can be rescued through PKA phosphorylation of NCLX.[85] Note that PINK1 has itself been shown to activate PKA.[86,87] PINK1 has also been shown to phosphorylate a H^+/Ca^{2+} exchanger, (LETM1) on mitochondria. The absence of PINK1-dependent phosphorylation at T192 of LETM1 is proposed to lead to a reduction in its activity and consequent mishandling of Ca^{2+} (Figure 2).[88] This provides a further example, beyond MICC60 (and possibly NDufA10) where PINK1 phosphorylates an inner mitochondrial membrane protein.

Calcium is transferred from the ER to the mitochondria at specific ER-mitochondrial junctions, also known as mitochondria–endoplasmic reticulum contacts (MERCs).[89] These contact sites are disrupted

in neurodegenerative disease models.[90,91] PINK1 has been proposed to localise to MERCs upon its accumulation on mitochondria following depolarisation.[92] Furthermore, PINK1 and Parkin degradation of MFN2 leads to rapid dissociation between ER and mitochondria.[45] However, PINK1 arrests at the TOMM complex, whose components are not evidently enriched at ER contact sites. The exception is the receptor subunit TOM70, which has alternative functions in regulating calcium transfer into mitochondria.[93] Direct evidence for PINK1 interaction with TOM70 is currently lacking and conventional wisdom would say that PINK1 interacts with the TOM20 receptor sub-unit. In *Drosophila* PINK1 mutants, SNc Da neurons have enhanced MERCs and elevated intra-mitochondrial Ca^{2+} levels. Interestingly this phenotype can be recapitulated by MIRO over-expression and rescued by MIRO depletion.[91]

The increase in intra-mitochondrial Ca^{2+} associated with defective PINK1 is observed across multiple studies and models.[84,88,91] Increased ER contact sites provide a satisfactory explanation, consistent with the predominant topology of PINK1. If Ca^{2+} stress is a frequent cause of mitochondrial damage and/or depolarisation, then enlisting PINK1 to uncouple mitochondria from the source of Ca^{2+}, would be a simple way of maintaining homeostasis.

PINK1 is linked to innate and adaptive immune signalling

In adaptive immunity, antigens of intracellular proteins are expressed on the cell surface bound to MHC molecules, allowing for the detection of infected or cancerous cells by cells of the immune system.[94] It has been shown that autophagy can lead to antigen presentation on both Class I and Class II MHC molecules.[95] Conceptually, promoting mitophagy via the PINK1 and Parkin pathway could provide a means to enable presentation of mitochondrial antigens (mitAP). These antigens could be delivered to endosomal compartments via MDVs as depicted in Figure 1C. In fact, the opposite appears to be the case. Although, a distinct MDV species is proposed for the mitAP pathway, PINK1 and Parkin repress the presentation of mitochondrial matrix-targeted antigens[96] (Figure 3). This leads to the proposal that derepression of autoimmune mechanisms contribute to the aetiology of PD.

Patients diagnosed with inflammatory bowel disease have an increased risk of PD in later life.[97] Intestinal infection with Gram-negative bacteria in $PINK1^{-/-}$ mice is resolved as effectively as in controls, but the $PINK1^{-/-}$ mice exclusively go on to develop PD-like phenotypes, which are accompanied by the appearance of $CD8^{+}$ T cells in the brain. As the bacterial infection also induces the presentation of mitochondrial antigens, the immune suppressive role of PINK1 is a plausible link to the symptoms.[98] In our opinion, it is still not entirely clear if this effect is specific to mitochondrial antigens or a more global effect on antigen presentation.

PINK1-Parkin defects have also been linked to the innate immune system via the activation of the STING pathway. This can be linked to mitophagy, which acts to limit the release of mitochondrial DNA after mitochondrial damage.[99] In the absence of efficient mitophagy, cytosolic mtDNA activates STING, which in turn elicits release of pro-inflammatory cytokines.[100]

$PINK1^{-/-}$ and $Parkin^{-/-}$ mice show no discernible PD phenotypes unless additional stresses are applied. When $PINK1^{-/-}$ mice are subjected to exhaustive exercise, and separately in the case of $Parkin^{-/-}$; mutator mice (which accumulate mutations in mitochondrial DNA), a strong inflammatory phenotype is observed. This can be rescued by the concurrent deletion of STING.[99] The $Parkin^{-/-}$; mutator mice show loss of dopaminergic neurons and movement defects that are also rescued by STING deletion. Thus, there is strong experimental evidence for the relevance to PD of this pathway, which is normally repressed by mitophagy. Accordingly, human patients with biallelic PINK1 and Parkin mutations show elevated levels of IL6 and mtDNA in the plasma, which could provide useful biomarkers for disease state and progression.[101]

Mitochondrial Antiviral Signalling Protein (MAVS) is a key component of the anti-viral innate response, downstream of RIG-1. RNA virus infection triggers MAVS to aggregate in prion-like structures, which then signal to activate the transcription of pro-inflammatory cytokines.[102,103] Recently PINK1 has been shown to interact with and inhibit the formation of these MAVS prion-like structures, with PINK1 deficiency leading to enhanced aggregation, although the exact mechanism is unclear.[104] The MAVS pathway can also be activated by release of mtRNA, recalling the mtDNA/STING connection described above.[105] There are multiple established means of cross-talk between the STING and RIG-1/MAVS pathways.[106] PINK1 is now serving us with a further embodiment of this principle

Potential biological functions of cleaved PINK1

As noted previously, under basal conditions newly translated PINK1 is continuously cleaved following mitochondrial import. The 54 kDa cleavage product (cPINK1) containing the intact kinase domain is released into the cytosol and degraded.[107] cPINK1 is nevertheless detectable in multiple physiological contexts and has been shown to increase during the differentiation of mouse primary cortical neurons, in which ~75% of cPINK1 is cytosolic. In these neurons, the basal levels of cPINK1 far exceed full length PINK1.[108] Similarly, in SHSY5Y neuroblastoma cells, retinoic acid induced neuronal differentiation is accompanied by increased levels of cPINK1. The unrestricted diffusion of cPINK1, affords an opportunity to expand its sphere of influence. Is this significant? Recall that exogenous expression of cytosolic PINK1 provides a protective effect for neurons against the neurotoxin MPTP, as described in the introductory section.[27,28] One caveat of this result is that a fraction of 'cytosolic' PINK1 may otherwise associate with mitochondrial localised binding partners such as MIRO.[53] Biochemical sub-cellular fractionation experiments have found that both phosphorylated ubiquitin and cPINK1 are also present in the nucleus following mitochondrial depolarisation.[109] Phosphoproteomics suggests that PINK1 phosphorylates nuclear proteins directly and also enables their modification by phospho-ubiquitin.[109,110]

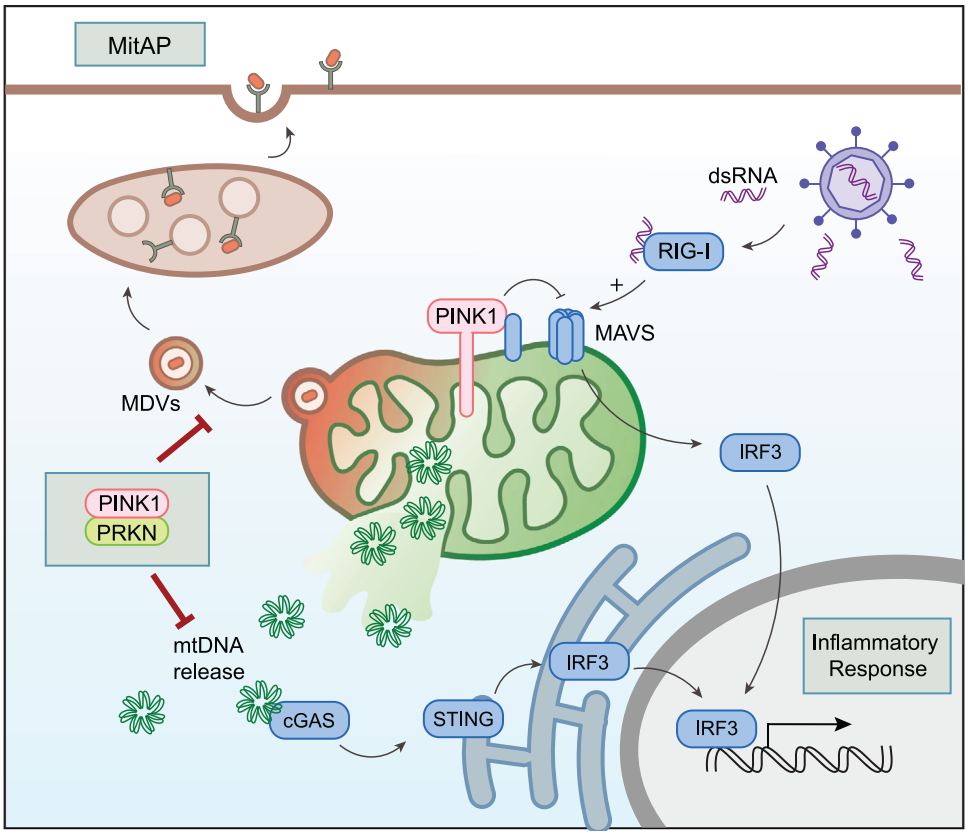

FIGURE 3 PINK1 and Parkin are linked to innate and adaptive immune responses.
Some mitochondrial derived vesicles (MDVs) are proposed to traffic mitochondrial cargo to specialized endosomes, for processing and loading onto MHC-II molecules. This, as well as cross-presentation on MHC-I (not shown), allows for mitochondrial antigen presentation (MitAP) on the cell surface. PINK1 inhibits this process in a Parkin dependent manner. Viral dsRNA is recognised by the receptor RIG-I, leading to aggregation of MAVS on mitochondria, and upregulation of the inflammatory response via multiple transcription factors including IRF3. PINK1 directly interacts with MAVS in a Parkin-independent manner, preventing its aggregation and inhibiting the viral dsRNA signalling response. Mitochondrial DNA (mtDNA) released into the cytosol from compromised mitochondria likewise induces an inflammatory response. This is mediated through mtDNA binding to the cytosolic DNA sensor cGAS and STING, promoting activation of multiple transcription factors, also including IRF3. PINK1-Parkin mediated mitophagy is proposed to limit this process by preventing mtDNA release

One feature of PD is the loss of neuronal plasticity in cortical and limbic structures of the brain.[111] In PINK1-deficient mice, exogenous expression of a cytosolic form of PINK1 lacking a mitochondrial targeting sequence, is sufficient to rescue a decrease in dendritic arborization of cortical neurons.[86] The intracellular levels of brain derived neurotrophic growth factor (BDNF), a modulator of dendrite complexity, are correspondingly increased by ectopic expression of a cytosolic form of PINK1, but only marginally by the full length mitochondrial targeted form. This requires kinase activity and has been attributed to PINK1-dependent activation of Protein Kinase A (PKA).[108] In a separate study, PINK1 was again shown to promote dendritic arborization and to activate PKA. Here the authors suggest that PINK1 additionally provides a bridge between PKA and the VCP/p47 complex, leading to PKA phosphorylation of p47, which underpins the dendritogenesis.[87]

The rapid accumulation of cPINK1 observed under conditions of proteasome inhibition, renders it well placed to act as an early sensor of proteasomal stress.[107,112] Following proteasome inhibition, a fraction of cPINK1 is recruited to ribosomes, where it phosphorylates the translation elongation factor eEF1A1 and inhibits protein synthesis.[113] Consequently, fibroblasts from PD patients with mutant PINK1 are sensitised to cell death by proteasomal inhibitors. Conversely, cytoplasmic PINK1 over-expression has been shown to protect cells against proteasomal stress induced cell death.[114,115]

Concluding remarks

PINK1 both controls normal mitochondrial physiology and acts as a sensor of mitochondrial damage. The PINK1 co-ordinated response to mitochondrial damage is multilayered and likely operates on different time scales. Activation of the ubiquitin E3 ligase Parkin is well understood, and critical to some, but by no means all, functions of PINK1.[116] PINK1 can also regulate mitophagy in cells that do not contain Parkin.[117] The damage response is co-ordinated from the

mitochondrial surface but some basal effects of PINK1 may require access to the inner mitochondrial membrane or be mediated by a cleaved form released into the cytosol.

The ATP analogue, kinetin triphosphate (KTP), has been shown to specifically activate PINK1; wild type and at least some defective mutants.[118] This has opened the way for development of small molecules that will provide interesting tool compounds for researchers and ultimately potential therapeutic opportunities. Assessing these compounds in vivo will require a holistic appreciation of the complex PINK1 biology.

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AUTHOR CONTRIBUTIONS

Michael J. Clague and Liam Pollock drafted the manuscript and Sylvie Urbé and Jane Jardine drafted the figures. All authors provided critical input to further iterations of both.

CONFLICT OF INTEREST

The author declares no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable–no new data generated.

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