

When more PINK1 is not better

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Received: 2 July 2026 | Accepted: 20 July 2026

PTEN-induced kinase 1 (PINK1) is well known as a mitochondrial fitness sensor that initiates mitophagy. Our recent study shows that PINK1 signaling also needs timely restraint, linking mitophagy fine-tuning to neuronal function and Alzheimer's disease (AD) [1, 2].

Neurons are among the longest-lived cells in the body. Over decades, they must maintain a functional mitochondrial network to sustain synaptic transmission, axonal transport, and local energy demand. This long-term dependence on mitochondrial integrity places mitochondrial quality control at the center of brain aging and neurodegenerative disease. In AD, impaired mitophagy has been observed in postmortem brain samples and disease models, whereas genetic or pharmacological enhancement of mitophagy reduces amyloid- β and tau pathologies and improves cognitive phenotypes in AD model systems [3, 4]. Evidence from multiple AD models further points to a protective role for PINK1. Restoration of PINK1 signaling attenuates amyloid pathology and mitochondrial dysfunction, whereas loss of PINK1 exacerbates mitochondrial and synaptic defects [5]. Together, these studies support a protective role for PINK1-dependent mitophagy in maintaining neuronal mitochondrial homeostasis and limiting AD-related pathology.

However, the view that increasing PINK1 is invariably beneficial needs to be reconsidered. PINK1-dependent mitophagy is built on a tightly controlled damage-sensing mechanism [6]. In healthy mitochondria, PINK1 is imported, cleaved by mitochondrial proteases, and rapidly degraded by the proteasome. Upon mitochondrial depolarization, full-length PINK1 accumulates on the outer mitochondrial membrane, phosphorylates ubiquitin and parkin RBR E3 ubiquitin protein ligase (PRKN), and initiates a feed-forward ubiquitin signal that recruits mitophagy receptors such as optineurin (OPTN) and calcium binding and coiled-coil domain 2 (CALCO2/NDP52). These receptors then bridge damaged mitochondria to the autophagy machinery, promoting autophagic engulfment and subsequent lysosomal degradation. While this activation step is essential for mitochondrial clearance, how cells regulate full-length PINK1

after mitophagy has been initiated remains less clear.

In our recent study, we found that full-length PINK1 is not maintained at high levels throughout mitochondrial damage [1, 2]. After its initial accumulation and activation of the ubiquitin-dependent mitophagy signal, full-length PINK1 gradually declines through a ubiquitin-proteasome-dependent mechanism. This decline helps to keep PINK1 within a range that supports productive mitophagy. STIP1 homology and U-box containing protein 1 (STUB1) catalyzes K48-linked polyubiquitination of full-length PINK1, which is then extracted from damaged mitochondria by valosin containing protein (VCP/p97) and targeted for proteasomal degradation. Importantly, this pathway degrades PINK1 in its full-length form, without prior cleavage, and is therefore distinct from the basal N-end rule degradation of cleaved PINK1. This damage-induced turnover of full-length PINK1 provides a mechanism to restrain PINK1 signaling after it has initiated PRKN-dependent mitophagy. Consistent with this fine-tuning model, STUB1 depletion stabilizes full-length PINK1 but does not improve mitophagy. Instead, excessive PINK1 promotes PRKN turnover and hampers the recruitment of downstream machinery that is required for mitochondrial clearance. These findings suggest that PINK1 levels need to be properly maintained, as insufficient PINK1 weakens mitochondrial damage sensing and mitophagy initiation, whereas excessive PINK1 compromises the PRKN-dependent pathway. This balance may be particularly important in aging neurons, where chronic mitochondrial stress, declining proteostasis, and reduced resilience increase susceptibility to PINK1-PRKN dysregulation [7]. In support of this idea, knockdown of STUB1 or VCP/p97 orthologs in *C. elegans* suppresses neuronal mitophagy and impairs olfactory associative learning and memory, while hippocampal tissues from patients with AD show reduced STUB1 and VCP/p97 together with decreased PRKN. Thus, impaired PINK1 fine-tuning may contribute to PRKN loss and inefficient mitophagy in aged or AD-vulnerable neurons, indicating that effective mitochondrial quality control depends not only on PINK1 activation but also on maintaining appropriate PINK1 signaling (Fig. 1).

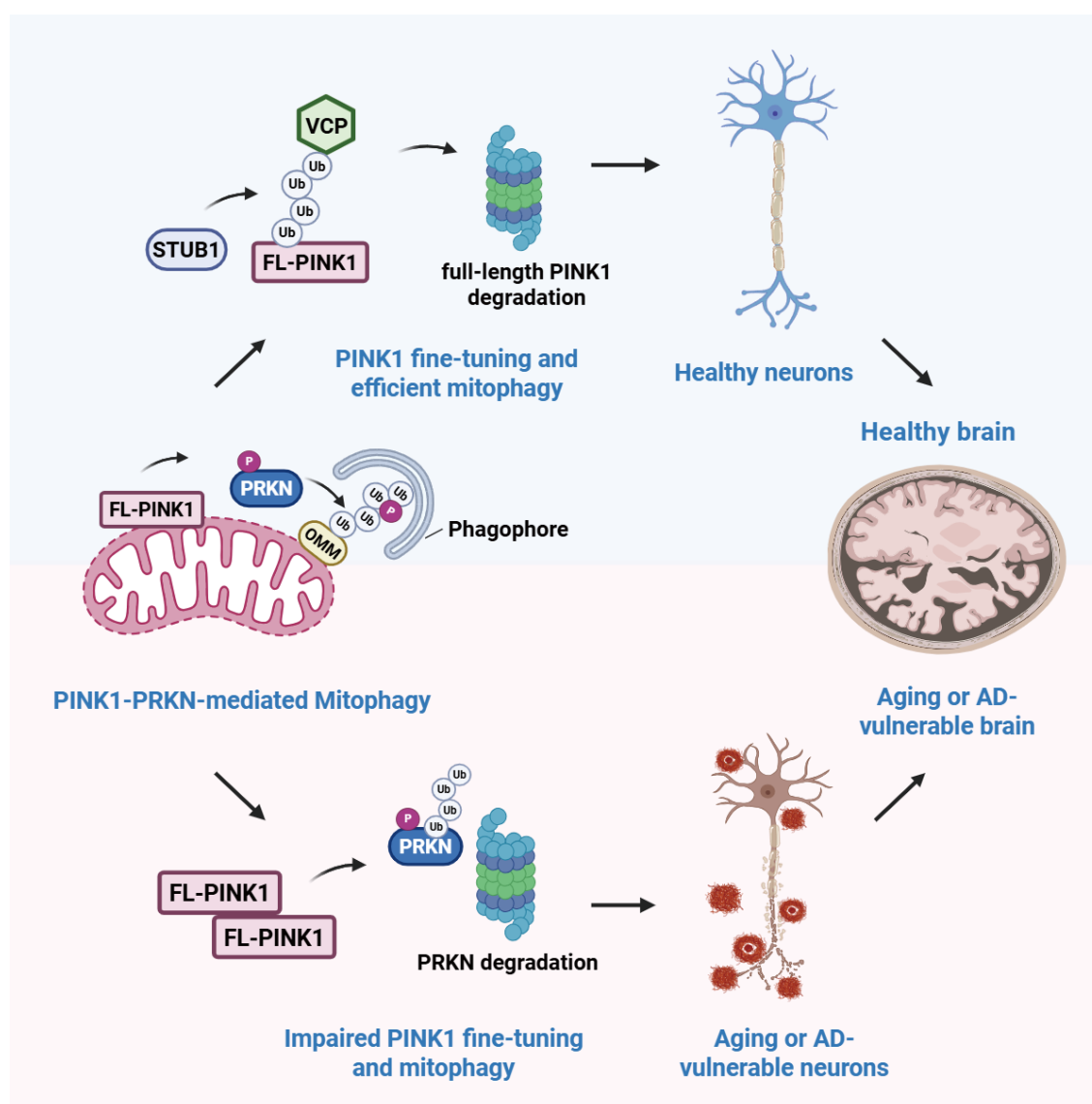


Figure 1 PINK1 fine-tuning in neuronal mitophagy and Alzheimer's disease (AD). In healthy or resilient neurons, mitochondrial damage induces the accumulation of full-length PINK1 on the outer mitochondrial membrane, leading to PRKN activation, mitochondrial ubiquitination, and phagophore recruitment for PINK1-PRKN-mediated mitophagy. As mitophagy proceeds, the STUB1-VCP complex promotes ubiquitination and removal of excess full-length PINK1, thereby preventing prolonged PINK1 signaling, preserving PRKN availability, and supporting efficient mitochondrial clearance. This balanced PINK1 fine-tuning may help maintain neuronal integrity and brain health. Defects in PINK1 fine-tuning may lead to sustained PINK1 signaling, enhanced PRKN degradation, defective mitophagy, and the buildup of damaged mitochondria. Such failure to properly resolve PINK1 signaling may contribute to neuronal vulnerability and AD-related brain dysfunction. The diagram is generated using BioRender (<https://BioRender.com>).

In summary, our study highlights the importance of fine-tuning PINK1 signaling after mitochondrial damage. By showing that excessive full-length PINK1 disrupts mitophagy, this work suggests that neuronal mitochondrial fitness depends not only on PINK1 activation but also on the fine-tuning of PINK1 signaling throughout the mitochondrial quality control process. Several important questions remain to be addressed in future studies. First, it remains unclear whether impaired PINK1 fine-tuning occurs early during brain aging or AD progression. Second, future studies should determine whether restoring proper PINK1 signaling dynamics can improve mitophagy and cognitive function in mammalian and non-human primate disease models. Third, the identification of patient genetic variants that impair PINK1 degradation may help define potential risk factors for AD pathology. At the same time, it will be important to

establish biomarkers that distinguish productive mitophagy, as elevated full-length PINK1 alone may not reflect increased mitophagic activity and should be interpreted together with downstream indicators such as PRKN and cargo receptor engagement. Addressing these questions may help refine mitophagy-based strategies for AD and other age-related neurodegenerative diseases.

Author contributions

Jin-Yi Lin contributed to visualization, writing original draft, and writing-review and editing. Hayden Weng Siong Tan contributed to writing original draft and writing-review and editing. Guang Lu contributed to conceptualization, supervision, visualization, writing original draft, and writing-review and editing. All authors reviewed and approved the final manuscript.

Conflict of interests

The authors declare no competing interests.

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