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The PINK1 advantage: recycling mitochondria in times of trouble?

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ABSTRACT

Parkinson disease remains a debilitating neurodegenerative disorder, despite the discovery of multiple causative genes that account for familial forms. Prominent among these are *PRKN/Parkin* and *PINK1*, whose protein products participate in mitochondrial turnover, or mitophagy. But our poor understanding of the basic biological mechanisms driven by those genes in neurons limits our ability to target them therapeutically. Here, we summarize our recent findings enabled by a new platform to track individual mitochondria in neurons. Our analysis delineates the steps of PINK1- and PRKN-dependent mitochondrial turnover, including the unexplored fates of mitochondria after fusion with lysosomes. These studies reveal unexpected mechanisms of mitochondrial quality control, which may contribute to the reliance of neurons on PINK1 under conditions of stress.

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The mechanisms of PINK1- and PRKN-dependent mitophagy have been elucidated in great detail in cell lines, but there have been relatively few such studies in neurons. However, neurons are preferentially vulnerable to disruptions in PINK1 and PRKN in Parkinson disease (PD), and also have fundamentally different responses to mitophagy triggers. In particular, the mitochondrial uncouplers FCCP and CCCP fail to clear mitochondria from neurons, whereas they remove essentially all mitochondria in many cell lines. Interestingly, neurons continue to turn over mitochondria even when PINK1 and PRKN are absent, and *PINK1* KO and *PRKN* KO neurons have normal complements of mitochondria.

Does this mean that neurons do not require PINK1 and PRKN for mitochondrial turnover, and that disruptions in mitochondrial quality control do not contribute to the pathophysiology of PINK1- and PRKN-dependent PD? While this possibility remains, the robust convergence of PINK1 and PRKN on mitochondria across model organisms suggests a key role in disease pathogenesis.

In fact, while not required for basal mitophagy, PINK1 and PRKN can become indispensable for mitochondrial turnover in stressed neurons. To investigate this process, we used neurons lacking the mitochondrial fission protein DNM1L/Drp1, a stress condition that markedly increases the toxicity of losing PINK1 to midbrain dopamine neurons [1]. Importantly, *dnm1l* KO mitochondria have a characteristic swollen shape and are far more segregated and less mobile than those in wild-type cell lines, which allowed us to track their individual fates and functions for up to 21 h. Moreover, we combined this approach with correlative light electron microscopy/CLEM, which allowed us to resolve the ultrastructure of mitochondria labeled with fluorescent markers. Using this approach, we visualized the initial phases of PINK1- and PRKN-based mitophagy in neurons and delineated their kinetics. As observed in studies of PRKN-based mitophagy in cell lines, these early steps included first the recruitment of PRKN by depolarized mitochondria, followed by their engulfment by phagophores and their eventual fusion with lysosomes to form mitolysosomes.

By tracking individual mitochondria, we also gained unprecedented insight into their fate after targeting to lysosomes. We found that the formation of highly acidic mitolysosomes depends largely on PINK1 and PRKN. Moreover, rather than being inert structures that are rapidly degraded, mitolysosomes that emerge from PINK1-PRKN targeting are dynamic, and often long-lived structures that interact closely with neighboring mitochondria. Remarkably, some mitolysosomes are even engulfed by other, apparently healthy mitochondria. Ultimately, both *dnm1l* KO and wild-type mitolysosomes formed via PINK1-PRKN targeting burst, and release their contents, including functional proteins, into the cytosol. Interestingly, the mitolysosomes deacidify before bursting, which we hypothesize represents the protective inactivation of lysosomal elements that could otherwise be detrimental to the cell.

The dynamic nature of the neurons' mitolysosomes argues against the common assumption that mitolysosomes are solitary structures whose sole function is to break down mitochondrial components into cellular building blocks. Instead, mitochondria may have evolved an ability to intercept and pillage mitolysosomes. We hypothesize that the close interactions between mitolysosomes and healthy mitochondria allow the recycling and exchange of still salvageable components of the degrading mitochondria stuck inside a lysosome: engulfment supplies recycled materials to the healthy mitochondria, while bursting releases other mitochondrial components to the cytosol. If true, this could lead to important energy and resource savings by avoiding the rebuilding of new mitochondrial parts from scratch. While this particular function may be dispensable in times of plenty, it

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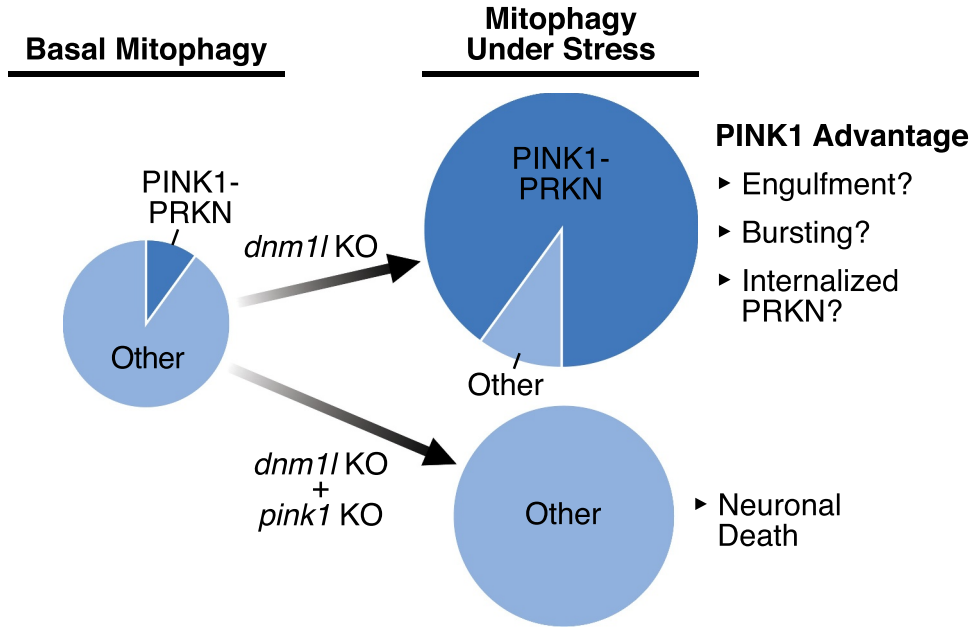

Figure 1. PINK1's value-add? Considerable evidence points to PINK1 and PRKN not being required for basal mitophagy. However, in stress conditions, mitophagy increases and PINK1-PRKN appear to underlie the bulk of that increase. If either one is absent in those conditions, neuronal survival may be compromised. New mechanisms of mitochondrial turnover identified in our study may contribute to this neuroprotective effect.

could be of critical importance in conditions of scarcity associated with stressful environments, especially for cells such as neurons with high metabolic demands.

We speculate that bursting and engulfment may also have signaling functions. Bursting, in particular, which we hypothesize occurs primarily in stressed cells, may bridge PINK1-PRKN mitophagy and the immune system. By releasing mitochondrial components not typically present in the cytosol, bursting may alert the immune system to threats that are putting pressure on the cell. Alternatively, bursting could serve as a negative feedback regulator of mitophagy that prevents the deletion of too many mitochondria.

In addition to the highly acidified mitolysosomes, we observed mildly acidified mitochondria that contained PRKN in their matrix. How could PRKN, a cytosolic protein lacking a mitochondrial targeting sequence, gain access to a sheltered mitochondrial compartment, and what is its function there? The presence of PRKN inside these mitochondria appears to have physiological relevance, because it depends on PINK1, a detector of mitochondrial damage. We speculate that these mitochondria might have engulfed mitolysosomes, which would explain both their acidification and their harboring PRKN. Alternatively, they may have some defect that somehow led PRKN to get in. Regardless, further experiments are required to determine whether PRKN inside these mitochondria mediates the local degradation of dysfunctional structures, for instance through ubiquitination, or contributes to mitochondrial repair through other mechanisms.

To summarize, we have identified new mechanisms of PINK1- and PRKN-based mitochondrial quality control – engulfment, bursting, and PRKN internalization – that may also contribute to the vulnerability of neurons to loss of PRKN and PINK1 under conditions of stress. However, our work raises new questions, including whether these processes are unique to PINK1-PRKN mitophagy, and whether abrogating them worsens neuronal survival. If true, they could underlie the "value-add" of PINK1 and PRKN mitophagy (Figure 1). Beyond providing new insights into how PINK1 and PRKN dysfunction may contribute to PD pathogenesis, these processes may be important areas of focus for basic biology studies investigating mitochondrial and cellular homeostasis.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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