Autophagy ›
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Autophagic Punctum

Long time-lapse imaging reveals unique features of PARK2/Parkin-mediated mitophagy in mature cortical neurons

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Abstra

Prope is essential to en n onto damage . However, direct ev ontroversial, leaving u PARK2-mediate on. We applied the slow but dynamic subsequent degradation through the autophagy-lysosomal pathway. In comparison with non-

neuronal cells, our study reveals unique features of PARK2-mediated mitophagy in mature neurons, which will advance our understanding of pathogenesis of several major neurodegenerative diseases characterized by damaged mitochondria or a dysfunctional autophagy-lysosomal system.

Keywords: :

mitochondria Parkin PARK2 lysosome autophagosome autophagy depolarization mitochondrial mobility neuronal mitophagy mitochondrial membrane potential mitochondrial quality control

This article refers to:

Mitochondria are essential organelles for neuronal function, development and survival. Throughout a neuron's lifetime, aged and damaged mitochondria undergo dynamic recycling via fusion/fission or are ultimately eliminated via mitophagy, an autophagic pathway specific for mitochondrial degradation. Dysfunctional mitochondria not only produce energy less efficiently, but also release harmful reactive oxygen species and initiate a enesis of several d mitocho lysosomal system echanisms. Mutation t Parkinson disease. es mitopha ondrial degr is overex wever, evidence nd degrada missing or controve gy has some unique f focused on addressi (2) whether this tran ochondrial mobility is altered during the mitophagic process; and (4) where PARK2-targeted

mitochondria are spatially distributed in neurons to facilitate their elimination through the autophagy-lysosomal system.

First, we speculate that the quality of neuronal culture is critical for allowing us to observe PARK2 translocation following CCCP-induced dissipation of mitochondrial membrane potential ($\Delta\psi_m$). If the optimal conditions are not met, the uncoupled mitochondria will quickly trigger apoptosis before PARK2 translocation can be observed. We established a high quality culturing condition of primary cortical neurons such that they survive long enough to exhibit PARK2 translocation. CCCP treatment for 24 h induces 26.67% of neurons to undergo PARK2 translocation onto depolarized mitochondria. Co-treatment with CCCP and lysosomal inhibitors (LIs) results in a doubling in the percentage (55.87%) of neurons with PARK2 translocation. Thus, proper lysosomal function is critical to avoid the accumulation of PARK2-associated mitochondria in neurons upon dissipating $\Delta\psi_m$. Second, we examined PARK2 translocation kinetics by imaging neurons at various time points during CCCP treatment. PARK2 translocation between 0.5–6 h was exceptionally rare, occasionally observed as early as 12 h, and became increasingly frequent after 18 h of CCCP treatment. We further imaged the dynamic recruitment of endogenous PARK2 to mitochondria in mature neurons following CCCP/LIs treatment. To confirm this, we alternatively isolated the mitochondria-enriched membrane fraction from mature cortical n is present in the cy ion of substant 3-II and SQSTM1 indicate the recruitm tochondria in matur

Next, we rgeted mito nd accum control neurons, electrocl isplay significa ectively targets t us PARK2 is required eurons impairs t mulation of mitochondria with reduced TMRE intensity. Thus, our results support the hypothesis

that PARK2-mediated mitophagy is one of the neuronal mechanisms maintaining mitochondrial quality.

Intriguingly, PARK2 forms typical ring-like structures surrounding the fragmented mitochondria in the soma and proximal dendritic regions, but it is hardly detectable in axons and the distal dendrites. We further observed that in neurons with PARK2 translocation, anterograde axonal transport of mitochondria is reduced, whereas retrograde transport is relatively increased. Thus, altered mitochondrial mobility may be attributed to the unique distribution pattern. PARK2-tagged depolarized mitochondria are restricted to the soma for degradation, where lysosomes are predominately located, while healthy mitochondria are distributed distally to support synaptic functions. To test this hypothesis, we utilized syntaphilin, an axonal mitochondria docking protein, to artificially immobilize mitochondria in distal processes. To our surprise, we found that PARK2 is recruited to stationary mitochondria anchored by syntaphilin in distal processes. Therefore, the PARK2-mediated process prevents dysfunctional mitochondria from traveling peripherally, leading to their accumulation in somatodendritic regions. In addition, our long time-lapse imaging exhibits dynamic PARK2 recruitment and degradation of depolarized mitochondria within the autophagy-lysosomal system. CCCP exposure results in LC3-labeled ring-like structures surrounding fragmented mitochondria in the somadendritic regions and enhances the recruitm urons.

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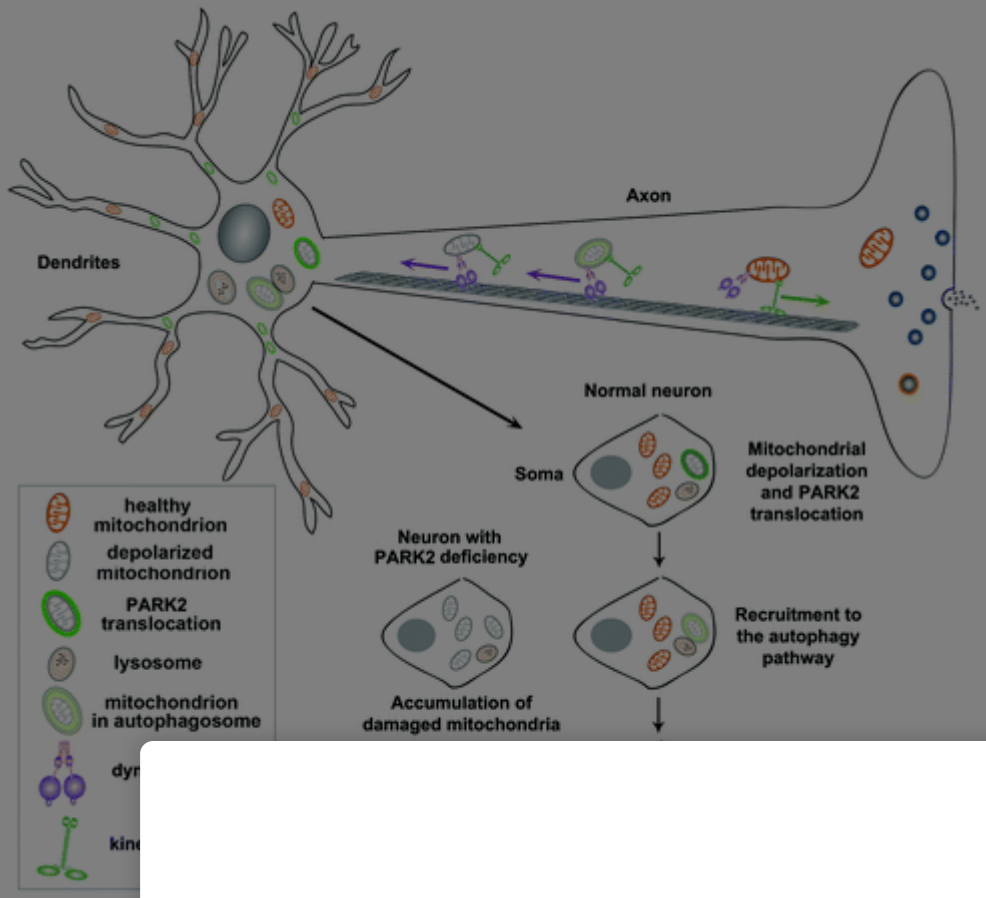
Figure 1 control via PARK2-m itochondria to form a oximal dendritic distal dendritic al transport of mitochondria is reduced, whereas retrograde transport is relatively increased.

Altered mitochondrial mobility is attributed to a unique distribution pattern: while healthy mitochondria are distributed distally to support synaptic function, PARK2-targeted depolarized mitochondria are restricted to the somatodendritic regions, where mature lysosomes are predominantly located. This spatial and dynamic process allows neurons to efficiently eliminate damaged mitochondria via the autophagy-lysosomal pathway for neuronal recovery. In contrast, PARK2 deficiency impairs the elimination of dysfunctional mitochondria.



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