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RESEARCH HIGHLIGHT

The TBK1-OPTN Axis Mediates Crosstalk Between Mitophagy and the Innate Immune Response: A Potential Therapeutic Target for Neurodegenerative Diseases

Lu He[1] · Linxi Chen[2] · Lanfang Li[1,2]

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Recently, Richter *et al*. [1] revealed the potential functions of the interaction between the serine/threonine kinase Tank-binding kinase 1 (TBK1) and the autophagy receptor optineurin (OPTN). The TBK1-OPTN axis targets damaged mitochondria for degradation via PINK1/parkin-mediated mitophagy [2, 3]. Indeed, TBK1 can phosphorylate OPTN at Ser177, Ser473, or Ser513 to enhance the binding capacity of OPTN with poly-ubiquitin (poly-UB) chains. Conversely, binding of poly-UB chains to OPTN is essential for the efficient recruitment and activation of TBK1 on mitochondria. These processes (Fig. 1) point toward an essential role of TBK1-OPTN signaling in mitochondrial quality control and maintaining cellular homeostasis. Currently, some studies have just focused on the role of the autophagy receptors OPTN, NDP52 (nuclear dot protein 52 kDa; also known as CALCOCO2, calcium-binding and coiled-coil domain 2), TAX1BP1 (Tax1 binding protein 1), and p62/sequestosome (SQSTM1) in damaged mitochondria [4–6]. However, only OPTN promotes auto-phagosome formation around mitochondria via the microtubule-associated protein light chain 3 (MAP1LC3/LC3)-interacting region (LIR) domain and is sufficient to trigger mitophagy.

The TBK1-OPTN axis participates in many pathophysiological processes. As an upstream binding partner for the autophagy receptor, TBK1 phosphorylates OPTN on damaged mitochondria, leading to the formation of a TBK1-OPTN complex. Inhibition and depletion of TBK1 or OPTN blocks the efficient turnover of depolarized mitochondria. The expression of amyotrophic lateral sclerosis (ALS)-associated TBK1 or OPTN mutants also interferes with mitophagy [2, 3, 7]. These defects in mitophagy are rescued by overexpression of TBK1 and OPTN. Notably, TBK1 or OPTN mutants are causative agents in the development of primary open angle glaucoma, Parkinson disease, ALS and frontotemporal lobar degeneration. In *in vitro* model systems, markers of these neurodegenerative diseases are reversed by the well-known TBK1 inhibitors BX795, MRT67307, and amlexanox [8, 9]. Thus, the mitophagy induced by TBK1-OPTN signaling may emerge as a potential therapeutic target for neurodegenerative diseases.

A growing body of evidence has also highlighted that TBK1-OPTN signaling is pivotal for the initiation of the innate immune responses in defense against viral pathogens. Expression of the TBK1-OPTN complex significantly inhibits the transcription of type I interferon β and phosphorylation of IRF3 (interferon regulatory factor 3) upon viral infection [10–12]. As noted above, TBK1 cooperates with OPTN to elicit the autophagic elimination of damaged mitochondria. Can the TBK1-OPTN axis leading to mitophagy also affect the innate immune signaling pathway? TBK1 mediates the crosstalk between autophagy and innate immunity. The TBK1-OPTN axis recruits cargoes that include ubiquitinated mitochondria into autophagosomes, leading to the innate immune response. Mitophagy also directly reduces the Toll-like receptor-dependent production of inflammatory cytosines, which affect the

Lu He and Linxi Chen have contributed equally to this work.

✉ Lanfang Li
llanfang6@126.com

[1] Department of Neurosurgery, First Affiliated Hospital, University of South China, Hengyang 421001, China

[2] Institute of Pharmacy and Pharmacology, Hunan Province Cooperative Innovation Center for Molecular Target New Drug StudyUniversity of South China, Hengyang 421001, China

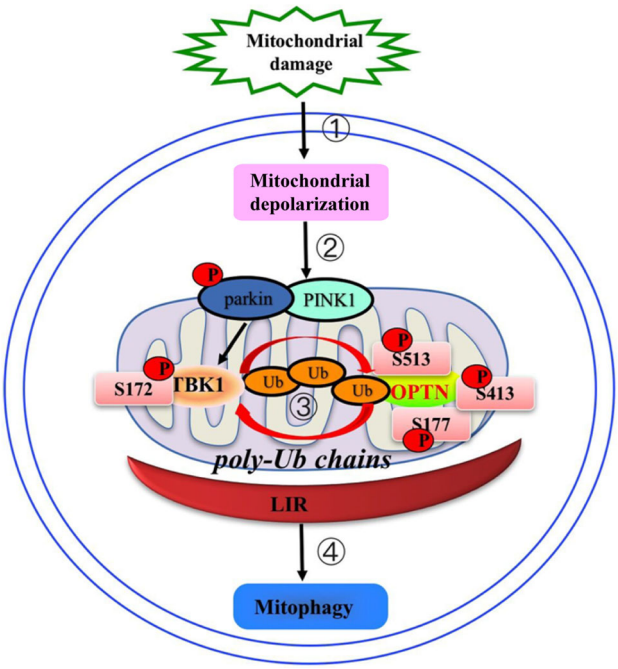

Fig. 1 TBK1-OPTN axis facilitates the turnover of impaired mitochondria via mitophagy. *Step 1*. Mitochondrial damage leads to depolarization induced by the uncoupler carbonyl-cyanide m-chlorophenyl-hydrazine. *Step 2*. Accumulation of PINK1 (PTEN-induced putative kinase 1) recruits the E3 ubiquitin ligase parkin, contributing to the ubiquitination of outer mitochondrial membrane proteins. *Step 3*. PINK1-parkin activation promotes TBK1 phosphorylation of S172 on mitochondria. TBK1 phosphorylates OPTN at Ser177, Ser473, and Ser513, thereby enhancing the capacity of OPTN to bind to poly-Ub chains. In turn, poly-Ub chain binding to OPTN is required for TBK1 recruitment and activation on mitochondria. *Step 4*. Thus, the TBK1-OPTN axis promotes autophagosome formation around damaged mitochondria via the LC3-interacting domain (LIR) and is sufficient for mitophagy.

innate immune response [13–15]. Surprisingly, innate immunity might be central to the pathophysiology of neurodegeneration [16, 17]. These reports support the viewpoint that antiviral signaling by the TBK1-OPTN axis leading to mitophagy may regulate the innate immune response and so contribute to a therapeutic strategy for neurodegenerative disorders and inflammation-associated diseases.

To sum up, TBK1-OPTN initiates self-reinforcing positive-feedback programs by eliminating damaged mitochondria via PINK1/parkin-dependent mitophagy. Disruption of TBK1 or OPTN results in the occurrence and development of neurodegenerative diseases. Yet, the PINK1/parkin-mediated mitophagy appears to be associated with the innate immune response. As TBK1-OPTN mediates the initiation of innate immune response by mitophagy, it may contribute to the pathogenesis of inflammation-associated diseases. The TBK1 antagonists BX795, MRT67307, and amlexanox eliminate the role of the autophagy receptor OPTN. Thus, the development and identification of TBK1 and OPTN agonists and antagonists that affect mitophagy and regulate the innate immune response may provide essential clues for the design of new therapeutic avenues for the pathogenesis of neurodegenerative and inflammation-associated diseases by targeted TBK1-OPTN axis interference.

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