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REVIEW
published: 18 March 2020
doi: 10.3389/fcell.2020.00171

Mammalian Mitophagosome Formation: A Focus on the Early Signals and Steps

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Specialty section:
This article was submitted to Cell Death and Survival, a section of the journal Frontiers in Cell and Developmental Biology

Received: *14 January 2020*
Accepted: *02 March 2020*
Published: *18 March 2020*

Citation:
Zachari M and Ktistakis NT (2020) Mammalian Mitophagosome Formation: A Focus on the Early Signals and Steps. Front. Cell Dev. Biol. 8:171. doi: 10.3389/fcell.2020.00171

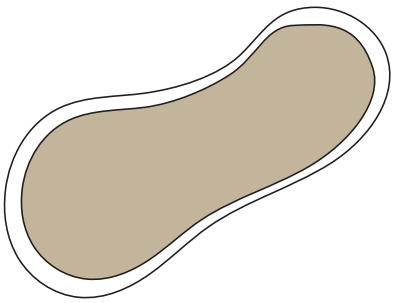

FIGURE 1 | (A) Cartoon of the PINK1/Parkin pathway. Upon loss of membrane potential (*1 9*), PINK1 stabilizes on the OMM, dimerizes and autophosphorylates. PINK1 next phosphorylates Ubiquitin attached onto OMM proteins, leading to the recruitment of Parkin, which also gets phosphorylated and activated by PINK1. Parkin further ubiquitinates OMM proteins leading to the recruitment of receptor proteins for the generation/recruitment of an autophagosome and subsequent degradation of the mitochondrion. **(B)** Representation of mitophagy pathways which do not rely on ubiquitin. Various mitochondrial proteins can act as mitophagy receptors including: (a) NIX/Bnip3, (b) FUNDC1, (c) Bcl2-L-13, and (d) FKBP8. **(C)** Ivermectin-induced mitophagy relies on mitochondrial fragmentation and ubiquitylation via TRAF2/CIAP1/CIAP2. Upon ubiquitylation, TBK1 is required for FIP200 recruitment, which results in optineurin recruitment and downstream activation of ATG13 and the rest of the autophagic machinery for mitophagy. **(D)** An alternative autophagy pathway which does not rely on LC3 lipidation can also mediate mitophagy. This pathway requires mitochondrial fission, ULK1 and Rab9-possitive membranes.

OCR and severe fragmentation of the mitochondrial network. This leads to induction of mitophagy, independently of PINK1 and Parkin, but dependent on the E3 ligases TRAF2, CIAP1, and CIAP2 which work synergistically (and potentially in complex) to conjugate ubiquitin onto fragmented mitochondria. Upon ubiquitination, TBK1 becomes activated in order to

a key role as a membrane source for mitophagy in general. It will be interesting to determine if the di□erent ER proteins that have been reported to be involved in autophagosome biogenesis upon amino acid starvation are also important for mitophagy as well (Walker and Ktistakis, 2019; Ktistakis, 2020). It was recently reported that in yeast mitochondria-ER contact sites are crucial for mitophagy (and pexophagy) to occur (Bockler and Westermann, 2014; Liu et al., 2018). Given the importance of ER-mitochondrial contacts in autophagosome formation in

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