A new sight: topology-dependent mitophagy

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Abbreviations

BCL2L13	BCL2-like 13	NBR1	NBR1 autophagy cargo receptor
BNIP3	BCL2-interacting protein 3	OPTN	Optineurin
BNIP3L/NIX	BCL2-interacting protein 3 like	PHB2	Prohibitin 2
CALCOCO2/NDP52	Calcium-binding and coiled-coil domain 2	PINK1	PTEN-induced putative kinase 1
FUNDC1	FUN14 domain-containing 1	PRKN/PARKIN	parkin RBR E3 ubiquitin protein ligase
GABARAP	Gamma-aminobutyric acid receptor-associated protein	P62/SQSTM1	Sequestosome 1
LIR	LC3-interacting region	ROS	Reactive oxygen species
MAP 1LC3/LC3	Microtubule-associated protein 1 light chain 3	TBK1	Tank-binding kinase 1
MFN1	mitofusin 1	$\Delta\Psi_m$	Mitochondrial membrane potential
MFN2	Mitofusin 2		
mPTP	Mitochondrial permeability transition pore		

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Mitochondria play an essential role as an energy ATP producer. In addition, mitochondria participate in various biological processes, such as apoptosis, reactive oxygen species (ROS) production, and Ca^{2+} signal. The elimination of damaged or unwanted mitochondria is essential to maintain the mitochondrial network function and cellular homeostasis. Currently, many pieces of evidence demonstrate that mitophagy, a selective autophagy for mitochondria, is critical for the developmental process, cell fate determination, and stress response (Song et al. 2016; Green and Levine 2014; Esteban-Martinez et al. 2017; Wu et al. 2016). The defects in mitophagy result in accumulation of damaged mitochondria, which is tightly associated with various diseases, such as heart failure (Shires and Gustafsson 2015; Zhou et al. 2020a), neurodegenerative disease (Reddy and Oliver 2019; Oliver and Reddy 2019), and aging-related diseases (Ding and Yin 2012).

Mitophagy plays a vital role in the maintenance of mitochondrial quality and quantity. Mitophagy is a multi-step process: (1) recognition of damaged or unwanted mitochondria; (2) engulfment by the phagophore, resulting in the formation of mitophagosomes; (3) fusion with lysosomes for recycling the contents. It is important to study the mechanisms and principles in selective mitophagy, which can expand our knowledge to understand mitochondrial function as well as their roles in diseases. Several mechanisms have been identified as responsible for specific recognition and selective elimination of damaged or unwanted mitochondria, such as the PINK1 (PTEN induced kinase 1)-PRKN/PARKIN (parkin RBR E3 ubiquitin protein ligase) pathway and receptor-mediated pathway.

The PINK1-PRKN can recognize depolarized mitochondria and add ubiquitin chains on mitochondrial membrane proteins to amplify and recruit autophagy receptors (Narendra et al. 2010; Jin et al. 2010; Lazarou et al. 2012; Matsuda et al. 2010). These receptors serve as a bridge between cargos and MAP1LC3/LC3 (microtubule-associated protein 1 light chain 3)

(Svenning and Johansen 2013; Stolz et al. 2014). Lazarou M et al. found that OPTN (Optineurin) and CALCOCO2/NDP52 (calcium-binding and coiled-coil domain 2) are the primary autophagy receptors, while P62/SQSTM1 (sequestosome 1) and NBR1 (NBR1 autophagy cargo receptor) are dispensable in PINK1-PRKN-mediated mitophagy (Lazarou et al. 2015). What's more, PHB2 (prohibitin 2), an inner mitochondrial membrane protein, is required for PINK1-PRKN-mediated mitophagy. PHB2 recruits LC3 through its LC3-interacting region (LIR) motif and promotes mitophagy after outer mitochondrial membrane rupture (Wei et al. 2017).

Besides the PINK1-PRKN pathway, mitophagy receptors such as BNIP3 (BCL2-interacting protein 3), BNIP3L/NIX (BCL2-interacting protein 3 like), FUNDC1 (FUN14 domain-containing 1), and BCL2L13 (BCL2-like 13), can mark damaged or unwanted mitochondria under mitophagic stimulus. These receptors that contain LIR motif can directly interact with LC3 or GABARAP (gamma-aminobutyric acid receptor-associated protein) to induce mitophagy (Hamacher-Brady and Brady

Fig. 1 Selective elimination of mitochondria by PINK1-PRKN pathway and receptor-mediated pathway

2016; Liu et al. 2014). Taken together, the selection of mitophagy is dependent on the accumulation of specific protein on damaged or unwanted mitochondria in the molecular level (Fig. 1).

Mitophagy and mitochondrial morphology, regulated by fusion and fission, are closely linked. Mitochondrial fission generates smaller mitochondria in size, which is easily enveloped by autophagosomes, while mitochondrial fusion generates elongated mitochondria (Gomes et al. 2011; Rambold et al. 2011; Okamoto et al. 2009; Twig et al. 2008). Given that the limited size of autophagosomes ranges from 0.5 to 1.5 μm (Pfeifer 1978; Schworer et al. 1981; Mizushima and Klionsky 2007), we take it granted that mitochondrial division precedes engulfment during mitophagy. However, Yamashita et al. showed that mitochondrial division could occur concomitantly with autophagosome formation. Autophagosome formation factors are essential for mitochondrial division to enable enwrapping of the maximum size of mitochondria to fit into autophagosome (Yamashita et al. 2016). Taken together, these findings demonstrate the importance of mitochondrial topology in mitophagosome engulfment. Recently, our lab showed a topology-dependent, bifurcated mitochondrial quality control model (Zhou et al. 2020b), which enriches the contents of selective mitophagy in organellar morphology-dependent manner (Fig. 2).

We found that mitochondria undergo different topological transformations during starvation, either swelling or forming donut shapes. Swollen mitochondria are associated with mitochondrial membrane potential ($\Delta\Psi_m$) dissipation and PRKN recruitment, resulting in the selective elimination by autophagy, while the donut topology maintains $\Delta\Psi_m$ and helps mitochondria resist autophagy. Importantly, donut mitochondria can undergo fission and fusion cycles, which could recover to tubular one. Mechanistically, donut topology resists autophagy even after depolarization, wherein the recruitment of autophagosome receptors CALCOCO2 and OPTN after PRKN recruitment and ubiquitination is prevented.

It would be interesting to investigate how donut mitochondria prevent mitophagy after outer membrane protein ubiquitination. One important issue may be the integrity of mitochondrial structure which guarantees the function of mitochondria after topology transformation. The crista structure is one of the fundamental structures for the oxidative phosphorylation system. We showed that the crista structure maintains well in donut mitochondria, while it is not so abundant in swollen ones, indicating the functional integrity of the donut structure. A mitophagy receptor PHB2 localized in crista may be exposed in swollen mitochondria as the structure rupture and mediate mitophagy in the PINK-PARKN pathway. Furthermore, as the externalization of

Fig. 2 Mitochondrial topology and mitophagy

cardiolipin to the outer mitochondrial membrane is a mitophagy signal, it would be interesting to observe the distribution of cardiolipin in donut and swollen mitochondria. LC3 contains cardiolipin-binding sites, which is important for the engulfment of mitochondria by the autophagic system (Chu et al. 2013). We hypothesize that cardiolipin is not transported to the donut mitochondrial surface; thus, it could not be enveloped by LC3 even though ubiquitination.

Donut mitochondria have been described long time ago (Laubert 1982; Funk et al. 1999), and the roles of the outer mitochondrial membrane localized GTPases (mitofusin 1/2) were initially described in yeast (Mozdy and Shaw 2003; Messerschmitt et al. 2003; Hermann et al. 1998). Similarly, we also showed that mitochondrial fusion is indispensable for donuts, for which no donuts are observed in mitofusin 1/2 double-knockout (*mfn1/2* KO) MEF cells. Donut-shaped mitochondria, not swollen mitochondria, are reversible to linear one. We also discussed the formation of donuts, which is triggered by the opening of mitochondrial permeability transition pore (mPTP) or K^+ channels, and as a result of osmotic pressure changes. We showed the extent of channel opening is very important in producing both donuts and swelling. For example, valinomycin, a K^+ ionophore, induced mitochondrial swelling, and donut formation at high (5–500 nM) and low (0.25–0.5 nM) concentration, respectively. What's more, donut mitochondria are able to tolerate the swelling volume of mitochondria than tubular mitochondria (Liu and Hajnoczky 2011). The Gibbs energy model of donut mitochondria we developed previously figures out that the donut is a lower-energy state compared with tubular one under stress (Long et al. 2015). In apoptosis, tubular mitochondria turn to swollen mitochondria after mitochondrial fission and swelling (Frank et al. 2001). Hence, to what extent the opening of channels plays a role in producing both types of mitochondria and to what extent both types of mitochondrial morphology are linked to the activation of apoptosis would be very interesting.

Donut mitochondria are observed in many physiological and pathological conditions, such as hypoxia-reoxygenation (Liu and Hajnoczky 2011), neuron degeneration (Hara et al. 2014), aging (Laubert 1982; Hara et al. 2014), and osteosarcoma (Jackson et al. 2018). The formation of donut has been suggested to be a hallmark of stress (Picard and McEwen 2014). Ahmad T et al. provided computational correlations of mitochondrial shape change with the level of mitochondrial ROS generated by cells. Mitochondria transform to donut under mild stress

and to blob form during high oxidative stress (Ahmad et al. 2013). This is consistent with our result that the transition from tubular to donut is reversible. The appearance of donut mitochondria indicates that cells are in stress and could recover if the stress withdraws. On the other hand, with prolonged time of depolarization, donut mitochondria finally turn into swollen mitochondria.

The selective elimination of mitochondria in the molecular and organellar level is crosslinked (Yoo and Jung 2018). For example, PINK1-PRKN could separate damaged mitochondria within a small size from normal ones by inhibiting mitochondrial fusion, for which PRKN can ubiquitinate MFN1/2 (mitofusin 1/2) and activate ubiquitin-proteasome system (Gegg et al. 2010). BCL2L13 not only serves as a receptor of mitophagy but also takes part in mitochondrial fission (Murakawa et al. 2015). Similarly, FUNDC1 not only mediates mitophagy but also involves in mitochondrial fission (Liu et al. 2012; Wu et al. 2016; Chen et al. 2016). In addition, modification of many proteins involved in mitophagy by phosphatase and phosphokinase precisely controls the process of mitophagy. For example, Tank-binding kinase 1 (TBK1) phosphorylates OPTN at S473, which enhances its binding to ubiquitin chains and promotes selective autophagy of mitochondria (Richter et al. 2016).

The mechanism of mitophagy is regulated by a multi-level network that many mitochondrial and cellular machineries are involved in. We just briefly propose a new sight in mitochondrial topology-dependent model of mitophagy. The new model we constructed provides a new strategy in selective removing mitochondria in a topology-dependent manner. It indicates that the topology of mitochondria not only represents the state of mitochondria but also serves as a role in selective mitophagy. It needs further study in the interaction between mitochondrial topology and mitophagy, as well as its roles in contributing to the pathology of chronic diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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