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Graphical Review

Mitochondrial dynamics and mitochondrial quality control

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ABSTRACT

Mitochondria are cellular energy powerhouses that play important roles in maintaining cell survival, cell death and cellular metabolic homeostasis. Timely removal of damaged mitochondria via autophagy (mitophagy) is thus critical for cellular homeostasis and function. Mitochondria are reticular organelles that have high plasticity for their dynamic structures and constantly undergo fission and fusion as well as movement through the cytoskeleton. In this review, we discuss the most recent progress on the molecular mechanisms and roles of mitochondrial fission/fusion and mitochondrial motility in mitophagy. We also discuss multiple pathways leading to the quality control of mitochondria in addition to the traditional mitophagy pathway under different conditions.

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Introduction

Mitochondria are the “power house” of the cell because they are the major site of ATP production for cell survival and many other vital cellular functions. It is well known that mitochondria act as central executioners of cell death including apoptotic and necrotic cell death. Therefore, mitochondrial quality must be well controlled to avoid cell death. Multiple mechanisms have been utilized by mitochondria to maintain their homeostasis. First, mitochondria have their own proteolytic system, allowing them to degrade misfolded proteins that could potentially disrupt mitochondrial function [1,2]. Second, damaged outer mitochondrial membrane proteins can be degraded by the proteasome [3]. Third, mitochondria can undergo constant fission and fusion to repair damaged components of the mitochondria, which allows for segregation of damaged mitochondria via the fission process and exchange of material between healthy mitochondria via the fusion process [4,5]. Fourth, a portion of mitochondria can bud off and

Abbreviations: APAP, acetaminophen; Bag4, Bcl2-associated athanogene 4; Bcl2L1, Bcl-2 like 1; BNIP3, Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3; CCCP, m-chloro phenyl hydrazine; Clec16a, C-type lectin domain family 16, member A; Drp1, dynamin-related protein 1; Fis1, mitochondrial fission 1; FUNDC1, Fun14 domain containing 1; Hif-1, hypoxia-inducing factor 1; HSPA1L, heat shock 70 kDa protein 1-like; LC3, microtubule-associated protein 1 light-chain 3; LIR, LC3-interacting region; MEFs, mouse embryonic fibroblasts; Mff, mitochondria fission factor; Mfn1, mitofusin 1; Mfn2, mitofusin 2; MDV, mitochondria-derived vesicles; MID49, mitochondrial dynamics protein of 49 kDa; Miro, mitochondrial Rho GTPase; MUL1, mitochondrial ubiquitin ligase 1; Nrdp1, neuregulin receptor degradation protein 1; OPA1, optic atrophy 1; PARL, presenilin-associatedrhomboid-like; PGAM5, phosphoglycerate mutase family member 5; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species; Smurf1, Smad-specific E3 ubiquitin protein ligase 1; SQSTM1, sequestosome 1; SNPH, syntaphilin; TOMM7, translocase of outer mitochondrial membrane 7; TOMM20, translocase of outer mitochondrial membrane 20; UBA, ubiquitin-associated; Usp30, ubiquitin-specific peptidase 30; VDAC, voltage-dependent anion channel

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form mitochondria-derived vesicles (MDV) under oxidative stress conditions, which further fuse with lysosomes to degrade oxidized mitochondrial proteins within MDV [6]. Fifth, damaged mitochondria can form mitochondrial spheroids and acquire lysosomal markers to possibly serve as an alternative pathway for removal of damaged mitochondria [7–9]. Finally, damaged mitochondria can be enveloped by autophagosomes to trigger their degradation in the lysosome via mitophagy [10–12]. This graphic review will focus on the current understanding of mitochondrial dynamics and the multiple mechanisms that regulate mitochondrial homeostasis.

Current mechanisms of mitochondrial quality control

Multiple mechanisms regulating mitochondrial quality control in yeast and mammals have been discovered recently. Below, we discuss regulation of mitochondrial quality control by various mechanisms including mitochondrial fission and fusion, Parkin-dependent and Parkin-independent mechanisms, MDV and mitochondrial spheroid formation.

Mitochondrial fission and fusion and motility in mitophagy

Mitochondria are dynamic organelles that continuously undergo fission and fusion, which are necessary for cell survival and adaptation to changing conditions needed for cell growth, division, and distribution of mitochondria during differentiation [4].

Mitochondrial fusion in mammals is mediated by the fusion proteins mitofusin 1 (Mfn1) and Mfn2 and optic atrophy 1 (OPA1). Mfn1 and Mfn2 are dynamin-related GTPases that are responsible for fusion of outer mitochondrial membranes. OPA1 is also a dynamin-related GTPase, which is responsible for fusion of inner mitochondrial membranes (Fig. 1A). Presenilin-associatedrhomboid-like (PARL) [13] and paraplegin (an AAA protease present in the mitochondrial matrix) [14] induce alternative splicing and alternative processing of OPA1 to generate eight OPA1 isoforms. However, OPA1 processing still occurs in PARL or paraplegin knockout MEF cells, suggesting that other factors may also be involved in OPA1 processing [15]. Yme can further cleave OPA1 under normal conditions to generate Short and Long forms of OPA1 (S-OPA1 and L-OPA1) [16], where L-OPA1 is integral in the inner membrane and S-OPA1 is located in the intermembrane space. L-OPA1 is further cleaved by the inducible protease OMA1 when mitochondria are depolarized by the mitochondrial uncoupler carbonyl cyanide m-chloro phenyl hydrazine (CCCP), resulting in mitochondrial fragmentation by preventing mitochondrial fusion [17,18]. The mitochondrial deacetylase SIRT3 is capable of deacetylating OPA1 and elevating its GTPase activity [19].

Mitochondrial fission in mammals is mediated by dynamin-related protein 1 (Drp1), which is also a large GTPase. Drp1 is a cytosolic protein that can be recruited to the outer mitochondrial membrane to constrict mitochondria resulting in eventual division of a mitochondrion into two separate organelles. Drp1 interacts with four mitochondrial receptor proteins: fission 1 (Fis1), mitochondria fission factor (Mff), mitochondrial dynamics protein of 49 kDa (MID49) and MID51 (Fig. 1B). In mammalian cells, it seems that the interaction between Fis1 and Drp1 has a minor role in regulating mitochondrial fission whereas the interactions of Drp1 with the other three receptor proteins play prominent roles for fission [20–24]. In addition, Drp1 can also localize at the endoplasmic reticulum–mitochondria contact site, and the endoplasmic reticulum may play a role in the process of mitochondrial fission [25]. Accumulating evidence indicates that posttranslational modification of Drp1 is an important mechanism for regulating its function. During cell division, mitochondrial

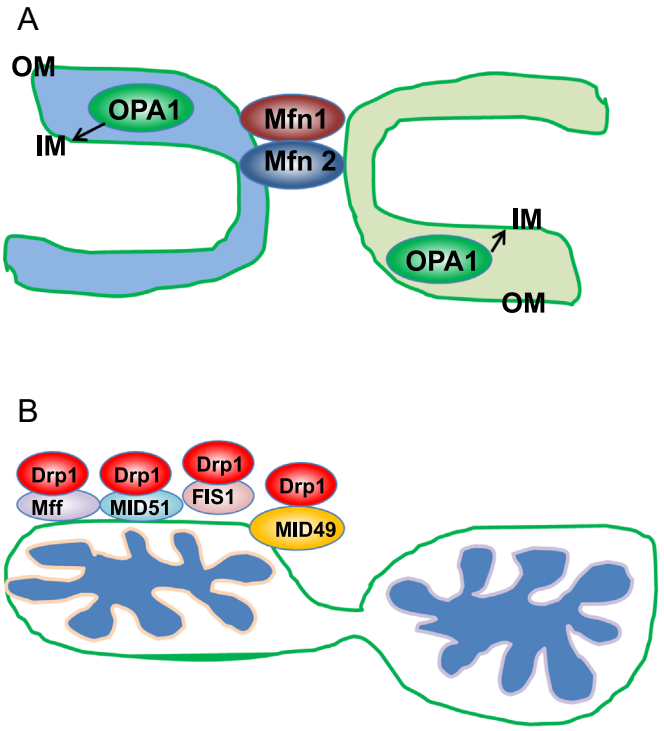

Fig. 1. Mitochondrial fusion and fission in mammalian cells. (A) Mitochondrial fusion is mediated by large dynamin-related GTPase proteins Mfn1, Mfn2 and OPA1. Outer mitochondria membrane (OM) fusion is mediated by Mfn1 and Mfn2, whereas inner mitochondria membrane (IM) fusion is mediated by OPA1. (B) Mitochondria fission requires the recruitment of Drp1 from cytosol to mitochondria. Drp1 is also a dynamin-related GTPase protein that binds to four Drp1 receptor proteins Fis1, Mff, MID49 and MID51, which are mitochondria OM proteins.

fission is essential for separating mitochondria into two daughter cells. At the onset of mitosis, Drp1 is phosphorylated by Cdk1/Cyclin B at Ser585, which increases Drp1 GTPase activity [26]. In contrast, reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase (PKA) and its dephosphorylation by phosphatase calcineurin at Ser656 leads to elongated mitochondria [27]. In addition, the mitochondrial phosphatase phosphoglycerate mutase family member 5 (PGAM5), dephosphorylates Drp1 at Ser637 and recruits Drp1 to mitochondria to induce mitochondrial fragmentation. This PGAM5-Drp1-mediated mitochondrial fragmentation was initially thought to play a critical role in programmed necrosis, but this notion has been challenged by recent findings that Drp1 knockout mouse embryonic fibroblasts (MEFs) were equally as sensitive to necrosis as wild type MEFs [28,29]. In addition to phosphorylation, Drp1 can also be ubiquitinated by MARCH V, a mitochondrial E3 ligase, or sumoylated by SUMO-1. The ubiquitination and sumoylation of Drp1 can either regulate the stability of Drp1 or recruit Drp1 to the actual mitochondrial dividing site and in turn regulate mitochondria fission [30–32].

In addition to fission and fusion, the movement of mitochondria through the cytoskeleton is also important for the cellular distribution and turnover of mitochondria [33]. Mitochondria in mammalian cells are mostly transported on microtubules using a kinesin motor towards the plus end and a dynein motor towards the minus end of microtubules [34] (Fig. 2). The attachment of mitochondria to the kinesin motor is regulated by a series of molecular adapters. The adapter protein Milton directly interacts with the outer mitochondrial membrane protein Mitochondrial Rho GTPase (Miro) and in turn links mitochondria to kinesin [34]. Interestingly, both Mfn1 and Mfn2 interact with Miro and