In vivo functions of Drp1: Lessons learned from yeast genetics and mouse knockouts

Hiromi Sesaki*, Yoshihiro Adachi, Yusuke Kageyama, Kie Itoh, Miho Iijima

Department of Cell Biology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Mitochondria grow, divide, and fuse in cells. Mitochondrial division is critical for the maintenance of the structure and function of mitochondria. Alterations in this process have been linked to many human diseases, including peripheral neuropathies and aging-related neurological disorders. In this review, we discuss recent progress in mitochondrial division by focusing on molecular and in vivo analyses of the evolutionarily conserved, central component of mitochondrial division, dynamin-related protein 1 (Drp1), in the yeast and mouse model organisms. This article is part of a Special Issue entitled: Misfolded Proteins, Mitochondrial Dysfunction, and Neurodegenerative Diseases.

© 2013 Elsevier B.V. All rights reserved.

1. Introduction

Mitochondria play important roles in many cellular and physiological functions, including energy production, lipid and amino acid metabolism, body temperature control, calcium signaling, and cell death [1,2]. In many cell types, mitochondria consist of short tubular structures with occasional branches and are distributed throughout the cytoplasm. Mitochondria increase in size by importing proteins, nucleic acids, and lipids into one of four compartments—the outer membrane, inner membrane, intermembrane space, and matrix. In addition to growth, mitochondrial division and fusion are highly regulated under different physiological conditions and are mediated by three conserved dynamin-related GTPases. Dynamin-related protein 1 (Drp1) controls mitochondrial division, whereas mitofusin and optic atrophy 1 (Opa1) drive fusion [3–6]. Recent studies have shown that aberrations in these dynamic processes are associated with many human disorders [7–10]. A mutation in Drp1 leads to postneonatal death with developmental defects in the brain and eye [11]. Mutations in mitofusin 2 and Opa1 cause Charcot–Marie–Tooth disease type 2A and dominant optic atrophy 1, respectively. In addition, changes in mitochondrial division and fusion have been suggested to play major roles in the pathogenesis of aging-related diseases, such as Alzheimer’s disease, Huntington’s disease, and Parkinson’s disease [7,8,10]. In this review, we will discuss recent findings on the physiological function of mitochondrial division from studies using genetic model organisms, such as yeast and mice.

2. Molecular analysis of Drp1

The central components of mitochondrial division, Drp1 in mammals and Dnm1 in yeast, are high molecular weight GTPases that belong to the dynamin protein family [4,12,13]. Classic dynamin functions in membrane scission during vesicle formation at the plasma membrane and Golgi complex, whereas Drp1, mitofusin, and Opa1 function in membrane remodeling in mitochondria [14–18]. The majority of Drp1 molecules forms soluble dimers and tetramers in the cytosol, which are recruited to sites of mitochondrial division through interactions with several mitochondrial outer membrane proteins, including mitochondrial fission factor (Mff), fusion 1 (Fis1), and two homologous proteins, mitochondrial dynamics proteins of 49 and 51 kDa (Mid49 and Mid51). Mid49 and Mid51 are also called mitochondrial elongation factors 1 and 2 (MIEF1 and 2). Mff, Fis1 and Mid/MIEF are discussed in more detail below (Section 2.3. Receptors for Dnm1 and Drp1).

The diameter of mitochondrial tubules (~300 nm) is larger than the necks of coated pits (~50 nm) formed during endocytosis at the plasma membrane. Consistent with the larger diameter of mitochondria, purified Drp1 assembles into spirals with a diameter (~100 nm) larger than that of dynamin spirals (~50 nm) [19,20]. However, Drp1 spirals are still too narrow to encircle mitochondria by themselves, suggesting involvement of mechanisms upstream of Drp1-dependent constriction. Recent studies have shown that another intracellular organelle, the ER, mediates a step prior to those of Drp1 and Dnm1.

*Corresponding author.
E-mail address: hsesaki@jhmi.edu (H. Sesaki).

© 2013 Elsevier B.V. All rights reserved.

0925–4439/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbadis.2013.11.024
2.1. Structure and domains

Drp1 and its yeast homolog, Dnm1, contain four domains: an N-terminal GTPase domain, middle domain, variable domain (a.k.a. B domain), and C-terminal GTPase effector domain (GED) [12,13]. The GTPase domain hydrolyzes GTP and regulates self-assembly of Drp1 and Dnm1 [21,22]. GTP simulates polymerization of Drp1/Dnm1 and, in turn, the GTPase activity is enhanced in assembled Drp1. During GTP hydrolysis, the diameters of Drp1/Dnm1 spirals decrease which potentially drives constriction of mitochondria.

The middle domain is important for the self-assembly of Drp1 into dimers and tetramers, as well as higher-order oligomers. Crystal structures of dynamin and Drp1 show that three helices from the middle domain and one from the GED form a four-helix bundle that mediates Drp1–Drp1 interactions at the dimerization interface [23–25]. The surface of the bundle located opposite the dimerization interface may bring two dimers together to form tetramers and mediate further oligomerization of Drp1. Consistent with the structural data, mutations in this domain block oligomerization of Drp1 and, thereby, assembly-stimulated GTPase activity [26]. A spontaneous dominant negative mutation in this domain (A395D) leads to postnatal death in humans, with defective brain development [11].

The variable domain, which is located next to the middle domain, is less conserved among different organisms [27]. In Dnm1, the corresponding region contains the pleckstrin homology (PH) domain and targets Dnm1 to the plasma membrane through interactions with the phosphoinositide PIP2 [14,15]. Drp1 binds to a mitochondria-specific phospholipid, cardiolipin; however, the interaction depends on a positively-charged residue in the GTPase domain [28]. The role of the variable domain in cardiolipin association remains to be determined. The variable domain may, therefore, function in providing the specificity for the localization of Drp1 to mitochondria through proteins located in the mitochondrial outer membrane; however, its molecular function is unclear.

The C-terminal GED folds back and binds to the GTPase domain and stimulates GTPase activity [29,30]. Unlike other GTPases, such as ras-related GTPases, no guanine nucleotide exchange factors (GEFs) or GTPase-activating proteins (GAPs) have been identified for Dnm1 and Drp1, perhaps due to the GED and relatively low affinities for GDP. Self-assembly of Dnm1 carrying a mutation in this domain is increased in yeast, perhaps as a result of slowed disassembly of oligomers, due to reduced GTPase activity [30]. In contrast, when expressed in mammalian cells, GED mutants connect mitochondrial tubules, suggesting a defect in mitochondrial division [29]. Part of the GED contributes a helix to the self-association interface together with the middle domain.

2.2. Isoforms

The Drp1 gene contains three alternative exons and expresses multiple isoforms [31–33]. One of the alternative exons is located in the GTPase domain, and the other two are in the variable domain [34]. Whereas most Drp1 isoforms are present in the cytosol and mitochondria, isoforms expressing the third, but not the second, alternative exon are associated with microtubules [34]. Percentages of the microtubule-associated Drp1 isoforms vary depending on cell type, with immune cells expressing high levels of these forms. Instead of engaging mitochondrial fission, these two isoforms stabilize the microtubule cytoskeleton, and this activity is regulated via phosphorylation of Drp1 by cyclin-dependent protein kinase [34]. Because the microtubule-associated isoforms and mitochondria-associated isoforms copolymerize, these different isoforms may function cooperatively to anchor mitochondria to microtubules or to use microtubules as templates for Drp1 spirals to encircle mitochondria for division.

2.3. Receptors for Dnm1 and Drp1

Because yeast Dnm1 and mammalian Drp1 are present as unassembled forms in the cytosol, key mechanisms for mitochondrial division are mitochondrial recruitment of Dnm1/Drp1 and their subsequent assembly. These steps are mediated by their receptors and adapters located in the outer membrane.

2.3.1. Yeast

Dnm1 is recruited to mitochondria through the outer membrane protein Fis1 and two homologous, functionally-redundant adapter proteins, Mdv1 and Caf4 [35–38]. Both proteins lack transmembrane domains, but are constitutively associated with the outer membrane through Fis1. The adapter proteins assemble Dnm1 on the mitochondrial outer membrane. Purified Mdv1 stimulates the assembly of Dnm1 in vitro [39]. Therefore, the role of Fis1 may simply be to anchor Mdv1 to mitochondria. In support of this model, addition of a transmembrane domain of a mitochondrial outer membrane protein to Mdv1 bypasses the requirement of Fis1 for Dnm1 recruitment and mitochondrial division [40].

Dnm1 is also attached to mitochondria through another mechanism for mitochondrial division and distribution. This mechanism involves a cortical protein, Num1, which binds to the cortical actin cytoskeleton, and Mdm36, which connects Dnm1 to Num1 [41,42]. In budding yeast, short actin filaments form the actin cortex beneath the plasma membrane [43]. Yeast mitochondria are mainly associated with the actin cytoskeleton, in contrast to mammalian mitochondria, which are associated with microtubules [44]. The Dnm1–Mdm36–Num1 complex is required for both mitochondrial division and mitochondrial anchoring to the actin cortex [41,42]. In particular, this complex functions in the retention of mitochondria in mother cells [41,45]. Interestingly, this anchoring mechanism can be substituted by synthetic linker molecules that connect mitochondria to either the plasma membrane or the cortical ER, suggesting that mitochondrial dynamics and distribution coordinate with other cellular structures [42,45].

2.3.2. Mammals

To recruit cytosolic Drp1 to the site of mitochondrial division in mammalian cells, several outer membrane proteins have been identified, including Mff, Fis1, MiD49, and MiD51. These individual transmembrane proteins are diverse in their amino acid sequences and topologies. Supporting their roles as receptor proteins, knockout and knockdown of Mff, Fis1, and MiDs decreases mitochondrial fission and elongates mitochondria. The combined loss of these proteins additionally affects mitochondrial division [46]. Interestingly, when Drp1 is expressed together with Mff or MiD49 in yeast cells null for DNM1, FIS1, MDV1 and CAF4, four genes for mitochondrial division, each pair of proteins can induce mitochondrial fission [40]. These data suggest that Mff, Fis1, and MiDs function in mitochondrial fission independently. These Drp1-recruiting proteins may be regulated under different conditions in response to diverse physiological cues. Unlike yeast, no adaptor proteins have been identified for Drp1 in mammals. It appears that Drp1 receptor proteins have the ability to assemble on mitochondria after recruitment of Drp1.

Mff is a 33-kDa protein anchored to the outer membrane via its C-terminal transmembrane domain [47,48]. Mff forms punctate structures along mitochondrial tubules, and many of these are located at the contact site between mitochondria and the ER [49] (roles of the contact sites in mitochondrial division are discussed below—Section 2.4). Constriction of mitochondria by the ER and actin cytoskeleton). Purified Mff slightly enhances the GTPase activity of Drp1 [40].

MiD49 and 51 (MIEF1 and 2) are homologous proteins of ~50 kDa and are inserted into the mitochondrial outer membrane via an N-terminal transmembrane domain [50,51]. The role of these proteins has been controversial, and it has been suggested that they block mitochondrial division by sequestering Drp1 at the mitochondrial surface in...
studies have suggested the ER promotes mitochondrial division at transfer during lipid biosynthesis. In addition to these functions, recent through calcium signaling at the contact sites and through phospholipid [58]. It has been shown that mitochondria and the ER communicate actin polymerization at the coated pits to generate endocytic vesicles of the actin cytoskeleton in mitochondrial division is reminiscent of physically separating two daughter mitochondria. The involvement mitochondria, and then Drp1 drives completion of the constriction, fi

Moreover, involvement of the actin cytoskeleton in mitochondrial division has been implied as part of the pathogenesis of Alzheimer’s disease. Hyperphosphorylation and proteolytic cleavage of a microtubule-binding protein, tau, lead to its aggregation in Alzheimer’s disease. Hyperphosphorylation and proteolytic cleavage of tau cause activation of Drp1 in Alzheimer’s disease. Supporting this idea, Drp1 was associated with phosphorylated tau [66].

3. Physiological studies of Drp1

3.1. Yeast

3.1.1. Mitochondrial morphology

In budding yeast, mitochondria continuously fuse and divide during growth, sporulation, and mating (Fig. 1). The loss of Dnm1 connects mitochondrial tubules and generates a single net-like structure [67–69]. Despite the dramatic morphological changes, there are no obvious growth defects in dnm1Δ cells. dnm1Δ mitochondria maintain their respiratory function and are inherited normally by daughter cells. During mitosis, a portion of mitochondria extends toward daughter cells and is divided between daughter and mother cells by an unknown mechanism. This division process occurs without loss of mitochondrial function. The force of cytokinesis may separate mitochondria. However, during meiosis, mitochondrial segregation into spores is more dependent on Dnm1, and dnm1Δ cells are defective in proper segregation of mitochondria into four spores [70].

Simultaneous loss of Dnm1 and fusion components, such as Fzo1, Ugo1 and Mgm1, restores tubular mitochondria similar in morphology to wild-type mitochondria [67,71,72]. In addition to the overall morphology, structure of the inner membrane cristae is lost in cells defective in mitochondrial fusion, but these phenotypes are rescued by additional loss of Drp1 in double mutants lacking both Dnm1 and Mgm1 [72]. Although the exact role of Dnm1 in cristae morphology remains to be determined, Dnm1 may regulate inner membrane organization through the intramitochondrial contact site between the outer membrane and the inner membrane. Similarly, it has been shown that mammalian Drp1 also remodels inner membrane cristae during apoptosis [73].

3.1.2. Mitochondrial DNA (mtDNA) nucleoids

Mitochondrial division is also important for the morphology of mtDNA nucleoids in the budding yeast. Whereas dnm1Δ cells normally maintain mtDNA nucleoids, when inner membrane cristae structure is disorganized and cristae junctions are lost in cells lacking the protein complex containing Fcj1 [74–77], a yeast homolog of mitofillin, the lack of Dnm1 leads to the aggregation of mtDNA nucleoids and loss of mtDNA [78]. Therefore, inner membrane cristae and mitochondrial division may perform overlapping functions to partition mtDNA nucleoids in the matrix. Consistent with this model, mitochondrial division is spatially linked to nucleoids, resulting in their distribution into newly generated tips in the mitochondrial network [79]. Similarly, in the fission yeast, mitochondrial division takes place between two mtDNA nucleoids and appears to ensure that each mitochondrion contains mtDNA. The role of mitochondrial division in mtDNA nucleoids is conserved because Drp1 knockout (KO) mouse embryonic fibroblasts showed clusters of mtDNA [80], and Drp1-depleted cells aggregated mtDNA nucleoids [81].

3.1.3. Mitophagy

Mitophagy has been suggested as a mechanism for removal of damaged mitochondria. Because mitochondria are constantly exposed to oxidative stress, efficient clearance of damaged mitochondria is critical for the maintenance of mitochondrial functional competence. Mitochondria become smaller by division and are engulfed by autophagosomes as dnm1Δ cells showed decreased delivery of mitochondria to lysosomes [82]. In one possible mechanism, the scaffold protein for autophagy Atg11 binds to the mitochondrial outer membrane protein Atp32 and the Atp32–Atg11 complex marks mitochondria for degradation [83–85]. In addition, Atg11 binds to and recruits Dnm1 to promote mitochondrial division [83]. Interestingly, the Dnm1–Atg11–Atp32 complex is located at mitochondria–ER contact sites [83]. Both steady-state mitochondrial division and mitophagy-induced mitochondrial division may occur at the organelle contact site.
3.1.4. Aging

Considering the role of Dnm1 in mitophagy, the lack of mitochondrial division is expected to decrease turnover of mitochondria and, therefore, lead to accumulation of damaged mitochondria. This may potentially result in shortening of life span. However, it is surprising that life span is extended in dnm1Δ cells [86]. In aged wild-type cells, mitochondrial tubules become fragmented, whereas, in dnm1Δ cells, aging-related mitochondrial fragmentation and increases in reactive oxygen species were suppressed [86]. Similarly, extension of life span was observed in drp1 mutants of Caenorhabditis elegans. Knockdown of drp1 leads to dramatic

---

**Fig. 1.** Mitochondrial morphology in yeast and mammalian cells. Mitochondria were visualized in yeast cells (wild-type and dnm1Δ), cultured mouse embryonic fibroblasts (MEFs) (wild-type and Drp1KO), and cultured Purkinje cells in vitro (wild-type and Drp1KO). Mitochondria were also examined in Purkinje cells and granule cells in vivo. Mitochondria formed short tubules in wild-type and net-like structures in yeast dnm1Δ cells. In Drp1KO MEFs, elongated mitochondrial tubules are highly connected. Upon addition of reactive oxygen species (50 μM H2O2) to the culture medium, elongated mitochondria became large spheres in Drp1KO MEFs. In Drp1KO Purkinje cells, mitochondria formed large spheres, which looked similar to those seen in H2O2-treated Drp1KO MEFs. When Drp1KO Purkinje cells were treated with antioxidants (1 mM N-acetylcysteine, NAC), mitochondria showed elongated tubules without forming spheres, which were similar to mitochondria in Drp1KO MEFs. These observations suggest that the loss of Drp1 induces oxidative damage in Drp1KO Purkinje cells and transforms elongated tubules into large spheres. In Drp1KO granule cells, mitochondria appeared normal.

© Wakabayashi et al. [91] and Kageyama et al. (2012).
extension of life span in daf16 or age1 mutants, in which insulin signaling is reduced [87]. In contrast, these phenotypes are in contrast to those observed in mammalian neurons, where the loss of mitochondrial division increases oxidative damage in mitochondria and causes cell death due to impaired respiratory function [7,88,89].

3.2. Mice

3.2.1. Mitochondrial morphology

In contrast to elongation and excessive connection of mitochondria in dnm1Δ cells, the effect of loss of mammalian Drp1 on mitochondrial morphology varies depending on cell type [Fig. 1]. In cerebellar Purkinje cells, where Drp1 is highly expressed, the lack of Drp1 transforms organelle morphology in two phases [88]. First, an imbalance between mitochondrial fusion and division results in elongation and connection of mitochondrial tubules. These elongated mitochondria gradually accumulate oxidative damage and undergo additional morphological changes from elongated tubules into large spheres. The formation of mitochondrial spheres can be suppressed by antioxidants, such as N-acetylcysteine and coenzyme Q10 [88]. In contrast, granule cells, another type of neuron in the cerebellum, in which Drp1 levels are much lower than in Purkinje cells [88,90], maintain normal mitochondrial morphology after the loss of Drp1 [91]. Mitochondria in granule cells may divide at a very low frequency or use Drp1-independent mechanisms for mitochondrial division. In neurons of the forebrain, mitochondria become large spheres similar to those seen in Purkinje cells [92]. Interestingly, mouse embryonic fibroblasts lacking Drp1 show interconnection of elongated tubules, similar to yeast dnm1Δ cells, but enlarged spheres are rarely observed. These morphological differences may be explained by the level of oxidative stress, because addition of reactive oxygen species, such as hydrogen peroxide, transforms elongated tubules into spheres in Drp1KO mouse embryonic fibroblasts [88].

3.2.2. Embryonic and brain development

Drp1KO causes embryonic lethality in mice [91,92]. Drp1KO embryos die at approximately E 11.5 and are smaller than wild-type embryos, suggesting the requirement of Drp1 for cell growth, proliferation, and differentiation [91]. As a possible cause of the lethality, giant cells are missing in the placenta of Drp1KO embryos. In contrast, blood vessels are not grossly affected [91]. The architecture of the heart appears normal, although isolated cardiomyocytes show decreased beating rate, suggesting that functional defects in the heart may also contribute to embryonic death. Heterozygous Drp1KO mice have levels of Drp1 that are decreased by 20%–30%, but these animals are normal in birth, growth, and mating [91,93]. Mitochondrial morphology also appears normal in heterozygous Drp1KO mice, suggesting that mitochondrial division is not severely affected [93]. Partial decreases in Drp1 levels are, therefore, tolerated in mice.

Drp1 is highly expressed in the brain. To determine the effect of Drp1KO on brain development, Drp1 was knocked out in the cerebellum and surrounding regions using brain-specific Drp1KO with En1-Cre recombinase and floxed alleles of Drp1 [91]. Development of the cerebellum was dramatically decreased, and the mice died within 24 h of birth. In Drp1KO cerebella, proliferation of neurons was greatly decreased, and the number of Purkinje cells was dramatically decreased [91]. Similarly, when Drp1 was deleted in a broad region of the brain using Nes-Cre recombinase, brain development was inhibited and many apoptotic cells were observed in the premature, superficial-layer neurons and the deep cortical layers [92]. In neurons isolated from Nes-Cre Drp1KO mice, the size of mitochondria was increased and the number was decreased [92]. In particular, synapses lacked mitochondria, and synapse formation was defective in these neurons in culture [92]. These observations are consistent with findings in Drosophila mutants carrying mutations in Drp1 [94]. drp1 mutant flies failed to distribute mitochondria at the neuromuscular junctions, leading to defects in mobilization of the vesicle reserve pool, likely due to decreased amounts of ATP in this region [94]. As a result, when Drp1 mutants were exposed to high frequency stimulation to induce continuous neurotranscretion, the mutants were unable to maintain normal levels of neurotransmission [94]. In mammals, Drp1 may have a more direct role in endocytosis of synaptic vesicles. Drp1 forms protein complexes with components of clathrin-coated vesicles and controls the size of endocytic vesicles in response to synaptic stimulation [95].

The role of Drp1 in apoptosis seems to vary depending on cell type and physiological context. In Drp1KO embryos, developmentally-regulated apoptosis of neural crest cells was decreased during neural tube closure [91]. In contrast, apoptosis was increased in the neuroepithelium of the brain [92]. When apoptosis was examined in isolated Drp1KO mouse embryonic fibroblasts and embryonic stem cells, the release of cytochrome c and apoptotic cell death in response to different death stimuli were not affected in the absence of Drp1 [91,92]. In culture, Drp1KO neurons are sensitive to apoptotic induction.

It should be noted that a spontaneous dominant negative mutation in human Drp1 in the middle domain resulted in developmental defects in the brain and eye, and postneonatal death one month after birth [11]. The patient had elevated lactate levels in blood and brain fluid, suggesting decreased mitochondrial respiration. However, skin fibroblasts isolated from the patient showed normal respiratory capacity, even though mitochondria were elongated, as expected from failure of division. This observation is consistent with findings in fibroblasts isolated from Drp1KO mouse embryos [91,92]. Fibroblasts may tolerate the loss of Drp1 and mitochondrial division in terms of mitochondrial functions. The structure and respiratory function of mitochondria in the skeletal muscle of the patient also appeared normal.

3.2.3. Survival of postmitotic neurons

In addition to its role in brain development, Drp1 ensures the survival of postmitotic neurons in mice [88,89]. When Drp1 is knocked out in postmitotic Purkinje cells in the cerebellum using L7-Cre recombinase, mitochondria accumulated oxidative damage, became defective in respiration, and gradually degenerated over 6 months. As a consequence of the loss of Purkinje cells, L7-Drp1KO mice became defective in motor coordination behavior. Mitochondria became elongated and then became large spheres due to oxidative damage [88,89]. On the other hand, the distribution of mitochondria was not affected. These spherical mitochondria lacked a subunit of the electron transport chain complex IV, which is encoded by mtDNA, suggesting that the respiratory defect at least partly results from abnormalities in mtDNA. Mitochondria also accumulated components related to mitophagy, such as LC3 and p62, suggesting that mitophagy may be slowed, with accumulation of its intermediates [88,89]. Similarly, mitochondria are highly decorated with ubiquitin. The E3 ubiquitin ligase parkin has been suggested to ubiquitinate mitochondrial proteins during mitophagy to signal engulfment of mitochondria by autophagosomes [96]. However, when L7-Drp1KO mice were crossed with parkinKO mice, L7-Drp1–parkin double-KO mice maintained ubiquitination of mitochondria in the absence of parkin. Therefore, ubiquitination of mitochondria was mediated by other E3 ubiquitin ligases under these conditions. Another study has also suggested a parkin-independent mechanism for mitophagy [97]. It is of interest to identify the enzymes that ubiquitinate mitochondrial protein during mitophagy. When Drp1KO Purkinje cells were treated with the antioxidants N-acetylcysteine and coenzyme Q10, the degeneration of Drp1KO Purkinje cells was suppressed, suggesting that oxidative damage is a downstream event that leads to neurodegeneration when mitochondrial division is blocked [88,89].

In addition to mitochondrial division, Drp1 also controls peroxisomal division [98–100]. Consistent with this role, peroxisomes were elongated in Drp1KO mouse embryonic fibroblasts [91]. However, the morphology of peroxisomes was not affected in Drp1KO Purkinje cells [88]. Peroxisomal division may be less dependent on Drp1 in Purkinje cells. The degeneration of Drp1KO Purkinje cells likely results from defects in mitochondrial division.
4. Concluding remarks

Studies have shown the physiological importance of mitochondrial division and revealed many aspects of the molecular mechanism underlying this process. The knowledge has helped us better understand the pathogenesis of human diseases that are linked to mitochondrial division. In addition, these studies have raised many important questions. How do signaling mechanisms couple mitochondrial division and mitophagy? What is the exact mechanism by which the ER and mitochondrial division? In addition, these studies have raised many important questions. Addressing these questions will broaden our knowledge of mitochondrial dynamics and human diseases.

Acknowledgements

We thank many scientists who advanced our understanding of mitochondrial dynamics, and apologize that we were unable to cite all of the relevant research due to space restrictions. This work was supported by NIH grants to M.I. (GM084015) and H.S. (GM089853 and NS084154).

References
