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REVIEW

Mitochondrial dynamics in cell death and neurodegeneration

Dong-Hyung Cho · Tomohiro Nakamura · Stuart A. Lipton

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Abstract Mitochondria are highly dynamic organelles that continuously undergo two opposite processes, fission and fusion. Mitochondrial dynamics influence not only mitochondrial morphology, but also mitochondrial biogenesis, mitochondrial distribution within the cell, cell bioenergetics, and cell injury or death. Drp1 mediates mitochondrial fission, whereas Mfn1/2 and Opa1 control mitochondrial fusion. Neurons require large amounts of energy to carry out their highly specialized functions. Thus, mitochondrial dysfunction is a prominent feature in a variety of neurodegenerative diseases. Mutations of Mfn2 and Opa1 lead to neuropathies such as Charcot-Marie-Tooth disease type 2A and autosomal dominant optic atrophy. Moreover, both Aβ peptide and mutant huntingtin protein induce mitochondrial fragmentation and neuronal cell death. In addition, mutants of Parkinson's disease-related genes also show abnormal mitochondrial morphology. This review highlights our current understanding of abnormal mitochondrial dynamics relevant to neuronal synaptic loss and cell death in neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and Huntington's disease.

D.-H. Cho · T. Nakamura · S. A. Lipton (✉)
Center for Neuroscience, Aging, and Stem Cell Research,
Sanford-Burnham Medical Research Institute,
10901 North Torrey Pines Road, La Jolla, CA 92037, USA
e-mail: slipton@burnham.org

D.-H. Cho
Institute for Innovative Cancer Research, Asan Medical Center,
University of Ulsan College of Medicine, Pungpap-dong,
Songpa-gu, Seoul 138-736, Korea

D.-H. Cho
Graduate School of East-West Medical Science,
Kyung Hee University, Yongin, Gyeonggi 446-701, Korea

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Abbreviations

Drp1	dynamin-related protein 1
Opa1	optic atrophy protein 1
Mfn1/2	mitofusin1/2
AD	Alzheimer's disease
PD	Parkinson's disease
HD	Huntinton's disease
ADOA	Autosomal dominant optic atrophy
CTM2A	Charcot-Marie-Tooth neuropathy type 2A

Introduction

Mitochondria are highly dynamic organelles that continuously divide and fuse in healthy cells [1]. Mitochondrial dynamics (fission and fusion) control processes associated with the biogenesis, subcellular localization and distribution of mitochondria as well as their morphology [2, 3]. Several principal controllers of mitochondrial dynamics have been identified [4–9] (Fig. 1). Mitochondrial fission is regulated by dynamin-related protein 1 (Drp1), which shares common mechanisms with its homologue, dynamin, a large GTPase protein involved in endocytosis [10]. Drp1 is translocated from the cytosol into the outer mitochondrial membrane (OMM) to initiate fission [11]. Knockdown of Drp1 by RNAi or the overexpression of a dominant-negative Drp1 (K38A, with defective GTPase activity) inhibits fission and delays cytochrome *C* release and caspase activation, and eventually leads to cell death [11–13]. Mitochondrial fusion is mediated by three large GTPase dynamin-like proteins,

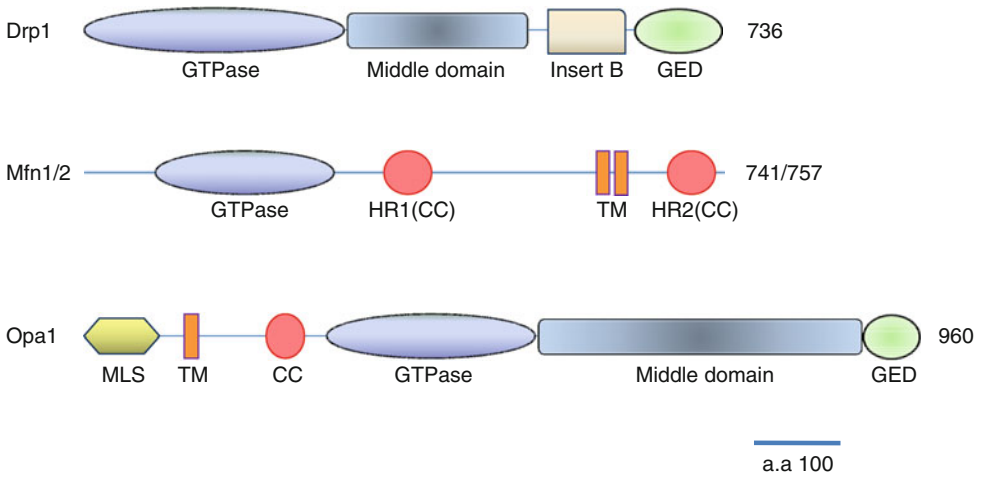

Fig. 1 Schematic structure of the domains of proteins involved in mitochondrial dynamics. The length and topology of amino acids for each region are shown. All proteins have a GTPase domain found in dynamin-related proteins for hydrolysis of GTP. Drp1 and Opa1 have a GED domain (*green*). Transmembrane domains (*orange*) are found in Mfn1/2 and Opa1, and a mitochondrial localization signal sequence in the N-terminus is found in Opa1. Coiled-coil domains are found in fusion proteins (*red*). *MLS* mitochondrial localization signal, *HR* heptad repeat domain, *CC* coiled-coil domain, *TM* transmembrane domain)

mitofusin 1 (Mfn1), mitofusin 2 (Mfn2) and optic atrophy protein 1 (Opa1) [3, 14]. OMM fusion is mediated by Mfn1/2, and inner mitochondrial membrane (IMM) fusion is associated with Opa1. Mitochondrial fusion functions in part as a cell protective mechanism. Silencing Mfn1/2 results in mitochondrial fragmentation and increases mitochondrial susceptibility to apoptotic stimuli. Similarly, loss of Opa1 induces disruption of mitochondrial cristae as well as spontaneous apoptosis [15, 16]. The proteins involved in mitochondrial fission and fusion are still being characterized, and the precise mechanisms underlying these structural modifications remain to be clearly elucidated.

In the past few years, emerging evidence has suggested that disruption of the dynamic balance of mitochondrial fission and fusion (collectively designated 'mitochondrial dynamics') contributes to neurodegenerative and metabolic disorders [17–20]. Dysfunction of mitochondrial dynamics and resulting disease can emanate not only from mutations of the genes encoding fission- or fusion-related proteins, but also, as our group has recently shown, from post-translational protein modifications that regulate their stability and activity. Mfn1/2 and Opa1 are affected in patients with Charcot-Marie-Tooth neuropathy type 2A (CMT2A) [21–23] and autosomal dominant optic atrophy (ADOA), respectively [7, 8, 17]. Drp1 activity can be regulated by phosphorylation, *S*-nitrosylation, sumoylation and ubiqutination, while Opa1 is activated by proteolytic processing [24–33].

Mitochondrial dysfunction is a hallmark of many common neurodegenerative diseases. Hence, in this review, we discuss effects of mitochondrial dynamics from the perspectives of cell death and neurodegeneration.

Mitochondrial fission and fusion machinery

Mitochondrial fission machinery

Despite extensive data currently available regarding the machinery of mitochondrial fission and fusion, the precise molecular mechanisms relevant to mitochondrial dynamics are not entirely understood. However, several key players in mitochondrial dynamics have been identified. Drp1 is a member of the conserved dynamin GTPase superfamily, which includes a broad range of membrane fission proteins [10, 11]. Drp1 exhibits specific fission activity on mitochondrial and peroxisomal membranes [34, 35]. Drp1 shows several functional domains, including an N-terminal GTPase domain, which is thought to provide mechanical force, a dynamin-like middle domain, an insert B domain and a GTPase effector domain (GED), which is located in the C-terminal region [1, 36]. Intra- and intermolecular interactions between the GTPase domain and GED or intermolecular interaction of GEDs are required for the assembly and promotion of higher order structures (dimers or tetramers) [37, 38]. Self-assembly and assembly-stimulated GTP hydrolysis are functionally essential features of the dynamin superfamily of proteins [39–42]. The GTP-binding defective mutant (K38A) inactivates Drp1 by sequestration of endogenous Drp1, thus inhibiting its mitochondrial localization; therefore, it acts as a dominant negative. GED is also involved in the regulation of GTPase activity and its assembly. Mutations in the GED domain also significantly change Drp1 activity [38].

The mechanism exploited in the recruitment of Drp1 to the mitochondrial membrane for spiral formation and fission remains unclear. Fis1, localized on the OMM,

functions as a Drp1 receptor. Fis1 overexpression accelerates mitochondrial fission, whereas Fis1 silencing by RNAi inhibits mitochondrial fragmentation [43, 44]. Although Fis1 acts downstream of Drp1, the role of Fis1 in Drp1 recruitment is still unclear because Drp1 still localizes to the OMM after RNAi knockdown of Fis1 [43–45]. Therefore, further studies will be required to understand the detailed mechanism for the interaction of Fis1 and Drp1.

Posttranslational modifications have been implicated as regulatory mechanisms that mediate a variety of Drp1 activities during mitochondrial fission (Table 1). The first of these modifications is phosphorylation. For example, during mitosis Drp1 is activated by the CDK1/cyclin B-mediated phosphorylation of serine 618 on the GED of Drp1 (serine 585 in rat) [29]. This phosphorylation events facilitate the proper distribution of mitochondria within daughter nascent cells. Another serine residue (serine 637) within the GED is also phosphorylated by cyclic AMP-dependent protein kinase (PKA) [27, 46]. Unlike CDK1, PKA-induced phosphorylation results in reduced activity by inhibiting the intramolecular interaction of Drp1. Overexpression of Drp1 (S637D), a phospho-mimetic mutant, significantly elongates mitochondria. Additionally, calcineurin is involved in dephosphorylation and regulates translocation of Drp1 to mitochondria [47]. In a recent study, it was demonstrated that Drp1 is also phosphorylated on serine 600 by calcium/calmodulin-dependent protein kinase I α (CaMKIα) [32]. This phosphorylation is regulated by calcium influx through voltage-dependent Ca^{2+} channels, is associated with increased translocation of Drp1 to mitochondria and results in increased affinity for Fis1. Finally, cyclin-dependent kinase 5 (CDK5) has been identified as another relevant mitochondrial fission-regulatory kinase, but whether or not CDK5 directly regulates Drp1 remains to be determined [48]. These reports thus suggest that phosphorylation of Drp1 may have positive or negative effects on its fission activity.

In addition to phosphorylation, our group and subsequently others have recently identified Drp1 as a substrate for reaction with nitric oxide (NO) species, leading to *S*-nitrosylation, or transfer of NO to a critical cysteine thiol, which regulates protein function [33, 49]. *S*-Nitrosylation of Drp1 (forming SNO-Drp1) enhances GTPase activity and oligomer formation, leading to excessive mitochondrial fission or fragmentation in neurons. By mutational analysis, we surmised that NO reacts with cysteine residue 644 of Drp1 within the GED. Mutation of this target cysteine prevented excessive mitochondrial fragmentation and ameliorated synaptic damage and neurotoxicity induced by NO or *β*-amyloid protein (A*β*, which indirectly increases NO) [33]. Cyclic AMP and calcium, as well as NO, are key second messengers in the control of cellular metabolism and homeostasis. Thus, current findings suggest that intracellular signals control and alter mitochondrial morphology by regulating Drp1 activity.

Sumoylation also affects Drp1 activity. Small ubiquitin-related modifier 1 (SUMO1) is bound to the insert B domain of Drp1 and functions as a Drp1-stabilizing protein via sumoylation, thereby resulting in mitochondrial fission [24, 50]. In contrast, sentrin/SUMO-specific protease (SENP5) works as a desumoylation enzyme on Drp1 [31]. Overexpression of SUMO1 evokes mitochondrial fragmentation, while SENP5 rescues SUMO-induced mitochondrial fragmentation [24, 31]. Beside sumoylation, ubiquitination also regulates mitochondrial dynamics. Mitochondrial-anchored protein ligase (MAPL) and mitochondrial E3 ligase protein (MARCH5/MITOL) function as ubiquitin E3 ligases for Drp1 [26, 51–53]. However, the effect of MARCH5 on mitochondrial dynamics has not been clearly identified. MARCH5-deficient cells (produced by small interfering RNA knockdown) or cells with a MARCH5 mutant lacking ubiquitin ligase activity manifested aberrant mitochondrial morphology, including fragmentation, in previously reported studies [26, 51]. However, Karbowski et al. [52] reported that MARCH5 RING mutants and knockdown of MARCH5 by RNAi resulted in abnormal elongation and interconnections of mitochondria. Therefore, Drp1 sumoylation is believed to

Table 1 Posttranslational modification of Drp1

Regulator	Modification	Functional effect	Reference
CDK1	Phosphorylation at Ser 618	Increase	[29]
PKA	Phosphorylation at Ser 637	Decrease	[27, 46]
CaMKIα	Phosphorylation at Ser 600	Increase	[32]
CDK5	Phosphorylation	Increase	[48]
Calcineurin	De-phosphorylation at Ser 637	Increase	[47]
Nitric oxide	*S*-Nitrosylation at Cys 644	Increase	[33]
SUMO1	Sumorylation	Increase	[24, 50]
SENP5	De-sumorylation	Decrease	[24, 31]
MAPL	Ubiquitination	Increase	[53]
MARCH5	Ubiquitination	Increase/decrease	[51, 52]

protect against degradation, but the function of ubiquitination of Drp1 warrants further study.

Mitochondrial fusion machinery

Mitochondrial fusion is a well-coordinated process in which the inner and outer membrane fuse separately. The key components of the machinery of mitochondrial fusion are the mitofusin proteins (Mfn1/2) and Opa1. Mfn1 has been identified as a mammalian homologue of *Drosophila* protein FZO, which mediates mitochondrial fusion in fly cells [4, 9]. Mfn1/2 is localized to the OMM with both its N- and C-termini facing into the cytosol [54]. Structurally, the mitofusins harbor a GTPase domain in the N-terminus, a bipartite transmembrane domain, and two heptad repeat (HR) coiled-coil domains in the middle and C-terminal regions [55]. Mfn1/2 function is dependent on GTPase activity. Loss of function mutations in the GTPase domain (K88T, T109A mutants) disrupts Mfn fusion activity, whereas the gain-of-function mutant (Mfn2 (G12V)) exhibits increased Mfn fusion activity [56–58]. The HR2 domain initiates mitochondrial fusion via oligomerization of Mfn, which leads to tethering of two adjacent mitochondria. Thus, mutations in the HR region also inhibit the fusion activity of Mfn [59]. Knockout of Mfn1 or Mfn2 results in the formation of small fragmented mitochondria, suggesting that both Mfn1 and Mfn2 mediate mitochondrial fusion [60, 61]. Mfn2 is predominantly expressed in heart and skeletal muscle, in contrast to the more general expression of Mfn1. Mfn1 depletion results in a more pronounced phenotype than Mfn2 [57, 62, 63]. Moreover, Opa1 functions in a Mfn1- but not Mfn2-dependent manner, in the mitochondrial fusion pathway [64]. Therefore, the various isoforms may perform specific roles with distinctive activities.

Opa1 is another key factor implicated in mitochondrial fusion and cristae remodeling. The mitochondrial localization sequence (MLS) in the N-terminal region of Opa1 imports is responsible for importing the protein into the mitochondrial inner membrane (IMM). In addition to the MLS, a transmembrane domain anchors Opa1 in the IMM. In the middle region, Opa1 also contains a GTPase domain that is crucial for activity. Mutations in this GTPase domain are associated with the generation of fragmented mitochondria [65]. The middle domain, which is located next to the GTPase domain, is involved in tetramerization and higher order assembly of Opa1 [41]. The C-terminus harbors a coiled-coil region thought to present in the GED domain, which is also involved in oligomerization and activation of Opa1 [10].

Similar to the effect of mitofusin proteins, RNAi against Opa1 leads to fragmentation of mitochondria [15, 63]. This may be attributable to an increased mitochondrial division rate or to a reduction in the fusion capacity of the mitochondria. It has been reported that overexpression of Opa1 leads to complicated responses, such as mitochondrial elongation or fragmentation, depending on the overexpression system [15, 63, 64, 66]. However, the mechanism of this paradoxical effect remains to be elucidated.

Alternative mRNA splicing and proteolysis are also involved in the regulation of Opa1 activity. Different forms of Opa1 can be generated by alternative splicing of exon 4 and 5 [67]. Opa1 isoforms are composed of two long forms (L1 and L2) anchored to the membrane and three soluble short isoforms (S3, S4 and S5), resulting from proteolytic cleavage [25]. Both membrane potential and mitochondrial proteases, such as presenilin-associated rhomboid-like protease (PARL), i-AAA metalloprotease (YmelL) and m-AAA metalloprotease (Paraplegin), regulate Opa1 cleavage [25, 68–72]. It is possible that disparate Opa1 isoforms manifest distinct subcellular localizations and functions [73]. A major function of PARL is generation of soluble Opa1, which controls the shape of mitochondrial cristae independently of fusion activity [69, 74]. The cristae are structurally and functionally distinct structures in the IMM. As the result of downregulation of Opa1, the cristae are disorganized, and their junctions widened. In contrast, cristae become more narrow in response to overexpression of Opa1.

Whereas outer and inner membrane fusion events are separable, their mechanisms are linked. For example, in yeast the protein Ugo1 functions as an adaptor by creating a complex with Fzo1 (the yeast homologue of Mfn) and Mgm1 (the yeast homologue of Opa1) that spans these membranes [75, 76]. Although no mammalian homologue has been identified that might coordinate outer and inner membrane fusion, an adaptor protein like Ugo1 may exist. The finding of a mammalian homologue of Ugo1 would enhance our current understanding of these complex dynamic machines.

Other regulatory proteins affecting mitochondrial dynamics

Recently, a number of proteins controlling mitochondrial dynamics have been identified. One of the key players in mitochondrial fission is Endophilin B1/Bif1, which has a BAR domain and interacts with BAX [77]. Similarly to Drp1, Endophilin B is mainly localized in the cytosol and translocates to mitochondria during apoptosis [78]. Endophilin B exhibits membrane binding and bending activities, and reduced expression by RNAi induces the formation of elongated OMM structures, suggesting that it functions as a mitochondrial fission molecule [78, 79]. The translocase of IMM 8 homologue A (Timm8a/DDP) is released from the intermembrane space of mitochondria and binds to

cytosolic Drp1 to promote its transition to mitochondrial fission sites [80]. Ganglioside-induced differentiation activated protein 1 (GDAP1), which is expressed principally in the nervous system, is anchored into the OMM and regulates mitochondrial networks. RNAi against GDAP1 results in a tubular mitochondrial morphology [81, 82]. Mutations in GDAP1 are known to cause Charcot-Marie-Tooth disease, as discussed further below [81, 83]. The mitochondrial ubiquitin ligase activator of NFκB (MULAN) has been identified as a linker protein between NFκB and mitochondrial dynamics [84]. Additionally, mitochondrial fission factor (MFF), carboxy-terminal modulator protein (CTMP) and gametogenetin-binding protein 1 (GGNBP1) have also been identified as fission-inducing proteins. Ectopic expression of these proteins increases mitochondrial fragmentation [85–87].

Mitochondrial phospholipase D (MitoPLD) is also a fusion regulatory protein. The manner in which the hydrolytic activity of MitoPLD regulates mitochondrial fusion remains unclear, but this phospholipase is required for normal mitochondrial fusion in an Mfn-dependent manner [88, 89]. Additionally, mitofusin-binding protein (Mib) controls mitochondrial morphology by interacting with the cytosolic domain of Mfn1 [90]. Peroxisome proliferatior-activated receptor gamma coactivator-1 beta (PGC-1β) increases Mfn2 promoter activity and expression by coactivation of estrogen-related receptor alpha (ERRα). Thus, PGC-1β increases mitochondrial fusion [91]. Stomatin-like protein 2 (SLP2) is another fusion-inducing protein. SLP2 is involved in stress-induced mitochondrial hyperfusion, which is an adaptive pro-survival response to stress [92].

In summary, although many regulatory proteins and mechanisms of mitochondrial fission and fusion have been elucidated, current models of mitochondrial dynamics remain far from complete. Therefore, future studies in this area are warranted.

Mitochondrial dynamics and cell death

Mitochondrial dynamics and apoptosis

Mitochondria play a pivotal role in cell death, mediating both intrinsic and extrinsic signaling pathways. Mitochondrial membrane permeabilization leads to increased ROS generation, reduced ATP levels and the release of several pro-apoptotic factors, including cytochrome *C*, Smac and apoptosis-inducing factor (AIF) [93, 94]. Mitochondrial membrane permeability is tightly regulated by Bcl-2 family proteins, and is determined by the ratio of pro- and anti-Bcl-2 protein complexes [95]. Mitochondria undergo extensive fragmentation during apoptosis, and Drp1 inhibition suppresses apoptosis, suggesting that mitochondrial fission is actively involved in apoptosis. Mitochondrial fragmentation occurs before caspase activation. Overexpression of a dominant-negative form of Drp1 inhibits not only mitochondrial fission, but also loss of mitochondrial membrane potential and cytochrome *C* release [12]. Moreover, inhibition of Fis1 also suppresses apoptosis, whereas overexpression of Fis1 induces both mitochondrial fission and cytochrome *C* release [43, 45]. Conversely, Mfn1/2 overexpression inhibits apoptosis [96]. Knockdown of Opa1 not only induces fission, but also induces spontaneous cytochrome *C* release and subsequent cell death [15]. Opa1 mutants defective in GTPase activity are incapable of protecting cells from apoptotic stimuli, indicating that the pro-survival and mitochondrial fusion effects of Opa1 might be linked [74].

Interestingly, Bcl-2 family proteins, which regulate mitochondrial permeabilization, functionally associate with mitochondrial fission and fusion proteins. For example, during apoptosis, Bax and Bak associate on the surface of the OMM, where they colocalize with Drp1 and Mfn2 [97]. Mitochondrial fragmentation is attenuated in Bak-deficient cells, and Bax activation is inhibited by a Mfn2 dominant-active mutant, suggesting that Bax and Bak also control mitochondrial fusion through Mfn2 [57, 58]. However, a recent study suggested that Bcl-2 family proteins might influence mitochondrial dynamics independent of anti-apoptotic activity [98]. Although Bax induces release of cytochrome *C* and apoptosis as well as mitochondrial fragmentation, overexpression of Bcl-xL protein only inhibits Bax-induced release of cytochorome c but not Bax-mediated mitochondrial fragmentation. In living neurons, Bcl-w and Bcl-xL appear to maintain proper spine or synaptic structures via regulation of mitochondrial morphology and biomass [99–101]. However, the mechanism whereby Bcl-2 family proteins regulate these events remains to be elucidated [102].

Calcium, one of the key regulators of both cell survival and cell death in response to various cell signals, may also be important in mitochondrial dynamics. p20, a caspase-cleavage product of the ER protein Bap31, and thapsigargin, an ER calcium-ATPase (SERCA) inhibitor, induce calcium release from the ER and activate Drp1-dependent mitochondrial fission and apoptosis [103, 104]. Moreover, Drp1 with Fis1 sensitizes cells to mitochondrial permeability transition via reduction in mitochondrial calcium retention capacity [105]. These results suggest that the relative rates of mitochondrial fission and fusion are important in regulating apoptotic events.

Nonetheless, increased mitochondrial fragmentation is not always necessary for apoptosis. For example, Fis1 stimulates mitochondrial fragmentation without apoptosis,

and inhibition of the mitochondrial fission machinery does not prevent Bax/Bak-mediated apoptosis [106, 107]. Moreover, in Mfn1/2-deficient cells, mitochondria are extensively fragmented, but apoptosis is not enhanced [60, 63]. In summary, current reports suggest that mitochondrial fission machinery may contribute to or regulate apoptotic events, but is not invariably linked to apoptosis. The exact nature between mitochondrial dynamics and apoptosis needs to be studied further.

Mitochondrial dynamics and autophagy

Autophagy is a catabolic process involving self-digestion and turnover of macromolecules and entire organelles. Autophagy is primarily a protective process in response to cellular stress, but it can also be associated with cell death [108, 109]. Autophagosomes are double membrane cytoplasmic vesicles, which fuse to the lysosomes to become autolysosomes, where they degrade cellular components. Although mitochondrial dynamics are associated with autophagy, the precise mechanisms by which this occurs remain poorly understood. Mitochondrial fission occasionally generates uneven daughter mitochondria, for example, with increased membrane potential in one and decreased membrane potential in the other. The depolarized mitochondria are much less likely to fuse and may undergo autophagy [110]. Indeed, overexpression of Fis1 selectively reduces mitochondrial mass and triggers autophagy [111]. In addition, overexpression of either Opa1 or Drp1 dominant negative reduces the level of autophagy [112]. These reports suggest that dysfunctional mitochondria are permissive for autophagy. Recently, it has also been demonstrated that PINK1 regulates mitochondrial fission and autophagy. Knockdown of PINK1 induces an increase in superoxide, contributing to both mitochondrial fragmentation and autophagy. Additionally, the autophagic machinery is required for PINK1 deficiency-induced mitochondrial fragmentation [113]. It has also been suggested that mitochondrial fission exerts a protective effect by facilitating the autophagic response under PINK1-deficient conditions. Mitophagy denotes selective autophagy for mitochondrial degradation. Recently, two different groups identified Atg32 as a mitochondrial transmembrane receptor in yeast that directs the formation of the autophagosome to mitochondria [114, 115]. However, no mammalian homologue of this receptor has yet been discovered, and its effect on mitochondrial dynamics remains to be demonstrated. Mitochondrial dynamics associated with mitophagy are thought to be an important event in the maintenance of cell homeostasis, but further work will be necessary to define the relationship of mitochondrial dynamics and autophagy.

Mitochondrial dynamics and neurodegeneration

Mitochondria are essential organelles for energy generation. Mitochondria are particularly important in neurons, owing to their high demands for energy because of their specialized functions, complex morphology and synaptic activity. Mitochondrial function is directly linked to mitochondrial dynamics, and vice versa. Additionally, mitochondrial dysfunction is strongly associated with neurodegenerative diseases [18]. Recent evidence suggests that an imbalance in mitochondrial dynamics may contribute to both familial and sporadic neurodegenerative diseases [20]. In this section we will discuss the effects of mitochondrial dynamics in neurodegenerative diseases.

Mitochondrial dynamics in genetic neurodegenerative diseases

Charcot-Marie-Tooth (CMT) disease is the most common inherited neuromuscular disorder, and affects the motor and sensory neurons. Mutations of Mfn2 cause CMT type 2A (CMT2A) [21–23]. More than 40 mutations of Mfn2 have been identified in CMT2A patients, and the majority of these mutations are missense mutations [1]. The mechanism by which Mfn2 mutations cause CMT2A has not been fully delineated, but many Mfn2 mutations found in CMT2A are detected within the GTPase domain. Overexpression of some of these Mfn2 mutants result in mitochondrial aggregation in rat dorsal root ganglion neurons, and additional Mfn2 mutants induce abnormal mitochondrial aggregation in mouse embryonic fibroblast (MEF) cells, whereas wild-type Mfn2 displays no effect on mitochondrial aggregation [116, 117]. In addition, transgenic mice expressing a Mfn2 mutant (T105) exhibit a phenotype consistent with the clinical symptoms of CMT2A, suggesting that Mfn2 mutations affect the pathogenesis of CMT2A [118]. GDAP1 mutations are associated with the type 4A CMT (CMT4A), the most frequently detected recessive form of CMT [83, 119]. In contrast to CMT2A, CMT4A is associated with segmental de- and re-myelination [120]. The GDAP1 mutations found in CMT4A patients are not targeted to mitochondria and do not display mitochondrial fragmentation activity [81].

Opa1 was initially identified as the gene mutated in ADOA, the most common optic atrophy affecting retinal ganglion cells and leading to reduced visual acuity [7, 8]. To date, more than 100 mutations of Opa1 have been identified, and almost 50% of the mutations result in premature truncation of the Opa1 protein [121]. The ‘hot spot’ of the cluster of Opa1 mutations is found within the GTPase domain, which is likely to abolish mitochondrial fusion activity. The GTPase mutations of Opa1 exert a dominant-negative effect in the presence of wild-type

protein; loss of Opa1 function produces mitochondrial fragmentation as well as spontaneous apoptosis, suggesting that these Opa1 mutations may be associated with ADOA [15, 45]. However, the question remains why Opa1 mutations specifically affect retinal ganglion cells, as opposed to other cells types, resulting in ADOA.

A recent case report of a patient with signs of both ADOA and CMT2A identified a heterozygous missense mutation of Drp1 (A395D), located in the dynamin-like middle domain [122]. This mutation functions as a dominant negative and inhibits fission of both mitochondria and peroxisomes. While the patient displayed a phenotype similar to those of CMT2A and ADOA, the Drp1 mutation resulted in more severe disease because of earlier onset. Taken together, these findings suggest that dysfunction of mitochondrial dynamics may contribute to the pathogenesis of several neurodegenerative diseases.

Mitochondrial dynamics in Alzheimer's disease

Alzheimer's disease (AD) is the most frequent age-related neurodegenerative disorder and currently has a prevalence approaching 40% among people 80 years of age or older. The clinical symptoms of AD are the consequence of deterioration of selective cognitive domains, particularly those related to memory function [123]. Accumulation of amyloid plaques, representing aggregates of Aβ protein, and neurofibrillary tangles, composed of hyperphosphorylated tau, is thought to contribute to the disruption of neuronal synapses, connectivity and plasticity, with eventual neuronal demise [124, 125]. Aβ is generated by proteolytic processing of amyloid precursor protein (APP) by β- and γ-secretase in the transmembrane region [123, 126]. Oligomers of Aβ may contribute to pathology by disrupting calcium homeostasis and synaptic function, possibly via increases in reactive oxygen/nitrogen species and inflammatory responses [127, 128].

Metabolic defects represent well-documented abnormalities in AD [129]. Not only are mitochondria damaged, but also the resulting oxidative stress has been shown to be present in AD. Moreover, several key molecules in oxidative metabolism have been shown to be defective in AD, consistent with the notion that mitochondrial dysfunction plays a prominent role in the pathogenesis of AD [49]. Aβ may directly induce mitochondrial dysfunction [130], and has been reported to be transported into mitochondria by TOM (translocase of the outer mitochondria membrane) [131]. Aβ may disrupt mitochondrial function via inhibition of key enzymes in respiratory metabolism, such as α-ketoglutarate dehydrogenase, pyruvate dehydrogenase and cytochrome oxidase [132, 133]. Additionally, ABAD, Aβ-binding alcohol dehydrogenase, interacts with Aβ and induces Aβ-mediated toxicity in mitochondria via ROS generation [134]. As discussed above, mitochondrial dynamics influence mitochondrial function; emerging studies indicate that abnormal mitochondrial dynamics may play a crucial role in the pathogenesis of AD [18, 49]. Indeed, as our group and others have shown, overexpression of APP or exposure to Aβ induces mitochondrial fragmentation and abnormal distribution, which results in mitochondrial and neuronal dysfunction [135–137]. We recently reported that NO can lead to mitochondrial fragmentation via *S*-nitrosylation of Drp1 at cysteine residue 644, which is located within the GED domain that regulates GTPase activity and oligomerization [33]. NO is a signaling molecule involved in several important physiological processes including neurotransmitter release and plasticity. However, when NO is excessively produced, it can contribute to neurotoxicity by inducing nitrosative stress, which contributes to the pathogenesis of neurodegenerative diseases. We found that exposure of neurons to oligomerized Aβ leads to *S*-nitrosylation of Drp1 (forming SNO-Drip1), thus hyperactivating this fission protein and causing mitochondrial fragmentation. This fragmentation of mitochondria contributes to synaptic damage and subsequent neuronal cell death (Fig. 2).

Importantly, substitution of an alanine for cysteine residue 644 in Drp1 suppresses Aβ-induced synaptic damage and cell death, suggesting that SNO-Drp1 is a critical step in the Aβ-mediated pathogenesis of AD. Susbsequently, it was reported that the expression of levels of Drp1, Opa1 and Mfn1/2 are significantly decreased in hippocampal neurons of human AD brains, whereas Fis1 levels are increased [49]. The overall expression level of Drp1 is reduced in AD brains compared to controls. Nonetheless, the level of mitochondrial Drp1 is similar in neurons from AD samples or even increased after exposure to oligomerized Aβ protein [or Aβ-driven diffusible ligands (ADDLs)]. Interestingly, phosphorylated or *S*-nitrosylated Drp1, which increases Drp1 activity, is upregulated in AD tissues and ADDL-exposed neurons [29, 33, 49]. In summary, emerging evidence suggests that impaired mitochondrial dynamics are involved in the pathogenesis of AD.

Mitochondrial dynamics in Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease following AD, and the most common movement disorder, affecting approximately 1% of people aged 60 years or older. It is characterized by the progressively diminished ability to initiate voluntary movements owing to the loss of dopaminergic neurons in the substantia nigra [138]. Mitochondrial dysfunction has long been implicated in the pathogenesis of PD.

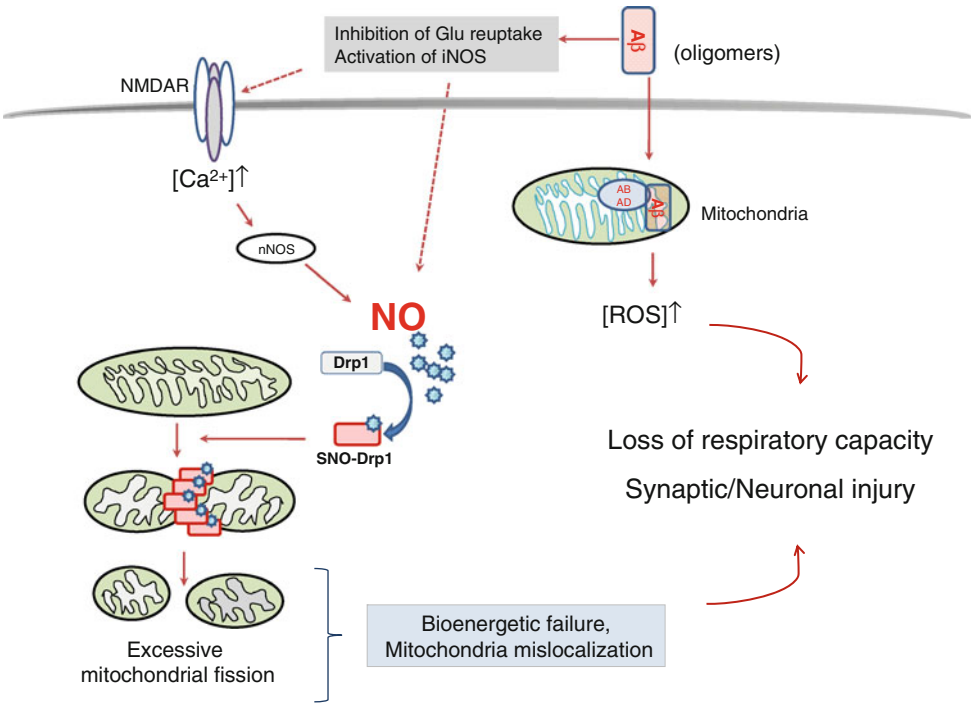

Fig. 2 Proposed model of amyloid-β peptide (Aβ)-induced mitochondrial fission in Alzheimer's disease. Aβ oligomers may interact with ABAD protein in mitochondria to generate ROS, inducing synaptic and neuronal injury. Aβ oligomers may also increase neuronal nitric oxide (NO) production by both NMDA receptor-dependent and -independent mechanisms. NO produces *S*-nitrosylation of Drp1 (forming SNO-Drp1). SNO-Drp1 contributes to synaptic and neuronal injury by leading to excessive mitochondrial fission and bioenergetic impairment

Mitochondrial respiratory electron transport chain NADPH dehydrogenase (Complex I) activity is reduced in the substantia nigra of PD patients, and complex I inhibitors, such as rotenone, MPP^+ and pesticides, result in neuropathological changes similar to PD [139]. Not only are levels of multiple mitochondrial proteins altered in postmortem samples of PD brains, but also PD-linked genetic mutations in PINK1, Parkin and DJ-1 have been identified, suggesting that mitochondrial function may be altered [138, 140].

Recent evidence suggests that abnormal mitochondrial dynamics may contribute to neuronal injury and death in animal models of PD. For example, both rotenone and 6-hydroxydopamine have been shown to induce Drp1-dependent mitochondrial fragmentation as well as oxidative stress [135, 141]. Additionally, loss of function of PINK1 or Parkin leads to mitochondrial fragmentation, which is associated with enhanced mitophagy [113, 142, 143]. Further evidence comes from studies of PINK1 mutations. Mammalian fibroblasts carrying PINK1 mutations from PD patients (Q456X nonsense or V170G missense) also exhibit more fragmented mitochondrial networks [144]. However, the effects of PINK1 on mitochondrial dynamics have been contentious. In *Drosophila* the PINK1/Parkin pathway appears to promote mitochondrial fission or inhibits mitochondrial fusion [145–147]. PINK1 and Parkin not only function on mitochondrial morphology, but also regulate mitochondrial degradation by mitophagy [148–151]. After translocation by PINK1, mitochondrial Parkin ubiqutinates VDAC1 and Mfn, which may promote autophagic clearance of damaged mitochondria. Although further studies will be needed to understand the significance of these findings for the pathogenesis of PD, it is clear that PD-associated genes are related to mitochondrial dynamics.

Mitochondrial dynamics in Huntington's disease

Huntington's disease (HD) is an incurable neurodegenerative genetic disorder characterized by the loss of capacity to control movements, cognition and emotional expression. Unlike AD and PD, HD is a purely genetic disease caused by mutations that result in CAG expansion in the first exon of the Huntingtin gene (Htt), with more than 35 CAGs being pathogenic and resulting in polyglutamine expression [152, 153]. Mitochondrial dysfunction is also associated with pathogenesis of HD [154]. Respiratory electron transport chain activity and ATP levels are decreased in mitochondria from HD patients and Htt transgenic mice [155, 156]. Additionally, the complex II inhibitor, 3-nitroprotionic acid (3-NP), causes a movement disorder similar in many respects to HD [157]. Moreover, mutant Htt directly impairs mitochondrial membrane potential, calcium homeostasis and mitochondrial axonal trafficking [158, 159]. Recently, Wang et al. [160] demonstrated that expression of mutant Htt sensitizes cells to oxidative stress-induced mitochondrial fission and reduces ATP levels by inhibiting mitochondrial fusion. Overexpression of the Drp1 dominant-negative (K38A) or the fusion protein Mfn2 reduces mutant Htt-induced

mitochondrial fragmentation as well as ATP loss and cell death. Importantly, RNAi against Drp1 reduces the motility defect in a worm model of HD. In addition, 3-NP treatment induces increased mitochondrial fragmentation in an NMDA receptor-dependent manner in cortical neurons [161]. Remarkably, we have also observed *S*-nitrosylation of Drp1 in HD brains similar to that seen in AD brains, raising the possibility that this redox event may play a pathogenic role in HD in addition to AD. Collectively, these studies suggest that alternations in mitochondrial dynamics may be involved in the pathogenesis of HD.

Conclusions

Mitochondria are highly dynamic organelles, which divide and fuse continuously. Over the past decade, a significant number of studies regarding mitochondrial dynamics have accumulated. Fusion requires the activity of large GTPase proteins such as Mfn1/2 and Opa1. Additionally, another large GTPase, Drp1, represents the principal component of the mitochondrial fission machinery. Mitochondrial fission and fusion have important roles not only in the modulation of mitochondrial morphology, but also in other cellular processes including bioenergetics, maintenance of mitochondrial DNA, synaptic integrity, cell death and aging. An impaired balance of mitochondrial dynamics between fission and fusion is strongly implicated in the pathogenesis of several neurodegenerative diseases. CMT2A and ADOA are caused by mutations of Mfn2 and Opa1. Oligomerized Aβ and mutant Htt can induce mitochondrial fragmentation through regulation of Drp1. Additionally, Parkinson's disease-related genes also induce abnormal mitochondrial morphology. Abnormal mitochondrial dynamics may represent a common final pathway leading to neuronal dysfunction and suggest that mitochondria may be a therapeutic target for neurodegenerative diseases including AD, PD, and HD.

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