Acta Med. Okayama, 2011
Vol. 65, No. 1, pp. 1–10


Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

*Review*

# Regulation of Mitochondrial Dynamics and Neurodegenerative Diseases

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**Mitochondria are important cellular organelles in most metabolic processes and have a highly dynamic nature, undergoing frequent fission and fusion. The dynamic balance between fission and fusion plays critical roles in mitochondrial functions. In recent studies, several large GTPases have been identified as key molecular factors in mitochondrial fission and fusion. Moreover, the posttranslational modifications of these large GTPases, including phosphorylation, ubiquitination and SUMOylation, have been shown to be involved in the regulation of mitochondrial dynamics. Neurons are particularly sensitive and vulnerable to any abnormalities in mitochondrial dynamics, due to their large energy demand and long extended processes. Emerging evidences have thus indicated a strong linkage between mitochondria and neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and Huntington's disease. In this review, we will describe the regulation of mitochondrial dynamics and its role in neurodegenerative diseases.**

**Key words**: mitochondria, phosphorylation, ubiquitination, SUMOylation, neurodegeneration

Mitochondria are cellular organelles well known for their important function in ATP synthesis through oxidative phosphorylation, and traditionally regarded as the cell's powerhouse units. However, mitochondria are more than simple powerhouses; they are also critical to many other cellular functions, such as intermediary metabolism, calcium homeostasis, cell proliferation, development and apoptosis [1–4]. On the other hand, mitochondria are highly dynamic. They continuously move throughout cells and change their morphology by frequent fusion and fission events in response to cellular energy demands and environmental challenges [5]. Under physiological condition, mitochondrial fission is well balanced with fusion to maintain the normal morphology, number and function of the mitochondria [6, 7]. Mitochondria often appear as thread-like or tubular in morphology and form a dynamic network in most cells. Although the precise molecular mechanisms are still not entirely understood, some large GTPases and mitochondrial proteins, such as Drp1, Fis1, Mfn1, 2, OPA1 and so on, have been identified as key molecular factors in mitochondrial fission or fusion [8–10]. However, it is

Received June 7, 2010; accepted August 18, 2010.
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still a mystery how mitochondria can respond to intra- or extra-cellular signals and stimulation through alterations in morphology. Recent studies have suggested that some specific signaling pathways and post-translational modifications, including phosphorylation, ubiquitination or SUMOylation of mitochondria-related proteins, may be involved in the regulation of mitochondrial dynamics [11].

Although mitochondria are critical organelles for all cells, neurons are also extremely dependent on normal mitochondrial function. Neurons are highly specialized cells with long extended processes including axons and dendrites. Additionally, the long extended neuronal processes are highly active in intercellular signal transduction by neurotransmitter release from synapses, which requires large amounts of energy [12]. Therefore, the ability of mitochondria to fuse, divide and migrate to provide energy throughout the extended neuronal processes is particularly important for synaptic functions (Fig. 1). In addition to energy supply, mitochondria also play a critical role in synaptic plasticity through the maintenance of calcium homeostasis in the synaptic microenvironment by calcium buffering (Fig. 1B) [13]. Furthermore, an accumulation of mtDNA mutations is found in the brain with age and neurodegeneration [5, 12, 14]. The coordinated mitochondrial fusion is important for the maintenance of mitochondrial DNA (mtDNA) stability [15, 16]. Taken together, these findings demonstrate that neurons are very sensitive and vulnerable to mitochondrial dysfunction. Emerging evidences also show that impaired mitochondrial dynamics and function are involved in the pathogenesis of neurodegenerative diseases, such as Alzheimer's

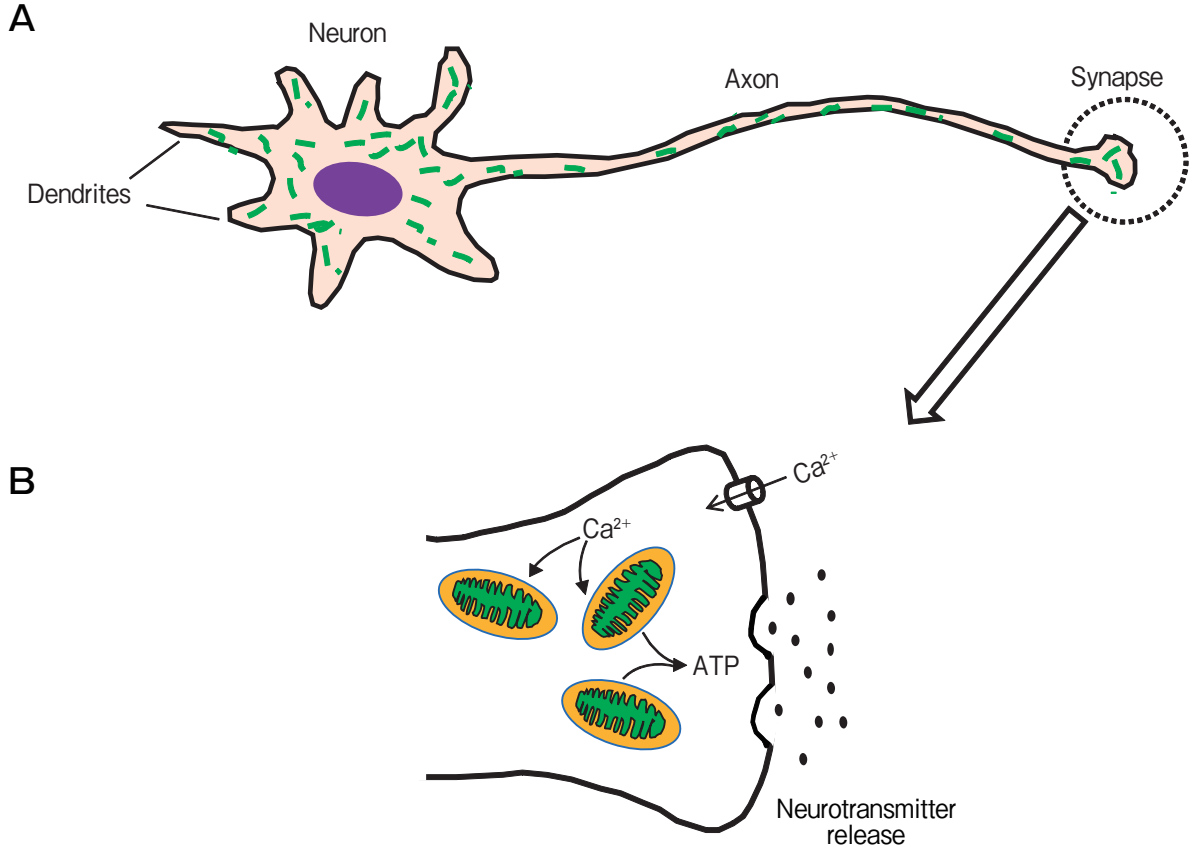


Fig. 1 Mitochondria play important roles in neuronal functions. **A**, In neurons, mitochondria not only distribute in the cell body but also travel to the long extended neuronal processes, including the dendritic and axonal termini; **B**, In synapses, mitochondria provide sufficient ATP for synaptic activities, such as neurotransmitter release and action potential firing. In addition, uptake of calcium by mitochondria is important for the maintenance of calcium homeostasis, synaptic functions and plasticity.

disease, Parkinson's disease and Huntington's disease [5, 7, 14].

In this review, we will describe the current understanding of the regulation of mitochondrial dynamics, and discuss the impact of mitochondria on cellular function, especially in neurodegenerative diseases.

## Mitochondrial Fission and Fusion

In structure, mitochondria are unique organelles containing a double membrane system. The double membrane system separates mitochondria into 4 intra-organelle compartments: the outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM), intermembrane space (IMS), and matrix. The IMM is highly folded into cristae, within which the complexes of the electron transport chain and ATP synthases are enclosed. Interestingly, there is a unique 16-kilobase circular mitochondrial DNA (mtDNA) genome containing 37 genes essential for mitochondrial respiratory function, although some mitochondrial proteins can be encoded by nuclear genes and subsequently transported into mitochondria [17, 18].

Mitochondria are also remarkably dynamic. They transport throughout cells with frequent changes in morphology. Mitochondrial morphology is controlled by a dynamic balance between fission and fusion. The first observation of mitochondrial fission and fusion events was in yeast [19, 20], but this phenomenon has since been observed in all mammalian cells. Under physiological conditions, the coordinated mitochondrial fission and fusion maintain mitochondria as thread-like or tubular morphology in most cells [6]. Disruption in the balance between fission and fusion not only changes the mitochondrial morphology, but also influences the mobility of mitochondria and their distribution in cells [21–23]. In addition, an abnormality in mitochondrial fission or fusion may lead to mitochondrial pathology and influence cell survival [1, 5, 24]. Emerging evidences also indicate that the mitochondrial dynamics may be altered in response to physiological demands, environmental stimulations or pathological conditions [5].

In recent genetic studies, some proteins have been identified as key molecular factors in the regulation of mitochondrial fission and fusion. Interestingly, the proteins required for fission are different from those required for fusion in both yeast and mammalian cells (Table 1). In yeast, mitochondrial fusion requires Fzo1 and Mgm1 [25, 26]. Fzo1 is an OMM protein, containing an N-terminal GTPase domain for outer membrane fusion and a C-terminus for mitochondrial location [26]. In contrast, Mgm1 localizes to the IMM and is responsible for fusion of the IMM [25]. In mammalian cells, mitofusin 1, 2 (Mfn1, 2) and optical atrophy 1 have been identified as the orthologues of Fzo1 and Mgm1, respectively. It has been shown that Mfn1 and Mfn2 have similar topologies and share 81% homology [9]. Mfn1 and Mfn2 are OMM proteins with a C-terminal coiled-coil structure homologous to Fzo1 and an N-terminal dynamin-like GTPase domain for mitochondrial fusion. On the other hand, OPA1 is an IMS protein with an N-terminal mitochondrial targeting sequence, a transmembrane domain, a central dynamin-related GTPase domain and

**Table 1** The proteins involved in mitochondrial fusion and fission in yeast and mammalian cells, respectively

| | Name of proteins | Location in mitochondria | Function |
|---|---|---|---|
| Yeast | Fzo1 | OMM | OMM fusion |
| | Mgm1 | IMM and IMS | IMM fusion |
| | Dnm1 | Cytosol and OMM | OMM fission |
| | Fis1 | OMM | Receptor of Dnm1 |
| | Mdv1 | Cytosol and OMM | Adaptor of Dnml and Fis1 |
| Mammalian cells | Mfn1, 2 | OMM | OMM fusion |
| | OPA1 | IMM and IMS | IMM fusion |
| | Drp1 | Cytosol and OMM | OMM fission |
| | hFis1 | OMM | Receptor of Drp1 |

a C-terminal helical domain [8]. Therefore, these proteins for mitochondrial fusion are all large GTPases and respectively localized to the IMM, OMM and IMS. Recent evidences suggest that Fzo1, Mfn1 and Mfn2 mediate OMM fusion by tethering outer membranes together via interactions of their coiled-coil domains *in trans* (Fig. 2A) [27]. In yeast, Mgm1 tethers IMM through the interaction with itself *in trans* [28]. Considering the sequence similarity between Mgm1 and OPA1, the mechanism of IMM fusion in mammalian cells may be similar to that in yeast (Fig. 2A). In mitochondrial fusion, the OMM and IMM should fuse simultaneously in order to maintain the organelle integrity. However, it is still unclear how the fusion of OMM and IMM are coordinated under physiological conditions.

In mitochondrial fission, a distinct set of evolutionarily conserved proteins (Table 1) are utilized. Mitochondrial fission in yeast is regulated by dynamin 1 (Dnm1) and Fis1, a small protein on OMM [29], while in mammalian cells dynamin-related protein 1 (Drp1) and hFis1 are required for mitochondrial fission [10]. Dnm1 and Drp1 share highly similar amino acid sequences and domain structures with dynamin, which is a well known large GTPase involved in the regulation of vesicular traffic and endocytosis [30, 31]. There are 3 conserved domains in Dnm1 and Drp1: an N-terminal GTPase domain, a GTPase domain and a GTPase effector domain (GED), the latter of which regulates self-assembly and activation of GTP hydrolysis in the process of mitochondrial fission [30]. Without the pleckstrin homology (PH) domain for mitochondrial membrane targeting, Dnm1 and Drp1 are mostly distributed in the cytoplasm under physiological conditions [5, 32]. In mitochondrial fission, Dnm1 and Drp1 can cluster into large foci at the fission sites (Fig. 2B) [33–35]. It has been proposed that Dnm1 and Drp1 may be recruited to the OMM via their respective molecular adaptors Fis1 and hFis1, which localize to the OMM by a C-terminal conserved transmembrane helix [10, 29]. In yeast, Mdv1 is found to facilitate the interaction between Dnm1 and Fis1 (Fig. 2B) [36]. A recent study also suggests that Fis1 can directly bind Dnm1 *in vitro*, and this interaction is negatively regulated by a short N-terminal region of Fis1 [37]. However, the N-terminal region of Fis1 is not well conserved in mammals; Mdv1 is also not found in mammalian cells. Additionally, hFis1 cannot rescue the phenotype of yeast cells lacking Fis1 [38, 39]. In mammalian cells, the interac-

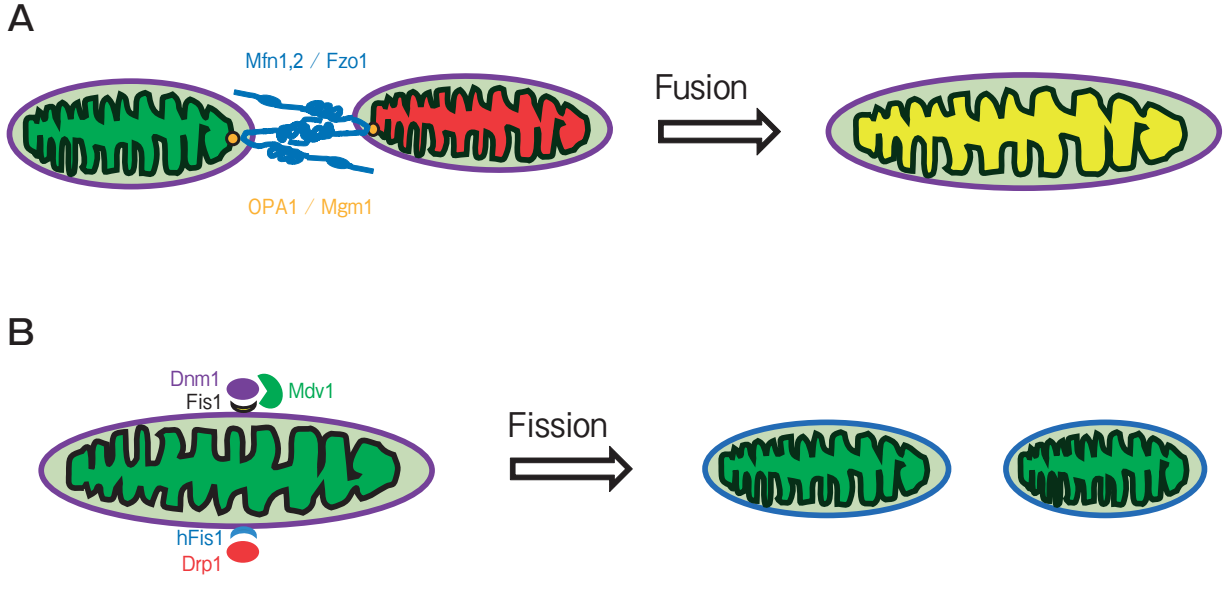


Fig. 2 Schematic model of mitochondrial fusion and fission. **A**, In mitochondrial fusion, Mfn1, Mfn2 and Fzo1 mediate OMM fusion by tethering outer membranes together via interactions of their coiled-coil domains in trans. Coordinately, OPA1/Mgm1 tethers IMM through an interaction with itself in trans. Mitochondrial fusion also serves to mix and unify the mitochondrial compartments; **B**, In mitochondrial fission, Drp1 and Dnm1 are respectively recruited to the OMM via their molecular adaptors hFis and Fis1. In yeast, Mdv1 facilitates the interaction between Dnm1 and Fis1. Scission of the mitochondrial membrane is induced under the GTPase activity of Drp1 and Dnm1.

tion between Drp1 and hFis1 can be detected by fluorescence resonance energy transfer and immunoprecipitation experiments, although the interaction is transient and weak [10, 40]. Therefore, the interaction between Drp1 and Fis1 in mammalian cells is likely to be a little different from those occurring between the equivalent proteins in yeast. When Dnm1 or Drp1 are recruited to the OMM, they may self-assemble into spirals and cluster into large foci around mitochondria [33–35]. As mechanoenzymes similar to dynamin, Dnm1 and Drp1 might reduce the mitochondrial diameter at possible fission sites and induce mitochondrial membrane constriction and scission by GTP hydrolysis [33, 35].

What is the role of fission and fusion in mitochondrial and cellular function? First, mitochondrial number and morphology depend on the dynamic balance between fusion and fission [6]. Fusion might maintain mitochondria in an extended interconnected long thread-like or tubular network, which is required for the intramitochondrial exchange of metabolic substrates and the maintenance of respiratory capacity [41]. Moreover, mtDNA is particularly vulnerable to reactive oxygen species (ROS)-mediated mutation [18]. The mutations accumulate with age and might result in mitochondrial dysfunction. Mitochondrial fusion might serve to mix and unify the mitochondrial compartments (Fig. 2A), which allows the complementation of mtDNA and counteracts respiratory deficiencies [15, 16]. Furthermore, the connectivity of the mitochondrial network is important for response to calcium signals [42]. The fusion of mitochondria is also an essential step in certain developmental processes, such as embryonic development and spermatogenesis [3, 4]. In contrast, in mitochondrial fission, the tubular mitochondrial network divides and splits into numerous morphologically distinct small and isolated spherical organelles. Mitochondrial fission is very necessary in dividing cells, since it ensures a sufficient number of functional mitochondria and the inheritance of mitochondria in newly formed daughter cells [2]. Fission is also important for the formation of synapses and dendritic spines in neurons [13]. However, excessive mitochondrial fission results in a breakdown of the mitochondrial network, loss of the mtDNA, respiratory defects and an increase in ROS, which actively participates in apoptosis [1, 5].

## Regulation of Mitochondrial Dynamics

Mitochondrial fusion and fission are well balanced to meet with cellular energy needs, cell growth, differentiation and extracellular environmental stimuli. How can mitochondrial dynamics respond effectively to these events? Recent studies have shed light on the mechanism underlying the regulation of mitochondrial fusion and fission. Emerging evidences indicate that three main posttranslational modifications of mitochondria-related proteins *i.e.*, phosphorylation, ubiquitination and SUMOylation are likely involved in the regulation of mitochondrial fusion and fission [11]. These modifications are also known to modulate protein-protein interactions, subcellular localization, protein degradation, and activation of signaling pathways.

***Phosphorylation.*** Phosphorylation of Drp1 is likely to be an effective regulation of mitochondrial fission. During mitosis, mitochondrial fission occurs at the early mitotic phase, and the interconnected mitochondrial networks begin to be restored in the late mitotic phase, and subsequently divided into daughter cells. Notably, Drp1 was found to be specifically phosphorylated by Cdk1/cyclin B at Ser 585 in mitosis. Knockdown of endogenous Drp1 or expression of unphosphorylated mutant Drp1 S585A effectively reduces mitotic mitochondrial fission [43]. In our studies [23], mitochondrial fission and the translocation of Drp1 from cytoplasm to mitochondria were triggered by high $K^+$ stimulation in neurons. In the presence of high $K^+$ stimulation, Drp1 was also specifically phosphorylated by CaMKI$\alpha$ at Ser600, which is close to the phosphorylation site of Cdk1/cyclin B. We also found that CaMKI$\alpha$-mediated phosphorylation of Drp1 facilitated the interaction between Drp1 and hFis1 *in vitro*. In addition, overexpression of Drp1 S600A significantly inhibited high $K^+$ induced mitochondrial fission. Together, these results indicate that phosphorylation of Drp1 by Cdk1/cyclin B and CaMKI$\alpha$ promotes mitochondrial fission in response to mitosis and neuronal excitation, respectively. On the other hand, CaMKI and protein kinase A (PKA) are known to have overlapping substrate specificity. For example, a common serine residue in synapsin I has been found to be phosphorylated in response to high $K^+$ treatment or increased cAMP levels [44]. Recently, PKA was also found to phosphorylate Drp1 at Ser637 in the variable domain of humans and Drp1

at Ser656 in the conserved GED in rats. Conversely, PKA phosphorylation has been shown to significantly decrease the GTPase activity of Drp1 and inhibit mitochondrial fission [45, 46]. Therefore, further studies will be needed to fully clarify the conflicts in the effects of phosphorylations induced by different kinases. Additionally, cyclin-dependent kinase 5 (Cdk5) has also been shown to act as a key upstream regulator of mitochondrial fission. Overexpression of Cdk5 and p25 or p35 induces significant caspase-independent mitochondrial fission. Conversely, knockdown of Cdk5 by RNAi reduces mitochondrial fission [47, 48]. Therefore, it will be very interesting to further examine whether Cdk5 regulates mitochondrial fission by phosphorylating some mitochondria-related proteins.

***Ubiquitination.*** Ubiquitination is mediated by the conjugation of ubiquitin, a small conserved peptide, to substrate proteins through a series of complex enzymatic reactions [49]. Ubiquitination plays an important role in selective protein degradation, membrane protein trafficking, and regulates a variety of cellular processes, including the cell cycle, signal transduction and cell transformation [50]. In recent studies, MARCH5, a mitochondrial E3 ubiquitin ligase, was identified as a critical regulator of mitochondrial dynamics through the ubiquitylation of certain mitochondrial proteins, including Drp1 and Fis1 [51]. MARCH5 is an OMM protein consisting of an N-terminal RING finger domain critical for the ubiquitin transfer activity of several E3 ubiquitin ligases and four transmembrane domains [51–53]. MARCH5 activity is likely to regulate the subcellular trafficking of Drp1 through the correct assembly at scission sites or through the disassembly of fission complexes [53]. However, the effect of MARCH5 on mitochondrial dynamics is still controversial, with various groups reporting different results. In the studies of Nakamura and Yonashiro, it was found that mutations in the MARCH5 RING domain or MARCH RNAi caused mitochondrial fission. Overexpression of MARCH5 promoted mitochondrial fusion in an Mfn2-dependent manner [51, 52]. Conversely, in Karbowski's studies, MARCH5 RING mutants and MARCH RNAi induced mitochondrial fusion through the inhibition of fission [53]. Therefore, the mechanism and role of ubiquitination in mitochondrial dynamics may still require more comprehensive investigation in the future.

***SUMOylation.*** SUMOylation is another highly transient post-translational protein modification enzymologically parallel to ubiquitination. Four mammalian SUMO isoforms have been identified, *i.e.*, SUMO1～4 [54–56]. In SUMOylation, substrate proteins are conjugated to SUMO by a number of specific enzymes to form SUMO-substrate complexes. The SUMO-protein complex is in a transient state, and can again be divided into SUMO and free substrate proteins for the next round of modification. SUMOylation thus facilitates rapid response to environmental cues by cells [57]. In recent studies [56, 58, 59], Drp1 has been identified as a target protein of SUMO modification. Drp1 interacts with the SUMO-conjugating enzyme Ubc9 as a prerequisite for SUMO modification [56]. Two clusters of lysine residues within Drp1 have also been identified as noncanonical conjugation sites for SUMO. Additionally, SUMO1 often colocalizes with Drp1 at mitochondrial fission sites in living imaging [58]. The overexpression of SUMO1 protects Drp1 from degradation, resulting in a more stable, active pool of Drp1, and dramatically enhances mitochondrial fission [58]. On the other hand, the cytosolic pool of SENP5, a SUMO specific protease, catalyzes the cleavage of SUMO1 from Drp1, and regulates the sensitivity of Drp1 to degradation. Overexpression of SENP5 protects mitochondria from SUMOl-induced fission. While silencing of SENP5 increases Drp1 SUMOylation and induces mitochondrial fission [59]. Recently, it is also found that three SUMO isoforms, SUMO1～3, are all involved in the SUMOylation of Drp1 [56]. Taken together, these evidences strongly support the notion that SUMOylation plays an important role in the regulation of mitochondrial dynamics.

## Mitochondrial Dynamics and Neurodegenerative Diseases

Neurons are metabolically active cells with high energy demands. In morphology, neurons are also unique, containing many long extended processes, such as axons and dendrites. In some motor neurons, the axons even extend up to one meter. As a result, the supply of energy throughout distant neuronal processes is highly dependent on mitochondrial dynamics (Fig. 1A). In addition, the ability of mitochondria

to buffer calcium, which modulates neurotransmitter release and action potential firing is very important for the maintenance of synaptic functions (Fig. 1B) [12, 13]. Therefore, neurons are much more sensitive and vulnerable to mitochondrial dysfunction than any other cells. A mutation in mitochondria-related proteins may cause abnormal mitochondrial dynamics and neuropathy [60–63]. For example, a mutation in the GTPase domain of OPA1 causes dominant optic atrophy (DOA), resulting in retinal ganglion cell death and progressive loss of vision [60, 61]. Mutation in Mfn2 leads to Charcot-Marie-Tooth subtype 2A (CMT2A), a peripheral neuropathy with axonal degradation in sensory and motor neurons [62, 63]. Aside from DOA and CMT2A, emerging evidences show that dysfunction in mitochondrial dynamics has a strong linkage with neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and Huntington's disease [5, 7, 14].

***Alzheimer's disease.*** Alzheimer's disease (AD) is the most common neurodegenerative disorder and is pathologically characterized by neuronal death, neurofibrillary tangles and beta-amyloid (A$\beta$) plaques in cerebral cortex. The symptoms of AD include progressive cognitive dysfunction and memory impairment. Recent evidences indicate that synaptic loss and dysfunction make important contributions to the memory impairment and cognitive dysfunction in AD [64, 65]. It has also been reported that mitochondria are important for synaptic development and plasticity, with abnormalities in mitochondrial dynamics leading to synaptic dysfunction and loss [13]. In the brains of AD patients, significant alterations in mitochondrial cristae, the accumulation of osmiophilic material and significant decreases in mitochondrial size are found prominently in neurons [66]. Mitochondria are redistributed away from axons in the pyramidal neurons [67]. The levels of mitochondrial fission and fusion proteins are also changed, *e.g.*, the levels of Drp1, OPA1, Mfn1 and Mfn2 are significantly decreased and the levels of hFis1 are increased [22, 67, 68]. In the brains of AD model mice, A$\beta$, the key mediator of AD, localizes to mitochondria, and promotes mitochondrial dysfunction and oxidative damage [68]. These evidences indicate the strong link between mitochondrial dynamics and the pathogenesis of AD. *In vitro*, the overexpression of amyloid precursor protein (APP) in M17 cells has been associated with significant mitochondrial fragmentation, decreased levels of Drp1 and OPA1, and redistribution of mitochondria around the perinuclear area [68], which is very similar to the phenotype *in vivo*. Interestingly, oligomeric amyloid-beta-derived diffusible ligands (ADDLs) cause mitochondrial fragmentation, and also reduce the mitochondrial density in neuronal processes. More importantly, the ADDL-induced synaptic changes, such as loss of dendritic spines and synapses, correlate with abnormal mitochondrial distribution [67]. The overexpression of Drp1 can prevent ADDL-induced synaptic loss, likely through the repopulation of neuronal processes with mitochondria [67]. Furthermore, Cdk5 has been identified as an important mediator in AD pathogenesis through the hyperphosphorylation of some microtubule-associated proteins such as Tau [69, 70]. Recently, it has also been reported that Cdk5 can act as an upstream mediator of mitochondrial fission [47, 48]. Taken together, these evidences strongly indicate that abnormal mitochondrial dynamics plays an important role in AD pathogenesis.

***Parkinson's disease.*** Parkinson's disease (PD) is the second most common neurodegenerative disease; PD is caused by the loss of dopaminergic neurons in the substantia nigra, and is characterized by progressive symptoms of movement disorder. Both chemical and genetic evidences have strongly suggested that mitochondrial dysfunction is associated with PD [14, 71]. A deficiency in complex 1 of the electron transport chain has been found in the substantia nigra from PD patients [72–74]. The toxin 1-methyl 4-phenyl-1, 2, 3, 6-tetra hydropyridine (MPTP), which impairs respiratory complex 1, can also evoke Parkinson's-like disease in human and animal models [75, 76]. More recently, mutations in two genes, Pink1 and Parkin, were identified in hereditary PD [14, 71, 72]. Pink1 is a serine/threonine kinase localized to both mitochondria and cytoplasm, and acts upstream of Parkin in a common genetic pathway [77]. In *Drosophila*, the 2 genes are also important for mitochondrial dynamics through promotion of fission and/or inhibition of fusion events [78, 79]. In human dopaminergic neurons or primary cultured mouse neurons, Pink1 deficiency results in an age-related reduction in basal viability accompanied by mitochondrial morphometric abnormalities [80]. Moreover, a Parkin-defective mutation in *Drosophila* leads to dop-

aminergic degeneration and mitochondrial abnormalities [81]. In addition, Parkin-knockout and Parkin-mutant transgenic mice also exhibit mitochondrial respiratory defects and morphological abnormalities [82].

***Huntington's disease.*** Huntington's disease (HD), the hereditary autosomal dominant neurodegenerative disorder, is caused by an expansion of CAG repeats within the *huntingtin* (Htt) gene. Abnormalities in mitochondria, such as reduced mitochondrial movement and mitochondrial ultrastructural changes, have also been found in HD patients or mouse transgenic HD models [83, 84]. The direct experimental evidence linking neurodegeneration in HD to mitochondria is the effect of 3-nitropropionic acid, an irreversible inhibitor of complex II. It has been shown that 3-nitropropionic acid can induce significant mitochondrial fragmentation in rat cortical neurons, and causes HD-like symptoms in animal models [85]. Additionally, overexpression of the mutant Htt74Q leads to significant mitochondrial fission and cell death, which can be rescued by overexpression of Drp1K38A or Mfn2 [86]. Importantly, the fragments of Htt have been found to associate with mitochondria, and to interfere with their microtube-associated transport, which leads to abnormal axonal trafficking of mitochondria to and from the synapses [84]. This suggests that Htt overexpression may alter the mitochondrial dynamics, although the molecular mechanism remains to be determined.

## Conclusions

We here discussed the mechanism of mitochondrial dynamics and its linkage with neurodegenerative disease. Mitochondrial fission and fusion are not isolated events. Under physiological conditions, they are well coordinated to meet with the energy demands and various activities of cells. Mitochondria-related GTPases and their posttranslational modifications, including phosphorylation, ubiquitination and SUMOylation, are involved in mitochondrial fission/fusion. An improved understanding of mitochondrial fission and fusion and their mechanisms would be of great benefit in evaluating their functions in physiology and pathology. Although the precise molecular mechanisms of mitochondrial dynamics in neurodegenerative diseases are still not entirely understood, it is becoming increasingly clear that the disruption of balance between mitochondrial fission and fusion plays an important role in neurodegenerative diseases. An improved understanding of the linkage between mitochondrial dynamics and neurodegeneration would be invaluable in the development of new therapeutic interventions which target mitochondrial fission and fusion for the treatment of neurodegenerative diseases.

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