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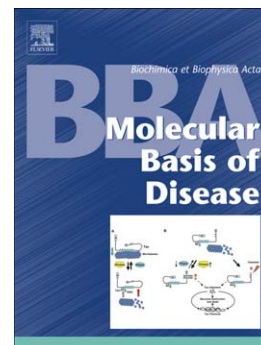
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Abnormal Mitochondrial Dynamics and Neurodegenerative Diseases

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Abstract

Mitochondrial dysfunction is a prominent feature of various neurodegenerative diseases. A deeper understanding of the remarkably dynamic nature of mitochondria, characterized by a delicate balance of fission and fusion, has helped to fertilize a recent wave of new studies demonstrating abnormal mitochondrial dynamics in neurodegenerative diseases. This review highlights mitochondrial dysfunction and abnormal mitochondrial dynamics in Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and Huntington disease and discusses how these abnormal mitochondrial dynamics may contribute to mitochondrial and neuronal dysfunction. We propose that abnormal mitochondrial dynamics represents a key common pathway that mediates or amplifies mitochondrial dysfunction and neuronal dysfunction during the course of neurodegeneration.

Key Words: Mitochondrial Dynamics, Mitochondrial Dysfunction, Mitochondrial Distribution, Synaptic Dysfunction, DLP1, Alzheimer Disease, Parkinson's disease

Introduction

Mitochondria, organelles found in virtually every eukaryotic cell, are involved in a number of cellular functions and are essential to both life and death. The many functions of mitochondria include, but are certainly not limited to, 1) the production of cellular ATP; 2) participation in the synthesis of key metabolites; 3) the regulation of apoptosis; 4) calcium buffering and 5) the primary source of endogenous reactive oxygen species [1, 2]. Neurons are particularly sensitive to changes in mitochondrial function since they are extremely energy dependent with many neuronal activities such as synaptic transmission, axonal/dendritic transport, ion channels, and ion pump activity being great energy taxing processes [3]. The maintenance of calcium homeostasis is critical for neuronal synaptic function [4]. Synaptic mitochondria are important in calcium clearance either by direct calcium removal or by providing ATP for the plasma membrane $\text{Na}^+/\text{Ca}^{2+}$ exchanger [5] which become the dominant players at sites where endoplasmic reticulum (ER) vesicles are absent [6]. Additionally, as postmitotic cells with membranes enriched in polyunsaturated fatty acid, neurons are sensitive to oxidative stress [2]. Not surprisingly, mitochondrial injury can have severe consequences for neuronal function and survival. On top of these reasons, compared to other cell types, the complex morphology of neurons leads to functional heterogeneity in neuronal segments, thus translating into different energy and calcium buffering demands that require local adaptation of metabolism and local cellular signals interconnecting neuronal and mitochondrial activities. Indeed, mitochondria are highly mobile in both anterograde and retrograde directions in neurons and can be positioned in neuronal segments with high metabolic demands such as active growth cones and synapses [3]. Therefore, neurons are also particularly sensitive to changes in mitochondrial movement and distribution.

Studies in the past decade revealed that mitochondria are highly dynamic organelles that constantly divide and fuse with each other [7]. Depending on physiological conditions, mitochondria can form giant tubule networks within a cell and allow rapid exchange of mitochondrial contents or divide into individual rod-like mitochondrion and allow deep penetration into side short-diameter neurites [7]. In fact, this highly dynamic balance of mitochondrial fission and fusion not only controls mitochondrial morphology, length, size and number, but also regulates mitochondrial function and

distribution. Therefore, it is not surprising that alterations in mitochondrial fission and fusion significantly impact neuronal function, and the prevalence of neuronal disease associated with mutations in mitochondrial fission/fusion genes underscores the important functional relationship between mitochondrial dynamics and neuronal function [7]. For example, mutations in *Mfn2* are associated with Charcot-Marie-Tooth disease 2A, a peripheral neuropathy targeting the axons of sensory and motor neurons, and mutations in *OPA1* cause autosomal dominant optic atrophy characterized by progressive degeneration of the optic nerve [7]. Alterations in mitochondrial dynamics are also increasingly implicated in neurodegenerative diseases that may not necessarily be associated with mutations in mitochondrial fission and fusion genes, and it in fact may become a common pathway underlying mitochondrial abnormality and dysfunction and neuronal dysfunction and degeneration in these neurodegenerative diseases [8, 9]. In this paper, we will summarize the current evidence indicating a potential involvement of abnormal mitochondrial dynamics in Alzheimer disease, Parkinson disease, and other neurodegenerative diseases and discuss the potential underlying mechanisms.

Mitochondrial Dynamics: A Tightly Controlled Delicate Balance between Fission and Fusion

Mitochondria are formed by two membranes: the outer membrane is permeable for ions and small molecules while the inner membrane is almost impermeable, thus allowing the formation of an electron gradient that is critical for mitochondrial function. Recent studies indicate that mitochondria are dynamic organelles that continuously change in number and morphology within a cell [7, 9]. This highly dynamic phenomenon is regulated by a delicate balance between two opposing processes: mitochondrial fission and mitochondrial fusion [7, 9]. When mitochondria divide, both the inner and outer membrane have to be cut and the mtDNA and other critical mitochondrial contents redistributed to the daughter mitochondria and mitochondrial transform into isolated, small, round organelles. Although the precise mechanisms remain to be fully elucidated, mitochondrial fission involves at least two proteins in mammals: A large GTPase, dynamin-like protein 1 (DLP1, also referred to as Drp1) and a small molecule, Fis1 [7, 9]. DLP1, a member of the conserved dynamin large GTPase superfamily that controls membrane tabulation and fission, is primarily a cytosolic protein and is recruited to punctuate spots on mitochondrial

surface. Similar to dynamin, DLP1 can also oligomerize and form large complexes. It is believed that once a ring-like complex structure is formed along the mitochondrial surface, DLP1 uses GTP hydrolysis to constrict and twist tubule to initiate fission [10]. Fis 1 is a mitochondrial outer membrane protein that evenly resides on the surface of mitochondria [11]. It is suggested that Fis1 acts as a receptor to recruit DLP1 to mitochondria which appears to be a limiting factor during fission. Mitochondrial fission produces two spherical daughter mitochondria accompanied with cristae and other inner structure remodeling that is not entirely clear [7, 9]. On the other hand, mitochondrial fusion is regulated by three large GTPase proteins: Mitofusin 1 (Mfn1), Mitofusin 2 (Mfn2) and optic atrophy protein 1 (OPA1) [7, 9]. Both Mfn1 and Mfn2 are mitochondrial transmembrane proteins localized to the outer membrane and appear to play similar roles in mitochondrial fusion, although they function independently of each other and have different rates of GTP hydrolysis [12, 13]. During mitochondrial fusion, through interactions of their coiled-coil domains, Mfn 1 and Mfn 2 could form homo-oligomeric and hetero-oligomeric complexes, and thus tether outer membranes of neighboring mitochondria together [13, 14]. For inner membrane fusion, it has been proposed that OPA1, an inner membrane protein that faces intermembrane space, is primarily involved and OPA1 requires Mfn1, but not Mfn2, to mediate this process [12, 15].

In mammalian cells, mitochondrial dynamics are sensitive to various stimuli [7, 9] and the mechanisms underlying the regulation of mitochondrial dynamics are only beginning to become understood. Most studies have focused on DLP1 and demonstrated that mitochondrial fission is regulated through post-translational modifications such as the phosphorylation, sumoylation, ubiquitylation, and nitrosylation of DLP1 [16-21]: DLP1 can be phosphorylated at least at two sites (i.e., Ser 616 and Ser 637). While it is suggested that phosphorylation at Ser616 (e.g., Ser585 in rat) by mitosis promoting factor (MPF, also referred to as cyclin-dependent kinase 1) facilitates mitochondria fission [16, 17, 21], there is still debate over the effect of phosphorylation at Ser 637 on mitochondrial fission activity with two groups reported that DLP1 phosphorylated at Ser637 by PKA inhibits mitochondrial fission [16, 17] and its calcium-dependent dephosphorylation by calcineurin promotes mitochondrial fission [22], while another group reported that calcium-dependent phosphorylation of this site by CaM kinase 1 α induces DLP1 translocation to mitochondria and enhances mitochondrial fission [23]. DLP1 can be ubiquitinated, a

process that is believed to facilitate its degradation [24]. On the other hand, sumoylation of DLP1 by SUMO-1 protects DLP1 from degradation, enlarges the stabilized DLP1 pool and facilitates the translocation of DLP1 from cytosol to the mitochondria [18]. Most recently, it is reported that S-nitrosylation of DLP1 activates GTPase activity and mitochondrial fission [25].

Mitochondrial Dysfunction and Abnormal Mitochondrial Dynamics in Alzheimer Disease

AD is a neurodegenerative disorder of the elderly that leads to progressive memory loss, impairments in behavior, language, visuo-spatial skills, and ultimately death. The disease is characterized by a progressive neuronal loss and the presence of extracellular deposits of amyloid- β ($A\beta$) as senile plaques and tau-containing intracellular neurofibrillary tangles in the brain. Mutations in $A\beta$ precursor protein (APP), presenilin 1 and 2 cause early-onset familial form AD. Substantial data from positron emission tomography (PET) consistently demonstrates a reduced cerebral metabolism in temporoparietal cortices in AD [26] and an increased oxidative utilization, in comparison with glucose utilization, is also well documented [27, 28]. Damage to both the components and the structure of mitochondria as well as increased oxidative stress are extensively reported in AD [29, 30]. The most consistent defect in mitochondrial components in AD has been a deficiency in several key enzymes of oxidative metabolism including α -ketoglutarate dehydrogenase complex (KGDHC) and pyruvate dehydrogenase complex (PDHC), two enzymes in the rate-limiting step of the tricarboxylic acid cycle, and cytochrome oxidase (COX), the terminal enzyme in the mitochondrial respiratory chain that is responsible for reducing molecular oxygen [31-37]. Altered calcium homeostasis is also reported in AD cytoplasmic hybrid (cybrids) made from mtDNA of AD subject [38, 39]. Sporadic mtDNA rearrangement (e.g., the common 5-kb deletion) and many more sporadic mutations in the mtDNA control region is significantly increased in AD patients compared with control cases [40-42]. High incidence of mtDNA base changes are also found in Down's syndrome [43]. Presenilin 1 is found in mitochondria and mutant presenilin 1 affects axonal transport of mitochondria presumably by affecting phosphorylation of kinesin light chain through effects on GSK3 β [44]. APP is also found in mitochondria and recent results suggest that APP accumulates exclusively in the protein import channels of mitochondria of human AD

brains but not in age-matched controls and the levels of translocationally arrested mitochondrial APP directly correlate with mitochondrial dysfunction and severity of the disease [45]. A β localizes to mitochondria and specifically interacts with certain mitochondrial proteins, which potentiates mitochondrial, neuronal and synaptic stress [46, 47].

Earlier ultrastructural morphometric studies on mitochondria revealed that AD neurons contained a significantly lower percentage of normal mitochondria and a significantly higher percentage of the mitochondria with broken cristae compared to age-matched control group [41]. Most interestingly, significant changes in mitochondrial size and number occurred in vulnerable neurons in AD [41], suggesting that a potential change in mitochondrial dynamics may be involved. Such a notion is further supported by the finding that fibroblasts from AD patients demonstrated abnormal mitochondrial dynamics compared to normal healthy fibroblasts from age-matched control patients [48]. Indeed, expression levels of DLP1, OPA1, Mfn1 and Mfn2 are significantly reduced while Fis1 levels are increased in hippocampal tissues from AD patients compared with age-matched controls [49]. Because immunocytochemical studies demonstrate that they primarily expressed in neurons, these findings thus confirm a tipped balance of mitochondrial fission and fusion in pyramidal neurons of AD. In addition to morphological changes of mitochondria, one likely outcome of the altered expression of these fission and fusion proteins is abnormal mitochondrial distribution since manipulations of these proteins in neurons mimicking these changes in AD neurons all caused reduced dendritic mitochondrial coverage [49]. In fact, this is consistent with the finding that mitochondria accumulate in the soma and are reduced in neuronal processes in vivo in AD pyramidal neurons [49]. Earlier studies demonstrated that exposure of primary neurons to preaggregated A β_{25-35} induces acute impairment in mitochondrial axonal transport [50] and striking mitochondrial fragmentation prior to neuronal demise [51], presumably through enhanced nitric oxide (NO) production and increased S-nitrosylated DLP1 formation which activates GTPase activity and mitochondrial fission [25]. Indeed, increased S-nitrosylation of DLP1 is also found in AD brain tissues [25, 49]. More detailed studies suggest that overexpression of APP and the familial AD-causing APP^{sw} mutant and treatment with ADDLs induce mitochondrial fragmentation and abnormal distribution under conditions that no cell death occurs [49, 52], suggesting that A β -induced abnormal mitochondrial dynamics may play important roles at early stages

during the pathogenesis of AD. In this regard, it is of interest to note that synaptic dysfunction is one of the early and most robust correlate of AD-associated cognitive deficits and abnormal mitochondrial dynamics likely play an important role in ADDLs-induced synaptic abnormalities because ADDLs-induced loss of dendritic spine and PSD95 puncta correlated with abnormal mitochondrial distribution and DLP1 overexpression, likely through repopulation of neuronal processes with mitochondria, preventing ADDLs-induced synaptic loss [49, 53].

Mitochondrial Dysfunction and Abnormal Mitochondrial Dynamics in Parkinson Disease

Parkinson disease (PD) is the second most common neurodegenerative disease after AD. PD is characterized by the progressively diminished ability to initiate voluntary movement owing to the loss of dopaminergic neurons in the substantia nigra. Genetic studies indicated that most PD cases are sporadic, but a small fraction of PD cases do exhibit evidence of heritability. Molecular and genetic studies in familial PD have identified pathogenic mutations in five genes including alpha synuclein, PINK-1, Parkin, DJ-1 and most recently, Leucine-rich repeat kinase 2 (LRRK2) [54, 55]. Compelling evidence suggest that mitochondrial dysfunction could represent a critical event in the pathogenesis of PD: 1) in idiopathic PD, consistent and significant deficits in subunits and activity of mitochondrial respiratory chain complex 1 was reported in the substantia nigra and blood platelets of PD patients as well as in cybrids cell lines [56]; Accumulation of mtDNA deletions occurs in SNpc dopaminergic neurons [57] and transfer of mtDNA from platelets of PD patients into cells depleted of their own mtDNA causes complex I deficiency [58]. 2) complex 1 inhibitors such as MPP⁺ and rotenone induce a Parkinson-like clinical syndrome in human [59, 60]. 3) Several recently identified familial PD genes are localized to and involved in mitochondrial functions including PINK-1, Parkin and DJ-1 [56].

Increasing evidence suggests that abnormal mitochondrial dynamics is involved in mitochondrial dysfunction or mediates neuronal death in PD models. In CV1-4A cells, rotenone induces a rapid DLP1-dependent mitochondrial fragmentation with intact internal mitochondrial structure which can be reversed after the removal of the inhibitor, suggesting that mitochondrial (dys)function can elicit reversible mitochondrial morphological changes [61]. This observation was confirmed in

neuronal cells in which rotenone induces rapid mitochondrial fragmentation prior to neuronal death, and prevention of mitochondrial fission by overexpressing Mfn1 or dominant negative DLP1 mutant also prevented rotenone-induced neuronal death [51]. Similarly, 6-OHDA also induces DLP1-dependent mitochondrial fission which precedes and mediates neuronal apoptosis [62], suggesting that excessive mitochondrial fission might be mediating neurotoxicity induced by complex I inhibition. Genetic factors associated with PD also cause changes in mitochondrial dynamics. For example, DJ-1 knock-out MEFs demonstrated reduced mitochondrial connectivity due to fragmentation which can be rescued by overexpression of wild type human DJ-1 [63]. PINK1-deficient *Drosophila* demonstrated prominent mitochondrial abnormalities including fragmented cristae and hollow-appearing mitochondria or mitochondrial enlargement and disintegration which can be rescued by Parkin overexpression [64-66], suggesting that PINK1 and Parkin converge within a single pathway related to mitochondrial damage. More detailed genetic screening studies by manipulating expression of mitochondrial fission/fusion proteins in PINK1-deficient or Parkin-deficient flies from several different groups suggest an emerging consensual view that the PINK1/Parkin pathway promotes mitochondrial fission and/or inhibits mitochondrial fusion in *Drosophila* [67-70]. Such a notion is also supported by some studies in mammalian cells. For example, mitochondria of fibroblasts from patients carrying Parkin mutations demonstrated more branching networks although no changes in mitochondrial length were noted [71]. PINK1 knockdown in COS-7 cells leads to elongated mitochondria which can be inhibited by DLP1 or Fis1 overexpression [70]. However, emerging evidence in mammalian cells have shown very different effect of PINK1/Parkin on mitochondrial morphology: siRNA knockdown of PINK1 or Parkin in HeLa cells or neuroblastoma cells leads to mitochondrial fragmentation [69, 72, 73] which is coordinated with enhanced mitochondrial turnover by autophagy [74]. DLP1 overexpression exacerbate the PINK1 deficiency phenotype while DLP1 knockdown or expression of dominant negative DLP1 mutant rescue them [75]. Primary fibroblasts from PD patients carrying PINK1 mutations also demonstrated a fragmented mitochondria network in a noticeable minority of cells [73, 76]. Despite the discrepancy, it is apparent that the role of these PD-associated genes in regulating mitochondrial function, and how dysregulation of these genes resulted in PD are just beginning to be unraveled and it is very likely an altered mitochondrial dynamics is a common pathogenic pathway.

Mitochondrial Dysfunction and Abnormal Mitochondrial Dynamics in Other Neurodegenerative Disease

Amyotrophic Lateral Sclerosis: Human amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a neurodegenerative disease characterized by a progressive and fatal degeneration of the large pyramidal neurons in the motor cortex and associated corticospinal tracts as well as lower motor neurons originating in the brainstem nuclei and spinal cord anterior horn, resulting in loss of motor function, muscle atrophy and eventual paralysis, speech deficit and death. Apparently sporadic in 90% of cases, ALS also presents as a familial, usually autosomal dominant, disease, 20% of which cases are due to mutations on the SOD1 gene and it is considered to be a toxic gain of function rather than a loss of normal SOD1 activity [77]. Biochemical studies revealed decreased complex IV activity in the spinal cord and individual spinal motor neurons [78, 79]. Such mitochondrial defects were also found in peripheral tissues from ALS patients [80, 81]. Levels of the "common 5-kb deletion" are also increased in the motor cortex and skeletal muscle of ALS cases [80, 82]. Consistently, respiratory deficits indicative of mitochondrial function abnormalities are widespread and appear early in the course of the disease in mutant SOD1 transgenic mice [83]. Interestingly, a proportion of the predominantly cytosolic SOD1 localizes to mitochondria in brain samples from ALS patients and mutant SOD1 mice [84], which could presumably damage mitochondrial function. Multiple lines of studies suggested mitochondrial morphological abnormalities in ALS patients and animal models. Earlier studies demonstrated the presence of aggregates of mitochondria in the subsarcolemmal region of muscles [85] and appearance of dense conglomerates of mitochondria in anterior horn neurons of the lumbar spinal cord of ALS patients [86]. Strikingly vacuolated and dilated mitochondria with disorganized cristae and membranes [87], presumably deriving from expansion of the outer mitochondrial membrane and intermembrane space [88], are present in motor neurons devoid of any apoptotic features at asymptomatic stages of the disease in mutant SOD1 transgenic mice. Continuous expression of G93A SOD1 mutant induces an extensive fragmentation of mitochondrial network and cristae remodeling in NSC-34 motoneuronal-like cells but not in N18TG2 neuroblastoma cells or non-neuronal cells [89], suggesting that excessive mitochondrial fission may be involved in the selective vulnerability of motoneuronal mitochondria to SOD1 mutation.

Huntington's disease: Huntington's disease (HD) is a genetic neurodegenerative disease characterized by loss of capacity in movement control, cognition, and emotional regulation due to the striatal neuronal loss caused by a CAG repeat expansion (>35 CAGs) in the first exon of the Huntingtin (Htt) gene which becomes translated into long stretches of glutamines [90]. Growing evidence suggest that mitochondrial dysfunction is involved in the pathogenesis of HD either directly or indirectly [91]. Positron emission tomography imaging studies have revealed hypometabolism in the caudate, putamen, and cerebral cortex of symptomatic HD subjects and nonsymptomatic known HD gene carriers [92]. Significant defects in mitochondrial respiratory enzymes, including mitochondrial succinate dehydrogenase (SDH, complex II) and aconitase, have been consistently reported in brain tissues from HD patients [93]. More importantly, SDH inhibitors including 3-nitropropionic acid and malonate cause medium spiny neuronal loss and clinical and pathological features reminiscent of HD in rodents and non-human primates [94, 95]. mtDNA damage and deletion were documented in HD patients and animal models [96, 97]. Htt aggregates are associated with mitochondria and mutant Htt directly impacts mitochondrial membrane potential, calcium handling [98] and mitochondrial trafficking in axon [99, 100]. Most recently, it is reported that mutant Htt causes mitochondrial fragmentation, likely through the inhibition of mitochondrial fusion, along with reduced ATP levels [101]. Remarkably, overexpression of Mfn2 or dominant negative DLP1 mutant not only prevents mitochondrial fragmentation, but also restores ATP levels [101], suggesting that mutant Htt-induced excessive mitochondrial fission mediates mutant Htt-induced mitochondrial dysfunction (e.g., ATP levels). More importantly, DLP1 knockdown rescues the motility defects associated with expression of mutant Htt in a *C. elegans* model of HD [101], suggesting that mutant Htt-induced excessive mitochondrial fission also mediates neuronal dysfunction that leads to motility deficit. SDH inhibition by 3-nitropropionic acid caused excessive mitochondrial fission and consequent neuronal death [102].

Abnormal Mitochondrial Dynamics: A Common Pathway Mediating Mitochondrial Dysfunction and Neuronal Dysfunction?

Despite the fact that different neuronal populations are affected in the various neurodegenerative diseases discussed above, one common phenomenon is that

abnormal mitochondrial dynamics is likely involved in these diseases, which suggests that altered mitochondrial dynamics may not be involved in the selective vulnerability of specific neuronal populations, but rather may represent a common pathway mediating or amplifying mitochondrial dysfunction and neuronal dysfunction during the course of neurodegeneration.

Mitochondrial Function:

It is assumed that every mammalian cell maintains a delicate balance of fission and fusion as reflected by its distinctive mitochondrial shape and network. Therefore, unbalanced fission or fusion will likely have deleterious impact to mitochondrial functions. Indeed, in addition to controlling mitochondrial number and morphology, mitochondrial dynamics is critical for maintaining various mitochondrial functions: Mfn1/2-null cells and OPA-1 deficient cells with excessively fragmented mitochondria demonstrate greatly reduced endogenous and uncoupled respiratory rates which is due to attenuation of electron transport rates in respiration complexes I, III, and IV and demonstrated reversible interorganellar heterogeneity in membrane potential and inhibition of cell growth [12, 103]. Purkinje cells of Mfn2 conditional knockout mouse have aberrant electron transport chain activity [104]. Similarly, excessive fusion induced by genetic inhibition of DLP1 causes a reduced rate of mitochondrial ATP synthesis due to a significant decrease in complex-IV activity and an inefficient OXPHOS system [1]. Sustained elongation of mitochondria induced by Fis1 knockdown was also associated with decreased mitochondrial membrane potential [105]. Mitochondrial Ca^{2+} uptake and intramitochondrial Ca^{2+} diffusion is impaired in cells with fragmented mitochondria, suggesting an imbalance between mitochondrial fission and fusion can disrupt normal Ca^{2+} ion homeostasis [106, 107]. Recently it was demonstrated that mitochondrial fragmentation mediated by the fission process is a necessary component to increase high glucose-induced respiration and to ROS overproduction, and inhibition of mitochondrial fission prevented periodic fluctuation of ROS production during high-glucose exposure [108]. On the other hand, sustained elongation also leads to increased reactive oxygen species production [105, 109]. However, how excessive fission or fusion impact mitochondrial function is not clear.

As a dynamics process, the balance between mitochondrial fission and fusion is also sensitive to alterations in cellular metabolism, energy status and redox homeostasis. In

a recent report by Ichishita et al [110], the authors knocked down 719 genes predicted to code for most of mitochondrial proteins. Strikingly, >80% of them caused abnormal mitochondrial morphology, including fragmentation and elongation. This report strongly suggests that fundamental mitochondrial functions, including metabolism and oxidative phosphorylation, are necessary for maintenance of mitochondrial tubular networks as well as membrane fission and fusion. Consistent with this report, inhibitors of electron transport, ATP synthase, or the permeability transition pore (mtPTP) induced reversible mitochondrial fission [61]. [Sandebring et al.](#), suggested that PINK1 deficiency causes mitochondrial fission via impaired mitochondrial membrane potential [75]. Indeed, mitochondrial depolarization associated with sustained cytosolic Ca^{2+} rise causes mitochondrial fragmentation in which DLP1 phosphorylation at Ser637 appears to play a critical role [16, 17, 22, 23]. A more recent study suggested that inhibition of complex II by 3-nitropropionic acid causes mitochondrial fission, likely mediated by increased oxidative stress and nitrosative stress following glutamate receptor activation of the NMDA subtype, rather than energy deficits per se [102]. In this regard, it is known that short exposure to low levels of ROS causes transient changes in the mitochondrial morphology and fine structure by inhibiting both the fusion and fission processes through modulation of the expression of fission/fusion proteins [111]. That the balance between mitochondrial fission and fusion can significantly impact mitochondrial function, and is also rapidly affected by mitochondrial function, is likely critical for each and every cell to meet its physiological needs under certain and ever-changing environment and thus shapes distinctive mitochondrial network between different cell types. However, changes that exceed the equilibrium of the balance, leading to either excessive fission or excessive fusion, likely will cause a downward spiral (or vicious cycle) that exacerbates mitochondrial dysfunction. Such a downward spiral appears to play a role in mitochondrial dysfunction in both genetic factor-induced and mitochondrial toxin-induced neurodegeneration models, although it is unclear in the former whether genetic factor-induced dynamics changes or functional changes initiate the cascade.

mtDNA integrity:

One possible mechanism underlying excessive fission/fusion-induced mitochondrial dysfunction is through the loss of mtDNA integrity. mtDNA genome encoding 24 genes that are involved in local mitochondrial protein synthesis and 13 essential

protein subunits of the OXPHOS complexes I, III, IV and V. Therefore, the integrity of mtDNA is critical for proper mitochondrial function. Since each mitochondrion contains 1-10 copies of mtDNA and each cell contains hundreds of mitochondria, mitochondrial dysfunction and cellular dysfunction will manifest only after mtDNA defects accumulate to a certain threshold level. Mitochondrial fusion allows the mixture and exchange of mitochondrial contents including mtDNA and its encoded proteins. This will enable each individual mitochondrion that has suffered stochastic loss of essential components to rapidly replenish their stores, thus effectively lowering the effect of defect mtDNA. Therefore, inhibition of mitochondrial fusion will likely maximize and exacerbate the effect of defect mtDNA on mitochondrial function. Indeed, in *Mfn2* deficient cells where mitochondrial fusion is entirely abolished, mitochondrial fragmentation results in a majority of mitochondria lacking mtDNA [104]. Due to the lack of essential respiratory subunits encoded by mtDNA, these mitochondria lack electron transport activity. However, on the other hand, mitochondrial fusion that creates a shared compartment of mtDNA may cause expansion of mtDNA deletion mutants because of their survival advantage of rapid replication [112]. Indeed, preventing mitochondrial fission by down-regulating expression of DLP1 or Fis1 in mammalian cells favors the accumulation of mutant mtDNA, leads to a loss of mtDNA and a decrease of mitochondrial respiration coupled to an increase in the levels of cellular ROS [105, 109, 113]. Importantly, mitochondrial fission, coupled with fusion and followed by autophagy, allows sequestration and elimination of irreversibly damaged mitochondria and mitochondrial content, thus maintaining the integrity and homogeneity of mitochondria population throughout the cell [114]. Therefore, an altered balance between mitochondrial fission and fusion may affect the removal of damaged mtDNA and thus contributes to the accumulation of mutant mtDNA. In this regard, it is notable that accumulation of damaged or mutated mtDNA is almost an invariant feature of all these neurodegenerative diseases [40-42, 57, 80, 82, 96, 97] and it is likely that abnormal mitochondrial dynamics is involved.

Synaptic maintenance:

As a specialization for communication, synaptic function and maintenance are critical for neuronal function and survival. It is generally accepted that the intracellular distribution of mitochondria is adapted to and critical for cellular physiology so that

mitochondria concentrate in subcellular regions with high metabolic requirement [115]. Therefore, it is not surprising that, with the high energy demand and calcium buffering requirements, synapses are packed with mitochondria [116, 117]. To exert their synaptic roles, mitochondria must be transported from the soma to distal synapses via cytoskeleton and constantly reconfigure to meet synaptic needs [118]. While synapses are more sensitive to declines in mitochondrial function than soma, due to the considerable length and complex morphology, they are also much more vulnerable to interruption of mitochondrial distribution mechanisms. Not surprisingly, deficits in axonal transport, especially the transport of mitochondria, are indicated as common themes in neurodegenerative diseases and some of the genetic factors are implicated in the regulation of mitochondrial transport. For example, PINK1 is involved in mitochondrial trafficking through interaction with Miro and Milton [119], thus potentially affecting the distribution of mitochondria. Importantly, mitochondrial dynamics also impact mitochondrial movement and distribution since both fission mutants (i.e., DLP1) with elongated mitochondria [120] and fusion mutants (i.e., OPA1) with short, rounded mitochondria [121] caused mitochondrial distribution changes, although the mechanisms involved are not clear. Indeed, in primary neuronal cultures, perturbation of either mitochondrial fission or fusion proteins affected the number of dendritic mitochondria which in turn affected the number and plasticity of spines and synapses and there is a correlation between dendritic spine morphogenesis and recruitment of nearby mitochondria [49, 122]. ADDLs-induced loss of dendritic spine and PSD95-positive puncta correlated with reduced dendritic density of mitochondria and can be prevented by DLP1 overexpression which only restored normal dendritic mitochondrial density but had no effect on mitochondrial function [49]. In vivo, DLP1 mutations in *Drosophila* led to elongated mitochondria and failure to properly populate the distal axon with mitochondria [123]. It causes synaptic dysfunction including elevated basal calcium levels and failure to mobilize reserve pool vesicles during intense stimulation at neuromuscular junction (NMJ). Neuron-specific DLP1-deficient mouse die shortly after birth as a result of brain hypoplasia with apoptosis. Aggregated mitochondria that failed to distribute properly within the cell processes correlated with a decreased number of neurites and defective synapse formation, which is likely the cause of abnormal forebrain development [124]. Similarly, cerebellum-specific Mfn2-deficiency causes movement defect and lethality due to extensive degeneration of Purkinje cells [104]. Although Mfn2-

deficiency-induced excessive fragmentation which causes severe mitochondrial dysfunction is thought to play a major role, Mfn2-deficiency aberrant mitochondrial distribution in Purkinje cells likely also contributes to deficits in dendritic outgrowth, spine formation, and cell survival. Synaptic dysfunction is arguably the earliest event in most neurodegenerative diseases causing clinical symptoms such as memory loss, cognitive decline and motor dysfunction and an abnormal mitochondrial dynamics is likely a contributing factor causing the early manifestation of synaptic dysfunction via abnormal mitochondrial distribution.

Cell death:

Extensive neuronal death occurs in neurodegenerative diseases and despite the controversy, apoptosis is implicated. Mitochondrial dynamics are involved in the regulation of apoptosis with mitochondrial fragmentation being an early event during apoptosis that precedes cytochrome c release and caspase activation [125]. Upon apoptotic induction, Bax/Bak-dependent sumoylation and mitochondrial recruitment of DLP1 increases along with increased mitochondrial fission [126]. DLP1 downregulation by RNAi decreases mitochondrial fragmentation, cytochrome c release, caspase activation and cell death [125]. Similarly, DLP1 inhibitor, mdivi-1, inhibits DLP1 translocation to mitochondria and mitochondrial fission and cell death [127]. Mitochondrial fusion was found to be blocked during apoptosis [128]. Knockdown of Mfn1, Mfn2 or OPA1 increases the cellular vulnerability to apoptotic stimuli while overexpression of these fusion proteins renders resistance [129]. OPA1 also controls apoptotic cristae remodeling during apoptosis independent of fusion [130, 131]. Bcl-2 family members including Bax, Bak, Bcl-2 and Bcl-xL were found to affect mitochondrial dynamics and specifically interact with Mfn1 or Mfn2 which further links mitochondrial dynamics and regulation of apoptosis [132]. In general, inhibition of fission reduces apoptosis while inhibition of fusion facilitates cell death [125, 133, 134]. However, apoptosis can occur in the absence of mitochondrial fission and excessive mitochondrial fission may not necessarily cause apoptosis [61]. Moreover, it was also reported that DLP1-dependent mitochondrial fission blocks intraorganellar Ca^{2+} waves thereby protecting cells against Ca^{2+} -mediated forms of apoptosis [107]. Neuron specific DLP1 deficient mice die shortly after birth due to brain hypoplasia with apoptosis [124]. Apparently, further studies are needed to

elucidate the role of mitochondrial fission and fusion in the regulation of apoptosis and other types of cell death and its potential contribution to neurodegeneration.

Conclusion

There is no doubt that mitochondrial abnormalities and dysfunction are involved in neurodegenerative diseases, however, it is still a matter of debate whether or not such abnormalities are a cause or merely a consequence--among many--of the diseases. It is also not clear how mitochondrial abnormalities and dysfunction cause selective neurodegeneration in different neurodegenerative diseases. With the deeper understanding of dynamic nature of mitochondria characterized by a tightly controlled balance of fission and fusion, emerging evidence suggests that abnormal mitochondrial dynamics is involved in various neurodegenerative diseases. Although this recent development in the field will unlikely resolve the debate over a causal and selective role of mitochondrial dysfunction in neurodegeneration, given that mitochondrial dynamics significantly impacts mitochondrial genome integrity and bioenergetics and neuronal functions including synaptic maintenance and cell death, it is very likely that abnormal mitochondrial dynamics represents a key common pathway mediating or amplifying mitochondrial dysfunction and neuronal dysfunction during the course of neurodegeneration. Therefore, strategies to modify abnormal mitochondrial dynamics may be an attractive therapeutic intervention target for the treatment of neurodegenerative diseases.

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