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Abnormal Mitochondrial Dynamics—A Novel Therapeutic Target for Alzheimer's Disease?

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Abstract

Mitochondria are dynamic organelles that undergo continuous fission and fusion, which could affect all aspects of mitochondrial function. Mitochondrial dysfunction has been well documented in Alzheimer's disease (AD). In the past few years, emerging evidence indicates that an imbalance of mitochondrial dynamics is involved in the pathogenesis of AD. In this review, we discuss in detail the abnormal mitochondrial dynamics in AD and how such abnormal dynamics may impact mitochondrial and neuronal function and contribute to the course of disease. Based on this discussion, we propose that mitochondrial dynamics could be a potential therapeutic target for AD.

Keywords

Alzheimer's disease; Mitochondrial dynamics; Mitochondrial fission; Mitochondrial fusion; Drug; Dimebon

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder of the elderly that leads to progressive memory loss, impairments in behavior, language, visuospatial skills, and ultimately death. The disease is characterized by a progressive neuronal and synaptic loss and the presence of extracellular Aβ deposits as senile plaque and intracellular neurofibrillary tangles composed of aggregated tau proteins in brain. Most cases of AD occur sporadically, yet genetic studies revealed that mutations in amyloid β precursor protein (APP), presenilin 1 and 2 (PS1 and PS2), cause rare early-onset familial form AD. In addition to these deterministic genetic mutations, the apolipoprotein E4 allele (ApoE4) was identified to significantly increase susceptibility for late- and early-onset AD.

The currently prescribed drugs for treating AD include cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) and the glutamatergic agent memantine, which only provides symptomatic improvement with modest efficacy. There is an obvious urgent need for new treatment, both symptomatic and disease modifying, for AD. However, our search for a cure for this debilitating disease is hampered by our incomplete understanding of this disease as evidenced by the fact that drugs targeting amyloid precursor protein processing or Aβ lowering, based on the dominating amyloid cascade hypothesis, are faltering in recent clinical trials. This suggests that we may need to also target other aspects associated with the course of the disease.

Mitochondrial dysfunction in AD has been widely reported. A large number of studies implicate metabolic defects in AD, such that a reduced rate of brain metabolism is one of the best documented abnormalities in AD [1]. Most importantly, such cerebral metabolic rate abnormalities precede rather than follow any evidence for functional impairment by neuropsychological testing or of brain atrophy by neuroimaging [1]. Consistently, deficiency in several key enzymes of oxidative metabolism in mitochondria (i.e., KGDHC, PDHC, and COX) is well documented in AD brain [2]. Mitochondrial encoded genes were abnormally expressed in AD postmortem brains [2]. As the center of reactive oxygen species (ROS) production, damage to mitochondria may contribute to the widespread oxidative damage in AD brain [3]. Calcium homeostasis is also altered in AD and animal models of AD, and it is known that mitochondrial impairment enhances dysregulation of neuronal calcium homeostasis [4]. Additionally, damaged mitochondrial DNA (mtDNA) was found present in vulnerable neurons in AD [5], and mtDNA genetic markers have been linked to an increased incidence of AD [6, 7]. Studies from cybrid cell lines with mitochondrial DNA from AD patients also showed abnormal mitochondrial morphology, membrane potential, and ROS production, confirming mutant mitochondrial DNA in AD contributing to the pathology [8–10]. More recently, it is found that APP and/or Aβ are associated with mitochondria [11, 12]. Overall, these studies suggest that mitochondria may be a very promising therapeutic target for AD.

Although it has long been appreciated that mitochondria are very dynamic organelles, recent studies revealed that they constantly divide and fuse with each other [13], which represents one of the most exciting findings in the field in recent years. Detailed studies revealed that mitochondrial fission and fusion is a tightly regulated delicate balance that not only controls mitochondrial morphology and number but also impacts every aspect of mitochondrial function and distribution [13]. The fact that mutations in genes that are essential for mitochondrial dynamics directly led to degeneration of specific nerves and caused several human neurological diseases underscored the notion that neurons are particularly prone to defects in mitochondrial dynamics [13]. Not surprisingly, abnormal mitochondrial dynamics has therefore emerged as an important mechanism for the development of neurodegenerative

diseases including Alzheimer's disease and may prove to be a novel therapeutic target for AD.

Mitochondrial Dynamics

Mitochondria are dynamic organelles that are engaged in a delicate balance of fission and fusion within the cell [13]. Until now, several proteins have been identified to control fission and fusion; however, their precise mechanisms of operation remain to be fully elucidated. Mitochondrial fission involves at least two proteins in mammalians: a large GTPase, dynamin-like protein 1 (DLP1), and a small molecule, Fis1. The former is a primarily cytosolic protein, and during fission, DLP1 is recruited to punctuate spots on the mitochondrial surface. Like 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 [14]. Similarly, Fis1 assists in mitochondrial fission but is evenly distributed along the surface of the mitochondrial outer membrane [15]; although it is suggested to act as receptor to recruit DLP1 to mitochondria during fission [16], controversy remains since DLP1 can assemble on mitochondria in the absence of Fis1.

On the other hand, mitochondrial fusion is regulated by three large GTPases: mitofusin 1 (Mfn1), mitofusin 2 (Mfn2), and optic atrophy protein 1 (OPA1) [17, 18]. Both Mfn1 and Mfn2 are mitochondrial transmembrane proteins localized to the outer membrane and appear to play similar roles in mitochondrial fusion [19, 20]. During mitochondrial fusion, through interactions of their coiled-coil domains, Mfn1 and Mfn2 could form homo-oligomeric and hetero-oligomeric complexes and tether neighboring mitochondria together [20, 21]. OPA1 is localized to the inner membrane and is primarily involved in inner membrane fusion [19, 22, 23].

In mammalian cells, mitochondrial dynamics are influenced by various regulatory pathways and stimuli, the mechanisms of which are incompletely understood [17, 18]. Most notably, posttranslational modifications to the mitochondrial fission protein DLP1 have been associated with fission regulation. That is, phosphorylation, sumoylation, ubiquitylation, and nitrosylation of DLP1 influence its ability to orchestrate the fission process in various ways [24–29]. Specifically, it is suggested that phosphorylation of DLP1 at Ser616 (e.g., Ser585 in rat) by mitosis-promoting factor facilitates mitochondrial fission [24, 25, 29], while ubiquitination of DLP1 is believed to facilitate its degradation [30]. On the other hand, sumoylation of DLP1 by SUMO-1 protects DLP1 from degradation, enlarges the stability DLP1, and facilitates the translocation of DLP1 from cytosol to the mitochondria [26]. Most recently, it has been reported that S-nitrosylation of DLP1 activates GTPase activity and mitochondrial fission [31]. Although OPA1 is encoded by one single gene, eight splice variants are identified, and multiple proteases have been identified in OPA1 processing [32], providing multiple points of regulation. However, the detailed mechanisms remain elusive.

Growing evidence suggests that the delicate equilibrium between mitochondria fission and fusion is vital for mitochondrial functions including metabolism, energy production, Ca^{2+} signaling, ROS production, apoptosis, cell cycle, and senescence [19, 33–38]. It is 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 [39]. Importantly, mitochondrial dynamics can also impact cellular function by influencing mitochondrial distribution since both fission mutants (i.e., DLP1) with elongated mitochondria [40] and fusion mutants (i.e., OPA1) with short, rounded mitochondria [41] caused mitochondrial distribution changes, although the mechanisms involved are not clear.

Abnormal Mitochondrial Dynamics in AD

Initial implication of an abnormal mitochondrial dynamics in AD neurons comes from an ultrastructural morphometric study suggesting that mitochondria size and number are significantly altered in vulnerable neurons in AD [5]. This same study also confirmed lower percentages of normal mitochondria and significantly higher percentages of impaired mitochondria with broken cristae in these neurons, implicating that an abnormal mitochondrial dynamics may contribute to ultrastructural deficit of mitochondria. Indeed, in hippocampal tissues of AD patients, mitochondrial fusion/fission protein expression levels were also altered (compared to age-matched controls) [42]. That is, the expression levels of DLP1, OPA1, Mfn1, and Mfn2 were shown to be significantly reduced in AD, while those of Fis1 were seen increased in AD compared with control, thus confirming a tipped balance of mitochondrial fission and fusion in pyramidal neurons of AD. As a supplemental analysis of this notion, fibroblasts from AD patients were scrutinized to reveal profound alterations in mitochondrial dynamics in these cells [43]. More recently, it is demonstrated that over-expression of mutant APP in neuronal cells leads to increased mitochondrial fission and a defect in mitochondrial function and neuronal differentiation, due to altered expression of mitochondrial fission/fusion proteins [44]. Overexpression of DLP1 or OPA1 partially rescues different aspects of these mitochondrial defects, confirming the critical role of mitochondrial dynamics in causing these deficits. In addition, exposure of neuronal cells to Aβ also leads to increased mitochondrial fission and loss of dendritic spines and synapse which can be partially rescued by overexpression of OPA1 or DLP1 [44, 45]. Increased levels of S-nitrosylated DLP1 are found in neurons treated with Aβ and also in brain samples from AD patients and AD mouse models [31, 42], which, along with reduced OPA1 expression, is believed to contribute to enhanced mitochondrial fission observed in these models.

In addition to morphological abnormalities, altered distribution of mitochondria in neurons was observed in AD patients, where more mitochondria are accumulated in cell body rather than throughout the neuronal processes [42]. In fact, such an abnormal mitochondrial distribution is also found in AD-related in vitro models: For example, fibroblasts from sporadic AD cases and M17 cells over-expressing APP mutation cause clustering of mitochondria around the perinuclear area and mitochondria at more remote regions becoming sparse [43]. Primary neurons overexpressing APP mutation or exposed to Aβ demonstrated significantly reduced mitochondrial coverage in neuronal processes correlated with reduced spine density and synapses [42]. It appears that at least two mechanisms likely contribute to such an abnormal mitochondrial distribution: (1) Earlier studies showed that exposure of primary neurons to preaggregated Aβ25–35 induces acute impairment in mitochondrial axonal transport [46], and more recent studies demonstrated that soluble Aβ oligomers lead to significantly reduced mitochondrial axonal transport in both anterograde and retrograde direction. It is known that defects in both kinesin-based anterograde and dynein-based retrograde axonal transport can lead to reduced mitochondrial density in neuronal processes [47]; (2) It is known that alterations in the expression of mitochondrial fission or fusion proteins can alter the distribution of mitochondria [48]. The causal role of mitochondrial fission/fusion proteins in Aβ-induced abnormal mitochondrial distribution is reinforced by the finding that DLP1 overexpression can partially rescue such defects [42]. However, the relationship between mitochondrial fission/fusion regulation and mitochondrial transport/retention remains to be determined.

Effect of Tau, ApoE4, and Presenilin on Mitochondrial Dynamics

Tau is a major component of the neurofibrillary tangles (NFTs) in AD patients, and it has been proposed to play a key role in the pathogenesis of AD [49]. Tau is a microtubule-

binding protein expressed in neurons, and the normal function of tau relates to the modulation of the assembly, dynamic behavior, and spatial organization of microtubules in neurons [50]. Tau protein has more than 30 known phosphorylation sites and becomes hyperphosphorylated in NFTs in AD neurons with some sites being only phosphorylated in the AD-specific, soluble form of tau, termed PHF-tau [51]. Phospho-tau not only has impaired microtubule binding activity with phosphorylation at certain sites (e.g., Ser262), but it also sequesters normal tau and microtubule-associated proteins (MAP1 and 2) and causes inhibition of assembly and disruption of preformed microtubules [52]. In this regard, it is not surprising that some studies showed that overexpression tau protein led to mitochondrial perinuclear distribution [53–55]. Indeed, the mechanisms associated with regulation of mitochondrial distribution are through regulation of motor protein kinesin and dynein [55, 56].

On the other hand, in addition to hyperphosphorylation, tau proteins are cleaved by caspase 3 at Asp-421 [57, 58]. In cell culture models, truncated tau is toxic to neurons [59–61], and fragmented mitochondria are observed with decreased calcium buffering ability and increased ROS production [62]. However, the detailed mechanisms about the regulation of mitochondrial dynamics have not been investigated.

ApoE4 is a known risk factor for late onset of AD, and its genetic presence increases the risk and lowers the age of onset in a gene dose-dependent manner [63, 64]. Like tau protein, ApoE4 is cleaved into C-terminal-truncated fragments, and in AD brains, more cleaved ApoE4 fragments are observed as compared to age-matched controls [65]. In mouse models, truncated ApoE4 interacts with mitochondria and impairs mitochondrial functions and integrity [66], and recently, it has been shown to impair mitochondrial dynamics in neurons (ICAD, 2008, Chicago).

Presenilin mutations are associated with most of early onset of familial Alzheimer’s disease [67, 68]. Presenilins are integral membrane protein: In neurons, they localize in the endoplasmic reticulum, intermediate compartment, nuclear membranes, and growth cones [69–71], and recent evidence also shows their presence in mitochondria [72–74]. The effects of presenilins on mitochondrial function have been reported. In a PS1 mice models, mutant PS1 led to abnormal mitochondrial function [75, 76]. In mouse embryonic fibroblasts, deficiency of PS2 resulted in abnormal lower mitochondrial membrane potential and lower respiratory rate, implicating the important role of PS2 in keeping mitochondrial functional state [73]. Mutant PS1 also affects axonal transport of mitochondria presumably by affecting phosphorylation of kinesin light chain through effects on GSK3β [77].

Mitochondrial Dynamics—A Potential Therapeutic Target for AD?

In neurons, synaptic function and maintenance are critical for neuronal function and survival. Synaptic dysfunction is thought to be the earliest event in most neurodegenerative diseases, resulting in clinical symptoms such as memory loss, cognitive decline, and motor dysfunction. Depletion of mitochondria from the synapse via altered mitochondrial trafficking is likely to play a role. Our studies demonstrate that Aβ-derived diffusible ligands (ADDLs) induce loss of dendritic spines and PSD95-positive puncta, which correlates with reduced dendritic density of mitochondria, and DLP1 but not OPA1 overexpression can restore normal dendritic mitochondrial density, dendritic spine, and PSD puncta number [42], suggesting that DLP1-regulated mitochondrial distribution played an important role in ADDL-induced change of dendritic spine and synapse plasticity. Therefore, deficit in axonal transport, particularly transport of mitochondria, is a common theme in neurodegenerative disease, and mitochondrial dynamics proteins are likely to play a role as both fission (i.e., DLP1) and fusion mutants (i.e., OPA1) cause mitochondrial distribution changes [40, 41].

Recently, multiple studies have demonstrated alterations of mitochondrial dynamics through manipulations of the five fission/fusion proteins. Mfn1 and Mfn2 dull cells and OPA1 deficient cells with excessively fragmented mitochondria demonstrated attenuated electron transport rates in respiratory complex I, III, and IV, leading to greatly reduced endogenous and uncoupled respiratory rates [19, 78]. Genetic inhibition of DLP1 caused excessive fusion and reduced rate of ATP synthesis [79]; Fis1 knocking down also associated with decreased mitochondrial membrane potential [34]. Mitochondrial Ca^{2+} uptake and intramitochondrial Ca^{2+} diffusion is impaired in cells with fragmented mitochondria, suggesting that an imbalanced fusion and fission can disrupt normal Ca^{2+} ion homeostasis [80, 81].

A similar effect was observed in mtDNA alteration by disturbed fusion–fission balance. As the mtDNA genome encodes 24 genes that are involved in local mitochondrial protein synthesis and 13 essential protein subunits of the OXPHOS complex I, III, IV, and V, the integrity of mtDNA is critical to maintain mitochondrial function. Mitochondrial fusion allows exchange of mitochondrial contents, including mtDNA and its encoding proteins. Inhibition of mitochondrial fusion by Mfn2 knock out resulted in a majority of mitochondria lacking mtDNA [82]. However, mitochondrial fusion may also result in exacerbation of mtDNA deletion mutants because of their survival advantage of rapid replication, as fusion enables intercontent sharing [83]. Indeed, fission inhibition by Fis1 or DLP1 knock down favors accumulation of mutant mtDNA and leads to a loss of mtDNA and a decrease of mitochondrial respiration coupled to an increase in the level of cellular ROS [34, 84, 85]. Likewise, autophagy, followed by fission and fusion, allows sequestration and elimination of damaged mitochondria, thus maintaining the integrity and homogeneity of mitochondrial population [86]. Therefore, an altered mitochondrial fusion and fission balance may affect the removal of damaged mitochondria and, thus, contribute to the accumulation of mitochondria with damaged or mutant mtDNA. In this regard, it is notable that accumulation of damaged or mutant mtDNA is almost an invariant feature of all neurodegenerative diseases [5, 6, 87–92].

Furthermore, these proteins are associated with regulation of apoptosis and development. It is suggested that an inhibition of fission or an increase of fusion have protective effects against cell death. For example, upon apoptotic induction, more DLP1 was recruited to mitochondria, resulting in increased mitochondrial fission [93]. Decreasing of mitochondrial fission by inhibition of DLP1 by RNAi reduced mitochondrial fragmentation, cytochrome c release, caspase activation, and cell death [33]. Similarly, the DLP1 inhibitor, mitochondrial division inhibitor-1 (mdivi-1), inhibits DLP1 translocation to mitochondria and mitochondrial fission and cell death [94]. Mitochondrial fusion was found to be blocked during apoptosis [95]. Knockdown of Mfn1, Mfn2, or OPA1 increases the cellular vulnerability to apoptotic stimuli while overexpression of these fusion proteins renders resistance [96]. OPA1 also controls apoptotic cristae remodeling during apoptosis independent of fusion [97, 98]. 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 [99]. 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 [81]. Neuron-specific DLP1-deficient mice die shortly after birth due to brain hypoplasia with apoptosis [100]. Consequently, 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.

Overall, it is clear that by targeting mitochondrial dynamics, one can effectively impact mitochondrial structure, alter mitochondrial distribution, improve mitochondrial function, and influence the regulation of apoptosis. With an abnormal mitochondrial dynamics being increasingly implicated in mediating or amplifying mitochondrial dysfunction and neuronal dysfunction in Alzheimer's disease, it represents a novel therapeutic target.

Mitochondrial Targeting Drugs for Alzheimer's Disease

Metabolic Antioxidants

Since overproduction of ROS by mitochondria is one of the major factors that contribute to the course of AD, many drugs targeting mitochondria tested or in development belong to metabolic antioxidants including lipoic acid (LA) and coenzyme Q10 (CoQ10). It is known that oxidative stress induces mitochondrial fragmentation and altered mitochondrial distribution in vitro which can be prevented by antioxidants [43]; it would be of interest to determine whether improved mitochondrial dynamics is involved in the beneficial effect of these metabolic antioxidants in vivo and in AD patients.

Lipoic Acid—LA, as the coenzyme of mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, is a powerful antioxidant and can recycle other antioxidants such as vitamin C and E and glutathione. Supplement of LA significantly reduced hippocampal memory loss in aged Tg2576 mice [101]. The cognitive improvement was also observed in ApoE4 mice fed with LA and acetyl-L-carnitine (ALCAR) [102]. The beneficial effects of LA is at least by restoring mitochondrial integrity and function because damaged mitochondria are reduced with LA and ALCAR supplementation [103]. In addition to the improvement in mice and rat, in AD patients, supplement of LA stabilizes cognitive functions [104, 105], suggesting it to be a promising drug candidate. A meta-analysis of double-blind placebo-controlled prospective, parallel group comparison studies of at least 3-month duration revealed beneficial effects on both the clinical scales and the psychometric tests in MCI and mild AD patients.

CoQ10 and Mito Q—CoQ10 is an important cofactor of the electron transport chain where it accepts electrons from complex I and II; CoQ10 is a potent antioxidant. It preserves mitochondrial membrane potential during oxidative stress and protects neuronal cells against Aβ toxicity through inhibition of PTP opening. Aged PS1 transgenic mice fed with CoQ10 for 60 days partially attenuates Aβ overproduction and intracellular Aβ deposits. However, it must be mentioned that idebenone, a synthetic analog of CoQ10, failed to slow cognitive decline in AD patients during clinical trial. Since one limitation to antioxidant therapy is the inability to enhance the antioxidant levels within mitochondria, to enhance mitochondrial accessibility, Mito Q is produced by conjugation of the lipophilic triphenylphosphonium (TPP+) cation to coenzyme Q [106]. With help of TPP+, coenzyme Q penetrates into the membrane core, where it is reduced to its active form (the antioxidant ubiquinol) by complex II to decrease lipid peroxidation, resulting reduced oxidative damage [107]. In several cell models, Mito Q has demonstrated protective effects by reducing free radicals, decreasing oxidative damage and maintaining mitochondrial functions [108–110]. It showed good pharmacokinetic behavioral in phase I clinical trial in AD patients.

Dimebon: A Serendipitously Discovered Drug with Potential Mitochondria-Targeting Activity

Dimebon was originally approved in Russia as a nonselective antihistamine for the treatment of skin allergy and allergic rhinitis and was retired from the market when more selective treatments became available. Prior studies suggested that Dimebon is neuroprotective against Aβ25–35 in primary neuronal cultures [111] and preserves learning and memory in

an active avoidance conditioned learning tasks in a preclinical AF64A cholinergic lesion model [112, 113]. During the recent successful trial held in Russia, Doody and colleagues compared 20 mg Dimebon, three times a day, with placebo over 6 months. At 3 and 6 months, Dimebon was significantly superior to placebo on five out of five endpoints measuring cognition, global function, activity of daily living, and behavior, and the effects were still measurable at 12 months [114]. Despite being a very promising treatment for AD, there is no known mechanism of action for Dimebon. Based on the literatures and data released by Medivation Inc., the company that sponsored the Russian trial [115, 116] (http://www.alzforum.org/new/detailprint.asp?id=2257), Dimebon is a very weak cholinesterase inhibitor (>3,000-fold less potent comparing to donepezil) and NMDA receptor antagonist. Differences in the side-effect profile of Dimebon during trial from current antidementia drugs suggest that Dimebon has another mode of action. Indeed, Dimebon modulates mitochondrial function in cells with nanomolar potency and stabilizes mitochondria membrane potential and improves neuron survival in the setting of cell stress (http://www.alzforum.org/new/detailprint.asp?id=2257), suggesting that mitochondria are a likely target of this promising drug. Such a notion was supported by studies reported at recent scientific conference [117]. It is demonstrated that Dimebon causes neurite outgrowth, comparable to that of BDNF, presumably through improved mitochondrial distribution and function in neurites, implicating that improved mitochondrial dynamics may be involved. Obviously, it is of critical importance to decipher the underlying mechanisms of Dimebon which will not only improve our understanding of the pathogenesis of the disease but also will have the potential to help to design and develop new drugs for AD.

Potential Drugs Targeting Mitochondrial Dynamics

Mdivi-1—To search for small molecules that inhibit mitochondrial division, Cassidy-Stone and colleagues used yeast screens of chemical libraries and identified an inhibitor called mdivi-1 [94]. Mdivi-1 selectively inhibits GTPase activity of Dnm1 by blocking the self-assembly of Dnm1. It also inhibits mitochondrial fission in mammalian cells by inhibiting DLP1 assembly. It is demonstrated that cells treated with mdivi-1 are resistant to apoptosis upon apoptotic challenges, presumably by inhibiting mitochondrial membrane permeabilization. Since excessive mitochondrial fragmentation due to unbalanced ongoing fission is a feature of various diseases including Alzheimer's disease [118], it is suggested that mdivi-1 may be of therapeutic benefit in these conditions. Such a notion is supported by the finding that mitochondrial fragmentation occurred in proximal tubular cells in mice during renal ischemia/reperfusion and cisplatin-induced nephrotoxicity and mdivi-1 treatment attenuate both tubular cell apoptosis and acute kidney injury in vivo [119]. Nevertheless, its negative effect on mitochondrial distribution may be a concern in treating neurodegenerative diseases [94]. In this regard, more studies are needed to determine its usefulness in these diseases.

Peroxisome Proliferator-Activated Receptor-γ-Coactivator 1α Activation—Peroxisome proliferator-activated receptor-γ-coactivator 1α (PGC-1α) is a master transcriptional coactivator that regulates mitochondrial biogenesis and respiration [120–123]. PGC-1α null mice display a reduced basal expression of many mitochondria genes in liver, heart, skeletal muscle, and brain compared with wild-type mice [124–126] and are more sensitive to oxidative stress [127]. Notably, overexpression of PGC-1α protects neurons from degeneration induced by oxidative stress or mutant huntingtin [127, 128], and recently, a study demonstrated that overexpression of PGC-1α or PGC-1β leads to increased mitochondrial intensity in neurites, suggesting that targeting PGC-1α or PGC-1β may restore the distribution of mitochondria in neurites [129]. Given the abnormal mitochondrial distribution and decreased PGC-1a expression level in the AD brain [130], promotion of PGC-1α activity or expression may be a promising therapeutic strategy for AD.

Conclusion

Recently, in addition to AD, emerging evidence has suggested that mitochondrial abnormal dynamics are also a character in other neurodegenerative diseases including Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). In Parkinson's disease PINK1, Parkin (two genetic factor leading to Parkingson disease) have been demonstrated to play a role in mitochondrial dynamics in vivo and in vitro [131–136]; environmental toxin 6-OHDA, an environmental toxin that results in PD, also led to mitochondrial fragmentation [137]. Some reports also demonstrated abnormal mitochondrial dynamics in ALS and HD models, suggesting abnormal mitochondrial dynamics in these diseases [138–146]. Actually, some of the mutations in fusion and fission proteins cause some neuronal disorder. For example, Mfn2 mutations results in Charcot–Marie–Tooth neuropathy type 2A [21, 147], and OPA1 mutation causes inherited optic neuropathy [148, 149]. Therefore, abnormal mitochondrial dynamics most likely represents a common pathway that mediates neuronal dysfunction in the course of neurodegenerative diseases. Given that mitochondrial dynamics not only affects mitochondrial morphology but also the mitochondria trafficking, function, and cell death, and manipulation of fission/fusion proteins has showed some beneficial effect in some disease-related models in vivo and in vitro; the strategies that modify abnormal mitochondrial dynamics may be an attractive therapeutic intervention target for the treatment of AD and other neurodegenerative diseases.

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