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Abnormal Mitochondrial Dynamics in the Pathogenesis of Alzheimer's Disease

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Abstract

Mitochondrial dysfunction is one of the most early and prominent features in vulnerable neurons in the brain of Alzheimer's disease (AD) patients. Recent studies suggest that mitochondria are highly dynamic organelles characterized by a delicate balance of fission and fusion, a concept that has revolutionized our basic understanding of the regulation of mitochondrial structure and function which has far-reaching significance in studies of health and disease. Tremendous progress has been made in studying changes in mitochondrial dynamics in AD brain and models and the potential underlying mechanisms. This review highlights the recent work demonstrating abnormal mitochondrial dynamics and distribution in AD models and discusses how these abnormalities may contribute to various aspects of mitochondrial dysfunction and the pathogenesis of AD.

Keywords

Alzheimer's disease; mitochondrial distribution; mitochondrial dynamics; mitochondrial dysfunction; mitochondrial fission; mitochondrial fusion

INTRODUCTION

One of the most striking features of the human brain is its metabolic energy requirement: despite the fact that the human brain occupies less than 2% of total body mass, it receives 15% of cardiac output and consumes 20% of total resting metabolic energy [1]. Within the brain, most of the energy is consumed by neurons, which is driven by many energy-taxing neuronal processes such as ion channel/pump activities, synaptic transmission, and axonal/dendritic transport [2]. Limited neuronal glycolytic capacity makes them almost exclusively dependent on aerobic oxidative phosphorylation in mitochondria. In addition to ATP generation, neurons are also dependent on mitochondria for maintenance of calcium home-

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ostasis since synaptic mitochondria are important in calcium clearance either by direct calcium removal or by providing ATP for the plasma membrane Ca^{2+}-ATPase and Na^{+}/Ca^{2+} exchanger, which become the dominant player at sites where endoplasmic reticulum vesicles are absent [3]. On top of these challenges, the large size and complex morphology of neurons leads to functional heterogeneity in neuronal segments, thus translating into different energy and calcium buffering demands that requires mitochondria to be strategically localized to specific regions, which poses additional unique challenges to mitochondrial regulation in neuron [4]. There is no wonder that neurons are particularly sensitive to changes in mitochondrial function. Indeed, mitochondrial dysfunction is implicated in various neurodegenerative diseases including Alzheimer's disease (AD) [5]. Decades of studies from multiple groups revealed that almost all aspects of mitochondrial function are altered in AD neurons and peripheral cells, and mitochondrial dysfunction is a prominent and early feature of the disease which may play a critical if not causative role in the pathogenesis of AD [6].

Traditionally, the biochemistry of mitochondria has been investigated in cell free, isolated systems, leading us to imagine the mitochondrion as a discrete, lonely organelle working tirelessly to provide the energy required for life, an impression that was stereotyped by snapshot electron microscopic images. However, in the past decade, this view has dramatically changed as the real time examination of dynamic mitochondrial behavior within intact cells, made possible by newer approaches, led to renewed appreciation for the fact that the mitochondria structure is highly dynamic [7]. The concept that mitochondria constantly divide and fuse with each other revolutionizes our basic understanding of the regulation of mitochondrial structure and function, which has far-reaching significance in studies of health and disease [7]. Not surprisingly, alterations in mitochondrial fission and fusion significantly impact neuronal function which is underscored by the prevalence of neurological disease associated with mutations in mitochondrial fission and fusion genes [8]. Recent studies from our group and others demonstrated that mitochondria become fragmented in AD neurons and peripheral cells as well as in AD cell models [9–16]. These new findings and how they may impact our understanding of the underlying mechanism of mitochondrial dysfunction and synaptic/neuronal dysfunction critical to the pathogenesis of AD is the topic of this review.

Mitochondrial dynamics: A delicate balance of fusion and fission

Mitochondria exist in the cells as highly dynamic entities, ranging from giant tubular network to small round organelles through rapid and reversible fission and fusion processes [7]. They vary between different cell types, within individual cells, and under different cellular environments. Such malleability of mitochondria is invaluable in the metabolically heterogeneous environment of the neuron, where specific regions require different ATP or calcium buffering.

Mitochondrial dynamics are regulated by a delicate balance of two opposing processes: mitochondrial fusion and mitochondrial fission [17]. An increasing number of proteins are known to mediate these processes and several large dynamin-related GTPases are believed to play a central role. The large GTPase involved in mitochondrial fission is dynamin-like

protein 1 (DLP1, also known as dynamin-related protein, Drp1). DLP1 is a cytosolic protein and is recruited to the outer mitochondrial membrane (OMM) during mitochondrial fission where it oligomerizes into a ring-like structure to physically pinch a mitochondrion into two daughter mitochondria [18]. Oligomerization into higher order structure activates GTPase activity of DLP1 which is essential for mitochondrial fission. GTPase activity, mitochondrial recruitment, and stability of DLP1 are regulated by post-translational modifications such as phosphorylation, S-nitrosylation, sumoylation, and ubiquitination [13, 19–22]. Fis1, an OMM protein, was initially suggested to recruit DLP1 to the OMM. However, most recent studies suggest that Fis1 may not be a core component of the mitochondrial fission machinery, but rather plays a regulatory role. Instead, it was shown that mitochondrial fission factor, also an OMM protein, directly binds to DLP1 and is necessary and sufficient for mitochondrial recruitment of DLP1 during mitochondrial fission [23]. Additional OMM proteins that physically or functionally interact with DLP1 have been identified which probably play a regulatory role that likely creates more layers for delicate regulation of this extremely important process [24].

The mitochondrial fusion process involves the coordinated fusion of both mitochondrial outer membrane and inner membrane. Nevertheless, fusion of outer membrane and inner membrane can be functionally separated and involve different regulators which are also large GTPases: mitofusin 1 and 2 (Mfn1/2) responsible for outer membrane fusion, and optic atrophy 1 (OPA1) responsible for inner membrane fusion [7]. Mfn1 and Mfn2 are highly homologous, integral outer membrane proteins with both C-terminal coiled-coil domain and N-terminal GTPase domain being exposed to the cytosol. Mitofusins on neighboring mitochondria can form either homo or hetero-dimer via the interaction of coiled-coil domains to tether the two outer membranes together. However, the understanding of subsequent events and underlying mechanisms of outer membrane merge remain elusive. OPA1 is an inner membrane protein that is proteolytically processed into membrane-associated long isoforms and soluble short isoforms. A combination of both isoforms is necessary for inner membrane fusion, and changes in the balance between these two isoforms affect mitochondrial fusion. OPA1 is also important for cristae formation and mtDNA inheritance [25].

Mitochondrial dynamics and mitochondrial function/distribution

Mitochondrial dynamics are critical for mitochondrial integrity in eukaryotic cells. On one hand, mitochondrial fusion permits the exchanges of critical mitochondrial components within mitochondrial network such as lipid membranes, oxidative phosphorylation complexes, and mitochondrial DNA (mtDNA) such that dysfunctional mitochondria due to defective components remain at a minimum [7]. For example, in Mfn null and OPA1 null cells, which have no mitochondrial fusion activity at all, the majority of mitochondria show complete loss of mtDNA nucleotides that correlates well with the severity of mitochondrial membrane potential loss [26]. Mitochondrial elongation is also an important mechanism for mitochondria to escape autophagy-mediated destruction so as to sustain cell survival during starvation-induced macroautophagy by optimizing ATP production, likely via increased cristae surface [27–29]. Mitochondrial fusion is probably also important in maintaining the proper ultrastructure of mitochondria since fusion-deficient mitochondria are usually larger

in diameter and appear round as compared to thin tubular forms of normal mitochondria [26], and unopposed fission also causes ultrastructural deficits such as loss of cristae [30]. On the other hand, mitochondrial fission enables the sequestration and subsequent elimination through mitophagy of irreversibly damaged mitochondria and mitochondrial content [29]. Studies suggest that mitochondrial fusion is usually followed by mitochondrial fission and the shape and membrane potential of daughter mitochondria determines their fate with the ones of lower mitochondrial membrane potential being selectively degraded. This is perhaps the reason that excessive elongated mitochondrial phenotype is associated with senescence phenotype [31, 32] in which damaged mitochondrial components likely accumulate due to inefficient removal through mitophagy coupled with fission. Recently, it was suggested that mitochondrial fission may also play an important role in the proper assembly of mitochondrial electron transport chain complexes [33]. Not surprisingly, changes in mitochondrial dynamics significantly impact almost all aspects of mitochondrial functions including energy metabolism, calcium buffering, reactive oxygen species (ROS) generation, and apoptosis regulation [34–44].

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 such as synapses [45]. Recent studies suggest that the balance of mitochondrial fission and fusion is also important for the proper distribution of mitochondria [4]. Mitochondrial fission may facilitate small mitochondria to be better dispersed in small calibers such as distal end of axon and dendrites, a notion supported by the evidence that expression of DLP1 increased dendritic mitochondrial density while DLP1 knockdown deplete remote sites of elongated mitochondria. However, small round mitochondria due to excessive fission in Mfn null neurons also demonstrate mitochondrial distribution deficits such that mitochondria in dendrites are far fewer and tend to congregate at the triangular branch point and are unable to enter the distal, smaller diameter branches [26]. Therefore, enhanced mitochondrial fission alone is not sufficient for proper mitochondrial distribution. The possibility that mitochondrial fission/fusion proteins may directly impact mitochondrial transport independent of their roles in regulation of mitochondrial morphology cannot be ruled out. In this regard, it is reported that Mfn2 interacts with Miro and/or Milton, mitochondrial adaptor proteins involved in mitochondrial transport which likely contributes to the alterations in mitochondrial distribution [46]. However, whether this is also underlying DLP1-caused mitochondrial distribution deficits is unclear [9].

Mitochondrial dysfunction in Alzheimer's disease

Positive emission tomography analysis consistently revealed characteristic and progressive reduction in the cerebral metabolic rate for glucose in the posterior cingulate, parietal, and temporal cortex, and in the frontal cortex and whole brain in more severely affected AD patients, indicating defective glucose utilization and energy metabolism [47]. A recent genome-wide transcriptomic study analyzed the expression of nuclear ETC genes and TOM/TIM genes in laser-capture microdissected non-tangle-bearing neurons from various brain regions of AD patients and demonstrated that the nuclear encoded ETC genes are specifically under-expressed in metabolically affected brain regions such as the posterior cingulate cortex and the hippocampal field CA1, but not in metabolically spared brain

regions such as primary visual cortex or superior frontal gyrus compared to age-matched control [48], suggesting that neuronal mitochondrial dysfunction underlies the reduced energy metabolism in AD brain. Indeed, decades of studies from multiple groups demonstrated deficiency in several key enzymes involved in glucose metabolism in AD brain [47]. In one recent study, Gibson and colleagues systematically examined PDHC and all the enzymes of the TCA cycle and their correlation with clinical state and with plaque counts in AD brain [49]. They confirmed reduced PDHC and KGDHC and further found changes in other enzymes in TCA cycle. There is decreased activity of decarboxylating dehydrogenases while compensatory increase in dehydrogenases, alterations of which all significantly correlated with clinical state and plaque counts, suggesting a coordinated regulation of these enzymes in response to neurodegenerative condition in AD brain that likely contributes to the decline in glucose metabolism in AD [49]. Importantly, abnormal change in cerebral metabolic rate is an early event since it precedes, rather than follows, any evidence of functional impairment by neuropsychological testing or of brain atrophy by neuroimaging. Reduced brain glucose metabolism occurs in patients with mild cognitive impairment (MCI), a prodrome for AD, which further worsens after the transition to definite AD [50]. In fact, the reduction in glucose metabolism predicts the conversion from normal to MCI and progression from MCI to AD. Similarly, declines in enzymes involved in oxidative phosphorylation are also identified in the MCI tissues [51]. It is more clearly shown in transgenic mouse models that defects in mitochondria such as reduced PGDH and COX expression and activity, reduced respiratory control ratio occur much earlier than the appearance of pathology or cognitive dysfunction in the 3xTg AD mice [52].

Defective mitochondria could become more efficient producers of ROS, which therefore pose significant oxidative threat to the surroundings. Indeed, oxidative stress, as evidenced by increased oxidative modifications of various cellular components and decreased antioxidant capacity, is well documented in neurons and peripheral cells in AD as well as in animal models of AD [53]. That abnormal mitochondria contribute to increased oxidative stress in AD brain is evidenced by the strong positive correlation between mitochondrial abnormalities (e.g., mtDNA deletions) and the extent of oxidative damage in the cytoplasm (e.g., 8OHG staining) [54]. Increased oxidative stress may further damage mitochondrial components such as mtDNA and critical enzymes such as PDHC and KGDHC, leading to a vicious cycle that leads to a spiral worsening of brain energy metabolism and increased oxidative stress [49]. In fact, the mtDNA is more susceptible to accumulating oxidative damage than is nuclear DNA likely due to its proximity to ROS production as evidenced by higher 8OHdG levels in human brain mtDNA than nuclear DNA during aging process. Sporadic mtDNA rearrangement (i.e., the common 5-kb deletion), which adversely affect mitochondrial replication, was significantly increased in AD patients compared with control cases [55]. Moreover, significantly higher incidence of heteroplasmic mtDNA control region mutations, which preferentially altered known mtDNA regulatory elements, was identified in AD brains [56]. Some mutations were exclusively found in AD brain samples whereas others were predominantly expressed in AD.

Abnormal mitochondrial dynamics in Alzheimer's disease

In our early studies to characterize cytological abnormalities in vulnerable neurons in AD brain, we noticed significant structural damage of mitochondria as evidenced by broken cristae or sometimes near total loss of the inner structure in AD neurons which could be the structural basis of enhanced oxidative stress and decreased mitochondrial function observed in AD. Detailed morphometric measurement of the organelles of samples obtained at biopsy demonstrates there is, in fact, a significant decrease in mitochondria of vulnerable neurons in AD. Interestingly, we also noted a slight but significant increase in mitochondrial size in vulnerable neurons in AD brains [55]. These findings implicate that the normally strict regulation of mitochondria morphology is impaired in AD. Indeed, by re-analyzing the same set of electron micrographs for lengths and width of intact mitochondria, we found that AD neurons demonstrated significantly reduced mitochondrial length but increased width with a significant increase in overall size [14]. Interestingly, this round and fatter appearance of mitochondria was also noted in the brain of Mfn2 knockout mice where mitochondria become fragmented due to unopposed fission [26]. Consistent with the notion that mitochondria dynamics is disturbed in AD neurons, significant changes in the expression of proteins involved in mitochondrial fission and fusion were reported in AD brain: we and Manczak et al. demonstrated reduced expression of all the fusion proteins (i.e., OPA1, Mfn1, and Mfn2) and increased expression of fission protein Fis1 [9, 11]. However, there is controversy over DLP1 expression: reduced DLP1 expression in AD brain was reported by Wang et al. and by Bossy et al. [9, 57], but not by Manczak et al. who actually found increased DLP1 in AD [11]. Reduced DLP1 expression is also demonstrated in fibroblasts and lymphocytes from AD patients [10, 58]. Given that the majority of DLP1 in mammalian cells is cytosolic and mitochondrial recruitment of DLP1 represents a critical step during mitochondrial fission [18], mitochondrial DLP1 serves as a better indicator for mitochondrial fission. Our study of DLP1 levels in mitochondrial fraction demonstrated increased mitochondrial DLP1 in AD brains [9]. This is likely due to increased DLP1 phosphorylated at Ser616 in AD brains since phosphorylation of this site by Cdk1 allows translocation of DLP1 to mitochondria and stimulate mitochondrial fission, although the responsible kinase is not clear. Another study suggests that S-nitrosylation of DLP1 activates GTPase activity and mitochondrial fission, and there is reported increased S-nitrosylation of DLP1 in AD brain tissues [13]. However, the effect of S-nitrosylation on DLP1 function and the role of S-nitrosylation of DLP1 in AD are challenged by Bossy et al. [57], an issue which needs to be resolved. Nonetheless, despite the controversy on overall levels of DLP1, it is clear that DLP1 is subject to post-translational modification which increases its translocation to mitochondria and likely leads to increased mitochondrial fission in AD brain, consistent with the effect of increased Fis1 or decreased OPA1 and Mfn1/2 in AD neurons. Recent evidence suggests an interaction between Aβ and DLP1, yet how such interactions may impact mitochondrial dynamics is not clear [11]. Overall, these morphometric and biochemical studies suggest that there is excessive mitochondrial fission which results in fragmented mitochondria in vulnerable neurons in AD brain. Nevertheless, it remains to be determined whether the increased structural damage is due to excessive mitochondrial fission in AD.

Excessive mitochondrial fission is more unequivocally demonstrated in *in vitro* models of AD. Primary hippocampal neurons treated with Aβ derived diffusible ligands (ADDLs) demonstrated significantly shortened mitochondria in neurites compared to those treated with control peptide [9]. The readily discernible individual mitochondrion in distal neurites makes it possible to measure the occurrence of mitochondrial fusion and fission events. Time-lapse recordings revealed that mitochondria rapidly underwent constant fission and fusion in control neurons but occurred at a much slower frequency in neurons treated with ADDLs, suggesting that both mitochondrial fission and fusion were impaired in ADDLs-treated primary neurons [9]. This is consistent with the observation that expression of both mitochondrial fission and fusion proteins were altered by ADDL treatment [9], consistent with the findings in AD brain. Nevertheless, that mitochondria spent significantly less time in the post-fusion state compared to post-fission state in the ADDLs-treated neurons suggests that mitochondrial fusion is probably more severely affected which leads to the overall fragmented mitochondrial phenotype [9]. Confocal microscopy demonstrated that M17 cells overexpressing wild-type AβPP contain fragmented punctiform structure of mitochondria compared to normal short tubular forms of mitochondria in control cells [14]. The mitochondrial fragmentation pheno-type became more severe in M17 cells expressing familial AD-causing Swedish AβPP mutation. Interestingly, electron microscopy further confirmed that mitochondria became significantly shorter and fatter, with a slight but significant increase in size, and that total mitochondrial number was decreased while the number of damaged mitochondria in AβPPwt or AβPPswe M17 cells was increased compared with control cells, very similar to the observation in AD brains [14]. Using primary neurons isolated from Tg2576 transgenic mice expressing human AβPP Swedish mutation, Calkins and colleagues also found fragmented mitochondria and an altered expression of mitochondrial fission/fusion proteins comparing to control neurons [16].

Abnormal changes in mitochondrial morphology are also noted in fibroblasts from sporadic AD patients [10]; although in contrast to what is found in AD brain, mitochondria become significantly elongated and form a highly connected network in AD fibrob-lasts which is distinctively different from age-matched normal human fibroblasts where mitochondria are predominantly sausage shaped. These morphological differences may be due to the different pattern in the expression of fission/fusion proteins since we found decreased DLP1 but unchanged OPA1 in AD fibrob-lasts. The discrepancy in mitochondrial morphology between peripheral phenotype and brain suggests that mitochondrial morphological response between neuron and peripheral cells to disease condition is different, supported by studies on Parkinson's disease which also noted difference between fibroblasts and neurons. For example, mitochondria of fibroblasts from patients carrying Parkin mutations demonstrated more branching networks [59] while Parkin-deficiency causes mitochondrial fragmentation in neuronal cells [60]. Similarly, increased mitochondrial elongation and interconnectivity were observed in fibroblasts from skin biopsy taken from Parkinson's disease patients with the G2019 S LRRK2 mutation [61], while fragmented mitochondria were found in neurons expressing G2019S mutant LRRK2 [62].

Abnormal mitochondrial distribution/transport in Alzheimer's disease

Interestingly, a consistent pattern of redistribution of mitochondrial fission/fusion protein and other mitochondrial membrane protein (i.e., COX I) and mtDNA from even distribution among soma and neu-rites in hippocampal neurons in the control brain to only soma in hippocampal neurons in the AD brain [9] is noted, suggesting an altered mitochondrial distribution such that mitochondrial become accumulated in the soma and are reduced in neuronal processes in AD pyramidal neurons. In fact, abnormal mitochondrial distribution in a similar pattern is also noted in AD cell models. Perinuclear accumulation of mitochondria was noted in AD fibroblasts and in M17 cells overexpressing mutant AβPP [10, 14]. Primary hippocampal neurons expressing mutant AβPP or exposed to ADDLs also demonstrated reduced mitochondrial density in neurites [9]. Recent studies in Aβ-overexpressing *Drosophila* indicated that the depletion of presynaptic mitochondria was the earliest detected phenotype [63]. Since fast axonal transport (FAT) of mitochondria underlies the uniform distribution of mitochondria along the axon [64], these findings suggest that an abnormal mitochondrial transport is likely involved.

Deficits in axonal transport may represent an early step in AD pathogenesis since axonal swelling and reduced axonal transport were observed before apparent AD hallmarks. A recent study demonstrating an overall disruption of FAT induced by soluble Aβ oligomers in isolated squid axoplasms [65]. Pigino and collaborators demonstrated that familial AD-associated presenilin 1 mutants impaired kinesin-based axonal anterograde transport including the transport of mitochondria both *in vitro* and in mouse models, likely by activating glycogen synthase kinase 3β, which leads to increased phosphorylation of kinesin light chains that reduce amount of kinesin-I bound to membrane-bound organelles [66, 67]. Earlier studies demonstrated that acute treatment of Aβ monomers and fibrils induces significant reduction in motile mitochondria [68]. We demonstrated that ADDL treatment of hippocampal neurons leads to impaired axonal transport of mitochondria in both anterograde and retrograde directions [69]. Aβ over-expression in *Drosophila* decreased mitochondrial velocity in both directions, which is associated with axonal depletion of mitochondria [63]. Du et al. found that low level of Aβ significantly impaired anterograde but enhanced retrograde axonal transport of mitochondria [70]. Calkin and coworkers demonstrated a specific impairment in anterograde transport of mitochondria without changes in the retrograde direction in primary neurons from Tg2576 AβPP transgenic mice [16]. While it remains to be resolved whether and how retrograde axonal transport of mitochondria is altered, it is generally agreed that it is the disturbed axonal transport of mitochondria that likely results in reduced mitochondrial density in neurites.

Interestingly, it was noted that abnormal changes in the expression of mitochondrial fission/fusion proteins observed in AD brain could lead to changes in mitochondrial distribution [9]. For example, decreased DLP1, OPA1, or Mfn1/2 or increased Fis1, as it occurs in AD brain, leads to perinuclear accumulation of mitochondrial in multiple cell types and also leads to decreased neuritic mitochondrial density in primary hippocampal neurons. This is unlikely due to the mitochondrial size effect since they cause differential effects on mitochondrial sizes and cell body may not pose much spatial restriction as small calibers of neurites. It perhaps suggests that mitochondrial fission/fusion and mitochondrial transport may be

mechanistically coupled. Such a notion is supported by the finding that Mfn2 interacts with Miro and Milton, two adaptor proteins involved in the regulation of mitochondrial transport [46]. However, how such interaction is coordinated with the fusion activity of Mfn2 is not clear. It is also not clear whether other fission/fusion proteins affect mitochondrial transport through Mfn2.

Potential consequences of abnormal mitochondrial dynamics in Alzheimer's disease

Structural damage and compromised bioenergetics—As noted earlier, larger diameter and round mitochondria with abnormal cristae structure as evidenced by abundant vesiculation of the inner membrane were present in neurons in Mfn2 null mice [26]. Similarly, loss of ChChd3, which also leads to excessive fission, caused mitochondria with lower crista density and more tubular crista and even mitochondria devoid or nearly devoid of cristae [30]. These studies likely suggest that excessive mitochondrial fission could lead to structural damage to mitochondria, although the possibility that these proteins may directly be involved in cristae remodeling could not be totally ruled out. Fat, round mitochondria with sometimes total loss of inner structure are common features in neurons from AD biopsied brain and in M17 cells expressing Swedish AβPP mutant where excessive mitochondrial fission occurs [14]. Therefore, it is reasonable to infer that excessive mitochondrial fission underlies the structural damage of mitochondria in AD brain and AD models. Because of the critical dependence on ion gradients between the inner membrane, mitochondrial function heavily relies on intact mitochondrial structure. Indeed, the combination of large-diameter mitochondria and abnormal cristae structure is often associated with compromised bioenergetics [71]. In addition, more recent study suggests that mitochondrial fission plays a critical role in the assembly of electron transport complex which has a more direct effect on mitochondrial bioenergetics [33]. In fact, in AD cell model, we demonstrated that, despite the net outcome of mitochondrial fragmentation, both mitochondrial fission and fusion are impaired [9], suggesting that disturbed mitochondrial fission/fusion likely contributes to decreased ETC activity in AD neurons. It remains to be determined whether mitochondrial fission/fusion also affects enzyme complexes involved in TCA cycle. Therefore, abnormal mitochondrial dynamics in AD could cause deficits in mitochondrial bioenergetics as observed in AD by both impairing the integrity of mitochondrial structure, and by directly impacting ETC assembly.

Calcium dyshomeostasis—Abnormal mitochondrial dynamics could contribute to calcium dyshomeostasis, a prominent feature observed in AD neurons, in several ways: the depletion of mitochondrial in remote sites deprives local calcium buffering capacity [9], a fragmented mitochondrial network and increased structural damage to mitochondria make them much less efficient in buffering calcium [37].

Oxidative stress—Neurons exposed to high concentrations of glucose demonstrated fragmented mitochondria along with a burst in ROS production [72]. Nitric oxide also induced mitochondrial fragmentation accompanied by ultra-structural mitochondrial damage and ROS production [15]. These studies suggest that excessive mitochondrial fission and/or ensuing mitochondrial structural damage correlates with increased oxidative stress. It is known that AβPP overexpression and ADDL treatment caused increased oxidative stress.

Recent studies demonstrated mitochondrial fragmentation and structural damage in these cells [9, 14]. More importantly, OPA1 expression restored the mitochondrial morphology and also reduced ROS production, which suggest that abnormal mitochondrial dynamics contributes to Aβ-induced oxidative stress [9].

mtDNA integrity—The mtDNA genome encodes 13 proteins essential for oxidative phosphorylation. Defects in mtDNA such as large deletions and increased mutations were found in AD brains which likely also contributes to mitochondrial dysfunction in AD. Recent study demonstrated that conditional deletion of Mfn1/2 causes severe mtDNA depletion and rapid accumulation of point mutations and deletions. Furthermore, disruption of mitochondrial fusion increases mitochondrial dysfunction in the presence of high levels of mtDNA mutations [73]. These suggest that mitochondrial fusion plays an important role in safeguarding mtDNA integrity and preserving mtDNA function in the presence of mutations. Therefore, an impaired mitochondrial fusion in AD neurons as evidenced by slower fusion rate and decreased expression of fusion proteins [9], which not only impairs the efficient exchange of critical components between neighboring mitochondria, but also prevents effective removal of damaged mitochondrial or components, likely underlies the deficits in mtDNA integrity observed in AD brain and AD models.

Synaptic dysfunction—Early changes in the AD brain include loss of synapses. Studies with biopsied AD cortex revealed a 25–35% decrease in the numerical density of synapses and a 15–35% decrease in the number of synapses per cortical neuron [74]. Synaptophysin immunoreactivity is also decreased ~25% in the cortex of patients with MCI or very mild AD [75]. In fact, among all the early changes, synaptic loss is the most robust correlate of AD-associated cognitive deficits [76–78]. Therefore, it is suggested that synaptic dysfunction plays a critical role in the pathogenesis of AD [79]. Importantly, synaptic terminals have abundant mitochondria and the paucity of mitochondria leads to synaptic dys-function in both dendrites and axons likely through negative impact on energy supply and calcium buffering [80, 81], suggesting their indispensable role at these sites. Aβ adversely affects long-term potentiation and synaptic transmission and ADDLs directly bind to dendritic spines [82] and induce abnormalities in spine composition, shape, and abundance [83]. Recent results suggested that these ADDLs-induced reduction in the number of spine and PSD-95 positive puncta correlates with reduced mitochondrial coverage in neurites [9]. Indeed, it has been repeatedly shown that mitochondria redistribute from an evenly distributed pattern to a depletion of mitochondria in remote sites and accumulate perinuclearly in various AD cell models. Importantly, correction of deficits in mitochondrial distribution by overexpressing DLP1 rescued ADDLs-induced reduction in the number of spine and PSD-95 positive puncta [9]. These findings suggest that abnormal mitochondrial dynamics mediates Aβ-induced synaptic dysfunction. Given the abnormal mitochondrial distribution in vulnerable neurons in AD brain and the changes in mitochondrial fission/fusion proteins leading to mitochondrial depletion in neurites, it is very likely that mitochondrial dynamics also plays a critical role in synaptic dysfunction *in vivo*.

CONCLUSION

Decades of studies from multiple groups demonstrated that mitochondrial dysfunction likely plays a critical role in the pathogenesis of AD. More recent advance in the field suggests that the usually tightly regulated balance of mitochondrial fission and fusion was tipped toward excessive fission in AD. Such a fundamental shift in mitochondrial dynamics negatively impacts all aspect of mitochondrial function such as impaired bioenergetics, increased structural damage, ROS production, and loss of mtDNA integrity, which causes synaptic dysfunction and neuronal dys-function that is critical to AD pathogenesis. Therefore, strategies to modify abnormal mitochondrial dynamics may be an attractive therapeutic intervention target for AD.

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