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Review Article

Alzheimer's disease: diverse aspects of mitochondrial malfunctioning

Renato X. Santos[1,2,3], Sónia C. Correia[1,2,3], Xinglong Wang[3], George Perry[3,4], Mark A. Smith[3], Paula I. Moreira[1,5], Xiongwei Zhu[3]

[1]Center for Neuroscience and Cell Biology of Coimbra, University of Coimbra, Coimbra, Portugal; [2]Faculty of Sciences and Technology, Department of Life Sciences, University of Coimbra, Coimbra, Portugal; [3]Department of Pathology, Case Western Reserve University, Cleveland, Ohio, USA; [4]UTSA Neurosciences Institute and Department of Biology, University of Texas at San Antonio, San Antonio, Texas, USA; [5]Faculty of Medicine, Institute of Physiology, University of Coimbra, Coimbra, Portugal.

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Abstract: Alzheimer's disease is a progressive neurodegenerative disorder, either assuming a sporadic, age-associated, late-onset form, or a familial form, with early onset, in a smaller fraction of the cases. Whereas in the familial cases several mutations have been identified in genes encoding proteins related with the pathogenesis of the disease, for the sporadic form several causes have been proposed and are currently under debate. Mitochondrial dysfunction has surfaced as one of the most discussed hypotheses acting as a trigger for the pathogenesis of Alzheimer's disease. Mitochondria assume central functions in the cell, including ATP production, calcium homeostasis, reactive oxygen species generation, and apoptotic signaling. Although their role as the cause of the disease may be controversial, there is no doubt that mitochondrial dysfunction, abnormal mitochondrial dynamics and degradation by mitophagy occur during the disease process, contributing to its onset and progression.

Keywords: Alzheimer's disease, mitochondria, mitochondrial dysfunction, mitochondrial dynamics

Introduction

Alois Alzheimer published for the first time an article in 1898 describing patients with signs of senile dementia. However, only several years later, in 1901, the young physician encountered his most striking case of dementia, a woman just over 50 years, representing a much earlier event than his first described cases. This hallmark patient in the story of Alzheimer's disease (AD) suffered from deteriorating memory, even of recent events, disorientation, decreasing speech abilities, and lack of judgment of the different surrounding situations. Indeed, these are some of the described clinical symptoms currently attributed to AD. In 1907 and 1911, Alzheimer published two case reports describing the clinical and histological hallmarks that characterized his demented patient [1, 2]. Ever since then, the efforts of the scientific community to gain insight into the molecular mechanisms of this disease are countless. Nevertheless, according to an Alzheimer's Association recent report [3], AD is still the seventh leading cause of death in the United States (fifth place among individuals aged 65 and older), causing an elevated financial burden in health care.

The main histopathological features of AD are massive neuronal loss, the deposition of senile plaques, which are extracellular aberrant amyloid-β (Aβ) protein aggregates, and neurofibrillary tangles composed of intracellular hyperphosphorylated tau protein [4]. AD has either an age-associated, late onset sporadic form, or an early-onset familial form with a genetic origin involving mutations in the amyloid-β protein precursor (AβPP) and presenilin 1 and 2 (PS1 and PS2) genes [4]. Despite this knowledge, the etiogenesis of sporadic AD remains largely unclear and several competing hypotheses have been proposed. Whereas the hypothesis that still drives the investigation of most authors is the amyloid cascade hypothesis with an added twist of new evidence suggesting that oligomeric Aβ, rather than the extracellular fibrillary accumulations of Aβ, may be the most toxic entity and culprit of the disease [5, 6], some authors implicate the cerebrovascular damage as a potential cause of AD [7, 8]. Others center their efforts on hyperphosphorylation of cytoskeletal proteins [9, 10], oxidative stress [11], abnormal cell cycle re-entry [12, 13], and inflammation [14].

Mitochondria are involved in vital cellular functions that are critical for life and death and it is crucial to maintain a healthy mitochondrial population within the cells which becomes increasingly challenging when long-lived cells such as neurons and the organism as a whole ages. Mitochondrial dysfunction is one of the earliest and most prominent features of AD and recent developments in the field support an involvement of mitochondrial-dependent mechanisms in the pathogenesis of AD [15, 16]. Indeed, mitochondria have been implicated in AD pathogenesis on a multitude of levels: 1) as triggers of disease [15-19]; 2) as mediators and targets of the harmful effects of Aβ [6], causing mitochondrial dysfunction and increased reactive oxygen species (ROS) production; 3) as potential sites of Aβ production, since AβPP was found in mitochondrial membrane [20] as well as an active γ-secretase enzymatic complex [21]. In this review the physiological mitochondrial function, the importance of organelle dynamics and mitophagy will be the focus, as well as the mitochondrial pathophysiological alterations that occur in AD.

Mitochondria: back to the basics

Mitochondria account for more than 90% of the cellular energetic production [22]. This bioenergetic production assumes its maximum importance in the brain since neurons have a limited glycolytic capacity, making them highly dependent on aerobic oxidative phosphorylation (oxphos); furthermore, neuronal function is extremely energy demanding [23].

Mitochondria generate energetic potential as electrons flow through the mitochondrial respiratory complexes I to IV, that constitute the electron transport chain (ETC), from donors with lower redox potentials to acceptors with higher redox potentials. The final acceptor of electrons is molecular oxygen that is reduced to water. During the flux of electrons across the mitochondrial respiratory chain, the respiratory complexes I, III, and IV pump protons across the inner mitochondrial membrane to the intermembrane space, generating potential energy that drives the phosphorylation of ADP to ATP by the FoF1-ATP synthase or mitochondrial complex V, “coupling” the oxidation with the phosphorylation processes [24, 25]. The potential energy generated by the ETC can also be dissipated as protons leak back to the mitochondrial matrix, producing heat [26]. The transport of the electrons through the mitochondrial respiratory complexes is a highly efficient process, however, during normal oxphos, 0.4-4.0% of all oxygen consumed is still converted to superoxide anion (O_2^-) in mitochondria by electron leak mostly in complexes I and III [27-30]. At low/ moderate levels, ROS act as second messengers within cells; however, exacerbated ROS production is deleterious for the cell, contributing to a variety of pathological processes [31, 32]. The level of ROS production is modulated by mitochondrial energetic state and is favored by high membrane potential values ($\Delta\Psi_m$) [33]. ROS production is also largely increased in cases of respiratory chain inhibition, as observed in mitochondrial disease, or in experimental and animal models of oxphos deficiencies [34]. The central nervous system (CNS) is especially prone to ROS-induced damage because of its greater oxygen availability and consumption, high levels of membrane polyunsaturated fatty acids susceptible to oxidative damage, its deficiency in antioxidant defenses, and high content of redox metals [35].

Mitochondria are intracellular “buffers” of cytosolic Ca^{2+}, internalizing it mainly via uniporter and releasing it by Na^+/Ca^{2+} or H^+/Ca^{2+} exchangers [36]. Abnormal cytosolic Ca^{2+} elevations trigger a rapid accumulation of the cation by mitochondria, which is particularly important in CNS given the role of Ca^{2+} in normal neurotransmission, short- and long-term plasticity and regulation of gene transcription [36-42]. Additionally, a deregulation in Ca^{2+} homeostasis can potentiate excitotoxicity, a phenomenon intimately associated with neurodegeneration [36, 43]. Decreased age-related Ca^{2+} buffering capacity has been shown in CNS, mitochondria being involved in this deregulated homeostasis [44].

A molecular link between increased ROS production, the deregulation of mitochondrial Ca^{2+} homeostasis and apoptosis induction is the opening of permeability transition pore (PTP), that enables the release of some small pro-apoptotic proteins, such as cytochrome c and apoptosis-inducing factor (AIF) to the cytosol, triggering the activation of the caspase cascade [45, 46]. The PTP is a voltage-dependent, high-conductance, non-selective pore that permeabilizes mitochondrial membranes to solutes/ molecules of less than 1.5 KDa in molecular weight [47]. The exact nature of the PTP is unknown, however, currently, it is believed that it is a multiprotein complex constituted by the adenine nucleotide translocator (ANT), located in the inner mitochondrial membrane, and the voltage-dependent anion channel (VDAC, porin), located in the outer mitochondrial membrane, both constituting the pore. Several other regulatory protein components are part of the pore: a peripheral benzodiazepine receptor (PBR), which provides ligand regulation of the pore; cyclophilin D (CypD), which senses matrix Ca^{2+} concentration and oxidative status; mitochondrial creatine phosphokinase that monitors intermembrane high energetic status; hexokinase (HK); Bax/Bcl2 protein family that modulate pore activation through direct interactions with ANT or VDAC [48].

Mitochondrial dynamics and mitophagy

Mitochondria have long been considered dynamic organelles because they migrate within the cells and are rapidly turned over by mitophagy. Studies in the past decade added one more fascinating feature to the concept of mitochondrial dynamics: rather than being depicted as isolated, bean-shaped structures, these organelles actually continuously divide and fuse with each other and can rapidly change in number and morphology within a cell. Mitochondrial dynamics enables their prompt adaptation to changes in cellular demands either due to physiological or environmental alterations [49]. The machinery of mitochondrial fission/fusion is governed by a group of GTPases, however, the mechanisms by which they rule those processes remain to be completely elucidated. In mammals, mitochondrial fission is directed by a large cytosolic GTPase that is recruited to the mitochondrial membrane upon a fission-like stimuli, dynamin-like protein 1 (DLP1 or DRP1), and a small mitochondrial molecule located in the outer membrane, Fis1 [50-52]. Mitochondrial fusion in mammals is directed by three large GTPases, Mitofusin 1 (Mfn1) and Mitofusin 2 (Mfn2), both located in the mitochondrial outer membrane, and optic atrophy 1 (OPA1) protein, located in the inner mitochondrial membrane [53-56]. Noticeably, OPA1 has also been implicated in mitochondrial cristae structure and release of cytochrome c from OPA1-dependent subcompartments of the cristae upon an apoptotic stimulus [57].

Mitochondrial dynamics is critical for maintaining various mitochondrial functions: fusion deficient cells demonstrate greatly reduced endogenous and uncoupled respiratory rates and demonstrate reversible interorganellar heterogeneity in membrane potential and inhibition of cell growth [54, 58]. Fission deficiency also causes a reduced rate of mitochondrial ATP synthesis due to a significant decrease in complex-IV activity and an inefficient oxphos system [59]. A fragmented mitochondrial network is less efficient in mitochondrial Ca^{2+} uptake and intramitochondrial Ca^{2+} diffusion, and the formation of a mitochondrial network facilitates Ca^{2+} propagation within interconnected mitochondria, suggesting that the balance of mitochondrial fission/fusion can significantly impact cellular Ca^{2+} ion homeostasis [60, 61]. Mitochondrial dynamics are also involved in apoptosis with mitochondrial fragmentation being an early event during apoptosis that precedes cytochrome c release and caspase activation [62]. Excessive mitochondrial fission is also correlated with increased ROS production [52, 63, 64].

The ability of mitochondria to move within the cells assumes its maximal importance in highly polarized cells, such as neurons, which have high energetic demands and several subcellular compartments with specialized functions [65, 66]. Defects in both fusion and fission have been shown to alter mitochondrial distribution, which is suggestive of altered mitochondrial movement [49, 52]. It is likely a size effect may play a role because neurons lacking mitochondrial fusion, also demonstrate an increased mitochondrial diameter that block efficient entry in neurites, which results in a scarcity of mitochondria in axons and dendrites leading to improperly developed neurons or neurodegeneration [67]. Similarly, reduced Drp1 expression induces a decrease in mitochondrial number in neurites, which is attributed to mitochondrial elongation, since large mitochondria accumulate in the base of dendritic protrusions ultimately leading to a loss of synapses and dendritic spines [68]. Accordingly, lack of mitochondrial transport results in neurotransmission defects during prolonged stimulation [69]. Recent studies demonstrated specific interactions between Mfn2 and Miro and Milton, members of the molecular complex that links mitochondria to kinesin motors, implicating mechanisms unrelated to fission/fusion may also be involved [70].

The process of mitophagy has been shown to be related to mitochondrial fission/fusion processes in mammalian cells, so that when depolarized (injured) mitochondria fail to undergo fusion and fission events, they are targeted for mitophagic clearance [71]. The mechanisms that tag mitochondria to mitochondrial elimination are not clear (for further readings, see [72]). Nevertheless it is quite accepted that fission events exert a protective effect against mitochondrial dysfunction through the segregation of damaged components into a mitochondrion that undergoes mitophagy. Indeed, inhibition of autophagy results in decrease $\Delta\Psi_m$ and fusion arrestment in rat myoblasts and human fibroblasts [73].

Mitochondrial dysfunction(s) in AD

It has been reported that mitochondrial abnormalities correlate with dystrophic neurites, the loss of dendritic branches and the pathological alteration of the dendritic spines present in the brains of AD cases [74]. Swerdlow and Khan [15, 16] proposed the mitochondrial cascade hypothesis to explain late-onset, sporadic AD, stating that Aβ deposition, neurofibrillary tangle formation and neurodegeneration are consequent events of mitochondria malfunctioning. This hypothesis emphasizes aging as the main risk factor for the development of the sporadic form of AD, the accumulation of Aβ being a consequence of aging [75] rather than the cause of the evolution of the neuropathology as is widely reported in the case of familial AD.

Multiple lines of studies suggest that reduced glucose metabolism is one of the best documented abnormalities in AD patients and its occurrence precedes clinical diagnosis. In longitudinal studies, the decline in mini-mental state examination (MMSE) scores in AD correlated with reduction in glucose metabolism as measured by positron emission tomography (PET) in the association areas (i.e., temporoparietal, frontal, and occipital cortices) which suggests that the clinical deterioration and metabolic impairment in AD are closely related. The analysis of the expression of 80 metabolically relevant nuclear ETC genes from laser-capture microdissected non-tangle-bearing neurons from autopsy brains of AD cases revealed that 60-70% of nuclear genes were significantly lower in those metabolically affected areas such as posterior cingulate cortex, middle temporal gyrus, and hippocampal CA1 but not in relatively spared visual cortex, suggesting that the cerebral abnormalities in metabolic rate for glucose found in fluorodeoxyglucose-positron emission tomography (FDG-PET) studies of AD may be associated with reduced neuronal expression of nuclear genes encoding subunits of the mitochondrial ETC [76]. Multiple studies suggest alterations in the activity of mitochondrial enzymes involved in tricarboxylic acid (TCA) cycle and ETC chains (**Figure 1**) [77, 78]. Bubber and colleagues [79] systematically examined pyruvate dehydrogenase complex (PDHC) and all the enzymes of the TCA cycle and found that there was reduced activity of decarboxylating dehydrogenases, yet a compensatory increase in dehydrogenases, alterations of which all significantly correlated with clinical state. Indeed, mitochondrial bioenergetic deficits are an early event that precedes AD pathology in animal models of AD [19, 80].

One question remains: what causes mitochondrial malfunction in sporadic AD? Based on the instability and irreparability of the mitochondrial genome due to the absence of histones and enzymatic repair systems [4, 81], it is possible that during aging, the accumulation of oxidative stress-induced mitochondrial DNA (mtDNA) damage and subsequent mitochondrial dysfunction may serve as a trigger of the appearance of the main AD histopathologic markers (**Figure 1**). In this regard, it is of interest to note that there was increased oxidation in both mtDNA and nuclear DNA bases in frontal, parietal, and especially, in temporal lobes of AD cases compared to age-matched controls, and that mtDNA oxidation was approximately 10-fold higher than nuclear DNA oxidation [82]. Some mtDNA mutations have been associated with increased incidence of AD [83, 84], in addition to brains having increased, unique mtDNA mutations com-

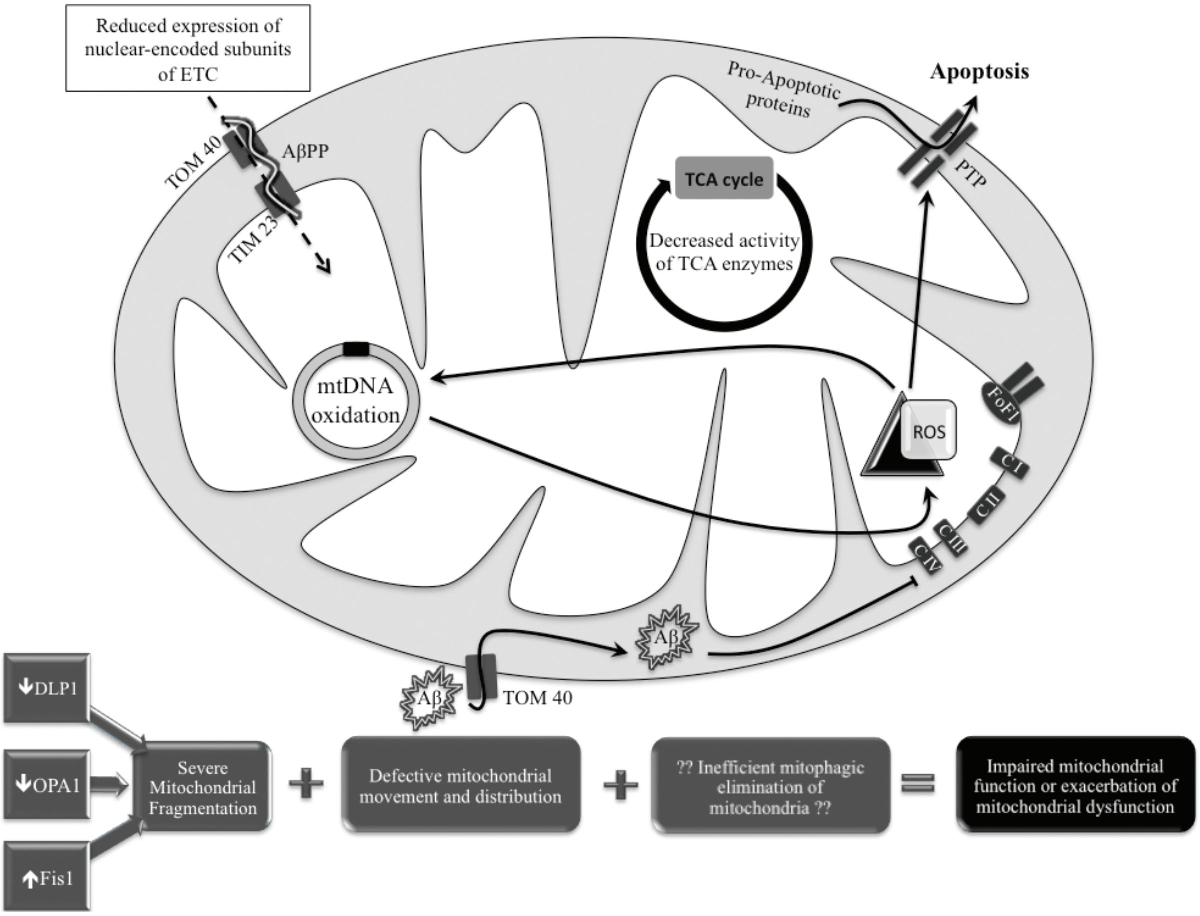

Figure 1. Mitochondrial abnormalities in Alzheimer's disease (AD). Mitochondrial respiratory chain is a major cellular producer of reactive oxygen species (ROS) that cause oxidative damage to several mitochondrial constituents, including mitochondrial DNA (mtDNA). mtDNA is prone to damage accumulation with aging due to the inexistence of protection/repairing systems. Since some complex subunits of the mitochondrial respiratory chain are mtDNA-encoded, age-associated mutations can occur that, in turn, decrease the electron transport chain (ETC) efficiency, further increasing ROS production. Accounting for an inefficient ETC, it has also been described a reduction in the expression of nuclear-encoded subunits of the respiratory complexes and that their translocation to mitochondria can be impaired due to the blockage of the translocase of the outer membrane 40 (TOM 40) and of the translocase of the inner membrane 23 (TIM23) by amyloid β precursor protein (AβPP). Aβ is present in the mitochondria and can have an inhibitory effect on mitochondrial complex IV (C IV). Recent evidence suggests that Aβ can be translocated into mitochondria by TOM 40. Ultimately, all these ROS production-enhancing events have positive regulatory effects in the opening of the permeability transition pore (PTP), increasing apoptotic cell death. In addition to the disturbances in the metabolic function of mitochondria caused by a defective function of ETC, also some enzymes of tricarboxylic acid (TCA) cycle were shown to have decreased activity. Mitochondrial dynamics and turnover are recognized to be functionally coupled with the mitochondrial function and between them. Indeed, an imbalance in expression and post-translational modification of mitochondrial dynamics-associated proteins has been described. This in association with defective mitochondrial movement and distribution, as well as an hypothetical, inefficient mitophagic process are also associated with the mitochondrial pathogenesis of AD. C I, C II, C III, C IV, mitochondrial electron transport chain complexes I, II, III, and IV respectively; FOF1, ATP synthase; optic atrophy 1, OPA1; dynamin-like protein 1, DLP1.

pared to control cases, this being further enhanced in an age-dependent fashion and preferentially in mtDNA regulatory elements, such as the control region [84]. Importantly those mutations in the control region of mtDNA could account for some of the mitochondrial defects in oxphos observed in AD, namely a reduction in the level of ND6 complex I transcript [84]. The impaired oxphos result in an exacerbation of ROS generation, promoting the augment of the number of mtDNA mutations in a vicious positive feedback cycle (**Figure 1**) [85, 86].

Increased Aβ can also be involved in mitochondrial dysfunction either directly or indirectly. In this regard, it is known that Aβ is present in mitochondria. The presence of a functional γ-secretase complex [21] and AβPP in mitochondria [20] suggest that mitochondria can be themselves sites of Aβ production, although the mitochondrial presence of a functional BACE1 is still lacking. Perhaps a more likely scenario is Aβ translocation into mitochondria by the translocase of the outer membrane (TOM) complex [87] or interaction with RAGE (**Figure 1**) [88]. Once inside mitochondria, Aβ has the ability to complex heme groups, which constitute critical redox centers of the subunit I of cytochrome oxidase (COX) (**Figure 1**) [89, 90], and interacts with Aβ-binding alcohol dehydrogenase (ABAD) increasing ROS generation (via impairment of COX activity) and cytochrome c release (activating caspase 3) and decreasing ATP [91-94]. Recently it has been demonstrated that Aβ and tau exert synergistic effects in the impairment of oxidative phosphorylation system in 3xTg-AD mice [95]. Mitochondrial-associated AβPP may also exert adverse effects on mitochondrial function as it appears to block the mitochondrial import channels TOM40 and TIM23 and disables the import of the nuclear-encoded COX subunits to reach the mitochondrial interior (**Figure 1**) [96].

Indeed, dysfunction of mitochondrial energy metabolism also culminates in Ca^{2+} buffering impairment [97]. Moreira and coworkers [98-100] demonstrated that Aβ decreases the capacity of mitochondria to accumulate and retain Ca^{2+} promoting the PTP opening. A molecular basis to explain this phenomenon was provided by Du and coworkers [101], in which Aβ interacts with CypD, a critical molecule involved in PTP opening modulation and cell death. Consistently, CypD deficiency protects neurons from Aβ-induced PTP formation and the resultant mitochondrial/cellular stresses, while improving learning, memory and synaptic function in an AD mouse model, as well as improving Aβ-mediated reduction of long-term potentiation (LTP) [101]. This increased predisposition to PTP opening creates more chances for cell death, as discussed in the previous section (**Figure 1**). Furthermore, a recent study showed evidence of AβPP interaction with heat shock proteins (HSPs) and Bcl-2 (an anti-apoptotic protein), decreasing their ability to protect against insults [102].

Abnormal Mitochondrial Dynamics in AD

Mitochondrial dynamics can be affected by changes in bioenergetic status in response to physiological or environmental alterations and impact all aspects of mitochondrial functions. AD brains show ultrastructural alterations in mitochondrial morphology such as reduced number, increased size and broken internal membrane cristae [103, 104]. We determined the state of mitochondrial fission/fusion events in fibroblasts from sporadic AD patients [56, 105] and M17 neuroblastoma cells overexpressing the Swedish variant of AβPP (AβPPswe) [64]. The Aβ–induced impairment in mitochondrial fission/fusion proteins occurs both by post-translational modification, such as S-nitrosylation [106] and phosphorylation [52], and by alteration of their expression [56, 64, 105]. While it is reported that in fibroblasts from sporadic AD patients DLP1 protein levels are decreased, thus impairing fission, which is translated into the development of elongated mitochondria (**Figure 1**) [56, 105], at the same time it is described in M17 neuroblastoma cells overexpressing AβPPswe that besides decreased levels of DLP1, OPA1 protein levels are decreased and Fis1 levels increased (**Figure 1**) [64]. Indeed, AβPP overexpression or ADDL treatment induces reduced fission and fusion with a net outcome of severe mitochondrial fragmentation phenotype in both M17 and primary hippocampal neurons [52, 64]. The discrepancy of mitochondrial morphology between fibroblasts from patients and neuronal cultures subject to disease-specific insults is also seen in Parkinson-related models [107, 108] which may reflect the fact that fibroblasts are less suseceptible than neurons in these disease conditions. Interestingly, AβPP-induced mitochondrial fragmentation underlies AβPP-induced deficits in mitochondrial function since overexpression of OPA1, which blocks fragmentation, could restore mitochondrial function, suggesting the fission-related structural basis for AβPP-induced functional changes.

One of the common features in all these models demonstrating abnormal mitochondrial dynamics is an abnormal mitochondrial distribution, i.e., perinuclear accumulation of mitochondria in AD fibroblasts or M17 cells overexpressing mutant AβPP or reduced mitochondrial density in neurites of primary hippocampal neurons (**Figure 1**). Indeed, our recent work also revealed that mitochondria accumulate in the soma and are reduced in neuronal processes in AD pyramidal neurons [52]. To explore the functional consequence of mitochondrial redistribution, we were able to demonstrate that overexpression of AβPP [64] or exposure to soluble Aβ oligomers [52] led to reduced neuritic mitochondrial density which correlated with reduced spine number and PSD95-positive puncta. More importantly, repopulation of neurites with mitochondria by overexpressing DLP1 in these cell models alleviates synaptic deficits, thus suggesting that abnormal mitochondrial localization is probably the most important contributing factor of synaptic dysfunction in the pathogenesis of AD. Such a notion is supported by the in vivo finding that in a fly model overexpressing Aβ, which demonstrates intracellular accumulation of Aβ in the soma and axon of a small group of neurons, the depletion of presynaptic and axonal mitochondria was the earliest detectable phenotype, preceding Aβ-induced presynaptic deficits in motor function [109]. Aβ-induced mitochondrial mislocalization is also confirmed in another Aβ-overexpressing fly model [110]. The depletion of mitochondria from axon or dendrite may impact synaptic function either directly through a lack of energy and calcium buffering support or indirectly through the removal of AMPA receptor [111].

Since fast axonal transport of mitochondria underlies the uniform distribution of mitochondria along the axon [65], these findings suggest that an abnormal mitochondrial transport may be involved (**Figure 1**). Deficits in axonal transport is implicated in AD pathogenesis since axonal swelling and reduced axonal transport were observed before apparent AD hallmarks [112]. Earlier studies demonstrated presenilin 1 mutant causes deficits in kinesin-mediated axonal transport including the transport of mitochondria through abnormal activation of GSK3β and phosphorylation of kinesin [113]. Acute treatment of Aβ monomers and fibrils induce a significant reduction in motile mitochondria [114]. We recently reported that soluble oligomers of Aβ are responsible for an abnormal axonal transport of mitochondria in primary hippocampal neurons, most likely contributing to an abnormal mitochondrial distribution [115]. Such a notion was supported by *in vivo* studies in one fly model [110] but not in the other similar fly model in which deficits in axonal transport occurs later than the presynaptic depletion of mitochondria [109]. Therefore, more studies, especially those in mammalian systems, are still needed.

Mitophagy in AD

Evidence showing mitophagy in AD is scarce; Moreira and coworkers [77, 116] showed that there is increased mitochondrial sequestration in autophagosomes in AD. Whether these mitochondria are degraded upon their autophagosomal sequestration or remain sequestered and accumulated within autophagosomal vesicles remains to be clarified. To date some findings gave some clues about this issue. Hirai and coworkers [103] demonstrated decreased mitochondria in vulnerable neurons in AD, this observation being region-specific in brain tissue. Furthermore, the same authors also demonstrate increased cytosolic accumulation of mitochondrial markers such as mtDNA and subunit I of COX [103], which is inconsistent with an efficient autophagic-lysosomal proteolytic degradation, even suggesting a leak of sequestered material from AVs. Supporting this hypothesis, it has been reported that Aβ induces lysosomal membrane permeabilization [117, 118], very recently being reported that multiple-oligomeric aggregates of $A\beta_{42}$, but not $A\beta_{40}$, insert into lysosomal membrane in a pH-dependent manner, contributing to its instability [119]. Accordingly it was also demonstrated that the overexpression of $A\beta_{42}$ in Drosophila neurons induced an age-dependent impairment of neuronal autophagy due to a leakage of postlysosomal autophagic vesicles (autolysosome), which caused a cytosolic acidification and damage of several cellular constituents [120]. Taken together these data suggest that an inefficient lysosomal system may be compromising the elimination of damaged mitochondria by mitophagy in AD (**Figure 1**). Moreover also the machinery involved in the induction of autophagy has been shown to be compromised in AD, since Beclin 1 deficiency was shown to be a feature of the brains of AD patients, a causal role being demonstrated in the exacerbation of the pathological markers of disease [121]. Another line of evidence that corroborates an impairment in efficient mitophagic elimination, comes from the impairment of mitochondrial fission/fusion events in AD. Since there are indications that mitochondrial fission and selective fusion tag damaged mitochondria for mitophagic elimination [71], and that mitochondrial fission/fusion events in fibroblasts from sporadic AD patients [56, 105] and M17 neuroblastoma cells overexpressing the Swedish variant of AβPP (AβPPswe) [64] is imbalanced, it is expected that mitophagic elimination of damaged mitochondria in AD brains is failing. Nevertheless, further clarification about the efficiency of the mitophagic turnover in AD brains is still needed.

Conclusion

Although AD etiogenesis is largely unknown, it is constantly growing in intricacy. Aβ and tau pathology are the most studied histopathological markers and considered by many authors as the cause of disease, particularly of genetic origin. Aβ and tau are unlikely causes of the sporadic, late onset form of AD, with mitochondria instead assuming a central stage, since these organelles are known to lose efficiency and progressively become dysfunctional with age, which is correlated with increased ROS production. Mitochondrial function has been shown to be impaired in AD in terms of metabolic energetic production and regulation of the levels of second messengers (ROS, Ca^{2+}), partially due to either accumulated damage to mtDNA or the direct harmful effects of oxidative stress or Aβ on mitochondrial components. Also mitochondrial dynamics has been documented to be altered in AD. Indeed, mitochondrial trafficking disruption in AD potentially compromises normal neurophysiological functions, such as neurotransmission. Moreover, mitochondrial fission/fusion and mitophagy disruption may have consequences on the maintenance of the homogeneity and a healthy cellular mitochondrial pool. In short, mitochondrial malfunctioning is one most likely major cause of onset and neurodegeneration in sporadic AD brains.

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Please address correspondence to: Xiongwei Zhu, PhD, Department of Pathology, Case Western Reserve University, 2103 Cornell Road, Cleveland, Ohio 44106, USA; Tel: 216-368-5903, Fax: 216-368-8964, E-mail: xiongwei.zhu@case.edu

References

[1] Dahm R. Alzheimer's discovery. Curr Biol 2006; 16: R906-910.
[2] Dahm R. Finding Alzheimer's disease. Am Sci 2010; 98: 148-155.
[3] Alzheimer's Association. 2010 Alzheimer's disease facts and figures. Alzheimers Dement 2010; 6: 158-194.
[4] Querfurth HW and LaFerla FM. Alzheimer's disease. N Engl J Med 2010; 362: 329-344.
[5] Haass C and Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol 2007; 8: 101-112.
[6] LaFerla FM, Green KN and Oddo S. Intracellular amyloid-beta in Alzheimer's disease. Nat Rev Neurosci 2007; 8: 499-509.
[7] Humpel C and Marksteiner J. Cerebrovascular damage as a cause for Alzheimer's disease. Curr Neurovasc Res 2005; 2: 341-347.
[8] Brenner SR. Neurovascular unit dysfunction: a vascular component of Alzheimer disease? Neurology 2008; 70: 243-244.
[9] Pei JJ, Sjogren M and Winblad B. Neurofibrillary degeneration in Alzheimer's disease: from molecular mechanisms to identification of drug targets. Curr Opin Psychiatry 2008; 21: 555-561.
[10] Chung SH. Aberrant phosphorylation in the pathogenesis of Alzheimer's disease. BMB Rep 2009; 42: 467-474.
[11] Smith MA, Rottkamp CA, Nunomura A, Raina AK and Perry G. Oxidative stress in Alzheimer's disease. Biochim Biophys Acta 2000; 1502: 139-144.
[12] Raina AK, Zhu X, Monteiro M, Takeda A and Smith MA. Abortive oncogeny and cell cycle-mediated events in Alzheimer disease. Prog Cell Cycle Res 2000; 4: 235-242.
[13] Raina AK, Zhu X, Rottkamp CA, Monteiro M, Takeda A and Smith MA. Cyclin' toward dementia: cell cycle abnormalities and abortive oncogenesis in Alzheimer disease. J Neurosci Res 2000; 61: 128-133.
[14] Pasinetti GM. Inflammatory mechanisms in neurodegeneration and Alzheimer's disease: the role of the complement system. Neurobiol Aging 1996; 17: 707-716.
[15] Swerdlow RH and Khan SM. A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. Med Hypotheses 2004; 63: 8-20.
[16] Swerdlow RH and Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis: an update. Exp Neurol 2009; 218: 308-315.
[17] Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chiba S, Atwood CS, Petersen RB and Smith MA. Oxidative damage is the earliest event in Alzheimer disease. J Neuropa-

thol Exp Neurol 2001; 60: 759-767.
[18] Pratico D, Uryu K, Leight S, Trojanoswki JQ and Lee VM. Increased lipid peroxidation precedes amyloid plaque formation in an animal model of Alzheimer amyloidosis. J Neurosci 2001; 21: 4183-4187.
[19] Hauptmann S, Scherping I, Drose S, Brandt U, Schulz KL, Jendrach M, Leuner K, Eckert A and Muller WE. Mitochondrial dysfunction: an early event in Alzheimer pathology accumulates with age in AD transgenic mice. Neurobiol Aging 2009; 30: 1574-1586.
[20] Keil U, Bonert A, Marques CA, Scherping I, Weyermann J, Strosznajder JB, Muller-Spahn F, Haass C, Czech C, Pradier L, Muller WE and Eckert A. Amyloid beta-induced changes in nitric oxide production and mitochondrial activity lead to apoptosis. J Biol Chem 2004; 279: 50310-50320.
[21] Hansson CA, Frykman S, Farmery MR, Tjernberg LO, Nilsberth C, Pursglove SE, Ito A, Winblad B, Cowburn RF, Thyberg J and Ankarcrona M. Nicastrin, presenilin, APH-1, and PEN-2 form active gamma-secretase complexes in mitochondria. J Biol Chem 2004; 279: 51654-51660.
[22] Chance B, Sies H and Boveris A. Hydroperoxide metabolism in mammalian organs. Physiol Rev 1979; 59: 527-605.
[23] Moreira PI, Zhu X, Wang X, Lee HG, Nunomura A, Petersen RB, Perry G and Smith MA. Mitochondria: a therapeutic target in neurodegeneration. Biochim Biophys Acta 2010; 1802: 212-220.
[24] Nelson DL and Cox MM: Lehninger Principles of Biochemistry. New York, W. H. Freeman, 2004.
[25] Scheffler IE: Mitochondria. Hoboken, NJ, John Wiley & Sons, Inc., 2008.
[26] Benard G and Rossignol R. Ultrastructure of the mitochondrion and its bearing on function and bioenergetics. Antioxid Redox Signal 2008; 10: 1313-1342.
[27] Shigenaga MK, Hagen TM and Ames BN. Oxidative damage and mitochondrial decay in aging. Proc Natl Acad Sci U S A 1994; 91: 10771-10778.
[28] Evans JL, Goldfine ID, Maddux BA and Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocr Rev 2002; 23: 599-622.
[29] Carreras MC, Franco MC, Peralta JG and Poderoso JJ. Nitric oxide, complex I, and the modulation of mitochondrial reactive species in biology and disease. Mol Aspects Med 2004; 25: 125-139.
[30] Balaban RS, Nemoto S and Finkel T. Mitochondria, oxidants, and aging. Cell 2005; 120: 483-495.
[31] Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M and Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007; 39: 44-84.
[32] Addabbo F, Montagnani M and Goligorsky MS. Mitochondria and reactive oxygen species. Hypertension 2009; 53: 885-892.
[33] Korshunov SS, Skulachev VP and Starkov AA. High protonic potential actuates a mechanism of production of reactive oxygen species in mitochondria. FEBS Lett 1997; 416: 15-18.
[34] Melov S, Schneider JA, Day BJ, Hinerfeld D, Coskun P, Mirra SS, Crapo JD and Wallace DC. A novel neurological phenotype in mice lacking mitochondrial manganese superoxide dismutase. Nat Genet 1998; 18: 159-163.
[35] Moreira PI, Carvalho C, Zhu X, Smith MA and Perry G. Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. Biochim Biophys Acta 2010; 1802: 2-10.
[36] Wojda U, Salinska E and Kuznicki J. Calcium ions in neuronal degeneration. IUBMB Life 2008; 60: 575-590.
[37] Zimmermann H. Neurotransmitter release. FEBS Lett 1990; 268: 394-399.
[38] Rizzuto R, Pinton P, Brini M, Chiesa A, Filippin L and Pozzan T. Mitochondria as biosensors of calcium microdomains. Cell Calcium 1999; 26: 193-199.
[39] Zucker RS. Calcium- and activity-dependent synaptic plasticity. Curr Opin Neurobiol 1999; 9: 305-313.
[40] Rizzuto R, Bernardi P and Pozzan T. Mitochondria as all-round players of the calcium game. J Physiol 2000; 529 Pt 1: 37-47.
[41] Soderling TR. CaM-kinases: modulators of synaptic plasticity. Curr Opin Neurobiol 2000; 10: 375-380.
[42] Sabatini BL, Maravall M and Svoboda K. Ca(2+) signaling in dendritic spines. Curr Opin Neurobiol 2001; 11: 349-356.
[43] Celsi F, Pizzo P, Brini M, Leo S, Fotino C, Pinton P and Rizzuto R. Mitochondria, calcium and cell death: a deadly triad in neurodegeneration. Biochim Biophys Acta 2009; 1787: 335-344.
[44] Buchholz JN, Behringer EJ, Pottorf WJ, Pearce WJ and Vanterpool CK. Age-dependent changes in Ca2+ homeostasis in peripheral neurones: implications for changes in function. Aging Cell 2007; 6: 285-296.
[45] Hengartner MO. The biochemistry of apoptosis. Nature 2000; 407: 770-776.
[46] Taylor RC, Cullen SP and Martin SJ. Apoptosis: controlled demolition at the cellular level. Nat Rev Mol Cell Biol 2008; 9: 231-241.
[47] Kroemer G, Galluzzi L and Brenner C. Mitochondrial membrane permeabilization in cell death. Physiol Rev 2007; 87: 99-163.
[48] Wallace DC and Fan W. The pathophysiology of mitochondrial disease as modeled in the mouse. Genes Dev 2009; 23: 1714-1736.
[49] Chen H and Chan DC. Mitochondrial dynamics--fusion, fission, movement, and mitophagy--in neurodegenerative diseases. Hum Mol Genet 2009; 18: R169-176.
[50] Smirnova E, Griparic L, Shurland DL and van

der Bliek AM. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Mol Biol Cell 2001; 12: 2245-2256.
[51] James DI, Parone PA, Mattenberger Y and Martinou JC. hFis1, a novel component of the mammalian mitochondrial fission machinery. J Biol Chem 2003; 278: 36373-36379.
[52] Wang X, Su B, Lee HG, Li X, Perry G, Smith MA and Zhu X. Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. J Neurosci 2009; 29: 9090-9103.
[53] Zuchner S, Mersiyanova IV, Muglia M, Bissar-Tadmouri N, Rochelle J, Dadali EL, Zappia M, Nelis E, Patitucci A, Senderek J, Parman Y, Evgrafov O, Jonghe PD, Takahashi Y, Tsuji S, Pericak-Vance MA, Quattrone A, Battaloglu E, Polyakov AV, Timmerman V, Schroder JM and Vance JM. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat Genet 2004; 36: 449-451.
[54] Chen H, Chomyn A and Chan DC. Disruption of fusion results in mitochondrial heterogeneity and dysfunction. J Biol Chem 2005; 280: 26185-26192.
[55] Ishihara N, Fujita Y, Oka T and Mihara K. Regulation of mitochondrial morphology through proteolytic cleavage of OPA1. EMBO J 2006; 25: 2966-2977.
[56] Wang X, Su B, Zheng L, Perry G, Smith MA and Zhu X. The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. J Neurochem 2009; 109 Suppl 1: 153-159.
[57] Perkins G, Bossy-Wetzel E and Ellisman MH. New insights into mitochondrial structure during cell death. Exp Neurol 2009; 218: 183-192.
[58] Chen H, Detmer SA, Ewald AJ, Griffin EE, Fraser SE and Chan DC. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. J Cell Biol 2003; 160: 189-200.
[59] Benard G, Bellance N, James D, Parrone P, Fernandez H, Letellier T and Rossignol R. Mitochondrial bioenergetics and structural network organization. J Cell Sci 2007; 120: 838-848.
[60] Frieden M, James D, Castelbou C, Danckaert A, Martinou JC and Demaurex N. Ca(2+) homeostasis during mitochondrial fragmentation and perinuclear clustering induced by hFis1. J Biol Chem 2004; 279: 22704-22714.
[61] Szabadkai G, Simoni AM, Chami M, Wieckowski MR, Youle RJ and Rizzuto R. Drp-1-dependent division of the mitochondrial network blocks intraorganellar Ca2+ waves and protects against Ca2+-mediated apoptosis. Mol Cell 2004; 16: 59-68.
[62] Frank S, Gaume B, Bergmann-Leitner ES, Leitner WW, Robert EG, Catez F, Smith CL and Youle RJ. The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis. Dev Cell 2001; 1: 515-525.
[63] Yu T, Robotham JL and Yoon Y. Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. Proc Natl Acad Sci U S A 2006; 103: 2653-2658.
[64] Wang X, Su B, Siedlak SL, Moreira PI, Fujioka H, Wang Y, Casadesus G and Zhu X. Amyloid-beta overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fission/fusion proteins. Proc Natl Acad Sci U S A 2008; 105: 19318-19323.
[65] Hollenbeck PJ and Saxton WM. The axonal transport of mitochondria. J Cell Sci 2005; 118: 5411-5419.
[66] Knott AB, Perkins G, Schwarzenbacher R and Bossy-Wetzel E. Mitochondrial fragmentation in neurodegeneration. Nat Rev Neurosci 2008; 9: 505-518.
[67] Chen H, McCaffery JM and Chan DC. Mitochondrial fusion protects against neurodegeneration in the cerebellum. Cell 2007; 130: 548-562.
[68] Li Z, Okamoto K, Hayashi Y and Sheng M. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell 2004; 119: 873-887.
[69] Guo X, Macleod GT, Wellington A, Hu F, Panchumarthi S, Schoenfield M, Marin L, Charlton MP, Atwood HL and Zinsmaier KE. The GTPase dMiro is required for axonal transport of mitochondria to Drosophila synapses. Neuron 2005; 47: 379-393.
[70] Misko A, Jiang S, Wegorzewska I, Milbrandt J and Baloh RH. Mitofusin 2 is necessary for transport of axonal mitochondria and interacts with the Miro/Milton complex. J Neurosci 2010; 30: 4232-4240.
[71] Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, Walzer G, Stiles L, Haigh SE, Katz S, Las G, Alroy J, Wu M, Py BF, Yuan J, Deeney JT, Corkey BE and Shirihai OS. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. EMBO J 2008; 27: 433-446.
[72] Tolkovsky AM. Mitophagy. Biochim Biophys Acta 2009; 1793: 1508-1515.
[73] Navratil M, Terman A and Arriaga EA. Giant mitochondria do not fuse and exchange their contents with normal mitochondria. Exp Cell Res 2008; 314: 164-172.
[74] Baloyannis SJ. Dendritic pathology in Alzheimer's disease. J Neurol Sci 2009; 283: 153-157.
[75] Swerdlow RH. Is aging part of Alzheimer's disease, or is Alzheimer's disease part of aging? Neurobiol Aging 2007; 28: 1465-1480.
[76] Liang WS, Reiman EM, Valla J, Dunckley T, Beach TG, Grover A, Niedzielko TL, Schneider LE, Mastroeni D, Caselli R, Kukull W, Morris JC, Hulette CM, Schmechel D, Rogers J and Stephan DA. Alzheimer's disease is associated with reduced expression of energy metabolism genes in posterior cingulate neurons. Proc Natl

Acad Sci U S A 2008; 105: 4441-4446.
[77] Moreira PI, Siedlak SL, Wang X, Santos MS, Oliveira CR, Tabaton M, Nunomura A, Szweda LI, Aliev G, Smith MA, Zhu X and Perry G. Autophagocytosis of mitochondria is prominent in Alzheimer disease. J Neuropathol Exp Neurol 2007; 66: 525-532.
[78] Fattoretti P, Balietti M, Casoli T, Giorgetti B, Di Stefano G, Bertoni-Freddari C, Lattanzio F and Sensi SL. Decreased numeric density of succinic dehydrogenase-positive mitochondria in CA1 pyramidal neurons of 3xTg-AD mice. Rejuvenation Res 2010;13:144-147.
[79] Bubber P, Haroutunian V, Fisch G, Blass JP and Gibson GE. Mitochondrial abnormalities in Alzheimer brain: mechanistic implications. Ann Neurol 2005; 57: 695-703.
[80] Yao J, Irwin RW, Zhao L, Nilsen J, Hamilton RT and Brinton RD. Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A 2009; 106: 14670-14675.
[81] Croteau DL and Bohr VA. Repair of oxidative damage to nuclear and mitochondrial DNA in mammalian cells. J Biol Chem 1997; 272: 25409-25412.
[82] Wang J, Xiong S, Xie C, Markesbery WR and Lovell MA. Increased oxidative damage in nuclear and mitochondrial DNA in Alzheimer's disease. J Neurochem 2005; 93: 953-962.
[83] Wallace DC, Stugard C, Murdock D, Schurr T and Brown MD. Ancient mtDNA sequences in the human nuclear genome: a potential source of errors in identifying pathogenic mutations. Proc Natl Acad Sci U S A 1997; 94: 14900-14905.
[84] Coskun PE, Beal MF and Wallace DC. Alzheimer's brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. Proc Natl Acad Sci U S A 2004; 101: 10726-10731.
[85] Petrozzi L, Ricci G, Giglioli NJ, Siciliano G and Mancuso M. Mitochondria and neurodegeneration. Biosci Rep 2007; 27: 87-104.
[86] Fukui H and Moraes CT. The mitochondrial impairment, oxidative stress and neurodegeneration connection: reality or just an attractive hypothesis? Trends Neurosci 2008; 31: 251-256.
[87] Hansson Petersen CA, Alikhani N, Behbahani H, Wiehager B, Pavlov PF, Alafuzoff I, Leinonen V, Ito A, Winblad B, Glaser E and Ankarcrona M. The amyloid beta-peptide is imported into mitochondria via the TOM import machinery and localized to mitochondrial cristae. Proc Natl Acad Sci U S A 2008; 105: 13145-13150.
[88] Takuma K, Fang F, Zhang W, Yan S, Fukuzaki E, Du H, Sosunov A, McKhann G, Funatsu Y, Nakamichi N, Nagai T, Mizoguchi H, Ibi D, Hori O, Ogawa S, Stern DM, Yamada K and Yan SS. RAGE-mediated signaling contributes to intraneuronal transport of amyloid-beta and neuronal dysfunction. Proc Natl Acad Sci U S A 2009; 106: 20021-20026.
[89] Atamna H and Frey WH, 2nd. A role for heme in Alzheimer's disease: heme binds amyloid beta and has altered metabolism. Proc Natl Acad Sci U S A 2004; 101: 11153-11158.
[90] Atamna H. Heme binding to Amyloid-beta peptide: mechanistic role in Alzheimer's disease. J Alzheimers Dis 2006; 10: 255-266.
[91] Anandatheerthavarada HK, Biswas G, Robin MA and Avadhani NG. Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. J Cell Biol 2003; 161: 41-54.
[92] Lustbader JW, Cirilli M, Lin C, Xu HW, Takuma K, Wang N, Caspersen C, Chen X, Pollak S, Chaney M, Trinchese F, Liu S, Gunn-Moore F, Lue LF, Walker DG, Kuppusamy P, Zewier ZL, Arancio O, Stern D, Yan SS and Wu H. ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. Science 2004; 304: 448-452.
[93] Takuma K, Yao J, Huang J, Xu H, Chen X, Luddy J, Trillat AC, Stern DM, Arancio O and Yan SS. ABAD enhances Abeta-induced cell stress via mitochondrial dysfunction. FASEB J 2005; 19: 597-598.
[94] Dell'agnello C, Leo S, Agostino A, Szabadkai G, Tiveron C, Zulian A, Prelle A, Roubertoux P, Rizzuto R and Zeviani M. Increased longevity and refractoriness to Ca(2+)-dependent neurodegeneration in Surf1 knockout mice. Hum Mol Genet 2007; 16: 431-444.
[95] Rhein V, Song X, Wiesner A, Ittner LM, Baysang G, Meier F, Ozmen L, Bluethmann H, Drose S, Brandt U, Savaskan E, Czech C, Gotz J and Eckert A. Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. Proc Natl Acad Sci U S A 2009; 106: 20057-20062.
[96] Devi L, Prabhu BM, Galati DF, Avadhani NG and Anandatheerthavarada HK. Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. J Neurosci 2006; 26: 9057-9068.
[97] Beal MF. Mitochondria take center stage in aging and neurodegeneration. Ann Neurol 2005; 58: 495-505.
[98] Moreira PI, Santos MS, Moreno A and Oliveira C. Amyloid beta-peptide promotes permeability transition pore in brain mitochondria. Biosci Rep 2001; 21: 789-800.
[99] Moreira PI, Santos MS, Moreno A, Rego AC and Oliveira C. Effect of amyloid beta-peptide on permeability transition pore: a comparative study. J Neurosci Res 2002; 69: 257-267.
[100] Moreira PI, Santos MS, Moreno AM, Seica R and Oliveira CR. Increased vulnerability of brain mitochondria in diabetic (Goto-Kakizaki) rats with aging and amyloid-beta exposure. Diabe-

tes 2003; 52: 1449-1456.
[101] Du H, Guo L, Fang F, Chen D, Sosunov AA, McKhann GM, Yan Y, Wang C, Zhang H, Molkentin JD, Gunn-Moore FJ, Vonsattel JP, Arancio O, Chen JX and Yan SD. Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. Nat Med 2008; 14: 1097-1105.
[102] Yang TT, Hsu CT and Kuo YM. Amyloid precursor protein, heat-shock proteins, and Bcl-2 form a complex in mitochondria and modulate mitochondria function and apoptosis in N2a cells. Mech Ageing Dev 2009; 130: 592-601.
[103] Hirai K, Aliev G, Nunomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, Vinters HV, Tabaton M, Shimohama S, Cash AD, Siedlak SL, Harris PL, Jones PK, Petersen RB, Perry G and Smith MA. Mitochondrial abnormalities in Alzheimer's disease. J Neurosci 2001; 21: 3017-3023.
[104] Baloyannis SJ. Mitochondrial alterations in Alzheimer's disease. J Alzheimers Dis 2006; 9: 119-126.
[105] Wang X, Su B, Fujioka H and Zhu X. Dynamin-like protein 1 reduction underlies mitochondrial morphology and distribution abnormalities in fibroblasts from sporadic Alzheimer's disease patients. Am J Pathol 2008; 173: 470-482.
[106] Cho DH, Nakamura T, Fang J, Cieplak P, Godzik A, Gu Z and Lipton SA. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. Science 2009; 324: 102-105.
[107] Mortiboys H, Thomas KJ, Koopman WJ, Klaffke S, Abou-Sleiman P, Olpin S, Wood NW, Willems PH, Smeitink JA, Cookson MR and Bandmann O. Mitochondrial function and morphology are impaired in parkin-mutant fibroblasts. Ann Neurol 2008; 64: 555-565.
[108] Lutz AK, Exner N, Fett ME, Schlehe JS, Kloos K, Lammermann K, Brunner B, Kurz-Drexler A, Vogel F, Reichert AS, Bouman L, Vogt-Weisenhorn D, Wurst W, Tatzelt J, Haass C and Winklhofer KF. Loss of parkin or PINK1 function increases Drp1-dependent mitochondrial fragmentation. J Biol Chem 2009; 284: 22938-22951.
[109] Zhao XL, Wang WA, Tan JX, Huang JK, Zhang X, Zhang BZ, Wang YH, YangCheng HY, Zhu HL, Sun XJ and Huang FD. Expression of beta-amyloid Induced age-dependent presynaptic and axonal changes in Drosophila. J Neurosci 2010; 30: 1512-1522.
[110] Iijima-Ando K, Hearn SA, Shenton C, Gatt A, Zhao L and Iijima K. Mitochondrial mislocalization underlies Abeta42-induced neuronal dysfunction in a Drosophila model of Alzheimer's disease. PLoS One 2009; 4: e8310.
[111] Rui Y, Gu J, Yu K, Hartzell HC and Zheng JQ. Inhibition of AMPA receptor trafficking at hippocampal synapses by beta-amyloid oligomers: the mitochondrial contribution. Mol Brain 2010; 3: 10.
[112] Stokin GB, Lillo C, Falzone TL, Brusch RG, Rockenstein E, Mount SL, Raman R, Davies P, Masliah E, Williams DS and Goldstein LS. Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. Science 2005; 307: 1282-1288.
[113] Pigino G, Morfini G, Pelsman A, Mattson MP, Brady ST and Busciglio J. Alzheimer's presenilin 1 mutations impair kinesin-based axonal transport. J Neurosci 2003; 23: 4499-4508.
[114] Rui Y, Tiwari P, Xie Z and Zheng JQ. Acute impairment of mitochondrial trafficking by beta-amyloid peptides in hippocampal neurons. J Neurosci 2006; 26: 10480-10487.
[115] Wang X, Perry G, Smith MA and Zhu X. Amyloid-beta-derived diffusible ligands cause impaired axonal transport of mitochondria in neurons. Neurodegener Dis 2010; 7: 56-59.
[116] Moreira PI, Siedlak SL, Wang X, Santos MS, Oliveira CR, Tabaton M, Nunomura A, Szweda LI, Aliev G, Smith MA, Zhu X and Perry G. Increased autophagic degradation of mitochondria in Alzheimer disease. Autophagy 2007; 3: 614-615.
[117] Yang AJ, Chandswangbhuvana D, Margol L and Glabe CG. Loss of endosomal/lysosomal membrane impermeability is an early event in amyloid Abeta1-42 pathogenesis. J Neurosci Res 1998; 52: 691-698.
[118] Ditaranto K, Tekirian TL and Yang AJ. Lysosomal membrane damage in soluble Abeta-mediated cell death in Alzheimer's disease. Neurobiol Dis 2001; 8: 19-31.
[119] Liu RQ, Zhou QH, Ji SR, Zhou Q, Feng D, Wu Y and Sui SF. Membrane localization of {beta}-amyloid 1-42 in lysosomes: A possible mechanism for lysosome labilization. J Biol Chem 2010;285:19986-19996.
[120] Ling D, Song HJ, Garza D, Neufeld TP and Salvaterra PM. Abeta42-induced neurodegeneration via an age-dependent autophagic-lysosomal injury in Drosophila. PLoS One 2009; 4: e4201.
[121] Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Jaeger PA, Small S, Spencer B, Rockenstein E, Levine B and Wyss-Coray T. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid beta accumulation in mice. J Clin Invest 2008; 118: 2190-2199.