The role of cell type-specific mitochondrial dysfunction in the pathogenesis of Alzheimer’s disease

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The decrease of metabolism in the brain has been observed as the important lesions of Alzheimer’s disease (AD) from the early stages of diagnosis. The cumulative evidence has reported that the failure of mitochondria, an organelle involved in diverse biological processes as well as energy production, maybe the cause or effect of the pathogenesis of AD. Both amyloid and tau pathologies have an impact upon mitochondria through physical interaction or indirect signaling pathways, resulting in the disruption of mitochondrial function and dynamics which can trigger AD. In addition, mitochondria are involved in different biological processes depending on the specific functions of each cell type in the brain. Thus, it is necessary to understand mitochondrial dysfunction as part of the pathological phenotypes of AD according to each cell type. In this review, we summarize that 1) the effects of AD pathology inducing mitochondrial dysfunction and 2) the contribution of mitochondrial dysfunction in each cell type to AD pathogenesis. [BMB Reports 2019; 52(12): 679-688]

INTRODUCTION
Alzheimer’s disease (AD) accompanied by extracellular amyloid plaques and intracellular neurofibrillary tangles exhibits memory impairment and cognitive deficit in patients with AD (1). However, the underlying mechanisms of the pathogenesis of AD remain unclear, and therapeutic approaches with AD (1). However, the underlying mechanisms of the pathogenesis of AD remain unclear, and therapeutic approaches with AD pathology (14, 15). In this review, we discuss the mitochondrial failure affected by AD pathology, and its implication in different cell types for the pathogenesis of AD.

MITOCHONDRIAL DYSFUNCTION INDUCED BY ALZHEIMER’S DISEASE PATHOGENESIS
Mitochondrial bioenergetics defects
The metabolism and glucose uptake of the brain tissue is down-regulated in patients with AD (16, 17). The investigation of bioenergetics profiles of fibroblasts from late-onset AD (LOAD) and health control demonstrates that the cells from LOAD, have the metabolic shift from the mitochondrial oxidative phosphorylation system (OXPHOS) to glycolysis, indicating reduced mitochondrial metabolic potential in LOAD (18). Mitochondria fractioned from triple transgenic AD model mice (3xTg-AD) brains show a decrease in mitochondrial membrane potential, ATP/ADP ratio and an impairment of the respiratory activities (19). The brain tissue of APP/PS1 AD model mice contains fewer ATP contents compared to the wild-type mice brain sample from 5 months old (20). When Aβ is specifically accumulated in mitochondria by using mitochondria-targeted Aβ construct, various mitochondrial functions were impaired, including the mitochondrial membrane potential and ATP generation (21)
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(Fig. 1). The genetic isoforms of apolipoprotein E (ApoE), the leading risk factor for the onset of LOAD, are also known to affect cellular metabolism (22). When each ApoE isoform is overexpressed in the mouse neuroblastoma cell line, the levels of hexokinase, one of the glycolytic enzymes, and the glycolytic activity are reduced in ApoE4-overexpressing cells as compared to other isoforms. In addition, it is shown that the oxygen consumption rate and the ATP amounts produced through the OXPHOS system are also shown to decrease when ApoE4 is overexpressed (23).

Many previous studies have investigated that there are distinct pathways how Aβ affects mitochondrial respiratory complexes. Both overexpression of amyloid precursor protein (APP) in cells and transgenic AD model mice represent reduced activities of adenosine 5'-triphosphate synthase (ATP synthase, mitochondrial complex V), but not other complexes, leading to reducing oxygen consumption and ATP production (24, 25). Using proteomic and functional analysis, differentially expressed proteins in P301L tau transgenic mice brain are identified as compared to wild-type mice brain, which are involved in a metabolism and mitochondrial respiration process (26). A decrease in complex I activity and ATP synthesis is observed in P301L mouse brain. In addition, human FTDP-17 patients with P301L tau mutation show reduced complex V levels in the cortex region of the brain. Here it is noted that the SH-SY5Y cell line overexpressing human P301L mutant tau exhibits decreased complex I activity, as accompanied by decreased ATP levels (27). When 3xTg-AD mouse model with both amyloid and tau pathology is compared with AD mouse model with distinct single pathology, the synergistic effects of both pathologies are the impact on the OXPHOS. In consistent with previous reports, mitochondrial complex I is down-regulated dependent of tau pathology whereas complex IV is affected by amyloid pathology at protein and activity levels (28). Together, each amyloid and tau pathology impact individually on the functions of mitochondrial components, and both pathologies synergistically induce mitochondrial failure in AD (Fig. 1).

Interaction of Aβ with mitochondrial components

It has been reported that Aβ is accumulated within the mitochondria of AD brain tissue (29, 30). Aβ can be translocated into mitochondrial matrix via the import machinery of mitochondria and APP is embedded in mitochondrial membrane, resulting in causing mitochondrial toxicity (21, 31, 32). Aβ located to the mitochondrial matrix can physically interact with mitochondrial components, thereby inhibiting their functions and producing excessive oxidative stress (Fig. 1) (33, 34). ATP synthase is localized in the inner membrane of mitochondria as the last component of the electron transport chain, where it produces ATP by the flux of a proton gradient across mitochondrial inner membrane (35). It has been reported that Aβ binds to ATP synthase and dysregulates its function, thereby inhibiting energy production. ATP synthase subunit α (ATP5A) activity which is regulated by the attachment of O-linked N-acetylglucosamine (O-GlcNAcylation) can be inhibited by the binding of Aβ to ATP5A. Aβ disrupts the interaction between ATP5A and O-GlcNAc transferase, resulting in blocking O-GlcNAcylation of ATP5A (36).

One of possible mechanisms to induce neuronal toxicity by Aβ is to form the mitochondrial permeability transition pore (mPTP), which activates the apoptotic pathway by the efflux of Ca2+ and apoptotic factors from the mitochondrial matrix (37, 38). Cyclophilin D, a peptidylprolyl isomerase, is known to regulate the opening of mPTP pore in the mitochondrial matrix (39, 40). The physical interaction of cyclophilin D with Aβ
occurs in the mitochondrial matrix, resulting in the inhibition of cyclophilin D to close mPTP pore. The pathological features of AD including mitochondrial toxicity and neuronal dysfunction can be reduced by genetic deletion of cyclophilin D, indicating that the cyclophilin D- Aβ interaction resulting in mPTP opening promotes Aβ-induced pathology of AD (41). Also, oligomycin sensitivity conferring protein (OSCP) subunit of ATP synthase involved in the formation of mPTP with cyclophilin D, also has the physical interaction with Aβ. The interaction leads to disrupting the stability and activity of ATP synthase, increased oxidative stress, and activated mPTP but the activities of other OXPHOS complexes are noted to be relatively unchanged (25).

Alcohol dehydrogenase, which catalyzes the reduction of the nicotinamide adenine dinucleotide (NAD⁺) to NADH using alcohol, is suppressed by Aβ in the mitochondrial matrix of AD patients and transgenic model mice (42). In these cases, Aβ induces to deform the active site of alcohol dehydrogenase, resulting in the inhibition of NAD⁺ binding. The mouse model in which alcohol dehydrogenase is overexpressed in an Aβ-rich environment exhibits a memory deficit dependent of the hippocampus, indicating that Aβ-induced mitochondrial toxicity occurs through the interaction between alcohol dehydrogenase and Aβ.

Mitochondrial proteins encoded by nucleus DNA possess the signal peptide to pull it into the mitochondrial matrix. After the import, the mitochondria-targeting sequence is cleaved by the mitochondrial processing peptidase (43). In the mitochondrial matrix, peptidase Cym1/PreP degrades presequence peptides of mitochondrial proteins. Aβ accumulated in mitochondria can disrupt PreP, thereby inhibiting the cleavage of presequence peptides. Consequently, an accumulation of undegraded presequence peptides cause feedback inhibition of preprotein processing. Damaged mitochondrial protein maturation induces mitochondrial toxicity and alteration of the mitochondrial proteome in AD patients (44).

**Mitochondrial dynamics and homeostasis**

Since mitochondrial morphology and dynamics are closely associated with mitochondrial functions and their homeostatic maintenance, it is shown that mitochondria respond to energetic demands through a process of fusion/fission dynamics (45, 46). Using an electron microscopy, an abnormal mitochondrial morphology is observed in the brain of AD (47-49). The long connected mitochondria termed mitochondria-on a string (MOAS) as a result of fission arrest, are observed in the hippocampus and entorhinal cortex of AD patients and AD model (47, 50, 51). In AD model mice (APP swe:PSN1ΔE9), mitochondrial loss and abnormal structure of mitochondria, particularly mitochondrial swelling, are observed near amyloid plaques. The neurons affected by near amyloid plaques contain highly fragmented mitochondria as compared to distinct neurons from amyloid plaques and neurons of wild-type mice (52). In addition, fibroblasts obtained from AD patients presents a decrease in the mitochondrial length (53). With morphological changes of mitochondria, the machinery required for mitochondrial dynamics, such as mitochondrial fusion proteins (OPA1, MFN1, and MFN2), is altered in the hippocampus of AD brain, seemingly without any change of the total levels of mitochondrial components (45). The activity of dynamin-related protein1 (DRP1), one of key regulators for mitochondrial fission, is elevated in the brain of subjects with AD, which can translocate to mitochondrial outer membrane and then leads to mitochondrial fission, but mitochondrial fusion proteins, such as MFN1, MFN2 and OPA1, are decreased in AD patients (54). The pharmacological inhibition of DRP1 can restore mitochondrial homeostasis and functions, including membrane potential, ATP production and reactive oxygen species production, and attenuates memory impairment in AD model mice (55, 56). Overexpression of APP and Aβ can affect the mitochondrial dynamics and homeostasis. APP-overexpressing cells exhibit fragmented mitochondria and altered mitochondrial distribution around the nucleus. The levels of DRP1 and OPA1 are decreased, but it is noted that the levels of FIS1 (mitochondrial fission 1 protein) are increased in APP-overexpressing cells (57). Furthermore, DRP1 oligomerization and recruitment on mitochondrial membrane are regulated by its posttranslational modification including phosphorylation of S-nitrosylation (58, 59). Aβ causes nitrosative stress to the cell which promotes S-nitrosylation modification on DRP1, leading to an increase in fission activity and further mitochondrial fragmentation (Fig. 1) (60, 61). Increased DRP1 activity due to abnormal interaction with phosphorylated tau can elucidate excessive mitochondrial fragmentation (62). In this case, the genetic reduction of DRP1 protect the mitochondrial dysfunction and impaired dynamics in P301L tau transgenic mice (63). In addition, truncated tau causes mitochondrial fission and a reduction of OPA1 levels in neurons, as compared to wild full-length tau, indicating that different forms of tau have a distinct impact on the mitochondrial dynamics (64). Additionally, CR6-interacting factor 1 (Cri1) involved in both the translation of OXPHOS proteins and their insertions into the mitochondrial inner membrane is down-regulated by Aβ-induced reactive oxygen species (ROS). As a result, a decrease of Cri1 results in fragmentation, dysfunction of mitochondria and even cell death in the subject with AD (65).

Extensive neurites of neuron require a wide coverage of energy and material supply to maintain neuronal functions. In fact, to deliver the mitochondria to nerve terminals, the neuron uses a microtubule axonal transport system, which can be regulated diverse post-translational modifications, including phosphorylation and acetylation. The levels of acetylated α-tubulin are decreased in AD patient’s brains and in the hippocampal neurons which are treated with Aβ. The inhibition of histone deacetylase 6 which deacetylates α-tubulin rescues the inhibited mitochondrial axonal transport by Aβ (Fig. 1).
(66). The patterns of mitochondrial distribution in hippocampal neurons are seen to be different in AD. Although mitochondria localize at both neuronal process and soma in control group, most mitochondria are confined to the soma area in AD (49). Since tau serves as microtubule-associated protein to stabilize microtubule, tau pathology is therefore associated with an abnormal mitochondrial transport in AD.

The overexpression of phosphorylated tau disrupts mitochondrial movement by regulating microtubule spacing (67). In other words, the mitochondrial distribution is altered in neurons with pathological tau aggregates of rTg4510 tau transgenic mice and AD patients. To this end, a reduction of soluble tau expression can restore the mitochondrial distribution, despite an existence of fibrillary tau inclusions (68). In addition to destabilizing microtubule network, tau also interact with kinesin motor protein, leading to preferential inhibition of anterograde transport along microtubules (Fig. 1) (69). These evidences suggest that amyloid and tau pathology affect mitochondrial dynamics to induce fragmentation and influence microtubule-based transport.

THE EFFECT OF MITOCHONDRIAL DYSFUNCTION ON EACH CELL TYPE IN ALZHEIMER’S DISEASE

Different cell types in the brain have distinct characteristics of metabolism, and exhibit specific roles related to their mitochondrial characteristics. Increasing evidences indicate that the mitochondria in different cell types vary in their function and morphology. Recently, the mitochondrial proteome of three major cerebellar cell types is identified, and it suggests that each cell type has differentially regulated mitochondrial proteins based on each biological role as utilized in the brain (70). In general, the metabolic coupling between neuron and astrocyte using mitochondria in different ways, manages and supports the functionality of the brain. In this case, the toxic fatty acids produced from hyperactive neurons are transferred into neighboring astrocytes, which can be stored in lipid droplets or detoxified by the β-oxidation process in mitochondria rather than processed in the neurons (71). Microglia undergo the metabolic reprogramming mediated by mitochondrial dynamics in response to external stimuli, which determine the inflammatory characteristics of microglia (72, 73). A better understanding of mitochondrial dysfunction as a pathological feature of AD requires a cell-type specific approach. We review mitochondrial dysfunction of each cell type, and note their contribution to AD pathogenesis.

Neuron

Neuron has different compartments with differentially functional units including axon and dendrite. The synaptic functions to release neurotransmitters and to respond signals at post-synaptic region require a high number of mitochondria, because of the high energy demand at the synapses (74). For this reason, the neuron has a high metabolic rate and the supply of glucose determines its functionality in the brain. The synaptic mitochondria especially have discrete metabolic characteristics that they are susceptible to the inhibition of complex I and Ca$^{2+}$ overload compared to non-synaptic mitochondria (75, 76). Since it is noted that the tau pathology has adverse effect upon mitochondrial complex I and Aβ activates synaptic terminals by the influx of Ca$^{2+}$ into cytosol, it seems likely that the synaptic mitochondria are impaired in AD (27, 28, 77). The existence of Aβ in synaptic mitochondria has been reported by the immunogold electron microscope (78). Moreover, the synaptic mitochondria contain higher amounts of Aβ as compared to non-synaptic mitochondria in Tg mAPP AD model mice, resulting in the impairment of synaptic mitochondrial respiration and accumulation of oxidative stress at synapses (Fig. 2) (78). The AD patient brain has local differences in the number of synaptic mitochondria as well as functional abnormality. For example, it is seen that the presynaptic region in AD has fewer mitochondria with abnormal morphology and structure, as compared to control subject, but there is no difference in those of a comparison post-synaptic region (79).

The synaptic communication between neurons is regulated by Ca$^{2+}$ signaling through the binding of neurotransmitters and their receptors at post-synaptic region. In fact, the synaptic mitochondria damaged by oxidative stress or AD pathology lose the capability to buffer excessive cytosolic Ca$^{2+}$ concentration. The expression of mitochondrial Ca$^{2+}$-exchange transporter NCLX, Na$^{2+}$/Ca$^{2+}$ exchanger, is decreased in the brain of AD patients and 3xTg-AD model mice. Furthermore, the genetic deletion of NCLX leading to impaired mitochondrial Ca$^{2+}$ efflux can cause memory loss, and aggravate both amyloid and tau pathology. Restoration of mitochondrial exchange transporter in neurons rescues mitochondrial dysfunction, cognitive impairment and AD pathology (Fig. 2) (80). Ca$^{2+}$ dysregulation of presynaptic mitochondria in mossy fiber synapses is exhibited in Tg2576 AD model mice. Moreover, it is shown that an exposure of Aβ to granule cells of the dentate gyrus causes Ca$^{2+}$ clearance failure. The results support that mitochondrial dysfunction by overproduced or existence of Aβ, particularly mitochondrial Ca$^{2+}$ regulation, is implicated in the synaptic dysfunction of mossy fiber-CA3 synapses (81). Similarly, impaired long-term potentiation and short-term plasticity at the mossy fiber synapses in Presenilin knockout mice are resulted from the altered mitochondrial Ca$^{2+}$ homeostasis in granule cells (82). The insulin-like growth factor-1 (IGF-1) signaling increased in AD patients and AD model mice is regulated by mitochondrial Ca$^{2+}$ homeostasis, which activates to release neurotransmitters and basal synaptic transmission (83-85). The pharmacological blockade of IGF-1 signaling can attenuate hippocampal hyperactivity in APP/PS1 model mice, indicating that mitochondrial dysfunction in AD conditions fails to control Aβ-dependent neuronal activation which is caused by excessive IGF-1 signaling (Fig. 2) (83).
Fig. 2. Cell type-specific mitochondrial dysfunction in AD pathogenesis. Many mitochondria are located in nerve terminals, contributing to supply energy for the production of neurotransmitters and the transport and release of synaptic vesicles. The damage of synaptic mitochondria causes abnormal synaptic activity in AD. Astrocyte regulates neuronal activity by buffering excess neurotransmitters at synapses through its mitochondria and metabolism. When astrocytic mitochondria are disrupted, neuronal hyperactivity may be triggered in AD. Also, since the β-oxidation process in astrocytic mitochondria exclusively consumes toxic fatty acids or lipid particles, astrocytic mitochondria play crucial roles in the removal of lipid particles associated with APOE in AD. The inflammatory status of microglia is determined by mitochondria and metabolic signaling in response to external stimuli. AD pathology cause metabolic reprogramming in microglia with the inflammatory response to become the activated or tolerance status.

**Astrocyte**

Astrocyte has crucial roles in the support of a neuron which includes the supply of metabolite, maintenance of synaptic plasticity and a control of neuronal activity in the brain (86). To preserve neural environment through buffering excessive glutamate as a neurotransmitter, it is known that astrocyte disposes of excessive released glutamate converting to glutamine by glutamine synthetase and the tricarboxylic acid (TCA) cycle of mitochondria (87). For this reason, it is seen that astrocytic mitochondria stay near glutamate transporter-1 (GLT-1, EAAT2) to regulate extracellular glutamate levels, which are followed by neuronal activation. When neuronal activity or glutamate uptake of astrocyte is inhibited, the proportion of mobile astrocytic mitochondria is increased instead of halting near GLT-1 to buffer glutamate (88, 89). In addition to mitochondria, glycolytic enzymes are co-localized with GLT-1. Although either the acute inhibition of glycolysis or the OXPHOS respiration in hippocampal slices cannot decrease glutamate uptake, simultaneous inhibition of both metabolisms reduce glutamate uptake, indicating that astrocytic metabolic state is a crucial factor for proper astrocytic functions (Fig. 2) (90). Using glia-specific mitochondrial gliotoxin being possible to impair selectively the OXPHOS system of glial cells, metabolic stress induced by mitochondrial dysfunction in glial cell inhibits the synaptic transmission (91). Thus, the differential metabolism of astrocyte satisfies the energetic demands of astrocytic functions, suggesting that the astrocytic metabolism has spatial and functional relation to the regulation of neuronal activity.

Astrocyte represents highly glycolytic metabolism compared to neurons (92, 93). For this reason, the pharmacological inhibition of glycolytic enzymes in astrocyte causes an accumulation of Aβ near or within astrocytes in the brain (94). It suggests that the glycolytic metabolism of astrocyte contributes to progress of AD pathogenesis. It is reported that 20% of energy supplied to the brain comes from fatty acid oxidation, which is known to occur mainly in astrocyte (95). Hyperactive neurons release toxic fatty acids through lipoprotein-like particles with ApoE. At that point, the astrocytic mitochondria are used exclusively for β-oxidation consuming lipid droplets or free fatty acids as an energy source than for TCA cycle (71). These evidences suggest that toxic fatty acids released from hyperactive neurons by Aβ can induce cytotoxicity, especially if they are not consumed due to...
damaged mitochondria of astrocyte. Moreover, if the secretion efficiency of toxic fatty acids depends on the ApoE polymorphism, it can be explained brain toxicity and high incidence of LOAD according to ApoE4 allele, which is a major risk factor for LOAD (Fig. 2).

Recently, research on the distinction of astrocytes between healthy individuals and AD has been investigated using an iPSC-derived model. Human iPSC-derived astrocyte model from early-onset familial AD (FAD) with PSN1 M146L mutations or late-onset sporadic AD (SAD) with ApoE4+/-+ exhibits morphological differences, as compared to those from healthy individuals. Moreover, most induced astrocytes from AD patients appear fibroblast-like cell morphology and display astrocytic atrophy, suggesting the alterations of astrocyte contribute to the pathogenesis of AD (96). Studies on the dysfunction of astrocytic mitochondria in AD have not investigated much more than those of other cell types in the brain. Astrocytes with PSN1 ΔE9 mutations derived from AD patients made using an iPSC-derived model represent metabolic reprogramming from glycolysis to OXPHOS respiration, thereby increasing ROS production and reducing lactate secretion which supports neuronal functions (97). The astrocyte transcriptome comparing healthy control and AD subjects, which is isolated from the posterior cingulate region by laser capture microdissection following the staining with anti-Aldehyde dehydrogenase 1 family, member L1 (ALDH1L1) antibody specific to astrocyte cell type, describes that differentially expressed genes in astrocyte of AD include mitochondria-related genes and immune responsive genes, indicating that astrocytic mitochondria are affected by the pathogenesis of AD (98).

In the AD brain, astrocytes have been reported to be exposed to oxidative stress, resulting in DNA damage and functional disability (99, 100). The increase of oxidative stress in astrocytes can be detected in old hAPP model mice, suggesting that astrocytic dysfunction by increased oxidative stress can contribute to the progress of AD pathogenesis (101). Additionally, an exposure of Aβ to astrocyte can induce mitochondrial fragmentation and depolarization, thereby leading to increased ROS production and mitochondrial impairment (102, 103). In addition, Aβ decreases the mitochondrial membrane potential of astrocytes but not the neurons, indicating the vulnerability of astrocytic mitochondria in AD (104). Another way of toxicity in astrocyte is an accumulation of poly-ADP-ribose polymers produced by poly-ADP-ribose polymerase that are activated by Aβ-induced oxidative stress. The increased poly-ADP-ribose polymers that limit the function of poly-ADP-ribose polymerase, which supports neuronal functions (105). A short exposure of Aβ to microglia induces acute inflammatory response, including production of cytokines and phagocytosis of Aβ. Microglia acutely treated with Aβ undergo metabolic reprogramming from OXPHOS to glycolysis via mTOR-HIF-1α pathway. In the AD brain, a long-term exposure of Aβ and senile plaques leads microglia to convert to a tolerance status, in which they have defective metabolic system and their inflammatory responses are reduced, indicating that health metabolic system is important to maintain inflammatory responses to external stimuli (Fig. 2) (106).

Using a method to generate iPSC-derived human microglia-like cells (iMGLs), the contribution of genetic backgrounds of AD, ApoE4, PSN1ΔE9, and APPswe, to functions and metabolism of iMGLs is elucidated. Both FAD mutations, PSN1ΔE9, and APPswe, have no effect on metabolic reprogramming. However, ApoE4 iMGLs exhibit lower oxygen consumption rate and can result in a decrease in all mitochondrial parameters related to cellular respiration. In addition, ApoE4 iMGLs, but not PSN1ΔE9 or APPswe iMGLs show reduced phagocytic capability (107). Additionally, hypomorphic variants of TREM2, a rare risk factor for LOAD associated with microglial responses, regulate microglial metabolism via mTOR signaling. Microglia in TREM2-deficient 5XFAD model mice have been shown to exhibit an accumulation of autophagosomes and impaired mTOR signaling due to down-regulated energy metabolism. These results suggest that TREM2 and mTOR-mediated metabolic activation mediates the function of microglia, such as the removal of amyloid plaques (Fig. 2) (108).

The mitochondria homeostasis is important to determine microglial inflammatory status, and its disruption can trigger neuronal death in neurodegenerative diseases. Recently, it has been suggested that microglial mitochondria are dysfunctional in neurodegenerative diseases, which are highly fragmented and released from microglia, thereby consequently inducing neuronal death. Dysfunctional mitochondria are detected in microglia-conditioned media when microglia are activated by Aβ. The treatment of P110 which is a selective inhibitor of mitochondrial fission and fragmentation, ameliorates glial activation and inflammatory responses in the brain of AD model mice (Fig. 2) (109). Reduced signaling of mitophagy that eliminate dysfunctional mitochondria has been identified as one of the pathological features of AD. An accumulation of defective mitochondria in microglia increases the release of cytokines and inhibits the removal of amyloid plaques, promoting the inflammatory responses in the brain. The restoration of mitophagy can mitigate inflammation and reduce the activation of NLRP3-inflammasome. Qualitative control of mitochondrial in microglia can alleviate AD pathogenesis by inducing an appropriate inflammatory response in the brain (110).
CONCLUSION
Mitochondrial dysfunction has been observed in the early stages of AD before the onset of clinical symptoms and interferes with the metabolism of the brain. Both Aβ and tau lesions induce the damage in various aspects of mitochondria, including the capacity of energy production, the control of homeostasis, and the transport of mitochondria along microtubules. Since various cell types that constitute the brain contribute to AD pathogenesis in different ways, an understanding of mitochondrial dysfunction in AD needs to be interpreted based on cell type-specific functions. Mitochondria affected by Aβ and tau pathologies cause a vicious cycle that induces the pathological features of AD pathogenesis at each cellular level. For this reason, a proper understanding of cell type-specific mitochondrial dysfunction contributing to AD pathogenesis leads to elucidating the underlying mechanisms of AD pathogenesis and the discovery of therapeutic targets for AD.

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CONFLICTS OF INTEREST
The authors have no conflicting interests.

REFERENCES
1. Querfurth HW and LaFerla FM (2010) Alzheimer's disease. N Engl J Med 362, 329-344
2. Cao J, Hou J, Ping J and Cai D (2018) Advances in developing novel therapeutic strategies for Alzheimer's disease. Mol Neurodegener 13, 64
3. Sanabria-Castro A, Alvarado-Echeverria I and Monge-Bonilla C (2017) Molecular Pathogenesis of Alzheimer's Disease: An Update. Ann Neurosci 24, 46-54
4. Marcus C, Mena E and Subramaniam RM (2014) Brain PET in the diagnosis of Alzheimer's disease. Clin Nucl Med 39, e413-422; quiz e423-416
5. Mosconi L, Bertl V, Glodzik L, Pupi A, De Santi S and de Leon MJ (2010) Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging. J Alzheimers Dis 20, 843-854
6. Patel JR and Brewer CJ (2003) Age-related changes in neuronal glucose uptake in response to glutamate and beta-amyloid. J Neurosci Res 72, 527-536
7. Beal MF (1995) Aging, energy, and oxidative stress in neurodegenerative diseases. Ann Neurol 38, 357-366
8. Mancuso M, Calsolaro V, Orsucci D et al (2009) Mitochondria, cognitive impairment, and Alzheimer's disease. Int J Alzheimers Dis 2009, 951548
9. Zhu X, Perry G, Smith MA and Wang X (2013) Abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. J Alzheimers Dis 33 Suppl 1, S253-262
10. Wang X, Su B, Zheng L, Perry G, Smith MA and Zhu X (2009) The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. J Neurochem 109 Suppl 1, 153-159
11. Swerdlow RH (2018) Mitochondria and Mitochondrial Cascades in Alzheimer's Disease. J Alzheimers Dis 62, 1403-1416
12. Swerdlow RH, Burns JM and Khan SM (2010) The Alzheimer's disease mitochondrial cascade hypothesis. J Alzheimers Dis 20 Suppl 2, S265-279
13. Swerdlow RH, Burns JM and Khan SM (2014) The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives. Biochim Biophys Acta 1842, 1219-1231
14. Cheng Y and Bai F (2018) The Association of Tau With Mitochondrial Dysfunction in Alzheimer's Disease. Front Neurosci 12, 163
15. Reddy PH and Beal MF (2008) Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. Trends Mol Med 14, 45-53
16. Szablewski L (2017) Glucose Transporters in Brain: In Health and in Alzheimer's Disease. J Alzheimers Dis 55, 1307-1320
17. Sun J, Feng X, Liang D, Duan Y and Lei H (2012) Down-regulation of energy metabolism in Alzheimer's disease is a protective response of neurons to the microenvironment. J Alzheimers Dis 28, 389-402
18. Sonntag KC, Ryu WI, Amirault KM et al (2017) Late-onset Alzheimer's disease is associated with inherent changes in bioenergetics profiles. Sci Rep 7, 14038
19. Carvalho C, Cardoso S, Correia SC et al (2012) Metabolic alterations induced by sucrose intake and Alzheimer's disease promote similar brain mitochondrial abnormalities. Diabetes 61, 1234-1242
20. Zhang C, Rissman RA and Feng J (2015) Characterization of ATP alternations in an Alzheimer's disease transgenic mouse model. J Alzheimers Dis 44, 375-378
21. Cha MY, Han SH, Son SM et al (2012) Mitochondria-specific accumulation of amyloid beta induces mitochondrial dysfunction leading to apoptotic cell death. PLoS One 7, e34929
22. Keeney JT, Ibrahim S and Zhao L (2015) Human ApoE Isoforms Differentially Modulate Glucose and Amyloid Metabolic Pathways in Female Brain: Evidence of the Mechanism of Neuroprotection by ApoE2 and Implications for Alzheimer's Disease Prevention and Early Intervention. J Alzheimers Dis 48, 411-424
23. Wu L, Zhang X and Zhao L (2018) Human ApoE Isoforms Differentially Modulate Brain Glucose and Ketone Body Metabolism: Implications for Alzheimer's Disease Risk Reduction and Early Intervention. J Neurosci 38, 6665-6681
24. Rhein V, Baysang G, Rao S et al (2009) Amyloid-beta leads to impaired cellular respiration, energy production and mitochondrial electron chain complex activities in human neuroblastoma cells. Cell Mol Neurobiol 29, 1063-1071

http://bmbreports.org
25. Beck SJ, Guo L, Phensy A et al (2016) Deregelation of mitochondrial F1FO-ATP synthase via OSCP in Alzheimer's disease. Nat Commun 7, 11483
26. David DC, Hauptmann S, Scherping I et al (2005) Proteomic and functional analyses reveal a mitochondrial dysfunction in P301L tau transgenic mice. J Biol Chem 280, 23802-23814
27. Schulz KL, Eckert A, Rhein V et al (2012) A new link to mitochondrial impairment in tauopathies. Mol Neurobiol 46, 205-216
28. Rhein V, Song X, Wiesner A et al (2009) Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. Proc Natl Acad Sci U S A 106, 20057-20062.
29. Manczak M, Anekonda TS, Henson E, Park BS, Quinn J and Reddy PH (2006) Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. Hum Mol Genet 15, 1437-1449
30. Caspersen C, Wang N, Yao J et al (2005) Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. FASEB J 19, 2040-2041
31. Devi L, Prabhu BM, Galati DF, Avadhani NG and Devi L, Prabhu BM, Galati DF, Avadhani NG and Prabhu BM, Galati DF, Avadhani NG (2004) Cyclophilin D: A marvellous rotary engine of the cell. Nat Rev 26, 9057-9068
32. Hansson Petersen CA, Alkhani N, Bebbahani H et al (2008) 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 105, 13145-13150
33. Chen JX and Yan SS (2010) Role of mitochondrial amyloid-beta in Alzheimer's disease. J Alzheimers Dis 20 Suppl 2, S569-578
34. Han SH, Park JC and Mook-Jung I (2016) Amyloid-beta-interacting partners in Alzheimer's disease: from accomplices to possible therapeutic targets. Prog Neurobiol 137, 17-38
35. Yoshida M, Muneyuki E and Hisabori T (2001) ATP synthase—a marvellous rotary engine of the cell. Nat Rev Mol Cell Biol 2, 669-677
36. Cha MY, Cho HJ, Kim C et al (2015) Mitochondrial ATP synthase activity is impaired by suppressed O-GlcNAcylation in Alzheimer's disease. Hum Mol Genet 24, 6492-6504
37. Halestrap A (2005) Biochemistry: a pore way to die. Nature 434, 578-579
38. Nicotra A and Parvez S (2002) Apoptotic molecules and MPTP-induced cell death. Neurotoxicol Teratol 24, 599-605
39. Zamzami N, Larochette N and Kroemer G (2005) Mitochondrial permeability transition in apoptosis and necrosis. Cell Death Differ 12 Suppl 2, 1478-1480
40. Javadov S and Kuznetsov A (2013) Mitochondrial permeability transition and cell death: the role of cyclophilin d. Front Physiol 4, 76
41. Du H, Guo L, Fang F et al (2008) Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. Nat Med 14, 1097-1105
42. Lusibaker J, Crillill M, Lin C et al (2004) ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. Science 304, 448-452
43. Vogtle FN, Wortelkamp S, Zahedi RP et al (2009) Global analysis of the mitochondrial N-proteome identifies a processing peptide critical for protein stability. Cell 139, 428-439
44. Mossmann D, Vogtle FN, Taskin AA et al (2014) Amyloid-beta peptide induces mitochondrial dysfunction by inhibition of preprotein maturation. Cell Metab 20, 662-669
45. Mishra P and Chan DC (2016) Metabolic regulation of mitochondrial dynamics. J Cell Biol 212, 379-387
46. Youle RJ and van der Bliek AM (2012) Mitochondrial fission, fusion, and stress. Science 337, 1062-1065
47. Zhang L, Trushin S, Christensen TA et al (2016) Altered brain energetics induces mitochondrial fission arrest in Alzheimer's Disease. Sci Rep 6, 18725
48. Shah SJ, Paine JG, Perez C and Ullah G (2019) Mitochondrial fragmentation and network architecture in degenerative diseases. PLoS One 14, e0223014
49. Wang X, Su B, Lee HG et al (2009) Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. J Neurosci 29, 9090-9103
50. Tymantsev MA, Stefanova NA, Kiseleva EV and Kolosova NG (2018) Mitochondria with Morphology Characteristic for Alzheimer's Disease Patients Are Found in the Brain of OXYS Rats. Biochemistry (Mosc) 83, 1083-1088
51. Trushina E (2016) A shape shifting organelle: unusual mitochondrial phenotype determined with three-dimensional electron microscopy reconstruction. Neural Regen Res 11, 900-901
52. Xie H, Guan J, Borrelli LA, Xu J, Serrano-Pozo A and Baeksi BJ (2013) Mitochondrial alterations near amyloid plaques in an Alzheimer's disease mouse model. J Neurosci 33, 17042-17051
53. Perez MJ, Ponce DP, Osorio-Fuenteaalba C, Behrens MI and Quintanilla RA (2017) Mitochondrial Bioenergetics Is Altered in Fibroblasts from Patients with Sporadic Alzheimer's Disease. Front Neurosci 11, 553
54. Manczak M, Callins MJ and Reddy PH (2011) Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: implications for neuronal damage. Hum Mol Genet 20, 2495-2509
55. Joshi AU, Saw NL, Shamloo M and Mochly-Rosen D (2018) Drp1/Fis1 interaction mediates mitochondrial dysfunction, bioenergetic failure and cognitive decline in Alzheimer's disease. Oncotarget 9, 6128-6143
56. Baek SH, Park SJ, Jeong JI et al (2017) Inhibition of Drp1 Ameliorates Synaptic Depression, Abeta Deposition, and Cognitive Impairment in an Alzheimer's Disease Model. J Neurosci 37, 5099-5110
57. Wang X, Su B, Siedlak SL et al (2008) Amyloid-beta
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overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fission/fusion proteins. Proc Natl Acad Sci U S A 105, 19318-19323
58. Knott AB, Perkins G, Schwarzenbacher R and Bossy-Wetzel E (2008) Mitochondrial fragmentation in neurodegeneration. Nat Rev Neurosci 9, 505-518
59. Westermann B (2009) Nitric oxide links mitochondrial fission to Alzheimer's disease. Sci Signal 2, pe29
60. Cho DH, Nakamura T, Fang J et al (2009) S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. Science 324, 102-105
61. Kang S, Byun J, Son SM and Mook-Jung I (2018) Thrombospondin-1 protects against Abeta-induced mitochondrial fragmentation and dysfunction in hippocampal cells. Cell Death Discov 4, 31
62. Manczak M and Reddy PH (2012) Abnormal interaction between the mitochondrial fission protein Drp1 and hyperphosphorylated tau in Alzheimer's disease neurons: implications for mitochondrial dysfunction and neuronal damage. Hum Mol Genet 21, 2538-2547
63. Kandimalla K, Manczak M, Fry D, Suneetha Y, Sesaki H and Reddy PH (2016) Reduced dynamin-related protein 1 protects against phosphorylated Tau-induced mitochondrial dysfunction and synaptic damage in Alzheimer's disease. Hum Mol Genet 25, 4881-4897
64. Perez MJ, Vergyara-Pulgar K, Jara C, Cabezas-Opazo F and Quintanilla RA (2018) Caspase-Cleaved Tau Impairs Mitochondrial Dynamics in Alzheimer's Disease. Mol Neurobiol 55, 1004-1018
65. Byun J, Son SM, Cha MY et al (2015) CR6-interacting factor 1 is a key regulator in Abeta-induced mitochondrial disruption and pathogenesis of Alzheimer's disease. Cell Death Differ 22, 959-973
66. Kim C, Choi H, Jung ES et al (2012) HDAC6 inhibitor blocks amyloid beta-induced impairment of mitochondrial transport in hippocampal neurons. PLoS One 7, e42983
67. Shapalsand K, Lernuira J, Saito T et al (2012) Regulation of mitochondrial transport and inter-microtubule spacing by tau phosphorylation at the sites hyperphosphorylated in Alzheimer's disease. J Neurosci 32, 2430-2441
68. Kopeikina KJ, Carlson GA, Pitstick R et al (2011) Tau accumulation causes mitochondrial distribution deficits in neurons in a mouse model of tauopathy and in human Alzheimer's disease brain. Am J Pathol 179, 2071-2082
69. Starner K, Vogel R, Thies E, Mandelkow E and Mandelkow EM (2002) Tau blocks traffic of organelles, neurofilaments, and APP vesicles in neurons and enhances oxidative stress. J Cell Biol 156, 1051-1063
70. Fecher C, Trovo L, Muller SA et al (2019) Cell-type-specific profiling of brain mitochondria reveals functional and molecular diversity. Nat Neurosci 22, 1731-1742
71. Ioannou MS, Jackson J, Shue SH et al (2019) Neuron-Astrocyte Metabolic Coupling Protects against Activity-Induced Fatty Acid Toxicity. Cell 177, 1522-1535.e1514
72. Park J, Choi H, Min JS et al (2013) Mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells. J Neurochem 127, 221-232
73. Orihuela R, McPherson CA and Harry GJ (2016) Microglial M1/M2 polarization and metabolic states. Br J Pharmacol 173, 649-665
74. Vos M, Lauwers E and Verstreken P (2010) SYNaptic mitochondria in synaptic transmission and organization of vesicle pools in health and disease. Front SYNaptic Neurosci 2, 139
75. Davey GP, Peuchen S and Clark JB (1998) Energy thresholds in brain mitochondria. Potential involvement in neurodegeneration. J Biol Chem 273, 12753-12757
76. Brown MR, Sullivan PG and Geddes JW (2006) SYNaptic mitochondria are more susceptible to Ca2+-overload than nonsynaptic mitochondria. J Biol Chem 281, 11658-11668
77. Zott B, Simon MM, Hong W et al (2019) A vicious cycle of beta amyloid-dependent neuronal hyperactivation. Science 365, 559-565
78. Du H, Guo L, Yan S, Sosunov AA, McKhann GM and Yan SS (2010) Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model. Proc Natl Acad Sci U S A 107, 18670-18675
79. Pickett EK, Rose J, McCrory C et al (2018) Region-specific depletion of synaptic mitochondria in the brains of patients with Alzheimer's disease. Acta Neuropathol 136, 747-757
80. Jadiya P, Kolmetzky DW, Tomar D et al (2019) Impaired mitochondrial calcium efflux contributes to disease progression in models of Alzheimer's disease. Nat Commun 10, 3885
81. Lee SH, Kim KR, Ryu SY et al (2012) Impaired short-term plasticity in mossy fiber synapses caused by mitochondrial dysfunction of dentate granule cells is the earliest synaptic deficit in a mouse model of Alzheimer's disease. J Neurosci 32, 5953-5963
82. Lee SH, Lutz D, Mossalam M, Bolshakov VY, Frotscher M and Shen J (2017) Presenilins regulate synaptic plasticity and mitochondrial calcium homeostasis in the hippocampal mossy fiber pathway. Mol Neurodegener 12, 48
83. Gazit N, Vertkin I, Shapiro I et al (2016) IGF-1 Receptor Differentially Regulates Spontaneous and Evoked Transmission via Mitochondria at Hippocampal Synapses. Neuron 89, 583-597
84. Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R and O'Neill C (2010) Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. Neurobiol Aging 31, 224-243
85. Zhang B, Tang XC and Zhang HY (2013) Alternations of mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells. J Neurochem 127, 221-232
and position mitochondria near glutamate transporters. J Neurosci 34, 1613-1624
89. Xu NJ, Bao L, Fan HP et al (2003) Morphine withdrawal increases glutamate uptake and surface expression of glutamate transporter GLT1 at hippocampal synapses. J Neurosci 23, 4775-4784
90. Genda EN, Jackson JG, Sheldon AL et al (2011) Co-compartmentalization of the astroglial glutamate transporter, GLT-1, with glycolytic enzymes and mitochondria. J Neurosci 31, 18275-18288
91. Canals S, Larrosa B, Pintor J, Mena MA and Herreras O (2008) Metabolic challenge to glia activates an adenosine-mediated safety mechanism that promotes neuronal survival by delaying the onset of spreading depression waves. J Cereb Blood Flow Metab 28, 1835-1844
92. Belanger M, Allaman I and Magistretti PJ (2011) Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 14, 724-738
93. Bouzier-Sore AK and Pellerin L (2013) Unraveling the complex metabolic nature of astrocytes. Front Cell Neurosci 7, 179
94. Fu W, Shi D, Westaway D and Jhamandas JH (2015) Bioenergetic mechanisms in astrocytes may contribute to amyloid plaque deposition and toxicity. J Biol Chem 290, 12504-12513
95. Ebert D, Haller RG and Walton ME (2003) Energy contribution of octanoate to intact rat brain metabolism measured by 13C nuclear magnetic resonance spectroscopy. J Neurosci 23, 5928-5935
96. Jones VC, Atkinson-Dell R, Verkhratsky A and Mohamet L (2017) Aberrant iPSC-derived human astrocytes in Alzheimer’s disease. Cell Death Dis 8, e2696
97. Oksanen M, Petersen AJ, Naumenko N et al (2017) PSEN1 Mutant iPSC-Derived Model Reveals Severe Astrocyte Pathology in Alzheimer’s Disease. Stem Cell Reports 9, 1885-1897
98. Sekar S, McDonald J, Cuypuran L et al (2015) Alzheimer’s disease is associated with altered expression of genes involved in immune response and mitochondrial processes in astrocytes. Neurobiol Aging 36, 583-591
99. Myung NH, Zhu X, Krumain, II et al (2008) Evidence of DNA damage in Alzheimer disease: phosphorylation of histone H2AX in astrocytes. Age (Dordr) 30, 209-215
100. Simpson JE, Ince PG, Haynes LJ et al (2010) Population variation in oxidative stress and astrocyte DNA damage in relation to Alzheimer-type pathology in the ageing brain. Neuropathol Appl Neurobiol 36, 25-40
101. Lee HP, Pancholi N, Esposito L et al (2012) Early induction of oxidative stress in mouse model of Alzheimer disease with reduced mitochondrial superoxide dismutase activity. PLoS One 7, e28033
102. Sarkar P, Zaja I, Bienengraeber M et al (2014) Epoxysiosatrienioic acids pretreatment improves amyloid beta-induced mitochondrial dysfunction in cultured rat hippocampal astrocytes. Am J Physiol Heart Circ Physiol 306, H475-484
103. Abeti R, Abramov AY and Duchen MR (2011) Beta-amyloid activates PARP causing astrocytic metabolic failure and neuronal death. Brain 134, 1658-1672
104. Abramov AY, Canevari L and Duchen MR (2004) Beta-amyloid peptides induce mitochondrial dysfunction and oxidative stress in astrocytes and death of neurons through activation of NADPH oxidase. J Neurosci 24, 565-575
105. Culmsee C, Michels S, Scheu S, Aroll V, Dammowski U and Alferink J (2018) Mitochondria, Microglia, and the Immune System-How Are They Linked in Affective Disorders? Front Psychiatry 9, 739
106. Baik SH, Kang S, Lee W et al (2019) A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer’s Disease. Cell Metab 30, 493-507 e496
107. Konttinen H, Cabral-da-Silva MEC, Ohtonen S et al (2019) PSEN1DeltaE9, APPswe, and APOE4 Confer Disparate Phenotypes in Human iPSC-Derived Microglia. Stem Cell Reports 13, 669-683
108. Ulland TK, Song WM, Huang SC et al (2017) TREM2 Maintains Microglial Metabolic Fitness in Alzheimer’s Disease. Cell 170, 649-663 e613
109. Joshi AU, Minhas PS, Liddelow SA et al (2019) Fragmented mitochondria released from microglia trigger A1 astrocytic response and propagate inflammatory neurodegeneration. Nat Neurosci 22, 1635-1648
110. Fang EF, Hou Y, Palikaras K et al (2019) Mitophagy inhibits amyloid-beta and tau pathology and reverses cognitive deficits in models of Alzheimer’s disease. Nat Neurosci 22, 401-412