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

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ABSTRACT

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.

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 directly targeting amyloid beta (Aβ) and tau have failed (2, 3). The development of ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) which visualizes the usage of glucose in the tissue, reveals the association between reduced metabolism in the brain and AD pathogenesis (4). In the progress of AD, since metabolic defect of the brain has appeared as the early symptoms of AD even before onset of AD pathological symptoms with brain atrophy and memory loss, the reduction of FDG-PET has long been used for the imaging biomarker of AD (5). Hypometabolism in the brain of AD is attributed to abnormal morphology and impaired functions of mitochondria (6, 7). For this reason it is noted that mitochondria are responsible for energy supply and maintenance of different functions of cells and mitochondrial failure has been reported in patients with AD (8). It has been suggested that mitochondrial dysfunction and impaired dynamics appear to be critical roles in the pathogenesis of AD (9, 10). The mitochondrial cascade hypothesis has been postulated to explain the onset of bioenergetics dysfunction involved in the pathogenesis of AD (11, 12). The hypothesis assumes that gene inheritance and environmental factors regulate mitochondrial functions, which in turn determines the vulnerability to AD (13). Also, Both amyloid and tau pathology can induce mitochondrial alterations *in vitro* and *vivo,* indicating that bioenergetics dysfunction is closely associated 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

1) 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) (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 mice 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

74 tau exhibits decreased complex Ⅰ activity, as accompanied by decreased ATP levels (27). When
75 3xTg-AD mouse model with both amyloid and tau pathology is compared with AD mouse model with
76 distinct single pathology, the synergistic effects of both pathologies are the impact on the OXPHOS.
77 In consistent with previous reports, mitochondrial complex Ⅰ is down-regulated dependent of tau
78 pathology whereas complex Ⅳ is affected by amyloid pathology at protein and activity levels (28).
79 Together, each amyloid and tau pathology impact individually on the functions of mitochondrial
80 components, and both pathologies synergistically induce mitochondrial failure in AD (Fig. 1).

81

82 **2) Interaction of Aβ with mitochondrial components**

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

95 One of possible mechanisms to induce neuronal toxicity by Aβ is to form the mitochondrial
96 permeability transition pore (mPTP), which activates the apoptotic pathway by the efflux of Ca^{2+} and
97 apoptotic factors from the mitochondrial matrix (37, 38). Cyclophilin D, a peptidylprolyl isomerase F,
98 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 relatiely 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, peptidasome 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).

3) 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 (*APPswe*:*PSEN1ΔE9*), 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 (60, 61) (Fig. 1). 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 (Crif1) involved in both the translation of OXHPHOS 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 Crif1 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 deacetylases α-tubulin rescues the inhibited mitochondrial axonal transport by Aβ (66) (Fig. 1). 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

177 microtubules (69) (Fig. 1). These evidences suggest that amyloid and tau pathology affect
178 mitochondrial dynamics to induce fragmentation and influence microtubule-based transport.

179

180 **The effect of mitochondrial dysfunction on each cell type in Alzheimer's disease**

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

195

196 **1) Neuron**

197 Neuron has different compartments with differentially functional units including axon and dendrite.
198 The synaptic functions to release neurotransmitters and to respond signals at post-synaptic region
199 require a high number of mitochondria, because of the high energy demand at the synapses (74). For
200 this reason, the neuron has a high metabolic rate and the supply of glucose determines its functionality
201 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 (78) (Fig. 2). 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 (80) (Fig. 2). 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 (83) (Fig. 2).

2) 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 (90) (Fig. 2). 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 *PSEN1 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 *PSEN1 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, therefore leading to increased ROS production and metabolic 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 availability of nicotinamide adenine dinucleotide as substrate, are also known to reduce mitochondrial membrane potential and result in neuronal death (103).

3) Microglia

Microglia, brain-resident immune cell, respond to surrounding stimuli and alert the immune response. Furthermore, mitochondria are required for the inflammatory responses of microglia and determining their metabolic status (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 (106) (Fig. 2).

Using a method to generate iPSC-derived human microglia-like cells (iMGLs), the contribution of genetic backgrounds of AD, *ApoE4*, *PSEN1*ΔE9, and *APPswe*, to functions and metabolism of iMGLs is elucidated. Both FAD mutations, *PSEN1*ΔE9, and *APPswe*, have no effect on metabolic

306 reprogramming. However, *ApoE4* iMGLs exhibit lower oxygen consumption rate and can result in a
307 decrease in all mitochondrial parameters related to cellular respiration. In addition, *ApoE4* iMGLs, but
308 not *PSEN1*ΔE9 or *APPswe* iMGLs show reduced phagocytic capability (107). Additionally,
309 hypomorphic variants of TREM2, a rare risk factor for LOAD associated with microglial responses,
310 regulate microglial metabolism via mTOR signaling. Microglia in TREM2-deficient 5XFAD model
311 mice have been shown to exhibit an accumulation of autophagosomes and impaired mTOR signaling
312 due to down-regulated energy metabolism. These results suggest that TREM2 and mTOR-mediated
313 metabolic activation mediates the function of microglia, such as the removal of amyloid plaques (108)
314 (Fig. 2).

315 The mitochondria homeostasis is important to determine microglial inflammatory status, and its
316 disruption can trigger neuronal death in neurodegenerative diseases. Recently, it has been suggested
317 that microglial mitochondria are dysfunctional in neurodegenerative diseases, which are highly
318 fragmented and released from microglia, thereby consequently inducing neuronal death.
319 Dysfunctional mitochondria are detected in microglia-conditioned media when microglia are activated
320 by Aβ. The treatment of P110 which is a selective inhibitor of mitochondrial fission and
321 fragmentation, ameliorates glial activation and inflammatory responses in the brain of AD model mice
322 (109) (Fig. 2). Reduced signaling of mitophagy that eliminate dysfunctional mitochondria has been
323 identified as one of the pathological features of AD. An accumulation of defective mitochondria in
324 microglia increases the release of cytokines and inhibits the removal of amyloid plaques, promoting
325 the inflammatory responses in the brain. The restoration of mitophagy can mitigate inflammation and
326 reduce the activation of NLRP3-inflammasome. Qualitative control of mitochondrial in microglia can
327 alleviate AD pathogenesis by inducing an appropriate inflammatory response in the brain (110).

328

329 **CONCLUSION**

330 Mitochondrial dysfunction has been observed in the early stages of AD before the onset of clinical
331 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.

FIGURE LEGENDS

Fig. 1. Mitochondrial alterations in AD. The effect of AD pathology on mitochondrial function for energy production, transport and dynamics.

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.

CONFLICTS OF INTEREST

The authors have no conflicting interests.

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Figure 1.

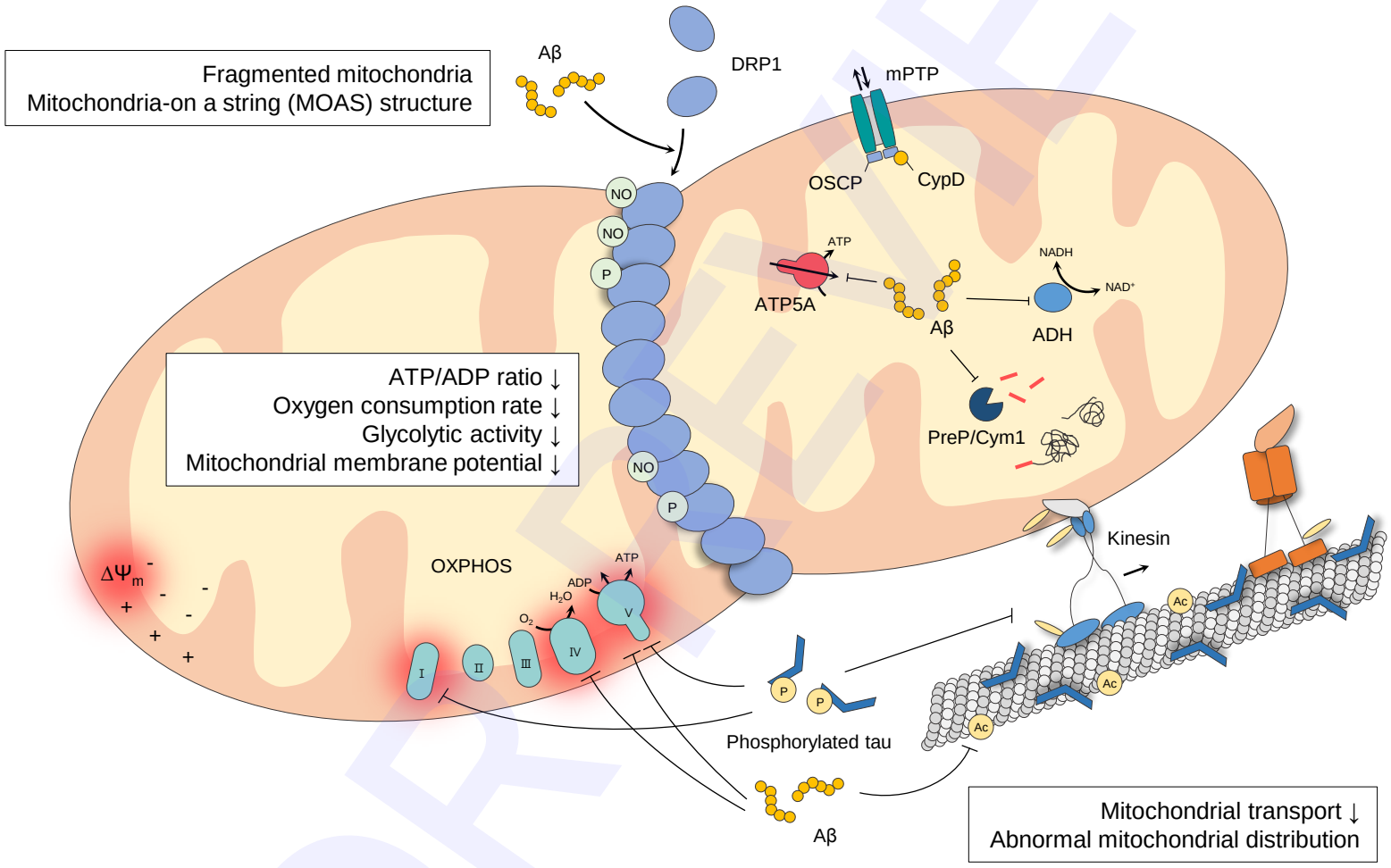
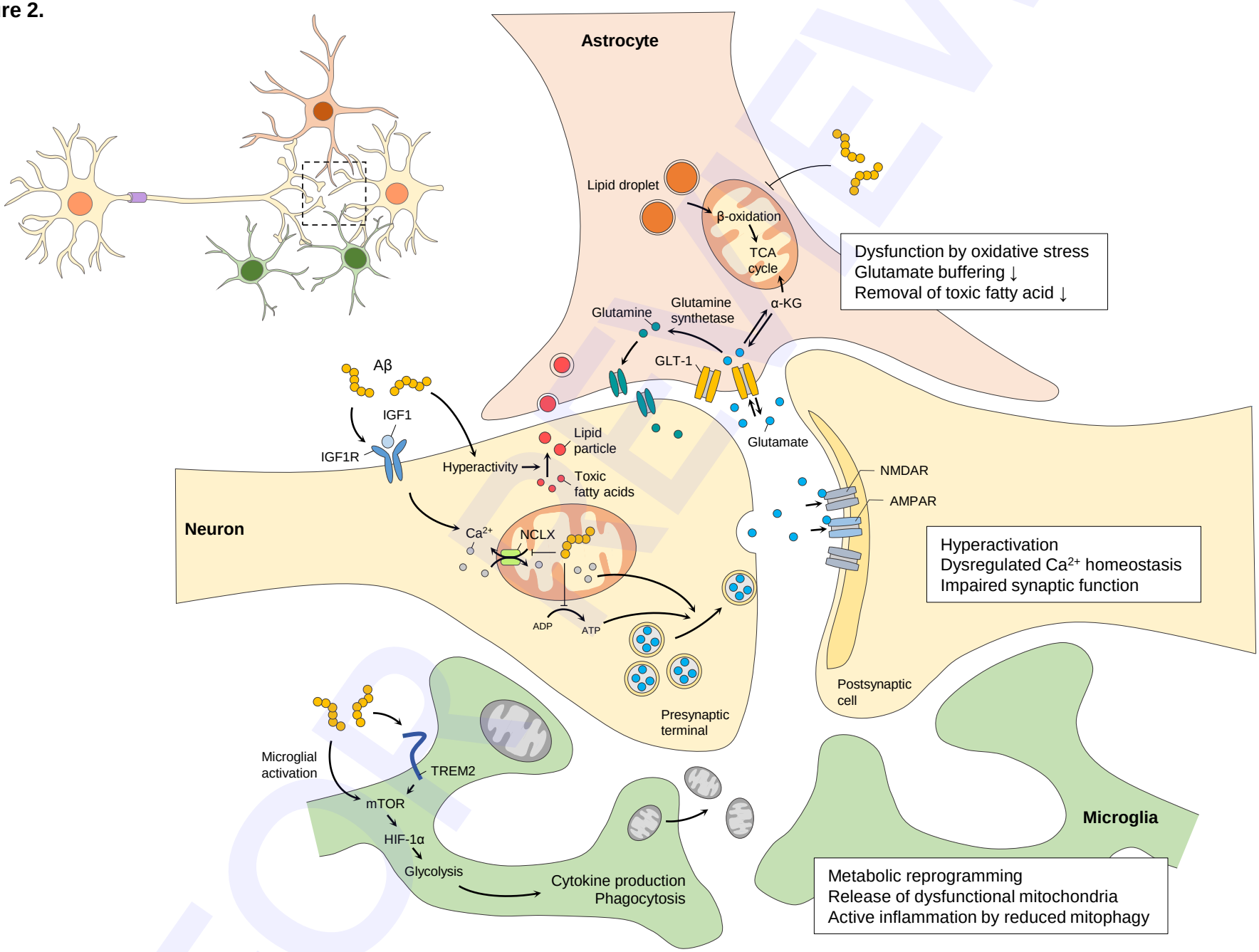

Fragmented mitochondria
Mitochondria-on a string (MOAS) structure
Aβ
DRP1
mPTP
OSCP
CypD
NO
NO
P
ATP
ATP5A
NADH
NAD+
Aβ
ADH
PreP/Cym1
ATP/ADP ratio ↓
Oxygen consumption rate ↓
Glycolytic activity ↓
Mitochondrial membrane potential ↓
NO
P
OXPHOS
ΔΨm
ATP
ADP
H2O
O2
I
II
III
IV
V
Kinesin
Ac
Ac
Ac
P
P
Phosphorylated tau
Aβ
Mitochondrial transport ↓
Abnormal mitochondrial distribution

Figure 2.


Astrocyte
Lipid droplet
β-oxidation
TCA cycle
Dysfunction by oxidative stress
Glutamate buffering ↓
Removal of toxic fatty acid ↓
Glutamine
Glutamine synthetase
α-KG
GLT-1
Glutamate
Aβ
IGF1
IGF1R
Lipid particle
Hyperactivity
Toxic fatty acids
Neuron
Ca2+
NCLX
ADP
ATP
NMDAR
AMPAR
Hyperactivation
Dysregulated Ca2+ homeostasis
Impaired synaptic function
Postsynaptic cell
Presynaptic terminal
Microglial activation
TREM2
mTOR
HIF-1α
Glycolysis
Cytokine production
Phagocytosis
Microglia
Metabolic reprogramming
Release of dysfunctional mitochondria
Active inflammation by reduced mitophagy