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Review Article

Amyloid Beta and Mitochondrial Perturbations: An Update on Mechanisms and Methods

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Abstract
Alzheimer's disease (AD) is a debilitating mental disorder that causes a gradual decline in cognitive function and memory loss. The disease is associated with the accumulation of amyloid beta (Aβ) peptide-containing plaques outside the cells and the formation of neurofibrillary tangles (NFTs) inside the neurons due to tau protein hyperphosphorylation. AD is considered a hypometabolic disease at the cellular level, characterized by decreased adenosine triphosphate (ATP) levels and elevated reactive oxygen species (ROS) levels. Mitochondria, the cellular powerhouse, provide energy for cellular metabolism and protect cells against excessive oxidative stress. During disease progression, toxic Aβ causes significant disruptions in mitochondria bioenergetics, proteolytic systems, electron transport chains, mitophagy, and mitochondria DNA (mtDNA), leading to an accumulation of damaged organelles. This results in a disruption of the cellular energy demands, ROS scavenging pathways, and autophagy. The compromised mitochondria function caused by toxic Aβ exacerbates the development and progression of AD. This review aimed to provide current insights into the interactions between mitochondria and Aβ in AD pathogenesis, highlighting the pivotal role of mitochondrial dysfunction in the disease's progression.
Keywords: Amyloid beta, Alzheimer's disease, Mitochondria, Mitophagy, ROS, ATP

Introduction

Alzheimer's disease (AD), the most prevalent and rapidly growing neurodegenerative disorder, dramatically puts a burden on individuals and societies, affecting 2% of the elderly in developed countries and accounting for nearly 50%–60% of all senile dementia cases.[1-3] The prevalence of AD rises significantly with age, particularly in people over 70 years old, and its incidence is estimated to triple by the year 2050.[4] AD clinical hallmarks are characterized by memory impairment, cognitive decline, and behavioral and personality deterioration. Histologically, AD is associated with the abnormal accumulation of extracellular amyloid beta (Aβ) plaques and the intracellular aggregation of hyperphosphorylated tau protein, known as neurofibrillary tangles (NFTs)[5,6] in the entorhinal cortex, hippocampus, basal forebrain, and amygdala.[7-9] Aβ is derived from the amyloid beta precursor protein (APP) through the proteolytic activity of two enzymes: the β-secretase (β-site APP-cleaving enzyme 1, BACE 1), and γ-secretase.[10,11] Initially, BCAE 1 cleaves APP to form soluble APP-β and membrane-bound APP-CTF. The APP-CFT is then cleaved by γ-secretase, releasing extracellular Aβ and the intracellular Aβ domain (AICD) for nuclear translocation.[12] Perturbation in the sequential proteolytic cleavage of APP by BACE1 produces neurotoxic Aβ assemblies, triggering a series of subsequent neurotoxic cascades, including tau hyperphosphorylation, NFT formation, oxidative stress, inflammatory reactions, and mitochondrial impairments.[13-16]

The human brain is a metabolically active organ that consumes nearly 16% of the body's total oxygen supply and uses up to 120 g of glucose daily.[17] Although the brain accounts for only 2% of the total body mass,[18,19] its energy demands are considerable.[17,18] The vital neuronal activity in the brain consumes energy derived from the mitochondria-dependent oxidative phosphorylation metabolism of glucose.[17] Neuronal cells can store only minimal amounts of glycogen, providing enough glucose to sustain normal functions for a few minutes.[19] Therefore, neurons must generate energy continuously to maintain their normal performance.[20,21] Unlike cells in peripheral tissues, neurons cannot tolerate drops in circulating glucose levels; hence, any decline in glucose results in altered cognitive functions, manifesting as confusion, coma, or, in extreme cases, death [19,21]. A reduction in glucose metabolism affects adenosine triphosphate (ATP) synthesis and increases the risk of oxidative stress, leading to harmful consequences for the brain.[22] It is suggested that some of the most prevalent neurodegenerative conditions such as AD and Parkinson's disease (PD) are

closely linked to brain bioenergetics impairments.[23,24] Accordingly, a substantial body of evidence, ranging from neuroimaging data in preclinical and clinical experiments to histopathological analyses in the brain of animal models, showed that disruptions in energy metabolism, bioenergetics, and mitochondrial homeostasis occur early in the progression of AD and play a pivotal role in Aβ-mediated adverse effects.[25-28] Moreover, it has been demonstrated that mitochondrial structural deficits and DNA abnormalities significantly affect AD occurrence.[29,30] Several pathways through which Aβ can induce mitochondrial malfunctions include APP-mitochondrial interaction, interaction with mitochondrial enzymes, insertion into mitochondria pores, Ca^{2+} cascade disruption, and inhibition of mitochondrial fission-fusion dynamics.[31] Overall, evidence highlights the involvement of various mitochondrial abnormalities as underlying cellular mechanisms in AD. This review focused on the multiple mitochondrial dysfunctions that lead to Aβ-induced neurotoxicity in AD.

Mitochondrial Homeostasis and Alzheimer's Disease

Mitochondria are important as the primary site of ATP production, Ca^{2+} homeostasis, and iron metabolism, and they also play executive roles in cell death, including necrosis and apoptosis. Although mitochondria have their genetic material, they are heavily dependent on their host cell for proper function. This connectivity allows mitochondria to respond to cellular metabolism under normal and stressful conditions, producing by-products such as reactive oxygen species (ROS).[32] Indeed, different mechanisms are involved in maintaining mitochondrial homeostasis, including the mitochondrial proteolytic system,[33,34] mitophagy,[35,36] mitochondrial fission and fusion,[37] and the formation of mitochondrial spheroids with lysosomes.[38,39]

Mitochondrial Proteostasis System in Alzheimer's Disease

Originating from bacteria descent, the mitochondrial genome encodes only a small number of mitochondrial proteins, which are involved in oxidative phosphorylation (OXPHOS) complexes. Almost all mitochondrial proteins (99%) are synthesized in the cytoplasm and imported into mitochondria.[40] Once imported to the mitochondria, a synchronized program assembles nuclear and mitochondria-encoded proteins, necessitating careful coordination between these two protein pools in the mitochondrial respiratory chain.[41] Cytosolic proteins have a mitochondrial targeting sequence (N-terminal peptide) recognized by mitochondrial outer membrane receptors. After binding to the receptors, proteins enter the mitochondria via the translocase of the outer membrane (TOM) complex and are then translocated to the matrix through the translocase of the inner membrane (TIM) complex.[42] Mitochondria are also the central site of oxidative damage caused by the OXPHOS cycle. Although mitochondrial ROS generated from the OXPHOS system can act as a retrograde signaling molecule that promotes cellular growth during homeostasis, ROS levels beyond physiological threshold can cause oxidative damage to proteins, lipids, and mitochondria DNA (mtDNA) during stress and aging.[43] The mitochondria proteome undergoes constant rearrangement in response to changes in cellular demand such as cell cycle progression, energy need alteration, and cellular stress.[44] All these mechanisms are regulated by a sophisticated degradation system in mitochondria to prevent the accumulation of unfavorable aggregates. At the protein level, interconnected networks of protease and chaperons monitor the number of damaged proteins. Protease quality control is a frontline of the mitochondrial defense system, which can considerably maintain protein turnover and mitochondrial integrity.[40] In healthy mitochondria, oxidatively damaged proteins resulting from ROS are degraded by the mitochondrial proteolytic system to prevent the accumulation of harmful aggregates. However, in AD and aging, disruptions in the mitochondrial proteostasis system, associated with abnormal mitochondrial proteolytic capacity, lead to the accumulation of damaged proteins.[34] The presequence protease (PreP), an independent protease located in the mitochondrial matrix, belongs to the pitrilysin family of proteases and contains an inverted zinc-binding motif. PreP is considered a mitochondrial presequence degradation enzyme which is a functional analog of an insulin-degrading enzyme.[45] Interestingly, human PreP (hPreP) contributes to the degradation of Aβ40, Aβ42, and Arctic Aβ40, a peptide associated with increased fibril formation and early onset of familial AD resulting from APP mutation.[46] Autopsy from AD patients demonstrated decreased proteolytic activity of hPreP in the temporal lobe, the most susceptible site for Aβ deposition, compared to healthy controls. Similarly, the degradation ability of PreP declined in transgenic (Tg) mice overexpressing Aβ without significant changes in PreP protein levels, suggesting functional alterations in enzyme activity through possible post-translational modifications such as protein oxidation in AD brains.[47]

It has been demonstrated that the formation of a complex between amyloid-binding alcohol dehydrogenase (ABAD) and Aβ within the mitochondria results in the reduction of ABAD activity, while simultaneously increasing ROS production and mitochondrial dysfunction. Interestingly, inhibition of the ABAD-Aβ complex decreased ROS and Aβ levels while enhancing hPreP activity.[48] Moreover, an in-vitro study of hPreP-knockout cerebral neurons showed higher levels of APP, Aβ, and the Aβ42/40 ratio, along with an enhanced mitochondrial stress response and clearance, indicating a strong relationship between mitochondrial matrix protease and AD.[49] In experimental models, mice that overexpress Aβ exhibited mitochondria accumulation as early as four months of age, even before the onset of AD pathology. However, in mice that overexpress neuronal PreP, there was a significant

decrease in Aβ deposition and receptor for advanced glycation end-product (RAGE) expression.[50] Indeed, RAGE is considered a cell-surface receptor that mediates chemotactic and inflammatory reactions in response to Aβ, promoting microglia activation in Aβ-enriched brains.[51] Interestingly, PreP-overexpressing mice exhibited decreased levels of proinflammatory mediators and improved learning and memory functions, indicating the positive role of PreP in alleviating Aβ toxicity.[52]

Mitophagy and Its Importance in Alzheimer's Disease

Mitophagy, one of the vital mechanisms in mitochondrial quality control, selectively degrades damaged mitochondria. During this process, the damaged organelles are sequestered as a double-layered membrane autophagosome, which then fuses with a lysosome to form an autolysosome, which is subsequently degraded by the lysosome's hydrolases.[53,54] In addition to removing damaged mitochondria, mitophagy is essential to regulate mitochondria numbers in response to changing cellular demands, ensuring steady-state mitochondrial turnover.[55,56] Mitophagy is activated by several cellular cascades such as increased ROS formation, mitochondrial permeability transition pore (mPTP) opening, hypoxia, and loss of mitochondria membrane potential.[57] There are various types of mitophagy, containing several signaling pathways and proteins, including dynamin-related protein 1 (Drp1), Fission 1 (Fis1), mitochondrial Rho GTPase protein (MIRO), mitofusin1 and mitofusin 2 proteins (Mfn1 and Mfn2), ptic atrophy 1 (Opa1), ubiquitin, PTEN-induced putative kinase 1 (PINK1), Parkin, Bcl-2 19-kilodalton interacting protein 3 (BNIP3), microtubule-associated protein 1A/1B-light chain 3 (LC3-1), NIX, optineurin (OPTN), FUN14 domain-containing protein 1 (FUNDC1), and Glycoprotein 78 (GP78).[55,58,59] PINK1 is a mitochondria-targeted serine/threonine kinase and acts as a mitochondria stress sensor that has proven role in neurodegenerative diseases. Parkin, a downstream of PINK1, acts as a cytoplasmic E3 ubiquitin ligase.[60] Upon mitochondrial damage, the depolarization of the inner mitochondrial membrane leads to PINK1 autophosphorylation and stabilization on the inner mitochondrial membrane. Phosphorylated PINK1 recognizes ubiquitin as a substrate and activates Parkin.[61-63] Activated Parkin targets fusion GTPase such as Mfn1 and Mfn2 as substrates, ceasing the mitochondria fusion process and segregating damaged mitochondria from healthy membrane proteins.[64] The activation of ubiquitin signaling by Parkin and PINK1 recruits autophagy receptors that induce the formation of mitophagosome and fusion of mitophagosome with lysosome for final degradation.[65] Other forms of mitophagy, namely receptor-mediated mitophagy, can occur independently of the ubiquitination pathway and are mediated by OMM adaptor proteins such as BNIP3, NIX, FUNDC1, and Bcl2-L-13, mostly under hypoxia. These receptors contain mitochondrial-targeting domains and LC3-interacting region motifs for mitochondria removal.[66,67] In AD, mitophagy impairments enhance the mass of large autophagic vacuoles in cell soma, particularly in dysfunctional neuritis. These vacuoles often fill with Aβ peptides, providing potential sites for Aβ aggression.[68] PTEN-PINK1 plays a significant role in damaged mitochondria removal by mitophagy; hence, mutations in this protein increase the mass of damaged mitochondria in neurons, causing AD pathogenesis.[69] Reports have shown a reduction in PINK1 function in AD patients; however, reestablishing PINK1 activity improved mitochondrial function.[70] AMP-activated protein kinase (AMPK), sirtuin (SIRT), and Akt are major pathways in mitochondrial function. Drp1 translocation from the cytosol to mitochondria is facilitated by Akt and inhibited by Akt inhibitors. Mitophagy and the reduction of Aβ are mainly regulated by AMPK, which is down-regulated in AD.[71] The SIRTs have been shown to have a protective effect on various age-related diseases, including AD. The SIRT family has seven isoforms, among which SIRT-I and SIRT-III have critical roles in mitophagy. Reduced levels of SIRT-I and SIRT-III have been associated with the accumulation of defective mitoplasts in AD.[72] The presenilin-1 (PS1) protein mutation, seen in early-onset of AD, impairs lysosomal degradation during mitophagy, exacerbating mitophagy disturbances. When the production of apoptotic proteases increases, mitophagy prevents protease production, thus leading to the inactivation of mitophagy and an increase in cell death.[73] Recent studies have identified massive apoptosis as one of the most fundamental events in AD pathology.[74] Autophagy deficiencies lead to the accumulation of Aβ in neural cells, causing neural impairment and memory loss.[75,76] Thus, manipulating mitophagy through novel pharmacological and genetic approaches is considered a potential therapeutic intervention in AD.

Mitochondrial Reactive Oxygen Species in Alzheimer's Disease Pathogenesis

Mitochondria are a cell's powerhouse, producing the required energy for cellular function through OXPHOS.[77,78] They regulate intracellular calcium levels, cells' redox activity, free radical clearance, and caspase-mediated apoptosis; hence, their normal performance is necessary for cellular bioenergetics and viability.[79] Unlike peripheral tissues, neurons have limited glycolytic ability, so they are extremely dependent on mitochondrial bioenergetics for energy production and survival.[80] Neurons contain a large number of mitochondria,[81] generating most of their energy via OXPHOS.[82] In the neural system, synapses have the highest energy consumption requirements.[83] Mitochondria are densely localized in these regions, providing energy and regulating Ca^{2+} concentration for neuronal synaptic functions.[84] ATP produced by synaptic mitochondria is necessary for ATP-dependent procedures such as neuronal communication, synaptic formation, action potentials generation, ion gradient maintenance,

neuronal and axonal transportation, neurotransmitters release, and uptake.[85-88] Oxidative stress resulting from cell metabolism is a double-edged sword that occurs from an imbalance between the production and accumulation of ROS.[89,90] Mitochondria are responsible for nearly half of ROS production in the cell; however, they are highly vulnerable to excessive ROS.[91] Cellular stress such as amyloid accumulation enhances bioenergetics demands, which causes mitochondria to produce more ATP to fulfill the cell's increased energy requirements at the cost of exacerbating ROS levels. ROS overproduction subsequently induces a chain of reactions, including excessive glutamate release, activation of glutamate receptors, and neuroinflammation, leading to more oxidative stress.[92] AD is characterized by hypometabolism that is associated with ATP dysfunction in mitochondria and ROS overproduction. ROS production and mitochondrial dysfunction exacerbate each other, resulting in further deficiency in AD.[24,93] ROS are mainly produced in the mitochondrial electron transport chain (ETC) complexes I and III during both physiological and pathological conditions.[94,95] Platelet mitochondria in AD patients showed a 15% decrease in cyclooxygenase (COX) activity and ATP levels, contrary to an increase in ROS levels.[96] Moreover, in-vitro studies reported that a COX inhibitor (e.g., sodium azide) and mitochondrial uncoupler such as carbonyl cyanide m-chlorophenylhydrazone (CCCP) cause bioenergetic perturbations that result in APP accumulation in the Golgi. Further in-vitro studies showed that glucose deprivation and glycolysis inhibitor (2-Deoxy-d-glucose) reduce sAPP levels. Additionally, COX inhibition by sodium azide can be reversed by GSH as an antioxidant.[97] Conversely, APP processing pathways can be influenced by glycolysis flux and the inhibition of the glycolysis-regulating enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB3), causing augmented APP accumulation and toxicity.[98]

In-vitro studies have shown that increased levels of damaged and abnormal mitochondria lead to amyloidogenic peptide overproduction.[99] Additionally, excessive ROS levels lead to Aβ deposition, which eventually causes lysosomal membrane degradation and neuronal death.[100] Aβ-mediated mitochondria dysfunction is reported early in the disease timeline progression. Oligomeric Aβ is a small hydrophobic molecule with soluble ability in the mitochondria membrane. The presence of membrane-resident Aβ induces mitochondrial oxidative stress before Aβ deposition in the AD brain.[101,102] Mitochondrial membrane potential defects observed in AD enhance the release of cytochrome c and caspase enzyme activity. Dysfunction of cytochrome c oxidase, one of the most prominent deficiencies in mitochondrial ETC in AD, enhances ROS production while decreasing energy storage and metabolism.[103] Oxidative stress induced by ROS targets lipids and proteins in the AD brain that are often measured as ROS biomarkers. Lipid peroxidation products such as 4-hydroxynonal and malondialdehyde (MDA), resulting from ROS attacks on lipids, have been observed in the hippocampus, pyriform cortex, and erythrocytes in AD brains. Furthermore, lipoxidation of ATP synthase, the main enzyme for synthesizing ATP from ADP in complex V, has been reported in the hippocampus and parietal cortex of patients with mild cognitive impairment. Localized Aβ can interact with and modify these proteins via oxidation, carbonylation, and nitrosylation.[101] Nitration of a-synuclein at tyrosine residues led to the tau protein accumulation in AD brains.[104] Interaction of Aβ with cytochrome c oxidase impairs protein activity and respiration, whereas interaction with cyclophilin-D (CypD) causes mPTP opening and inhibition of ATP synthase.[105,106] Aβ accumulation occurs early in AD, especially in synaptic mitochondria, which are extremely susceptible to synaptic Ca^{+2} changes due to high levels of CypD. CypD is a component of mitochondrial mPTP located in the matrix. As CypD transfers from matrix to mPTP, it stimulates pore formation in the inner membrane through interaction with adenine nucleotide translocase.[107,108] Persistent mPTP opening is followed by membrane potential decline, OXPHOS failure, mitochondrial matrix swelling, and mitochondrial membrane rupture, resulting in cytochrome c and apoptotic peptide release.[109] Aβ also interacts with the mitochondrial Ca^{2+} uniporter (MCU) complex, contributing to Ca^{2+} overload. Ca^{2+} accumulation in mitochondria increases ROS production, ATP synthase inhibition, mPTP opening, cytochrome c release, and eventually neurotoxicity.[110] Thus, it is assumed that inhibition of CypD, mPTP opening, and MCU can be considered a novel therapeutic option for future investigations in AD.

Mitochondria Fission and Fusion in Alzheimer's Disease

Mitochondria possess unique properties that allow them to fuse and form an interconnected reticulum. This reticulum can also divide through fission to either increase the number of mitochondria or isolate parts of the organelle for mitophagy.[111] The shape and size of mitochondria are regulated by fission and fusion, and an imbalance between them leads to abnormal mitochondrial elongation and fragmentation.[30,86,112,113] Mitochondria failure to alter their shape and size inhibits mitochondrial trafficking and, consequently, impairs mitochondrial movement and bioenergetics.[30] Mitochondrial trafficking depends on its morphology, controlled by fission and fusion. These mechanisms optimize mitochondrial morphology, and there is an equilibrium between fission and fusion in healthy neurons. Impairments in mitochondrial dynamics are associated with neurodegenerative diseases, including AD, Huntington's disease, PD, and Friedreich ataxia.[114] Evidence suggests that Aβ plays a fundamental role in perturbating mitochondrial dynamics and impairing the normal trafficking and distribution of these organelles.[80,115] Significant alterations in the size and

number of mitochondria were reported in AD patients' brains. Disturbance in the balance of fission and fusion mechanisms is associated with decreased mitochondrial number and increased mitochondrial size.[108,116] Enhanced mitochondria fission that is associated with synaptic loss has been reported as a histopathological hallmark of AD.[102] Morphological alterations of mitochondria are controlled by a set of dynamin-related GTPases. Fission is regulated by Drp1 and Fis1, whereas fusion is mediated by Mfn1, Mfn2, and Opa1.[117,118] Baek et al found that Drp1 inhibition in Aβ-treated cells and Tg mice APP/PS1 recovered Aβ-induced mitochondrial fragmentation, ROS overload, mitochondrial depolarization, and synaptic depression. They also showed that four weeks of Drp1 blockade significantly downregulated the protein and mRNA expression of BACE1 and APP CTF in APP/PS1 Tg mice,[119] indicating a positive interconnection between Aβ aggression and mitochondria fragmentation. In-vitro investigations have revealed that upregulation of mutant human APP enhances mitochondrial fission and collapse, possibly either due to Drp1 upregulation or Drp1 post-transcriptional alterations such as nitrosylation and phosphorylation.[120] Drp1 blockade was found to downregulate the protein and mRNA expression of BACE1 and APP CTF in APP/PS1 Tg mice. Moreover, postmortem analyses of human brains indicated an overexpression of Drp1 and Fis1 and downregulation of Mfn1, Mfn2, Opa1, and TOM40 genes and proteins in the frontal cortex of AD patients. Immunofluorescence analysis of AD brains also demonstrated the colocalization of Aβ and Drp1, inducing further mitochondrial fragmentation and abnormalities during disease progression.[121] Mitochondria fission and fusion abnormalities can occur due to mtDNA mutations following ROS elevation in mitochondria. Knockout of fusion proteins such as Mfn1, Mfn2, and Opa1 induces mitochondrial fractures and disrupts electron transport rates in complexes I, III, and IV.[122] Moreover, variations in mitochondrial morphology and distribution correlated with the loss of mitochondrial oxidative activity, the onset of amyloid plaque formation, and AD progression in Tg mice APP/PS1.[123-125] Rui et al reported that different Aβ fragments inhibit mitochondrial trafficking. They found that incubation of rat hippocampal neurons with Aβ within 10 minutes can block mitochondrial transportation.[126] Wang et al used two different mutants of M17 cells, namely, APP wild-type (WT) M17 and APP Swedish M17 cells, which were transfected with WT APP and APP Swedish mutant cDNA, respectively. Their findings revealed that although APP overproduction in mutant cells slightly altered the size and number of mitochondria, a significant correlation was not observed between APP levels and mitochondrial dynamic abnormalities. Conversely, they observed that Aβ secreted from these cells effectively altered both fission and fusion-related proteins and caused mitochondrial defects, consequently impairing trafficking function.[30] Similarly, Manczak et al showed that incubation of mice neuroblastoma cells with Aβ increases the expression of fission proteins, ultimately leading to swollen and fragmented mitochondria.[127]

Mitochondria Trafficking

Mitochondria can migrate from the cell's soma and accumulate in regions with high metabolic demands or increased Ca^{2+}concentration via an anterograde movement, while damaged mitochondria return to the cell body through retrograde transport.[86,116,128] These processes, known as mitochondrial trafficking, play a significant role in synaptic neurotransmission and mitigating neuronal dysfunctions such as excitotoxicity. Mitochondria can move along microtubule tracks or actin filaments. The MIRO is involved in the anterograde migration of mitochondria, interacting with the adaptor protein Milton and motor proteins kinesin 1 and kinesin 3, whereas retrograde transport of mitochondria is mediated by dynein and dynactin protein complexes.[129] Mfn2 also interacts with MIRO and is involved in mitochondria migration.[130] Mitochondria dynamics are highly dependent on environmental cues. For example, MIRO regulation occurs in response to increased Ca^{2+}levels. As Ca^{2+}levels increase in the cytoplasm, the ion binds to the MIRO's Ca^{2+}binding sites, inducing conformational changes in MIRO-Milton-Kinesin protein complexes. This interaction can inhibit mitochondria axon transport, either by disconnecting kinesin from the microtubule or dissociating Kinesin from MIRO-Milton-Kinesin protein complexes.[131] In AD, mitochondria dynamics dysfunctions exacerbate the toxic protein accumulation that is associated with axonal disintegration and neuronal loss [132]. Mitophagy dysfunctions associated with AD impair mitochondria trafficking [133]. In healthy neurons, damaged mitochondria are sent back to the soma to be replaced by new organelles. During this process, impaired mitochondria are sequestered in autophagic vacuoles and transported from synapses to the soma. This transportation involves the fusion of autophagosomes with late endosomes to form amphisomes, which are facilitated by dynein-snapin complexes. In diseased synapses, Aβ disrupts the dynein-snapin motor protein, consequently distorting retrograde transport.[134] In the AD model of Drosophila, overexpression of Aβ disrupts axonal transport, leading to mitochondria accumulation in the cell body and a reduced number of organelles in synapses.[135,136]

Intra-Mitochondrial Accumulation of Amyloid Beta

Aβ has been shown to accumulate in neuronal mitochondria in different parts of the central nervous system in AD patients. This intra-mitochondrial accumulation of Aβ precedes extracellular Aβ deposition, making mitochondria a crucial intra-neuronal site for APP and Aβ accumulation**.** Within mitochondria, APP interacts with mitochondrial import channels, and then the accumulated Aβ interacts with mitochondrial DNA,

proteins, and other components, leading to increased mitochondrial toxicity, neuronal death, and exacerbated AD.[80,137,138] Therefore, understanding the life cycle of intra-mitochondrial Aβ and the underlying mechanisms of its interaction with target proteins is crucial for developing effective therapeutic interventions for AD. Evidence has confirmed the roles of TOM, TIM, Omi protease, α/β-secretases, and γ-secretase in importing APP into mitochondria and producing Aβ. Another mechanism is the transport of Aβ to the mitochondria via endocytosis, RAGE vesicular transport.[139,140] In addition, mitochondria-associated endoplasmic reticulum membranes (MAM), which play vital roles in lipid synthesis and transport between the two organelles, fatty acid, glucose and cholesterol metabolism, Ca^{2+} homeostasis, and apoptosis, can be a potential site for Aβ synthesis and assembly in the vicinity to the mitochondria, suggesting the potential of this pathway as a cause of mitochondrial Aβ localization.[141,142]

Mitochondria DNA Modifications in Alzheimer's Disease

Although the majority of mitochondria OXPHOS elements are encoded by the cell's DNA, mtDNA also is involved in encoding mitochondria respiratory chain genes and proteins.[143] The lack of protective proteins such as histone, an efficient DNA repair system, and mtDNA proximity to the ROS production site, make it highly vulnerable to oxidative damage and increase the probability of mutations.[144] A strong correlation has been found between oxidative stress and mtDNA epigenetic manipulations, highlighting direct interactions between ROS levels and mtDNA epigenetics.[145] Recent studies have found that polymorphism in mtDNA may transfer to proteins, therefore affecting OXPHOS activity and resulting in free radical overproduction.[99,146-148] Since oxidative stress and ROS levels are significant contributors to AD progression, it is assumed that mtDNA alterations can strongly influence the disease's pathogenesis.[145,149] Data from an in-vitro study showed that oxidative stress induced by oligomeric Aβ causes S-nitrosylation of Drp1 at cysteine 644 (SNO-Drp1). Elevated SNO-Drp1 levels have also been found in the brains of AD patients, confirming the role of oxidative stress and mitochondria fragmentation in Aβ-induced epigenetic regulations.[150] S-nitrosylation accelerates the bioenergetics impairments and neuronal death through GTPase hyperactivity and elevated mitochondria fission.[151] Oxidative damage has been shown to induce single-strand double-point mutations, leading to mtDNA deletion. In addition, aging was found to be associated with high levels of mtDNA mutations, either as large deletions that produce smaller circular mtDNA molecules or as single base changes.[152,153] The number of point mutations and mtDNA deletions increases in the frontal cortex and hippocampus of AD individuals.[154] Notably, mtDNA deletions are approximately 15 times more frequent in AD individuals.[99] Higher levels of point mutations in the mtDNA control region were also observed in the AD brain, resulting in mtDNA transcription and replication errors.[154] Furthermore, A to G transitions were more prevalent in AD brains.[152] Research has reported that individuals with a maternal history of familial AD, the most inherited form of the disease, exhibit disruption in glucose uptake in the same brain regions as AD patients.[155] This confirms that the mtDNA modifications in AD patients may result from the maternal inheritance of the mitochondrial genome.[156]

Conclusion

Following the growing pace of the elderly population worldwide, the number of people suffering from AD increases year by year. Due to the multifaceted nature of the disease, which affects all parts of the organism from the cell to the genome, understanding the processes involved in AD's photobiology and pathogenesis is crucial for developing promising therapeutic strategies. Mitochondria are one of the main contributors to AD pathology. Emerging evidence shows that APP and Aβ proteins disrupt mitochondrial integrity and quality control, elevating ROS levels, oxidative stress, mitochondrial fragmentation, and mutation. Given the significant role of mitochondria dysfunctions in disease development and progression, targeting mitochondria as a main hub of ROS and ATP may contribute to effective treatment.

Authors' Contribution

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None.

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