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Review

Mitochondrial Dysfunction in Alzheimer's disease: Focus on Dynamics and Electron Transport Chain

Jiehui Li[1,2#], Gajendra Kumar[4#,*], Yuqing Yan[3#,*], Mengmeng Wang[1], Ling Xu[1], Haige Wu[2], Ye Gao[3], Yi wang[1*], Yingyi Fan[3], Ying Bai[1*]

[1]Department of Neurology, Dalian University Affiliated Xinhua Hospital, Dalian, Liaoning, 116021, China. [2]Graduate School, Dalian University, Dalian, Liaoning, 116622, China. [3]Institute of Brain Science, Shanxi Key Laboratory of Inflammatory Neurodegenerative Diseases, Medical School of Shanxi Datong University, Datong 037009, China. [4]Department of Neuroscience, City University of Hong Kong, Hong Kong.

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ABSTRACT: Alzheimer's disease (AD) is a progressive neurological disease characterized by a decline in cognitive abilities and memory loss. Mitochondrial dysfunction is a major factor in early pathological changes; however, its precise pathogenic mechanisms are not yet fully understood. Mitochondria are essential for neuronal energy generation, calcium ion balance regulation, apoptosis control, and production of reactive oxygen species. Among the various mitochondrial changes, the imbalance between fission and fusion is closely linked to β-amyloid deposition and tau pathology, forming a vicious cycle. The electron transport chain (ETC) produces more than 90% of cellular ATP and is damaged in AD. However, most studies simply refer to "mitochondrial dysfunction" in general terms without detailing specific changes in ETC complexes and their subunits. This review aims to provide a detailed overview of the dynamics and ETC complex dysfunction observed in AD for therapeutic targets.

Keywords: mitochondrial dysfunction, Alzheimer's disease, mitochondrial dynamics, electron transport chain, therapeutic strategies, neurodegeneration

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases affecting the elderly population, typically characterized by a gradual onset and a clinical course marked by persistent deterioration [1, 2]. AD is a pathological state characterized by general neuronal cell pathology with neurofibrillary tangles of highly phosphorylated tau proteins and extracellular senile plaques predominantly composed of β-amyloid (Aβ) peptides. According to epidemiological projections by Nichols et al., the global AD population may reach 100 million by 2050 [3]. The amyloid hypothesis proposes that Alzheimer's disease pathogenesis may be initiated by the deposition and subsequent aggregation of oligomeric or fibrillar forms of Aβ peptides. This hypothesis has been widely accepted for more than two decades [4]. However, therapeutic strategies targeting Aβ pathology have shown modest clinical efficacy. As reported by Boccardi et al., the correlation between Aβ plaque burden and cognitive deterioration is weak, and significant Aβ deposition is also observed in normal individuals within the elderly cohort [5]. Currently approved therapeutic drugs, such as acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the NMDA receptor antagonist memantine, can alleviate symptoms and slightly delay disease progression. However, these primarily target downstream clinical manifestations and cannot prevent or reverse neurodegeneration [6]. Increasing evidence indicates that mitochondrial dysfunction and

***Correspondence should be addressed to:** Dr. Yuqing Yan, Medical School of Shanxi Datong University, Datong, China. Email: 779734216@qq.com; Dr. Gajendra Kumar, City University of Hong Kong, Hong Kong. Email: gajendra.aiims@gmail.com; Dr. Yi wang, Dalian University Affiliated Xinhua Hospital, Liaoning, China. Email: wangyi226626@sina.com; Dr. Ying Bai. Dalian University Affiliated Xinhua Hospital, Dalian, Liaoning, China. Email: 1029981825@qq.com). #These authors contribute equally to this work.

dysregulation of mitochondrial dynamics play significant roles in the pathophysiology of AD (Fig. 1). Recent studies have suggested that targeting mitochondrial-related pathways may offer novel therapeutic approaches and strategies for early intervention and treatment of AD [2].

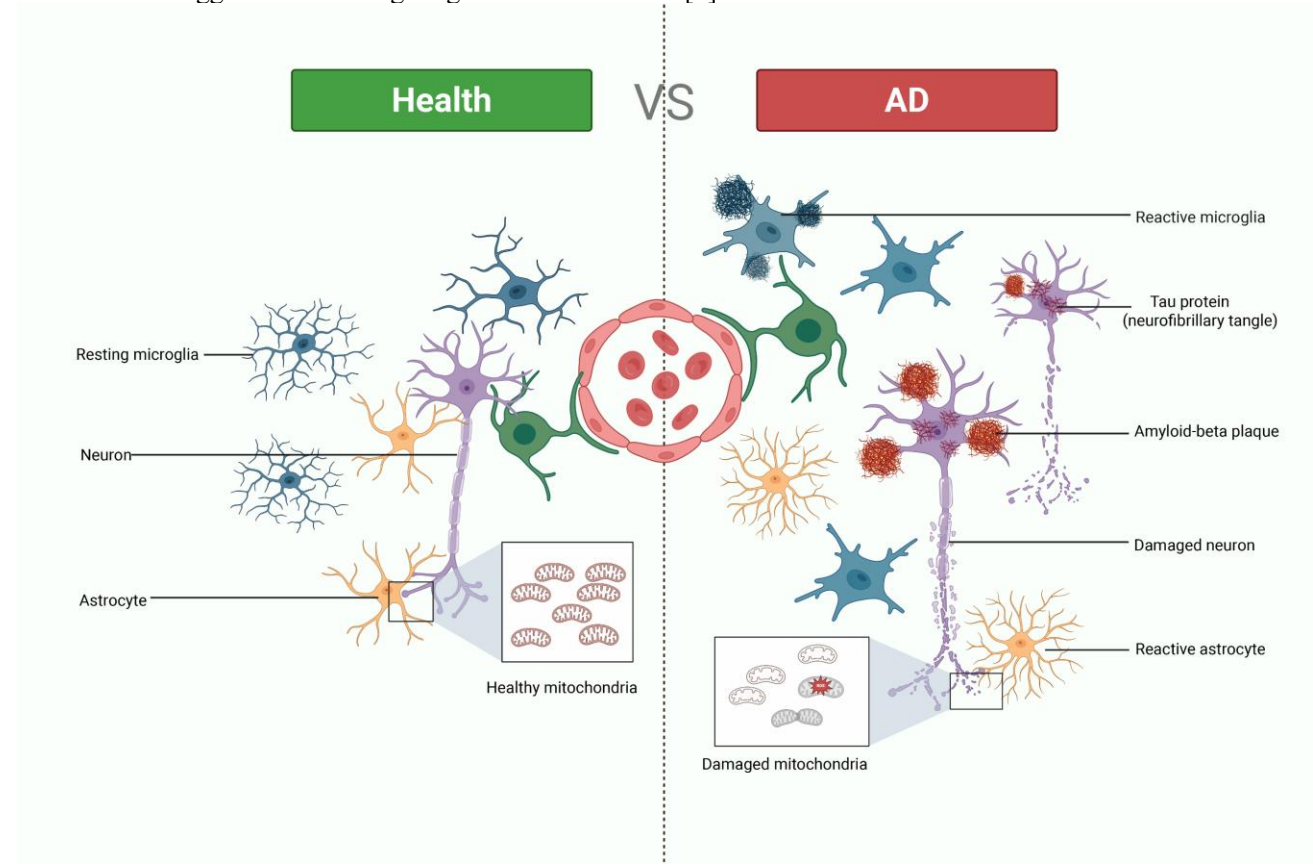

Figure 1. Schematic comparison of the brain microenvironment in healthy individuals and Alzheimer's disease (AD) patients. In the healthy brain (left), neurons, astrocytes, and microglia are in homeostasis, with resting microglia and intact mitochondria supporting normal function. In AD brains (right), reactive microglia and astrocytes, tau protein accumulation (neurofibrillary tangles), extracellular amyloid-beta plaques, neuronal damage, and severely impaired mitochondria are present. The figure points to mitochondrial dysfunction as an important pathological feature of neuroinflammation and neurodegeneration in AD.

Mitochondria are membrane-bound organelles that are primarily responsible for energy production and other cellular functions. Organelles are highly dynamic and highly regulated, enabling them to quickly adapt their shape and activity to physiological functions [7]. Fission, fusion, and autophagy are continuous dynamic cycles that control the location and number of mitochondria within cells. These processes maintain mitochondrial stability by maintaining balance [1]. Fusion allows adjacent depolarized mitochondria to merge and facilitates the formation of a fully functional mitochondrial network. Fission segregates damaged mitochondrial fragments from the normal mitochondrial network, targeting them for mitophagy. All four of these processes: fusion, fission, mitophagy, and biogenesis, help regulate mitochondrial dynamics. An accumulation of evidence has found that imbalanced mitochondrial dynamics are key for AD pathology [8-10].

Mitochondria typically provide over 90% of cellular energy through the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC), thereby generating ATP to power cellular processes [11,12]. Despite being only 2% of the body weight, the human brain uses 15% of the cardiac output and almost 20% of the total energy [13, 14]. Recent studies have shown that mitochondrial ETC dysfunction is not only an early pathological feature of AD but also a driving force in the progression of the disease. Defective ETC function results in a steep reduction in ATP production, resulting in neuronal energy deficit, which in turn gives rise to synaptic dysfunction and excitotoxic damage. ETC complexes control the leakage of excessive electrons, which produces more reactive oxygen species (ROS) and eventually causes oxidative damage to mitochondrial DNA (mtDNA) and probably to lipids and proteins. Such oxidative stress is accelerated by abnormal Aβ aggregation and hyperphosphorylation of tau proteins. Simultaneously, it

causes an imbalance in the mitochondrial membrane potential (ΔΨm), which disturbs cytoplasmic Ca^{2+} homeostasis and activates the apoptotic signaling cascade. The increased overload of Ca^{2+} into the cytoplasm and mitochondrial matrix under oxidative stress induces the opening of the mitochondrial permeability transition pore (mPTP) and activates cell death pathways. Furthermore, damage-associated molecular patterns (DAMPs) released by damaged mitochondria activate innate immune pathways, such as the NLRP3 inflammasome. This cascade of events causes a chronic neuroinflammatory microenvironment and further exacerbates neuronal injury and loss.

The ETC consists of five multi-subunit enzyme complexes embedded in the inner mitochondrial membrane: Complex I (NADH: ubiquinone oxidoreductase), Complex II (succinate dehydrogenase), Complex III (ubiquinol: cytochrome c oxidoreductase), Complex IV (cytochrome c oxidase), and Complex V (ATP synthase) [11, 15]. Each mitochondrial respiratory chain complex consists of several components [16]. The assembly and maintenance of these complexes maintain mitochondrial structural integrity and functional capacity. Disruptions in the function of even one subunit can lead to mitochondrial disorders and major pathological consequences. Mutations in NDUFA2 affect the function and assembly of Complex I [16, 17]. NDUFA4 mutations affect the function of complex IV (cytochrome c oxidase) subunits [18]. In AD, there are few comprehensive studies describing the regulatory characteristics of these complexes and their individual subunits. Few studies have systematically investigated the enzyme activity, dynamics, and subunits of ETC complexes during AD progression [19].

In our review, we focused on two aspects: mitochondrial dynamics imbalance and ETC dysfunction. Recent review articles have not discussed the changes in the individual subunits of mitochondrial complexes in AD. In the ETC, we addressed the detailed functional aspects of Complexes I, including subcomplex changes and protein abnormalities such as NDUFA1, NDUFA10, ND5, SDHB, UQCRC1, MTCO1, and ATP5H. We also discussed the impact of RNA modifications, such as N6-methyladenosine (m^6A) and N^1 -methyladenosine (m^1A), post-transcriptional regulation, and abnormal subunit localization on ETC activity. Finally, we summarized the list of new drugs targeting mitochondria and with the aim of providing new insight for early intervention in AD.

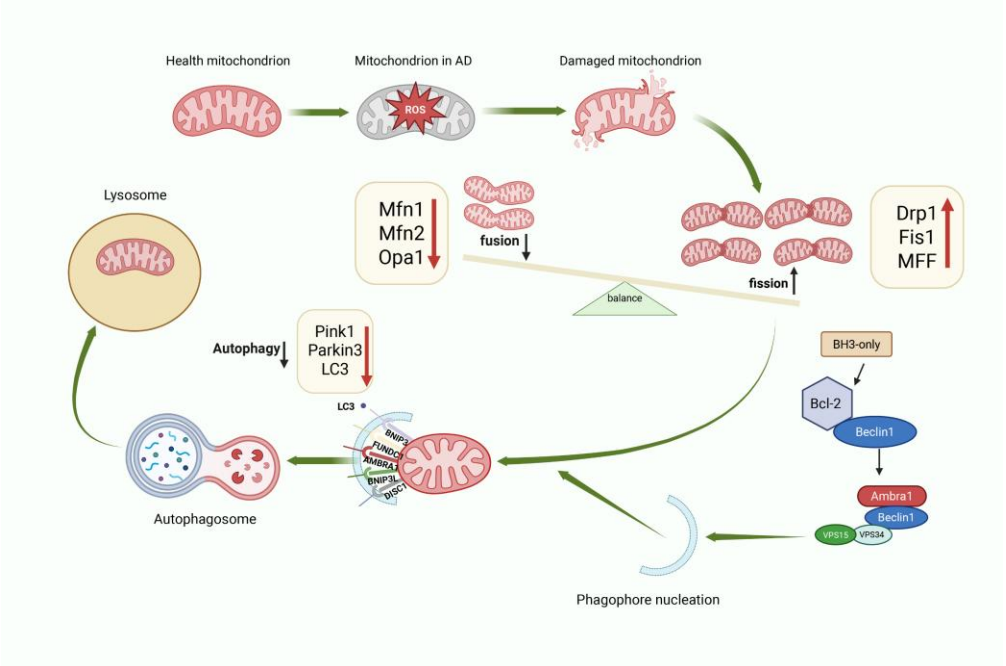

Figure 2. Schematic illustration of mitochondrial dynamic imbalance and defective mitophagy in AD. In AD, oxidative stress-induced mitochondrial damage disrupts the dynamic equilibrium between mitochondrial fusion and fission. The levels of fusion mediator proteins (Mfn1, Mfn2, Opa1) are reduced, while the levels of fission mediators (Drp1, Fis1, MFF) are elevated, resulting in excessive fragmentation of mitochondria. In normal cells, damaged mitochondria are selectively degraded by mitophagy pathways mediated by PINK1, Parkin, LC3, BNIP3, FUNDC1, and AMBRA1. These pathways are dysfunctional in AD, resulting in the accumulation of defective mitochondria. In addition, autophagy initiation is regulated by the Beclin1–VPS15–VPS34 complex, which is suppressed by Bcl-2 and BH3-only proteins. These disruptions collectively enable exacerbation of neuronal degeneration.

Mitochondrial Dynamics Dysfunction in the Pathogenesis of AD

Mitochondrial dynamics, which include ongoing fission and fusion processes, are essential for sustaining normal mitochondrial function, distribution, and quality (Fig. 2). Neurons have a high energy demand, and cells cannot be renewed by division as in other cell types; therefore, mitochondrial dynamics are particularly important [20, 21]. During the mitochondrial life cycle, fission facilitates the production of new mitochondria and the segregation of impaired organelles for elimination through mitophagy [22, 23]. Mitochondrial dysregulation, marked by excessive fission, is a significant pathological feature of AD. A detailed morphological analysis of neurons vulnerable to AD indicated a striking reduction in mitochondrial number, accompanied by an increase in mitochondrial volume [24-26]. Confocal and electron microscopy studies have confirmed that mitochondria in the brain tissue of patients with AD exhibit significant fragmentation and structural abnormalities. Mitochondria often display characteristics such as fragmentation, rounding, and shortening in length, which are often accompanied by vacuolization. The entire layout of the mitochondrial cristae was impaired and could not be distinguished. Furthermore, mitochondria exhibit typical changes in distribution within the cell bodies and axons, becoming sparse as opposed to the slender, filamentous interconnected network observed in healthy controls [27]. In brief, all the above-mentioned findings show the importance of mitochondrial dynamic impairment in both the early and late stages of AD pathogenesis.

Mitochondrial fission: This is a regulated process facilitated by dynamin-related protein 1 (Drp1). Drp1 oligomerizes into a spiral-like scaffold around mitochondrial constriction sites on the OMM and powers mitochondrial fission through GTP hydrolysis [28-30]. A study on N2a neuronal cells revealed that exposure to amyloid-β (Aβ) under AD conditions significantly increased the expression of Drp1 and Fis1. Patients with AD show higher expression of Drp1 and Fis1 in the brain than age-matched normal controls [31-33]. Aβ binds directly to Drp1, causing abnormal activation of Drp1 and leading to excessive mitochondrial fragmentation. Such interactions facilitate further ROS generation, whereby ROS increase the expression of Drp1 and Fis1 in a feed-forward loop, accentuating mitochondrial dysfunction and synaptic degeneration [1, 34].

Studies suggest that Aβ can cause mitochondrial dysfunction through some modification of Drp1. This modification could be due to the activation of LRRK2, which phosphorylates Drp1 at Ser616, Ser637, and Thr775 sites, causing an elevation in GTPase activity and fragmentation of mitochondria [35-38]. In addition, Aβ damages mitochondria through nitrosative stress. As the levels of reactive nitrogen species increase, Drp1 undergoes S-nitrosylation at the Cys644 site to form SNO-Drp1. This modification enhances Drp1 dimerization, increases its activity, and causes excessive mitochondrial fission and neuronal death [39]. In addition to its direct impact on mitochondrial fission, Aβ perturbs intracellular calcium homeostasis. It damages mitochondria-associated ER membranes (MAMs) and impairs calcium transfer between the endoplasmic reticulum and mitochondria. Aβ also interacts with L-type voltage-gated calcium channels and N-methyl-D-aspartate receptors (NMDARs), promoting abnormal calcium influx and aggravating the intracellular calcium overload [40-43]. Aβ-induced activation of Cdk5 promotes tau hyperphosphorylation, contributing to neurofibrillary tangle formation and neurodegeneration [44]. Drp1 relocation from the cytosol to the outer mitochondrial membrane interacts with fission, a process mediated by several OMM adapter proteins, including Fis1, mitochondrial fission factor (Mff), and mitochondrial dynamics proteins MiD49 and MiD51 [45]. Studies have shown that Aβ enhances the interaction between Drp1 and Fis1 in neurons and fibroblasts of patients with AD. Enhanced interaction between Drp1-Fis1 may be the primary mechanism by which Aβ contributes to mitochondrial fragmentation and cognitive impairment [45]. Mff recruits Drp1, regardless of the presence of Fis1. Knockdown of Mff results in elongated mitochondria, whereas overexpression of Mff promotes Drp1 recruitment and mitochondrial fragmentation [46, 47]. Synaptic loss is mediated by the reduction of mitochondrial numbers facilitated by Aβ oligomer-induced CAMKK2 and AMPK pathway activation, thereby phosphorylating Mff and promoting mitochondrial fission, which, together with ULK2-mediated mitophagy, acts as a destruction mechanism [48]. MiD49 and MiD51 are also important receptors for Drp1. MiD51 promotes Drp1 recruitment by binding ADP as a cofactor, whereas MiD49 directly takes Drp1 to the mitochondrial surface [49]. MiD51 function is independent of other regulatory factors, such as Mff, Fis1, and Mfn2. MiD49 plays a more critical role than Fis1 or Mff in mitochondrial fission [50]. There is no clear link between MiD49 or MiD51 and AD. The findings suggest that several mechanisms regulate Drp1 activity in AD, including phosphorylation, nitrosylation, calcium signaling, and interaction with mitochondrial adaptor proteins. Once Drp1 is hyperactive, it causes excessive mitochondrial fission, disrupts energy metabolism, and ultimately leads to neuronal death. These mitochondrial abnormalities act synergistically with tau-induced neurotoxicity, accelerating the progression of neurodegenerative diseases, such as AD.

Mitochondrial fusion: It is a two-phase procedure involving the merging of the outer and inner membranes. Outer membrane fusion is facilitated by Mfn1 and Mfn2, members of the dynein-associated GTPase family located on the outer mitochondrial membrane. Inner membrane fusion is controlled by Opa1, a member of the dynein-associated GTPase. Cells lacking Mfn1 and Mfn2 completely lose the ability of the outer membrane to fuse. Cells with Opa1 defects can complete outer membrane fusion; however, inner membrane fusion is impaired. Recent studies have revealed that mitochondrial fusion plays a crucial role in determining cell fate during neurogenesis [23]. After the division of cortical stem cells, the progeny cells undergo mitochondrial fusion and retain the characteristics of stem cells, whereas progeny cells with high levels of mitochondrial fission are more likely to differentiate into neurons [51]. Clinical studies have shown that compared to healthy individuals, patients with AD show significantly reduced expression of the mitochondrial fusion proteins Mfn1, Mfn2, and Opa1 in brain tissue. This suggests that mitochondrial fusion dysfunction may contribute to the mitochondrial dysfunction observed in AD [52].

Opa1 overexpression improves the structure of mitochondrial cristae, mitigates mitochondrial fragmentation, and promotes mitochondrial integrity and function in primary neurons [53]. Opa1 also orchestrates the function of microglia. Microglia are immune cells in the brain that clear Aβ protein deposits involved in AD. Studies have shown that increased Opa1 levels enhance ATP production, thereby supporting microglia in clearing more Aβ proteins [54]. Opa1 enhances microglial metabolism, possibly by reducing the glycolytic enzyme HK2. HK2 depletion in microglia shifts energy metabolism from glycolysis to oxidative phosphorylation by enhancing mitochondrial efficiency. Metabolic reprogramming may explain the functional improvement of microglia when Opa1 is upregulated. Therefore, Opa1 is a therapeutic candidate for AD through targeting mitochondrial dynamics.

Mitophagy dysfunction in the Pathogenesis of AD

Mitochondrial autophagy ensures the maintenance of mitochondrial homeostasis and functional integrity [55, 56]. Mitophagy is regulated by three mechanisms: the PINK1/Parkin pathway in response to mitochondrial depolarization; NIP3/NIX, involved during reticulocyte maturation, and FUNDC1 receptor-mediated autophagy, which acts at the mitochondrial outer membrane (OMM) [57]. The PINK1/Parkin pathway initiates the mitophagy signaling cascade [58, 59]. PINK1 is transported into the mitochondria and swiftly degraded [60, 61]. Consequently, in the presence of damaged or depolarized mitochondria, PINK1 fails to be imported and thus accumulates on the OMM, where it phosphorylates ubiquitin and Parkin [62, 63]. Physiologically, activated Parkin ubiquitinates outer mitochondrial membrane proteins, including voltage-dependent anion channels (VDACs), marking dysfunctional mitochondria for autophagosome sequestration and lysosomal degradation, thereby preserving cellular homeostasis [64]. The formation of autophagosomes is highly regulated by Beclin-1. This is achieved through the formation of the PI3K-III complex, along with Vps34 and Vps15. This interaction is modulated by Bcl-2 family proteins and through the phosphorylation of Beclin-1 by ULK1 [65]. Mitophagy occurs through Beclin-1-dependent and-independent pathways. It incorporates Rab and Atg9, which are often activated by specific stimuli or pathophysiological states. AMPK activation or mTORC1 inhibition triggers ULK1 phosphorylation and initiates mitophagy by recruiting PI3P effectors to form pre-autophagosome structures [66].

The BNIP3/NIX pathway facilitates mitophagy by directly interacting with LC3, a process that is critical during erythrocyte maturation and protective against ferroptosis [56, 67]. The FUNDC1 pathway promotes mitophagy under hypoxia by binding LC3 and coordinating mitochondrial protein quality control via interactions with HSC70 and TOM-TIM [68, 69]. Mitophagy declines progressively in AD and correlates with disease severity [70]. Key mitophagy proteins, including Bcl2L13, PINK1, BNIP3L/NIX, p-ULK1 (Ser555), FUNDC1, AMBRA1, and MUL1, are downregulated in the brains of patients with AD and iPSC-derived cortical neurons, indicating defective mitophagy [71]. PINK1 is elevated in early AD, whereas the levels of PINK1 and Parkin decrease in the late stage, accompanied by the accumulation of autophagy markers LC3-II/I and SQSTM1/p62, suggesting an initial compensatory response followed by pathway failure [70]. Impaired mitophagy results in the development of mitochondrial autophagosomes in neurons, disrupting synaptic structure and function and contributing to cognitive decline [72, 73].

Lysosomal dysfunction, marked by the downregulation of transcription factor EB (TFEB) and lysosomal proteins such as LAMP1, exacerbates mitophagy impairment in AD [74]. Aβ buildup in autophagic vesicles impedes their fusion with lysosomes, leading to mitochondrial dysfunction [75]. Therapeutic strategies that restore lysosomal function, such as nicotinamide riboside supplementation in APP/PS1 mice, enhance mitophagy, reduce Aβ pathology, and improve cognition [76]. Nicotinamide mononucleotides (NMNs) and Urolithin A promote neuronal mitophagy and ameliorate synaptic deficits in a preclinical AD model

[75]. Increased activation of the mitochondrial calcium uniporter (MCU) disturbs calcium balance within the organelle and results in mitophagy failure. Calcium overload promotes mitochondrial permeability transition pore (mPTP) opening and membrane depolarization, followed by mitochondrial swelling and the release of apoptotic factors, leading to neuronal death [77, 78]. Elevated calcium disrupts PINK1 stabilization on mitochondria and blocks Parkin recruitment and mitophagic clearance [79]. Pathological tau damages the normal function of the mitochondrial calcium uniporter (MCU) and aggravates mitochondrial calcium imbalance. It also amplifies defects in mitophagy and accelerates neuronal degeneration [80]. Impaired mitochondrial autophagy leads to the accumulation of misfolded proteins, including Aβ and hyperphosphorylated tau, exacerbating mitochondrial dysfunction and calcium homeostasis imbalance, and establishing a vicious cycle [81, 82]. Pathological changes in tau, particularly its interactions with Aβ, further impair mitochondrial transport and exacerbate oxidative stress. Phosphorylation of tau at specific sites cannot cause mitochondrial damage; rather, it is the cumulative effect of many pathological changes that accelerate neurodegeneration [83]. Superfluous expression of tau protein raises the level of base parkin but interferes with mitochondrial transport. When APP is simultaneously expressed, this inhibitory effect becomes more striking and points to a synergistic disruptive effect on mitochondrial autophagy [71, 84]. This finding may indicate that defective mitophagy is a common element involved in AD, with tremendous potential in therapeutic approaches aimed at mitophagy and lysosomal pathways.

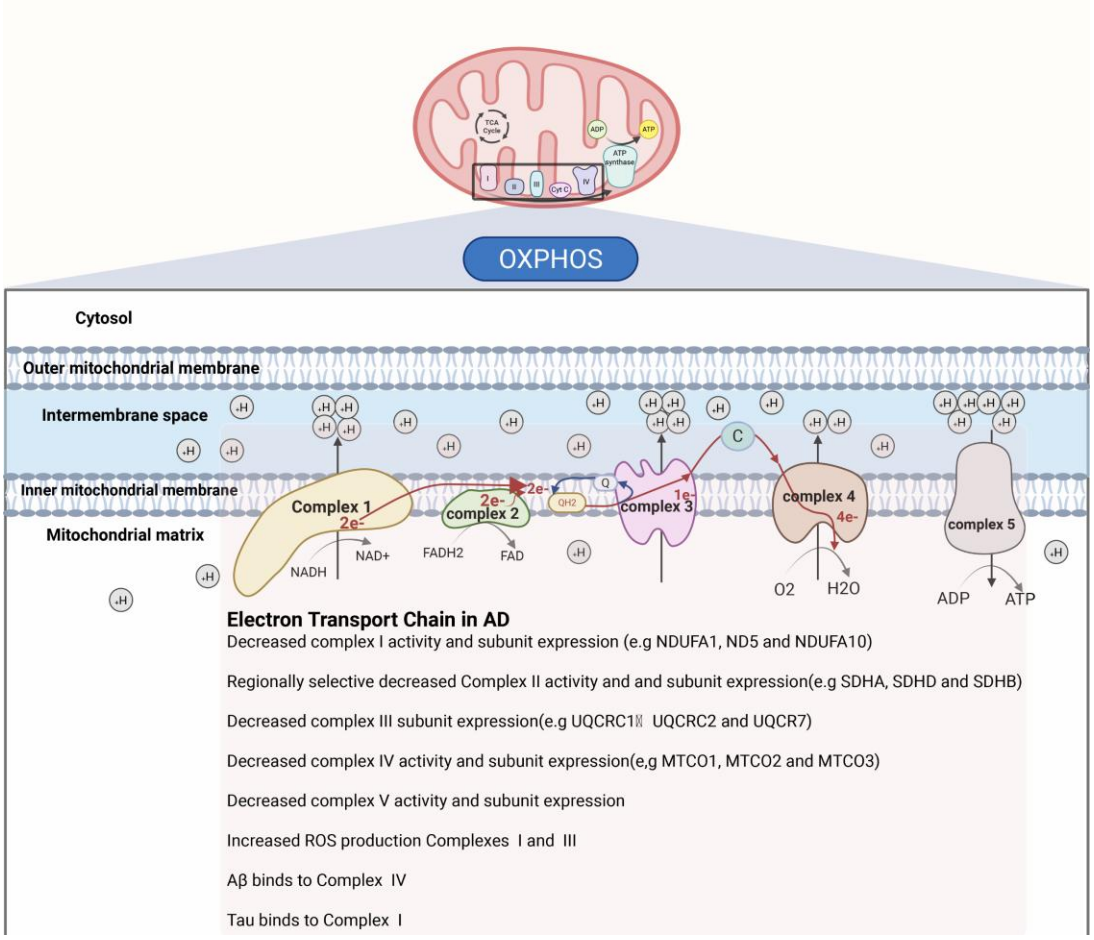

Figure 3. Mitochondrial electron transport chain (ETC) dysregulation in AD. The mitochondrial ETC is composed of five multi-subunit complexes (I–V) embedded in the inner mitochondrial membrane, responsible for oxidative phosphorylation (OXPHOS) and ATP synthesis. In AD, the activity and subunit expression of several ETC complexes are reduced. Complex I has diminished function and subunit expression of NDUFA1, ND5, and NDUFA10. Complex II contains regional deficiencies that include SDHA, SDHB, and SDHD. Complexes III and IV also display defective subunit expression (e.g., UQCRC1, UQCRC2, MTCO1, MTCO2), with amyloid-β (Aβ) being associated with complex IV and tau protein with complex I. These dysfunctions lead to enhanced production of reactive oxygen species (ROS), mainly from complexes I and III, thus contributing to mitochondrial dysfunction and neuronal degeneration.

Impact of ETC Complex Dysfunction on Neuronal Degeneration in AD

The ETC on the inner mitochondrial membrane generates ATP by the sequential passage of electrons and pumping of protons (Fig. 3). NADH carries electrons into the system through Complex I. Similarly, Complex II carries electrons from FADH2, but does not establish a proton gradient. Both electron routes combine at the ubiquinone site, where electrons are sequentially transferred to Complex III, cytochrome c, and finally Complex IV, which reduces oxygen to water. The resulting proton gradient drives Complex V (ATP synthase) to produce ATP. As the ETC is impaired, specifically in Complexes I and IV, oxidative phosphorylation efficiency declines and ROS levels increase. It is a significant component to the neurodegenerative pathology in AD.

Complex I (NADH Dehydrogenase): Complex I (NADH: ubiquinone oxidoreductase) is the most substantial multiprotein complex in the mitochondrial ETC and is pivotal in cellular energy metabolism. In the human body, Complex I consists of 45 subunits. These include 14 evolutionarily highly conserved "core" subunits responsible for catalytic functions such as NADH oxidation, ubiquinone reduction, and proton translocation, as well as 31 auxiliary subunits involved in the complex's structural stability, assembly, and regulation [85-87]. The seven core subunits encoded by mitochondrial DNA (ND1, ND2, ND3, ND4, ND4L, ND5, and ND6) form a hydrophobic membrane segment integrated within the inner mitochondrial membrane. The remaining core subunits (NDUFS1, NDUFS2, NDUFS3, NDUFS7, NDUFS8, NDUFV1, and NDUFV2) are encoded by nuclear DNA and form a hydrophilic arm that extends into the mitochondrial matrix. This hydrophilic arm contains redox cofactors, including flavin mononucleotide (FMN) and eight iron-sulfur (Fe–S) clusters, and plays a significant role in NADH oxidation and subsequent electron transport [85, 88].

Dysfunction of Complex I has been associated with the pathogenesis of AD. Proteomics analysis showed a significant reduction in the expression of multiple subunits of Complex I in postmortem brain tissue of patients with AD [19]. Alterations in the NDUFA4 and NDUFA9 subunits indicate instability between the membrane arm and the matrix arm [16]. Absence or reduction of NDUFA1 expression weakens the structure of Complex I, impairing its stability and function [89]. These defects are accompanied by a reduction in the total levels of mitochondrial protein (almost 2 – 4%) in AD brains, suggesting possible damage to mitochondrial biogenesis or protein synthesis machinery [90]. Post-transcriptional regulatory and RNA epigenetic modifications would also be involved. The ND5 subunit was found to be considerably decreased at the protein level in AD models and patient brain tissue but mRNA levels remained normal to even elevated. This difference is linked to abnormal m^1A methylation carried out by TRMT10C, inhibiting the translation of ND5 mRNA. Then there is Aβ-induced oxidative stress that increases TRMT10C expression, which in turn creates a positive feedback loop that worsens mitochondrial dysfunction [91]. Another finding is that NDUFA10, a nuclear-encoded subunit, is important for the assembly of Complex I. In the brain of AD cases, due to reduced METTL3 expression, m^6A methylation levels of NDUFA10 mRNA decreased and so does the protein level, resulting in impairment in Complex I functions. Such an abnormal epigenetic regulation may hamper the normal functioning of the electron transport chain, thus accelerating neurodegenerative damage [92].

Neuroimaging studies support regional Complex I activity impairment in the early stages of the AD. PET imaging using the new tracer [^{18}F] BCPP-EF indicates a significant decrease in Complex I activity in the medial temporal lobe (including the olfactory cortex and the hippocampal cortex) and prefrontal cortex regions. However, the decline in activity of the complex is negatively correlated with tau protein deposition, as determined by the Braak staging, whereas the same does not apply to Aβ accumulation. Thus, dysfunction of the complex might represent an early stage, tau-related event in pathological progression of AD [93]. Animal studies have also confirmed this. A remarkable decrease in mitochondrial complex I activity was observed in the hippocampus of TgF344-AD rats with APP/PS1 mutations, which also had impaired oxidative phosphorylation efficiency [94, 95]. In AD, increased activity of Complex I in peripheral lymphocytes represent a compensatory mechanism of cells to meet the enhanced energy requirements or possibly impairment of other components of the ETC [96, 97]. This idea was further supported by the study of fibroblasts from patients with SURF1 mutations, in which a reduced activity of complex IV caused its compensation by an increase in the expression and activity of complex I [98]. Notably, the pathology linked to Complex I seems to be more tightly associated with tau protein changes than Aβ. Imaging studies using [^{11}C]PBB3 showed that the functional decline of Complex I in certain brain regions is positively correlated with deposits of tau protein but has no significant association with amyloid deposition [93, 94]. These findings indicate that mitochondrial complex I not only plays a key role in the pathogenesis of AD but may also be a promising therapeutic target. Therefore, in-depth research into its regulatory mechanisms and potential applications in early diagnostic imaging and intervention is of great importance.

Complex II (succinate dehydrogenase; SDH): Mitochondrial Complex II, also called succinate-ubiquinone oxidoreductase or succinate dehydrogenase (SDH), consists of four subunits encoded by nuclear genes: SDHA is a flavoprotein that is covalently bound to FAD, SDHB is an iron-sulfur protein containing multiple iron-sulfur clusters, while the membrane-anchored SDHC and SDHD subunits possess heme [99]. Unlike complexes I, III, and IV in the respiratory chain, complex II is completely encoded by nuclear DNA. Thus, its function remains relatively intact in many diseases associated with mitochondrial DNA (mtDNA). In patients with mtDNA defects, cytochrome c oxidase (COX) activity is reduced, while succinate dehydrogenase (SDH) activity remains normal. However, dysfunction of complex II may play a role in the etiology of AD. Studies have shown regional variations in succinate dehydrogenase (SDH) activity within the brains of AD patients. Mutisya et al. observed a decrease in activity of Complex II in AD patients' occipital cortex, while no significant changes were noted in other cortical regions [100]. In mouse models, 3xTg-AD and APP/PS1 mice, Complex II activity gradually declines with age. Although APP/PS1 mice exhibit Aβ deposition as early as 4 months of age, the decline in Complex II activity typically becomes apparent around 9 months of age, suggesting that mitochondrial dysfunction may be a downstream consequence of Aβ pathology [101]. In addition to reduced enzyme activity, there are also changes in complex II subunits expression. Chua et al. found that amyloid precursor protein (APP) isoforms with Kunitz protease inhibitor domains, such as APP751, can downregulate Complex II subunits and thus impair mitochondrial function. This leads to an imbalance in the NAD^+/NADH ratio and mitochondrial membrane potential disruption [102]. Troutwine et al. demonstrated the possibilities of reduced SDHB-expression levels in AD brains [103]. Proteomics analysis by Adav et al., levels of SDHA and SDHD are significantly reduced in early-onset AD patients, whereas they were not significantly altered in either healthy elderly ones or late-onset AD patients. These observations suggest that expression changes are specific in this disease for the Complex II subunits [19]. AD has also been associated with structural abnormalities of SDH protein, besides being subject to alterations in expression levels. Changes have been detected in regard to lysine residue accessibility in the SDHB protein in brain tissue from AD patients, and this could be linked to protein misfolding or aggregation in neurodegenerative pathology [104].

Such dysfunctions involving Complex II are not confined to the brain and spinal cord; other studies show defects in peripheral tissues such as platelets in AD patients, suggesting that Complex II may have potential value as a systemic biomarker [105]. Neuroexosomes in the plasma of AD patients have shown marked reduction in the expression of SDHB. It suggests that low levels of SDHB, not only predict the development from mild cognitive impairment (MCI) to AD but also associate the structural changes, such as hippocampal atrophy and cortical thinning. Hence, it could be useful in diagnostic and prognostic assessment [106]. Lipopolysaccharide (LPS) activates SDH, promoting HIF-1 α stabilization, glycolytic reprogramming, and proinflammatory factor production, while drugs inhibiting the SDH (e.g., dimethyl propylene glycol) reduce inflammation and induce anti-inflammatory phenomena in microglia [107]. Succinate dehydrogenase (SDH) is essential for neuroinflammatory reaction and involved in AD. Being fully encoded by nuclear genes and with their functional activity well-maintained in case of mtDNA-related diseases, Complex II has been a "stable complex" in the mitochondrial respiratory chain. Recent studies, however, have revealed functional alterations in this enzyme in AD. Thus, mitochondrial dysfunction in AD entails energy deficits, post-transcriptional regulation, structural alterations, and immunometabolism disturbances.

Complex III (Cytochrome c Reductase): Mitochondrial complex III (CIII), also called the cytochrome bc1 complex (ubiquinol-cytochrome c reductase). The mammalian CIII monomer consists of three catalytically active subunits: cytochrome b (MTCYB), cytochrome c_1 (CYC1), and the Rieske iron—sulfur protein (UQCRFS1). There are also two core structural subunits (UQCRC1 and UQCRC2) and six low-molecular-weight subunits (UQCRH/QCR6, UQCRB/QCR7, UQCRQ/QCR8, UQCR10/QCR9, UQCR11/QCR10, and a cleavage product of UQCRFS1) [108, 109]. Among them, three catalytic subunits are encoded by mitochondrial DNA, whereas the remaining subunits are encoded by nuclear DNA. Functionally, CIII exists as a dimer ($CIII_2$, ~450 kDa), although the two monomers function independently or in a coordinated manner [110]. CIII dysfunction is associated with the pathogenesis of AD, particularly in early onset. Transcriptomic and proteomic studies have consistently demonstrated downregulation of CIII subunits including UQCRC1, UQCRC2, and UQCRB in brains of AD patients, with pronounced deficits in temporal cortex [19, 111].

However, findings from animal models suggest a more nuanced role for CIII dysfunction. In AD mouse model with an extra target deletion of an essential subunit of CIII (CIII^KO-AD), it was indeed paradoxical to observe a reduction in amyloid-β (Aβ) plaque burden notwithstanding increased oxidative stress and activity of the 20S proteasome [112]. These findings suggest that improved proteasome activity may contribute to the clearance of Aβ42 fragments as a compensatory response to mitochondrial dysfunction. This result goes against the

assumption of a mitochondrial OXPHOS obstruction necessarily leading to Aβ accumulation. Moreover, considering these, studies have also shown that complex III inhibition alone may not necessarily worsen amyloid pathology. In general, mitochondria play a role in AD, particularly in interventions targeting CIII and OXPHOS. The deficiency of CIII not only affects its own activity but also impairs the structure and function of mitochondrial respiratory super complex (SC). SC is a multi-enzymatic system composed of complexes I, III, and IV, and CIII2 dimer is important to maintain the stability and efficient electron transport of the whole complex. Mutations in the CIII subunit (e.g., the deletion of the mitochondrial cytochrome b gene MT-CYB) prevent the dimerization of CIII, resulting in abnormal intermediates and thereby disrupting the assembly and function of complex IV [113]. Previous studies have focused mainly on functional changes in individual complexes; further investigation is needed to focus on the dynamic assembly processes of mitochondrial super complexes, the interdependence between various complexes, and the roles of their synergistic interactions in overall mitochondrial function.

Complex IV (cytochrome C oxidase, COX): Mitochondrial complex IV (COX) in the ETC limits the oxidation phosphorylation. Its activity is used to assess mitochondria's respiratory performance and the overall energy status of cells. Complex IV consists of 13 subunits, three of which are encoded by mitochondrial DNA (COX1, COX2, COX3), and the remaining 10 structural subunits (COX4, COX5A/B, COX6C, COX7A/B/C, COX6A1/2) are encoded by nuclear genes. Due to "double genetic origin", COX functions are easily compromised as the transcription or translation of nuclear and mitochondrial genes becomes incompatible.

Reduced cytochrome c oxidase (COX) activity and abnormal subunit expression are widely recognized as characteristics of AD. A multitude of evidence indicates that COX activity is markedly diminished in postmortem brain tissue from AD patients, including the frontal, temporal, and parietal cortices, while the occipital cortex and nucleus accumbens are often spared [114, 115]. Notably, these alterations extend beyond the central nervous system. COX defects have also been observed in peripheral cells, such as platelets, suggesting its potential as a systemic biomarker for mitochondrial dysfunction in AD [115].

Abnormal expression involving mtDNA and nuclear DNA-encoded COX subunits has been noted in AD. Reduced mRNA expression of mitochondrial MTCO1 and MTCO2 subunits has been observed in the mesial temporal lobe, and, in general, nuclear-encoded OXPHOS components are generally downregulated across whole-genome microarray analyses in hippocampal tissue [116, 117]. Notably, few studies have reported paradoxical increases in COX protein levels and mtDNA content in the hippocampus, frontal lobe, and temporal cortex, despite reduced enzymatic activity. However, studies have shown that many of these proteins and mitochondrial DNA are not localized within the mitochondria but abnormally distributed in the cytoplasm. This phenomenon may indicate either accelerated mitochondrial renewal processes or malfunctions in protein degradation mechanisms [118, 119]. Research indicates that amyloid beta (Aβ) protein may directly interfere with normal mitochondrial function. In the brain tissue of Alzheimer's patients, Aβ was detected and aggregated within mitochondria and interacted with key components of the ETC [120-122]. More precisely, $A\beta_{1-42}$ attaches to the N-terminal region of cytochrome oxidase 1 (COX1) and thus inhibits the enzymatic activity, which ultimately impairs mitochondrial energy metabolism [123]. Experimental evidence shows the inhibition of cytochrome oxidase activity by Aβ exposure, decreased levels of adenosine triphosphate (ATP), and cognitive impairment, particularly in the hippocampal region [124]. Oxidative stress is among the critical pathologic manifestations of AD and further impedes the function of cytochrome oxidase. Some modifications induced by ROS could hamper the structural stability of the enzyme, thereby reducing its activity. Interestingly, some studies suggest decreased COX activity to be a direct pathological damage or compensatory response. Fukui et al. have shown the inhibition of COX activity to lower β-secretase activity and the ROS production, and thereby Aβ deposition. This indicates that under certain pathological conditions, COX downregulation may help alleviate oxidative stress [125]. Most of these studies are postulated to be late-stage AD models and thus treated, so it is not yet clear whether their conclusion applies to an early stage of either disorder. Complex IV dysfunction in AD stems from both the direct toxicity of Aβ and many other determinants such as oxidative stress, altered subunit expression, and disturbed mitochondrial-nuclear signaling. A deeper understanding in the regulation behind dysfunction of cytochrome c oxidase is the key to developing targeted therapies to restore mitochondrial function and consequently slow down neurodegenerative damage.

Complex V (ATP Synthase): Mitochondrial F_1F_0 ATP synthase (complex V) is a terminal enzyme in the oxidative phosphorylation system, converting the proton gradient created by the ETC into ATP. ATP synthase is composed of two major domains: the F_0domain is embedded in the inner membrane and is the proton channel, and the F_1 domain is in the matrix and converts ADP and inorganic phosphate into ATP [126, 127]. In mammals, F_1F_0 ATP synthase has a molecular weight of around 600 kDa and is made up of somewhere between

16 and 20 subunits. The F_1 catalytic domain has the stoichiometry $\alpha_3\beta_3\gamma\delta\varepsilon$ [128]. The F_0 complex is formed by several smaller subunits which carry out proton translocation and mechanical rotation. The ATP synthase structures exist in two forms, monomers and dimers. These dimers are crucial to conditioning the mitochondrial cristae and are also implicated in the formation of the mitochondrial permeability transition pore (mPTP), which takes part in cell death processes [129, 130].

Clinical studies, animal models and cellular experiments show severe impairment of the F_1F_0 type ATP synthase in AD [131-135]. In AD brain, ATP synthase subunits encoded by nuclear genes in four main brain regions: posterior cervical cortex, CA1 region in the hippocampus, medio temporal gyrus, and entorhinal cortex are impaired [136]. Early proteomics studies on mitochondria isolated from human tissues employing Blue Native-PAGE report decreased expression of intact ATP synthase complexes in the hippocampal regions of AD patients [137]. In AD, the α subunit of mitochondrial F_1F_0 ATP synthase serves as the central hub integrating several pathological signals including Aβ toxicity, oxidative stress, and disorders of energy metabolism. In Tg2576 transgenic AD mice, the expression of α-subunit increases significantly with Aβ deposition. The binding capacity of APP and Aβ domains by N-glycosylation is considered important in the process of AD pathogenesis [138]. These interactions on neuronal plasma membranes inhibit extracellular ATPase activity, thereby diminishing ATP supply at synapses and affecting neural signaling [139]. Immunohistochemical and ultrastructural analyses showed increased colocalization of the α-subunit with neurofibrillary tangles, suggesting a direct association of accumulation on cytoskeleton-related aggregates [133].
Beyond these structural interactions, post-translational modifications of the αsubunit also require attention [135]. In Braak stages I-II, preceding clinical symptom onset, the αsubunit may undergo modification by 4-hydroxy-2-nonenal (HNE), resulting in approximately 30% reduction in ATPase activity [140, 141]. The β subunit expression is typically downregulated in the brain tissue of AD patients and animal models, whereas few proteomics studies indicate upregulation [142-144]. These discrepancies may reflect compensatory responses across different brain regions or temporal variations in disease progression, or they may be related to differences in the experimental models. In addition, the δ subunit encoded by the ATP5D gene is upregulated in the brains of AD patients, while the d subunit encoded by the ATP5H gene shows reduced expression in the hippocampal region of 3xTg-AD mice and in the medial prefrontal cortex of human AD patients [19, 145, 146]. In genome-wide associations, ATP5H may represent a genetic susceptibility locus for AD [146], which further supports the notion that changes in the subunits may increase disease risk and promote the progression of pathological processes.

Systemic aging mechanisms

In addition to mitochondrial dysfunction in the brain, aging-related systemic changes lead to further deterioration of the brain's mitochondrial resilience, hence contributing to mitochondrial damage associated with AD. During the aging of the body, chronic low-grade inflammation may gradually develop in the whole of the body [147]. Cellular senescence is accompanied by the release of a series of inflammatory signals including IL-1α, IL-1β, IL-6, IL-8, and TNFα and collectively referred to as SASP (senescence-associated secretory phenotype) [148]. With increasing age, the levels of SASP increase, resulting in the accumulation of cellular metabolic by-products in the organism. Overproduction of ROS by mitochondria disturbs the permeability of the mitochondrial membrane and increases the oxidative damage caused by Aβ and tau proteins [147, 149]. At the same time, both aging and inflammation release DAMPs (like mtDNA, ATP, and HMGB1) from within and outside cells. These molecules interact with Toll-like receptors (TLRs) and the NLRP3 inflammasome, causing an inflammatory response and enhancing the release of ROS. It is coupled with mitochondrial injury and leads to a continuous chain of adverse events [150, 151]. Also, the processes of autophagy and mitophagy become less efficient with age and become unable to remove the damaged mitochondria on time. The accumulation of damaged mitochondria, release of ROS, lipid oxidation products and mtDNA, further exacerbates the inflammation response [152]. Insulin-like growth factor 1 (IGF-I) plays an important role in maintaining the homeostasis of the brain through neurogenesis, synaptogenesis, and neuroprotection. Elevated level of serum IGF-I has been reported to be associated with cognitive functions and overall brain health [153]. IGF-I level is modulated by AD pathology, including the accumulation of Aβ, loss of glucose metabolism, oxidative stress, chronic inflammation and neuronal death. In addition, as the levels of sexual hormones (such as testosterone) decrease with age, mitochondrial damage is exacerbated. In aged male rats, testosterone supplementation significantly improves mitochondrial dysfunction in the brain by increasing the levels of mitochondrial membrane potential, antioxidant enzymes expression/activity, and mitochondrial respiratory complex activity [154].

Therapeutic Strategies for Reducing Mitochondrial Dysfunction in AD

Research into the development of AD indicates that mitochondrial dysfunction is a primary contributor to neuronal death. Therefore, treatments targeting mitochondrial pathways or their regulatory factors are becoming increasingly prominent in the intervention of AD. Many mitochondrial-focused treatments are under development, including antioxidant strategies, agents that stimulate mitochondrial biogenesis and stability, and medications designed to preserve mitochondrial DNA integrity and respiratory chain activity (Fig. 4). This review deals with some of the most representative and promising approaches to mitochondria-targeted treatment in current AD research and aims to analyze the possible synergic effects that multi-targeted combined regulation may have in offering an answer to the extreme complexity in the pathophysiology of AD (Tables 1 and 2).

Table 1. Candidate drugs primarily exert their effects by regulating mitochondrial autophagy/dynamics and clearing pathological proteins.

Potential drug	Mechanism of action	References
Mdivi-1	Inhibits Drp1, attenuates oxidative stress, reduces the effects of Ca^{2+} overload and limits Aβ deposition	155-159
DDQ	Improves mitochondrial biogenesis and flux by inhibiting Drp1-Aβ Interaction	160-167
Rg1	Activates AMPK; inhibits p-Drp1; promotes mitochondrial fusion; reduces Aβ and tau pathology	168
Spermidine	Enhances autophagic flux; promotes protein clearance; reduces Aβ and tau pathology	169-177
Resveratrol	Promotes mitochondrial biogenesis and mitophagy; reduces oxidative stress and Aβ accumulation	178-182
Urolithin A	Activates PINK1/Parkin-mediated mitophagy; promotes clearance of damaged mitochondria; reduces ROS	71, 183-186
UMI-77	Binds MCL1 to induce mitophagy; promotes LC3-II recruitment; reduces Aβ pathology	187, 188
Metformin	Induces mitophagy by activating SIRT1, AMPK, and Parkin and suppressing the activities of complex 1 and mTOR	189-196
Rapamycin	Inhibits mTORC1; restores autophagosome formation; activates PINK1/Parkin and AMPK signaling	197-200

Inhibition of Mitochondrial Fission as a Strategy for Neuroprotection in AD

Mdivi-1: Mitochondrial Division Inhibitor-1 (Mdivi-1) is a small molecule compound that selectively inhibits mitochondrial fission protein Drp1. It regulates mitochondrial dynamics. Mdivi-1 has shown neuroprotective effects in AD models by maintaining mitochondrial functions and protecting neurons from damage. The possible mechanism may involve regulation of mRNA expression of ETC-related genes to reduce H_2O_2 production, decrease lipid peroxidation, and alleviating oxidative stress-induced cell damage [155 - 157]. Mdivi-1 also reduces Aβ deposition by alleviating neuronal toxicity resulting from Ca^{2+} overload and improves the bioenergetic of mitochondria for normal distribution and morphological maintenance [158, 159]. Mdivi-1 passes through the blood-brain barrier to enter the brain. After a month of oral Mdivi-1 treatment, APP/PS1 transgenic mice demonstrated improved spatial learning and memory in the Morris water maze, along with a significant reduction in amyloid plaque buildup within their brains [158]. It is believed that Mdivi-1 has the potential to modify the progression of AD by regulating mitochondrial fusion and fission processes and promoting mitochondrial autophagy. Currently, the project is in the initial research phase and has not yet reached clinical trials. The clinical application of this is constrained by issues such as safety testing, optimal dosing, and ensuring target specificity. There have been no human clinical trials conducted involving patients with AD till date.

DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has the redox ability to inhibit the pathological link between Drp1 and Aβ, helping to correct mitochondrial dysfunction associated with AD. Due to abnormal Aβ binding, Drp1-mediated mitochondrial fission is enhanced, thus resulting in tau hyper-phosphorylation and synaptic degeneration [160, 161]. DDQ decreased the formation of Drp1-Aβ42 complexes in neuronal cells, promoted mitochondrial fusion, and lowered Aβ-related cell toxicity [162]. DDQ was also tested on SH-SY5Y cells and a transgenic AD mouse model, leading to decreased levels of fission-related proteins (Drp1, Fis1) and increased levels of fusion-related proteins (Mfn1, Mfn2), which helped restore mitochondrial balance and enhance synaptic function [163 -165]. DDQ activates the PINK1/Parkin pathway, stimulates mitophagy, and reduces irregular tau phosphorylation levels [166, 167]. Research suggests that

DDQ may serve as a promising treatment option to enhance mitochondrial function and synaptic health in AD. Related studies are still in the preliminary and preclinical phases.

Ginsenoside Rg1: Ginsenoside Rg1 (Rg1) is a steroidal saponin derived from ginseng that has neuroprotective properties and has demonstrated notable effectiveness in animal and human research related to AD. Rg1 reduces pathological alterations in Aβ and tau, neuroinflammation, oxidative stress, and apoptosis. The mechanism behind this is likely the activation of AMPK by increasing p-AMPK protein levels and inhibiting p-Drp1 expression to abate the hyperactivation of Drp1 [168]. The above effects were accompanied by the upregulation of mitochondrial fusion-related proteins, such as optic atrophy-related protein 1 (OPA1), mitochondrial fusion protein 1 (Mfn1), and mitochondrial fusion protein 2 (Mfn2), suggesting that Rg1 promotes mitochondrial fusion and inhibits excessive fission. By reestablishing mitochondrial balance, Rg1 can significantly enhance synaptic activity and support neuron survival in mice modeled for AD. Although Rg1 has shown promising outcomes in experimental cognitive models, additional research is needed to confirm its effectiveness in treating AD patients.

Table 2. Candidate drugs primarily exert their effects through antioxidant mechanisms, improvement of respiratory chain function, and other pathways.

Potential drug	Mechanism of action	References
MitoVitE	Mitochondria-targeted antioxidant; reduces oxidative stress and preserves mitochondrial membrane potential	201-205
MitoQ	Mitochondria-targeted antioxidant; reduces Aβ accumulation, astrogliosis, and caspase activation	120, 206-213
SS-31	Stabilizes cytochrome c oxidase; improves bioenergetics and reduces oxidative stress	214-219
NDI1	Improves defects in mitochondrial complex I	220
DMM	Inhibition of succinate dehydrogenase (SDH)	107
Olesoxime	Enhances the activity of respiratory chain complexes and reverses complex IV activity	221
CP2	Increases mitochondrial respiratory control ratio, reduces proton leakage, prevents formation of Aβ aggregates from AD, inhibits mitochondrial complex I	222-228

Therapeutic Potential of Natural bioactive substances in AD: Targeting Mitophagy and Mitochondrial Dysfunction

Spermidine: Spermidine is a polyamine generated from natural sources and is extensively distributed in plant-based foods. Spermidine concentrations in the body decrease with age. This change has been strongly linked to disrupted cellular balance and a higher likelihood of age-related diseases [169 -171]. Emerging theories propose that spermidine might provide therapeutic benefits by boosting mitochondrial quality control [172]. In mice, spermidine reduces Aβ plaques and decreases the abnormal phosphorylation of tau protein. These effects might be caused by higher levels of autophagy and reduced oxidative stress. Lumkwana et al. have demonstrated that spermidine surprisingly boosts autophagic activity, improves protein removal, and shields against neurotoxicity caused by APP overexpression, indicating a potential protective effect in AD development [173]. Although spermidine shows potential benefits, its safety profile is still being researched. Initial reports highlighted the production of toxic byproducts during polyamine metabolism, like superoxide from spermine in Escherichia coli. However, preclinical and clinical studies showed improved safety profile [174-176]. There is ongoing controversy regarding the toxic profile of spermidine and its associated adverse impacts. Few studies suggest that spermidine may break down into harmful by-products [174]. Kumar et al. described spermidine-induced superoxide generation in Escherichia coli [175]. The FDA does not recognize spermidine as a supplement, and the GRAS application was withdrawn in 2020. Schwarz et al. (2018) reported no toxic effects in mice administered mixed polyamines. The Phase II study demonstrated that supplementation did not impact vital signs, blood chemistry, or other blood-related safety measures, leading to the conclusion that polyamine supplementation is well tolerated [176]. The 2023 toxicological assessment concluded that spermidine trihydrochloride is regarded as safe [177]. Numerous studies indicate that spermidine acts as an activator of cellular metabolism by promoting autophagy and improves mitochondrial function. Therefore, it can have therapeutic potential in AD, targeting metabolic issues and neurodegeneration.

Resveratrol (RV): Resveratrol (RV) is a naturally occurring non-flavonoid polyphenol found in plants like grapes and berries. It modulates mitochondrial function through multiple target sites [178, 179]. Karupagund et al. have shown that a diet high in resveratrol considerably reduced the accumulation of amyloid-β (Aβ) plaques in

genetically modified mice used as models for AD [180]. Recent research uncovered the key role of resveratrol in improving neuronal mitochondrial energy production and decreasing oxidative damage [181]. The results from a Phase II clinical trial indicated that resveratrol was considered safe and well-tolerated in individuals with mild to moderate AD [182]. Nonetheless, additional clinical studies are necessary to thoroughly evaluate the true effectiveness of resveratrol in treating AD. The FDA has not formally approved its use for clinical treatment and has revoked its "Generally Recognized as Safe" (GRAS) status granted in 2007. Resveratrol primarily faces challenges due to its limited solubility in water and its low rate of absorption in the body. Resveratrol possesses significant therapeutic potential for mitigating mitochondrial dysfunction linked to metabolic diseases and Alzheimer's by promoting mitochondrial autophagy and biogenesis. Resveratrol's effectiveness is improved by the antioxidant properties, especially in instances involving mitochondrial dysfunction. Resveratrol becomes highly attractive in the realm of adjunct supplements or when used alongside other treatment methods.

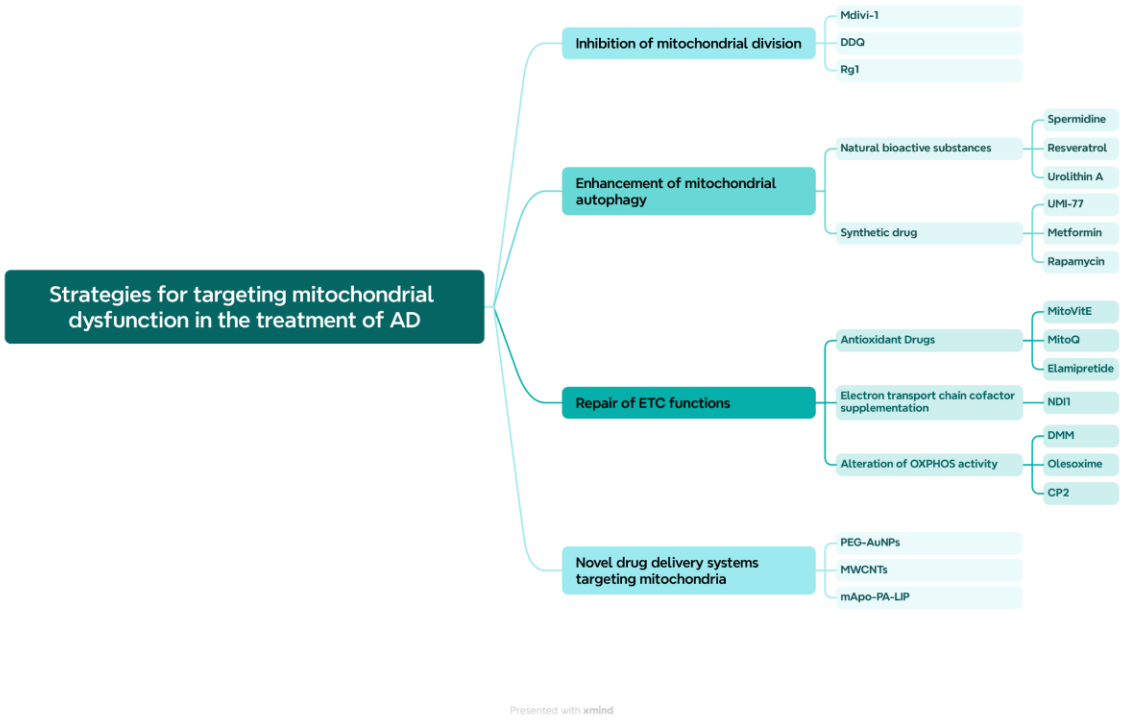

Figure 4. Therapeutic Strategies for Mitochondrial Dysfunction in Alzheimer's disease: A Systematic Overview.

Urolithin A: It is a potent modulator of mitophagy [183]. In AD animal models, UA promoted the selective clearance of dysfunctional mitochondria through PINK1/Parkin-mediated mitophagy, thereby reducing ROS accumulation and protecting neurons from oxidative stress, a major contributor to AD pathology [71]. In PC12 cells, UA treatment induces upregulation of the PINK1 and phospho-ubiquitin levels, indicating mitophagy activation [184]. Phase I clinical trials showed that oral administration of UA at 1000 mg daily for 28 days was safe and well tolerated, and it led to a dose-dependent increase in autophagy in skeletal muscle [185]. However, 40% of people are capable of metabolizing UA effectively, indicating the variability in gut microbiome composition [186]. Despite the need for further clinical validation, UA is a viable therapeutic candidate for alleviating mitochondrial dysfunction in AD and associated metabolic diseases.

Therapeutic Potential of Synthetic drug in AD: Targeting Mitophagy and Mitochondrial Dysfunction

UMI-77: MCL-1, a Bcl-2 family protein with anti-apoptotic properties, is well-known for cell survival. However, its role in AD remains insufficiently understood. MCL-1 is associated with the survival of the tumor due to its overexpression. Neuronal apoptosis, on the other hand, is controlled by several anti-apoptotic proteins, making the specific contribution of MCL-1 less prominent. In addition, the technical issue like delivery of drugs to the brain through the blood-brain barrier, have slowed the research. Hence, selective MCL-1 inhibitor

UMI-77 in AD models has been less explored. Preclinical evidence from cellular and animal studies indicates that UMI-77 is a pro-apoptotic BH3-mimetic that binds to MCL-1 and enhances the activity of the mitophagy receptor. This promotes LC3-II interaction and triggers mitophagy, reducing amyloid-β pathology and neuroinflammation [187]. It is classified as an MCL1-targeted mitophagy inducer [188]. Despite UMI-77's efficacy in modulating mitochondrial autophagy and mitigating Aβ pathology in both cellular and animal models, its long-term toxicity, dose range, and adverse effects remain inadequately assessed. Therefore, the clinical application of UMI-77 remains in the early preclinical stage.

Metformin: It is a natural compound extracted from the medicinal herb 'goat's-rue', Galega officinalis. It is an FDA-approved drug for the management of type 2 diabetes mellitus (T2DM). Enhancing insulin signaling in the brain (e.g., hippocampus) (e.g., with long-acting insulin medication) improves Aβ-induced memory dysfunction [189, 190]. Metformin has been shown to improve neuronal glucose metabolism and insulin sensitivity. Song et al. Demonstrated that metformin restores Parkin-mediated mitochondrial autophagy by inhibiting cytoplasmic p53. It indicates that metformin may modulate the relationship between Parkin and p53 to enhance mitochondrial autophagy [191, 192]. Chen et al. demonstrated that metformin enhances autophagy clearance and mitigates tau hyperphosphorylation generated by diabetes [193]. Kickstein et al. elucidated its mechanism of action involving the regulation of the mTOR/PP2A signaling pathway, affecting phosphorylation status of tau [188]. These results suggest that metformin affects autophagic activity by modulating tau phosphorylation and related signaling pathways such as mTOR/PP2A. Thus, metformin can be considered a multi-targeted autophagy modulator with potential effects on a wide range of pathological conditions. Daly et al. proposed that 500 mg/day of metformin may be used for individuals in the preclinical or prodromal stages of AD [194]. Clinical studies of metformin in AD and cognitive impairment are currently in Phase II or early exploratory stages [195, 196].

Rapamycin: It improves aging and longevity in animals. Its potential application in treating mitochondrial dysfunction associated with AD has also been investigated. Rapamycin therapy has been shown to increase mitochondrial activity and reduce the oxidative stress in a mouse model of AD [197]. Rapamycin, a powerful mTORC1 inhibitor, restores defective mitophagy in AD models by directly inhibiting mTORC1 activity. This antagonizes mTORC1-mediated suppression of autophagosome formation, while concomitantly activating PINK1/Parkin-mediated mitophagy and AMPK signaling [198]. Gonzales et al. (2025) conducted a single-site open-label phase 1 clinical trial (ClinicalTrials.gov: NCT04200911) to investigate the effects of rapamycin in humans. Rapamycin was not detected in cerebrospinal fluid, but biomarkers associated with AD and inflammation increased following treatment [199]. Svensson et al. conducted a six-month, single-arm, open-label Phase IIa biomarker-driven study to assess whether rapamycin could be repurposed for the treatment of AD [200].

Therapeutic Potential of ETC repair function in AD

Antioxidant Drugs

MitoVitE: Exogenous antioxidants like vitamins C and E aim to mitigate ROS-induced damage and improve mitochondrial function; however, they have limited clinical efficacy due to poor mitochondrial targeting and inability to cross the blood-brain barrier. A mitochondria-targeted form of vitamin E, MitoVitE, was conjugated with vitamin E to triphenylphosphonium cations to facilitate rapid mitochondrial uptake. MitoVitE protects mitochondria against oxidative stress by reducing the accumulation of hydrogen peroxide, blocking the activation of caspases to prevent apoptosis [201, 202]. Additionally, MitoVitE reduces oxidative stress-induced mitochondrial injury, preventing the loss of mitochondrial membrane potential in rat models [203-205]. MitoVitE is a promising mitochondria-targeted antioxidant therapeutic strategy.

MitoQ: MitoQ is composed of a covalent bond between coenzyme Q (Ubiquinone) and ammonium triphosphate ion, forming a Ubiquinone structure. MitoQ exerts neuroprotective effects by preventing the production of peroxide and superoxide directly and protects mitochondria from lipid peroxidation [206]. Furthermore, MitoQ improves expression of PGC-1 α and prevents mitochondrial dysfunction, including inhibition of membrane depolarization, reduction of free radical generation, and enhancement of cytochrome oxidase activity [207]. MitoQ has demonstrated significant neuroprotective effects across multiple preclinical models. McManus et al. reported that MitoQ prevented Aβ accumulation, astrogliosis, and caspase activation in AD mouse models and C. elegans AD models [208-210]. Long-term oral administration of MitoQ in AD mice prevented cognitive decline and disease-like pathology [208]. Several clinical trials have shown the safety of MitoQ up to one year without significant adverse side effects [211-213]. Higher concentrations (> 0.3 μM) of MitoQ are potentially neurotoxic, limiting the therapeutic window for treatment [120]. MitoQ is considered a promising therapeutic candidate for the treatment of metabolic diseases, based on its well-defined mechanism,

extensive preclinical evidence of efficacy, especially in models of neurodegenerative and metabolic diseases, and favorable human safety data.

SS-31: Elamipretide, referred to as MTP-131, SS-31, or Bendavia, is a mitochondria-targeted tetrapeptide of alternating aromatic and basic amino acids [214]. The peptide chain of Elamipretide contains residues of tyrosine and dimethyltryptamine, which scavenge oxygen free radicals generated by mitochondria and show significant antioxidant capacity [215]. The drug can successfully penetrate the blood-brain barrier, making it a potential treatment option for neurodegenerative conditions like AD [216]. Elamipretide demonstrates significant neuroprotective effects in preclinical models of AD. It stabilizes the cytochrome c oxidase in the mitochondrial ETC and improves the metabolism of mitochondrial energy while simultaneously reducing oxidative stress [217, 218]. Compared with vitamin E, Elamipretide more effectively preserves mitochondrial function [219]. Although SS-31 has shown potential to treat AD in animal models, clinical studies in patients with AD are still in the early stages. This can be attributed to the complex pathological mechanisms of the disease, individual variations among patients, and the challenges in the design of clinical trials.

ETC cofactor supplementation

Mitochondrial complex I disorder is increasingly recognized as a causative etiology in AD pathogenesis. Li Hongzhi et al. established an AD cellular model with $A\beta_{1-42}$-treated differentiated human neuronal cells and transfected the yeast-derived complex I homolog gene NDI1 with adeno-associated virus serotype 9 (AAV9). Similarly, in an AD mouse model developed with hippocampal $A\beta_{1-42}$ injection, AAV9-NDI1 was delivered into the hippocampus stereotactically. In both models, NDI1 expression effectively restored the function of the mitochondria and improved AD pathology. These findings suggest that gene therapy directed at mitochondrial complex I by NDI1 presents an effective treatment modality for AD types with mitochondrial involvement [220]. There are no clinical trials initiated on the application of NDI1 (yeast mitochondrial NADH dehydrogenase 1) in AD.

Alteration of OXPHOS activity

Inhibition of succinate dehydrogenase (SDH), a constituent of ETC complex II, by dimethylmalonate (DMM) reprograms the pro-inflammatory metabolic phenotype. DMM therapy reduces mitochondrial biogenesis and ROS production and promotes a microglial shift towards an anti-inflammatory phenotype while improving mitochondrial function [107]. Olesoxime (TRO19622) has been evaluated in AD models. This analogue of cholesterol has proved to revive mitochondrial function by enhancing the activity of respiratory chain complexes, improving the impairments in complex IV activity and mitochondrial membrane potential [221]. Olacimib has shown neuroprotective effects by inhibiting complex I, but concerns have been raised about its possible side effects: elevated $A\beta_{1-40}$ levels were observed in treated mice and HEKsw cells. Further studies are required to evaluate its long-term safety in AD. Moderate inhibition of oxidative phosphorylation (OXPHOS) at complex I may exhibit therapeutic benefits [222]. CP2 crosses the blood-brain barrier and selectively aggregates in mitochondria and exhibits a mild and specific inhibitory effect on complex I [223, 224]. Several studies have shown that CP2 reduces oxidative stress and neuroinflammatory processes, maintains neuronal function, and restores homeostasis without toxicity [225, 226]. CP2 also inhibits Aβ aggregation [227]. Metformin is a well-characterized complex I inhibitor and modulates mitochondrial signaling pathways by impairing cyclic AMP/protein kinase A signaling and activating AMPK. These effects have been associated with increased metabolic and inflammatory profiles relevant to AD pathogenesis [228]. These studies indicate that improving the function of the ETC and targeting selective inhibition of mitochondrial complexes, especially Complex I, can offer neuroprotective effects in AD and other neuro-degenerative disorders associated with age.

Mitochondria-Specific Drug Delivery Systems: A New Frontier in AD

Treatment of AD is often limited by the blood-brain barrier (BBB). Nanotechnology provides promising solutions to increase the drug penetration into the brain and to allow targeted release. Anthocyanin-rich polyethylene glycol-modified gold nanoparticles (PEG-AuNPs) significantly improved cognitive function in AD mice by activating the PI3K/Akt/GSK-3β pathway [229]. Polysorbate/phospholipid-coated multiwalled carbon nanotubes (MWCNTs) efficiently delivered berberine across the blood-brain barrier, providing controlled release and neuroprotective effects [230]. Liposome-based carriers modified by ApoE peptides (mApo), phosphate (PA), or curcumin derivatives (TREG) efficiently bind Aβ42 in cerebrospinal fluid, demonstrating potential for amyloid clearance and possible disease progression modification [231]. These nanocarrier strategies show a wide range of possibilities to overcome the limitations of blood – brain barrier in AD therapy.

Conclusive and outlook

Neuronal cells are highly dependent on mitochondrial homeostasis. Disruptions in the fission and fusion processes not only affect mitochondrial morphology and function but also affect interactions with Aβ and tau proteins, creating a vicious cycle that promotes the onset and progression of early pathology in AD.

Understanding of ETC dysfunction in AD is known; however, existing studies primarily focus on changes in overall activity, without sufficient emphasis on expression regulation and post-translational modifications of individual subunits. Furthermore, implementing targeted treatments aimed at specific ETC subunits could provide more accurate therapeutic outcomes than traditional antioxidant therapies, which tend to have a wider, less focused effect. The restoration of NDUFA13 function in complex I by either a small molecule or gene editing improves the neuronal energy metabolism. ETC subunits show potential as early diagnostic markers and targets for intervention in AD. This review focuses on exploring mitochondrial dysregulation and ETC dysfunction in AD and based on this, summarizes current potential intervention strategies targeting mitochondria (Fig. 5). Future research can be centered around three main avenues: (1) targeting mitochondrial dynamics for early intervention in AD pathology; (2) laying down detection techniques of very high sensitivity to dictate the expression and modification state of ETC subunits; (3) engineering refined cellular and animal models that reveal the exact mechanism of how ETC subunit dysfunction brings forth AD.

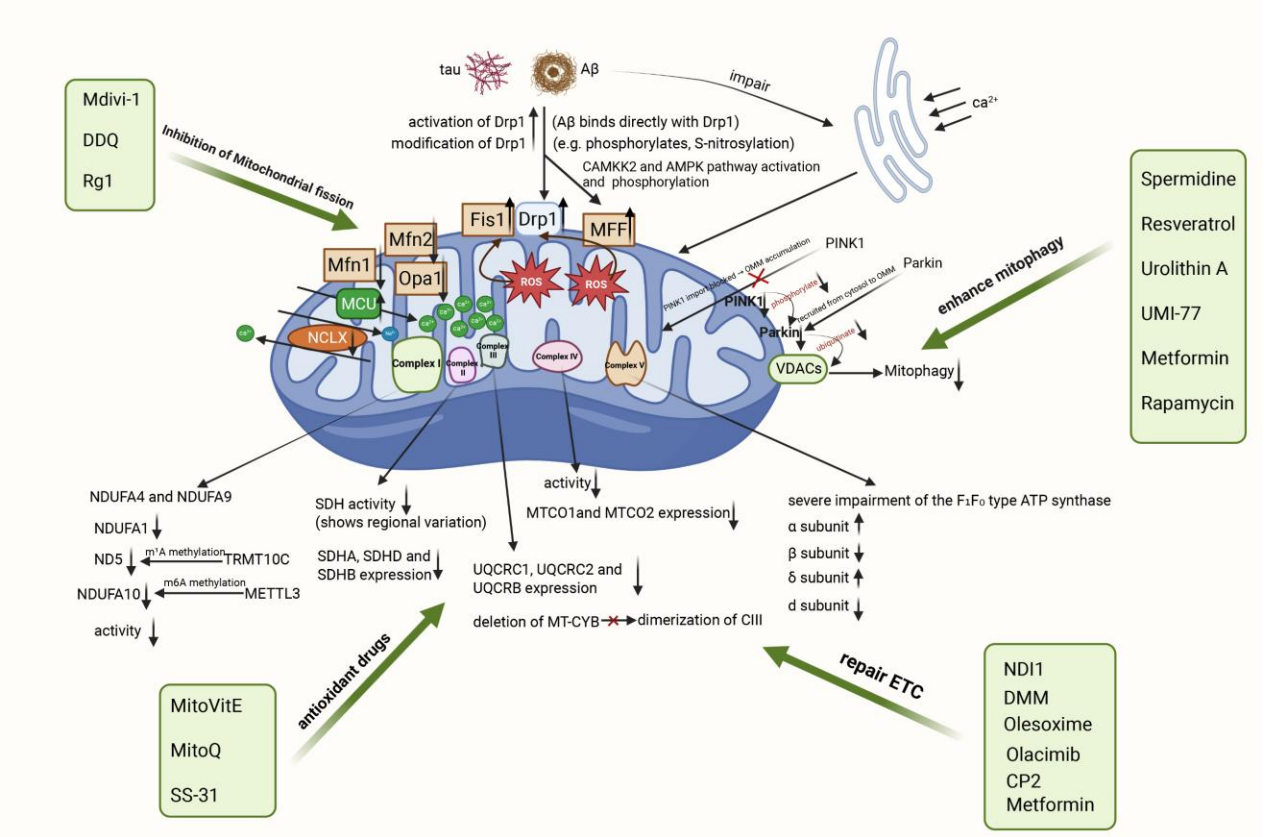

Figure 5. Molecular Mechanisms of Mitochondrial Dysfunction and Targeted Intervention Strategies in AD. In AD, Aβ and tau induce mitochondrial dysfunction by promoting excessive fission via Drp1, disrupting ER–mitochondria contacts and causing calcium overload, and impairing PINK1/Parkin-dependent mitophagy. ETC complexI–V and their subunits are also reduced in activity and expression, resulting in an increase in ROS production. Potential interventions include fission inhibition (e.g., Mdivi-1, Rg1), antioxidant protection (e.g., MitoQ, SS-31), enhancement of mitophagy (e.g., spermidine, resveratrol), and restoration of ETC function (e.g., NDI1, metformin).

In addition to mitochondrial dysfunction and the dysfunction of the electron transport chain, recent studies have shown several mechanisms understudied in AD, providing new insights into mitochondrial vulnerability and the development of targeted intervention strategies. Mitochondrial dysfunction is an important pathological change in the early stages of AD and plays a key role in calcium homeostasis. The accumulation of Aβ is strongly associated with increased calcium levels within mitochondria [80]. The mitochondrial calcium uniporter

(MCU) on the inner mitochondrial membrane transports calcium ions from the cytoplasm into the mitochondria, thereby maintaining intracellular calcium homeostasis [232]. Recent research indeed shows that an MCU deletion or inhibition can reduce the calcium overload in mitochondria and conversely ameliorate pathological changes and behavioral abnormalities in AD animal models. Hence, one may consider MCU a promising potential therapeutic target [233]. Mitochondrial sodium/calcium exchanger (NCLX) plays a crucial role as the primary channel responsible for calcium ion export from the mitochondria. Jadiya et al. provided additional evidence that just blocking calcium efflux through NCLX is sufficient to cause AD-like pathological manifestations, accentuating further the pathological functions of the mitochondrial calcium exchange system [234]. Furthermore, inhibiting the opening of the mitochondrial permeability transition pore (mPTP) mediated by cyclopeptide D similarly improves mitochondrial dysfunction and cognitive impairment in AD models. This suggests that targeting calcium homeostasis signaling pathways may represent a therapeutic strategy [235].

There has been notable epidemiological evidence of gender-related differences in mitochondrial dysfunction-dependent AD. Females tend to present with mitochondrial irregularities earlier than male mice. Female mice exhibited decreased hypothalamic mitochondrial functioning at about 2 months in the 3xTg-AD model of AD, while males usually developed overt changes only by around 13 months. In contrast, female mice tended to display significantly lesser cytochrome oxidase activity than males, thereby suggesting that mitochondrial damage may take place earlier during female AD development [236]. In female AD-stricken mice, mitochondrial autophagy and autophagosome levels were found to be elevated. Such an overactive autophagic process can further hamper mitochondrial functioning [237]. Studying these gender differences helps us understand the accentuation of females' vulnerability in AD, and it further elucidates early intervention and personalized therapeutic strategies.

The reprogramming of metabolism in glial cells is also a significant factor in AD. Baik et al. (2019) showed that microglial cells exposed to Aβ shift their energy metabolism from oxidative phosphorylation to glycolysis, leading to mitochondrial damage and exacerbating inflammatory reactions [238]. Fairley et al. (2021) highlighted that mitochondria play a central role in the immune metabolism of glial cells, and changes in metabolism can influence their immune phenotype by regulating mitochondrial function and contribute to the development of AD [239]. Inhibition of the mitochondrial pyruvate carrier (MPC) in astrocytes can significantly reduce the accumulation of Aβ and Tau proteins in 3xTg-AD mice's brains, further confirming the central role of mitochondrial metabolism in the development of AD [240].

Recent studies suggest that the metabolic interactions between neurons and astrocytes have a significant impact on the pathogenesis and progression of AD. Astrocytes produce lactate for neurons through glycolysis, lipid metabolism, and mitochondrial energy conversion mechanisms and regulate the mitochondrial pyruvate transporter (MPC). Multi-omic and functional studies have shown that fatty acid β-oxidation and cholesterol metabolism are altered in astrocytes at early stages of AD and manifested by CPT1A downregulation with free fatty acid accumulation. These changes cause mitochondrial stress, increase the level of ROS, and reduce the metabolic support capacity of astrocytes for neurons [241]. Animal studies have also shown that inhibition of MPC in astrocytes significantly reduces Aβ and tau protein deposition in the brain, suggesting that targeting astrocyte metabolism may offer new approaches for early intervention in AD [242].

Furthermore, the mitochondrial unfolded protein response (mito-UPR) maintains mitochondrial protein homeostasis in AD models. Studies have shown abnormal folding of mitochondrial proteins and elevated levels of molecular chaperone proteins such as HSP60 in AD models. This suggests that cells can maintain stable mitochondrial function by activating the mito-UPR [243]. Moderate activation of the mitochondrial UPR can promote mitochondrial repair through activating transcription factor 5 (ATF5)-mediated transcriptional pathways, potentially reducing neuronal damage [244]. However, extended activation over a long duration or through strong stimulation can inhibit the PINK1/Parkin pathway responsible for mitochondrial autophagy, potentially worsening energy metabolism issues and increasing oxidative stress [244]. Animal studies and human brain transcript analyses show that the mitochondrial UPR can protect nerve cells. However, mitochondrial problems still increase at certain stages of AD. This makes the mitochondrial UPR an important area for further research [245].

These new research directions collectively enrich our understanding of mitochondrial dysfunction in AD. Future research into these uncharted regions could lead to the development of new methods for early diagnosis and personalized treatments.

Author Contributions

Jiehui Li: Conceptualization, Writing – Original Draft, Visualization. Gajendra Kumar: Writing – Review & Editing, Intellectual input. Yuqing Yan: Conceptualization, Idea generation, Writing – Review &

Editing; Ying Bai: Supervision, Writing – Review & Editing, Project administration. Mengmeng Wang, Ling Xu, Haige Wu, Ye Gao, Yi wang and Yingyi Fan: Investigation, Data curation, Proofreading. All authors contributed to the article and approved the submitted version.

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