OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

A Stage-Dependent Model of Mitochondrial Dysfunction in Alzheimer's Disease: From Early Bioenergetic Vulnerability to Pathological Amplification

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ABSTRACT

Mitochondrial dysfunction is widely implicated in Alzheimer's disease, but its temporal and mechanistic relationship to classic AD pathology such as amyloid-beta and tau pathology remains largely unresolved. Some studies suggest that mitochondrial abnormalities occur before substantial plaque and neurofibrillary tangle (NFT) accumulation while others describe mitochondrial dysfunction as a downstream consequence. This review proposes a stage-dependent framework that reconciles these findings without treating mitochondrial dysfunction exclusively as a cause or consequence in Alzheimer's disease.

The first stage is characterized by the appearance of early bioenergetic vulnerabilities and declining mitochondrial biogenesis before substantial Aβ plaque deposition. In the second stage, accumulating Aβ and tau then promote mitochondrial decompensation through mechanisms such as impaired OXPHOS, disrupted mitochondrial dynamics, and defective mitophagic clearance. Finally, in the third stage, persistent mitochondrial stress contributes to further tau hyperphosphorylation and disrupted tau proteostasis, thereby reinforcing a cycle of MD and worsening AD pathology.

This framework suggests therapeutic targets across stages of disease progression from preserving mitochondrial resilience to ensuring tau clearance. However, the proposed stages are largely overlapping rather than concrete chronological phases. Much of the supporting evidence derives from transgenic animal models, cultured cells, postmortem tissue analysis, and human induced pluripotent stem cell-derived neurons, limiting causal conclusions. Longitudinal studies in sporadic AD and the development of disease-specific mitochondrial biomarkers are needed to validate the model.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia worldwide and a pressing public health issue of the twenty-first century. As of 2025, more than 7 million Americans live with Alzheimer's, a number projected to rise to nearly 13 million by 2050 (Alzheimer's Association, 2025). Despite extensive research on treatment aimed at halting or reversing disease progression, current therapeutic options

remain limited, and many treatments are symptomatic instead of disease-modifying (Yiannopoulou & Papageorgiou, 2020).

The neuropathology of AD is defined by two hallmark lesions: extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). Aβ peptides are produced when β-secretase and γ-secretase enzymes proteolytically cleave amyloid precursor protein (APP). This process generates Aβ isoforms —most commonly the Aβ38, Aβ40, and Aβ42 variants — which aggregate into insoluble fibers and initiate a toxic cascade in the brain. The formation of amyloid oligomers triggers a series of downstream effects, including local inflammation, oxidation, neurotoxicity, and tau hyperphosphorylation (Yiannopoulou & Papageorgiou, 2020). NFTs, the second major hallmark, are composed of insoluble fibrils of hyperphosphorylated tau. Under normal conditions, tau protein stabilizes microtubules and facilitates axonal transport; however, hyperphosphorylated tau dissociates from microtubules, disrupting intracellular transport and contributing to microtubule instability.

These pathological features form the basis of the amyloid hypothesis, which for decades has dominated explanations for the pathogenesis of AD. Critically, the hypothesis proposes that the deposition of Aβ is the primary initiating event that leads to amyloid plaque buildup, which then triggers hyperphosphorylated tau and the downstream pathology described above. The amyloid hypothesis provides a strong explanation for familial Alzheimer's disease (FAD), a rare early-onset form of AD accounting for 1–5% of all cases. It identifies three genes as causes for early-onset AD: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) (UpToDate, n.d.). However, this hypothesis faces limitations in explaining sporadic AD, which constitutes over 95% of AD cases and generally occurs without FAD-linked gene variants (Liu et al., 2019). If faulty Aβ production is not the trigger inherited by patients, this hypothesis does not adequately capture the initiating mechanisms of sporadic AD.

Because of this, emerging research has directed attention to the mitochondrial hypothesis, which proposes mitochondrial dysfunction (MD) as a central driver of the disease. Broadly, MD refers to disruptions in energy production by impaired oxidative phosphorylation, elevated reactive oxygen species (ROS), and defective mitophagy (D'Alessandro et al., 2025). Critically, several studies have identified mitochondrial abnormalities in AD-vulnerable brains occurring before substantial Aβ deposition, suggesting that mitochondrial dysfunction may not simply arise as a consequence of amyloid and tau pathology but may instead precede it. The temporal and mechanistic relationship between mitochondrial dysfunction, Aβ accumulation, and tau pathology remains a significant point of uncertainty and a central question.

Rather than treating mitochondrial dysfunction as simply a cause or consequence of AD pathology, this review argues that MD plays a stage-dependent role in AD progression. Early mitochondrial abnormalities may precede substantial plaque deposition or initially arise as a compensatory response, whereas the later accumulation of amyloid-beta and tau intensifies respiratory-chain dysfunction and abnormal mitochondrial dynamics. Over time, sustained mitochondrial stress may amplify tau pathology by promoting tau hyperphosphorylation and disrupting ubiquitin-proteasome clearance. This review therefore proposes a stage-dependent mitochondrial model of AD progression in which mitochondrial

dysfunction acts as an early and evolving contributor to AD. These stages represent overlapping mechanistic states and are intended to span both preclinical and symptomatic phases of AD. The review proceeds in four steps. First, it evaluates evidence that early mitochondrial abnormalities may represent disruptions in cellular bioenergetics or compensatory adaptation before major plaque accumulation. Second, it examines how Aβ and tau pathology drive mitochondrial decompensation through impaired oxidative phosphorylation (OXPHOS), abnormal mitochondrial dynamics, and defective mitophagy. Third, it argues that sustained mitochondrial stress becomes especially consequential when it disrupts tau proteostasis, allowing the accumulation of pathological tau species and initiating a cycle of neurodegeneration. Finally, this review considers therapeutic implications of this model and proposes stage-specific targets for future treatment.

METHODS

The temporal and mechanistic relationships between mitochondrial dysfunction and classic AD pathology are not well understood. Current literature is divided on whether mitochondrial dysfunction serves as an early driver of AD or occurs as a downstream consequence. Therefore, this review aimed to evaluate current evidence and clarify the role of mitochondrial dysfunction in AD. PubMed was used as the primary database. Search terms included "Alzheimer's disease," "mitochondrial dysfunction," "mitochondrial dynamics," "mitophagy," "mitochondrial biogenesis," "amyloid-beta," "tau hyperphosphorylation," "oxidative stress," and "tau proteostasis" combined using Boolean operators such as AND and OR. Approximately 70 articles were screened, of which 50 were included in the final synthesis.

Studies were screened initially by title and abstract to determine relevance to the research question. Full texts of potentially relevant papers were then reviewed with attention to the results and discussion sections to determine whether findings provided evidence for the proposed mechanisms. Inclusion criteria consisted of studies directly examining mitochondrial function in AD or linking mitochondrial dysfunction with neuronal pathology present in AD. Recent literature published after 2020 was prioritized, while older studies were retained when they provided foundational evidence or direct experimental results. Studies were excluded if they lacked evidence applicable to the proposed framework.

Experimental studies were prioritized when evaluating mechanistic and temporal relationships. For example, longitudinal and disease-model studies were used to assess early mitochondrial abnormalities, while experiments such as Rhein et al. (2009) and Samelson et al. (2026) provided evidence concerning OXPHOS disruption and tau proteostasis, respectively. Review papers, including D'Alessandro et al. (2025) and Liu et al. (2024), were mainly used to explain well-characterized processes such as mitochondrial dynamics, respiration, and mitophagy. Evidence was then qualitatively synthesized according to its temporal position and proposed mechanism to construct the three-stage model proposed in this review.

RESULTS

Stage 1: Early Mitochondrial Vulnerability

Emerging evidence suggests mitochondrial damage as a characteristic of early AD even before the appearance of substantial amyloid-beta (Aβ) plaque deposition and tau accumulation (D'Alessandro et al., 2025). In this stage, some mitochondrial abnormalities may reflect early dysfunction while others represent compensatory responses that temporarily preserve neuronal energy production. Interpretation of these changes first requires consideration of normal mitochondrial function.

Normal Mitochondrial Dynamics

Mitochondria maintain energy sources for neurons through oxidative phosphorylation (OXPHOS), while also supporting synaptic activity, calcium buffering, axonal transport, and redox balance (Misrani et al., 2021). Mitochondria maintain this capacity through coordinated processes of fission, fusion, mitophagy, and biogenesis. Because neurons are highly energy-dependent, mitochondrial quality control mechanisms are critical. Fission and fusion maintain mitochondrial shape, distribution, and network integrity while mitophagy removes damaged mitochondria and mitochondrial biogenesis generates new mitochondria through regulators such as PGC-1α, NRF1, NRF2, and TFAM (Sukhorukov et al., 2024; Lewis et al., 2018).

Early Bioenergetic Vulnerability and Mitochondrial Dysfunction

Altered brain energy metabolism in early AD suggests that mitochondrial vulnerability in bioenergetic homeostasis may precede severe neurodegeneration. Through PET scanning, Vlassenko et al. found that brain regions with high aerobic glycolysis in young adults spatially overlap with regions vulnerable to later Aβ deposition, suggesting a link between regional aerobic glycolysis and later AD progression (Vlassenko et al., 2010). In a later multi-tracer PET study, Vlassenko et al. found lower aerobic glycolysis to be associated with higher tau deposition in individuals with amyloid burden, including preclinical and mildly symptomatic AD cases (Vlassenko et al., 2018). These studies show that AD-vulnerable regions are characterized by altered energy regulation early in disease progression. Although aerobic glycolysis is a cytosolic process, it indicates broader disruption in neuronal energy regulation, a process that mitochondria regulate through OXPHOS and ATP production.

More evidence of early mitochondrial involvement comes from studies showing altered ATP production and oxidative stress in AD models. A study using an AD-Tg mouse model by Zhang et al. showed that ATP content was significantly reduced in the mouse models, suggesting impaired mitochondrial energy production (Zhang et al., 2015). A decline in ATP content is also linked to oxidative stress. When the electron transport chain (ETC) becomes inefficient, electrons may leak and lead to the production of reactive oxygen species (ROS) which can then impair mitochondrial function (Wang et al., 2014).

However, early MD may not necessarily appear as a decline in ATP production. In a longitudinal study of Thy1-APP751SL mice, Reutzel et al. followed Aβ levels, cognition, and mitochondrial function at 3, 7, and 13 months. At 7 months, ATP levels were significantly elevated despite early reductions in mitochondrial biogenesis markers, suggesting a compensatory response. By 13 months, when Aβ levels were the highest, mitochondrial Complex IV activity was significantly reduced (Reutzel et al., 2022). These findings refine the characteristics of Stage 1: early mitochondrial dysfunction in AD may appear as impaired energy production or as a temporary compensation for later respiratory-chain decompensation.

Mitochondrial Biogenesis Links Early Compensation to Later Vulnerability

Declining mitochondrial biogenesis can explain the transition from bioenergetic compensation into mitochondrial vulnerability. In early AD, neurons may temporarily preserve ATP production by increasing mitochondrial activity. However, this compensation is dependent on the cell's ability to regenerate mitochondria. When biogenesis regulators such as PGC-1α, NRF1, NRF2, and TFAM decline, neurons become less able to replace damaged mitochondria and will suffer from impaired OXPHOS. According to Sheng et al., reduced PGC-1α expression and impaired mitochondrial biogenesis signaling in AD brains and AD models were associated with weakened mitochondrial renewal capacity (Sheng et al., 2011).

Several studies also support the idea that impaired mitochondrial biogenesis occurs in early AD models. In a study conducted using 3xTg-AD mouse models, Singulani et al. found that impairment of biogenesis signaling mediated by PGC-1α preceded classic AD pathology and likely resulted in later mitochondrial dysfunction (Singulani et al., 2020). Impaired biogenesis before the development of AD pathology suggests that mitochondrial vulnerability may begin due to failed maintenance rather than immediate ATP collapse. Reutzel et al. further corroborate this by showing that 7-month-old Thy1-APP751SL mice experienced a decrease in mitochondrial transcription factor A (TFAM) and AMPK-activated protein kinase (β-AMPK), both of which are critical in mitochondrial biogenesis (Reutzel et al., 2022). ATP elevation occurring alongside decreased gene expression of TFAM and β-AMPK suggests that declining mitochondrial biogenesis may be driving the transition from a compensatory response to early vulnerability followed by mitochondrial dysfunction. A decline in mitochondrial renewal means the accumulation of damaged mitochondria which may then lead to impaired ROS regulation and oxidative stress. Under these conditions, early mitochondrial changes may begin as adaptive responses but become pathological when mitochondrial renewal can no longer support sustained energetic compensation.

Stage 2: Aβ- and tau-driven Mitochondrial Decompensation

Stage 1 established how early mitochondrial abnormalities may precede substantial plaque deposition in AD pathogenesis; however, as Aβ and tau accumulate, mitochondrial stress becomes more damaging. Stage 2 examines how classical AD pathology actively drives mitochondrial dysfunction. This section focuses on how Aβ and tau impair mitochondrial respiration, disturb the fission-fusion balance, and disrupt mitochondrial quality control in mitophagy.

Mitochondrial Respiration and Oxidative Phosphorylation

The electron transport chain (ETC) is the site of oxidative phosphorylation and cellular ATP production, generating reactive oxygen species (ROS) as a byproduct. While ROS are a normal part of functional metabolism, a dysfunctional ETC may leak electrons and generate superoxide radicals that damage mitochondrial proteins, lipids, and DNA (Spuch et al., 2012). As mentioned in Stage 1, bioenergetic vulnerabilities, including altered aerobic glycolysis and ATP decline, appeared early in AD models and are only made more persistent through direct impairment of OXPHOS and respiratory-chain activity in Stage 2 (Vlassenko et al., 2018; Zhang et al., 2015).

Evidence for synergistic Aβ-tau toxicity on mitochondrial respiration comes from Rhein et al., who conducted a comparative transgenic mouse study which revealed a potential molecular link between Aβ and tau protein in AD pathology. Using a triple-transgenic AD mouse model (pR5/APP/PS2) combining amyloid and tau pathologies, together with quantitative iTRAQ proteomics and mass spectrometry, Rhein's group found deregulation of 24 proteins, one-third of which were mitochondrial proteins associated with Complexes I and IV of the OXPHOS system. Functionally, complex I deregulation was mainly tau-dependent whereas complex IV was mainly Aβ-dependent. The synergistic toxicity of Aβ and tau also appeared to be age-associated: their combined effects were evident in 8-month-old tripleAD mice, while by 12 months, tripleAD mice exhibited the strongest defects in OXPHOS and ATP synthesis (Rhein et al., 2009). This study delineates the mechanisms by which Aβ and tau drive mitochondrial damage; they act on different respiratory complexes to create a combined bioenergetic deficit.

The mechanisms by which Aβ reaches mitochondria and disrupts the ETC have been extensively studied and characterized. Aβ peptides which were thought to accumulate exclusively as extracellular, insoluble plaques have been shown to localize to mitochondrial membranes where they can block nuclear-encoded proteins and components of the electron transport chain. Aβ interacts with the translocase of the outer mitochondrial membrane 40 (TOM40), disrupting protein import into the mitochondria, and also interacts with cytochrome c oxidase (Complex IV), directly impairing the final step of the ETC (Spuch et al., 2012). These interactions increase free radical production and contribute to a self-reinforcing cycle where impaired ETC function generates ROS and leads to further damage of mitochondrial components. Pagani and Eckert extended this analysis by mapping Aβ interactions across mitochondrial compartments, from the outer membrane through the intermembrane space to the inner membrane and matrix, establishing how Aβ permeates and targets every functional layer of the organelle (Pagani and Eckert, 2011).

Tau contributes to respiratory chain dysfunction through distinct but complementary mechanisms. As shown in the study by Rhein et al., hyperphosphorylated tau decreased the activity of NADH dehydrogenase at complex I and disrupted the mitochondrial membrane potential, thereby compromising the proton gradient necessary for ATP synthase function (Rhein et al., 2009). Site-specific phosphorylation of tau further modulates its effects. Isei et al. studied mouse hippocampal neuronal cells expressing either wild-type tau or phosphomimetic tau including Ser396/Ser404 (2EC) and Thr231/Ser235 (2EM) constructs. After measuring their impacts on various mitochondrial functions, Isei

et al. found decreased ATP levels in both 2EC and 2EM expressing cells and higher ROS production than cells expressing wild-type tau (Isei et al., 2023). These findings align with current evidence that hyperphosphorylated tau impairs mitochondrial bioenergetics and show that tau phosphorylation can affect mitochondrial function in a site-specific manner, linking pathological tau directly to ATP decline and oxidative stress.

Aβ and Tau Disrupt Mitochondrial Dynamics through Drp1-Driven Fragmentation

A second mechanism of sustained mitochondrial dysfunction is the disruption of mitochondrial dynamics, primarily fission and fusion. Normally, fission and fusion are complementary processes in mitochondria that divide and merge mitochondria, respectively, helping maintain mitochondrial network integrity. In AD, Aβ and phosphorylated tau shift mitochondrial dynamics towards excessive fission and fragmentation by interacting with the major GTPase proteins involved such as Drp1 (also known as DLP1), Fis1, OPA1, Mfn1, and Mfn2 (Wang et al., 2020).

The central mediator of mitochondrial fission is dynamin-related protein 1 (Drp1), a cytoplasmic GTPase recruited to the outer mitochondrial membrane where it oligomerizes, constricts, and severs the organelle (Sukhorukov et al., 2024). In healthy neurons, Drp1 activity is tightly regulated to maintain a balance between fusion and fission events. However, in AD, both Aβ and tau physically interact with Drp1, potentially contributing to excessive mitochondrial fission. Manczak et al. found that Aβ interactions with Drp1 in the frontal cortex of AD subjects as well as the cerebral cortex of AβPP/PS1 transgenic mice were associated with neuronal degeneration and partly responsible for initiating mitochondrial fragmentation (Manczak et al., 2011). Similarly, pathological tau seems to converge on the same fission pathway. In a later study, Manczak and Reddy extended the Aβ-Drp1 model by testing whether phosphorylated tau also interacts with Drp1 in AD. Using co-immunoprecipitation and immunofluorescence analyses, they were the first to demonstrate a physical association between phosphorylated tau and Drp1 in postmortem frontal cortex tissues from AD patients and in cortical tissues from APP, APP/PS1, and 3XTg.AD mice (Manczak & Reddy, 2012). They found significantly elevated mitochondrial fission-linked GTPase activity in these tissues and concluded that both Aβ- and tau-Drp1 interactions lead to excessive mitochondrial fragmentation which may contribute to neuronal dysfunction and cognitive impairment. These findings suggest that Aβ and phosphorylated tau may intensify mitochondrial dysfunction through a shared Drp1-mediated fragmentation pathway.

Further, the functional importance of Drp1 is supported by intervention studies. Baek et al. found that Drp1 inhibition led to reduced Aβ-mediated mitochondrial fragmentation, ROS production, and cognitive impairment in APP/PS1 2xTgAD mice (Baek et al., 2017). By showing that Drp1 inhibition also improved learning and memory in AD models, this study provides evidence that Aβ-driven Drp1 activation contributes not only to mitochondrial fragmentation but also later downstream cognitive decline. Similarly, Joshi et al. found that inhibiting Drp1/Fis1 interaction reduced Aβ accumulation and oxidative stress and improved behavioral performance in a 5xFAD mouse model (Joshi et al., 2017).

These studies highlight the role of excessive fission in cognitive impairment and suggest Drp1-mediated fission as a possible target for future disease-modifying therapies of AD.

Aβ and Tau Impair Mitophagy and Mitochondrial Quality Control (MQC)

A third mechanism by which Aβ and tau sustain mitochondrial dysfunction is through impaired mitophagy and mitochondrial quality control. Damaged mitochondria produced by excessive Drp1-mediated fragmentation are cleared through mitophagy, which isolates and degrades unhealthy mitochondria. Mitophagy can occur through several pathways, but two major forms are especially relevant. In PINK1/Parkin-dependent mitophagy, mitochondrial depolarization leads to PINK1 accumulation on the OMM, where it then recruits Parkin to ubiquitinate mitochondrial surface proteins. In receptor-mediated mitophagy, mitochondrial receptors such as BNIP3, NIX/BNIP3L, and FUNDC1 bind LC3 directly to recruit autophagosomal membranes (Liu et al., 2024). The major difference between the two pathways is the ubiquitin dependence; however, both work to prevent the accumulation of damaged mitochondria and, consequently, the buildup of excess ROS.

Various studies show that AD pathology interferes with mitochondrial clearance at multiple points. Reddy and Oliver described Aβ and phosphorylated tau association with abnormal mitophagy after observing significantly reduced cell survival and altered mitochondrial quality-control markers in mAPP-expressing HT22 mouse hippocampal cells (Reddy & Oliver, 2019; Reddy et al., 2018). Specifically, Reddy et al. found decreased levels of autophagy (ATG5, LC3BI, LC3BII) and mitophagy (PINK1, BNIP3L), suggesting that mutant Aβ impairs both general autophagy and PINK1-related mitophagy. Additionally, the group observed increased levels of mitochondrial fission genes (Drp1, Fis1) and decreased levels of fusion (Mfn1, Mfn2, Opa1) which were consistent with the disruption of mitochondrial dynamics described above. The link between Drp1 and mitophagy is further supported by experiments crossing APP x Drp1 +/- mice. In genetic studies crossing Drp1 heterozygous knockout mice with APP transgenic mice, 6-month-old APP x Drp1+/- mice were shown to have reduced expression of fission-related genes and increased expression of fusion, mitochondrial biogenesis, and synaptic genes (Manczak et al., 2016; Pradeepkiran & Reddy, 2020). Taken together, the mAPP-HT22 and APP x Drp1+/- experiments clarify the role mitophagy failure plays in Stage 2 mitochondrial decompensation. Aβ drives mitochondrial damage through respiratory dysfunction and excessive fission, and at the same time also reduces the clearance mechanisms needed to remove damaged mitochondria.

Persistent Mitochondrial Dysfunction Creates Sustained Oxidative Stress

The combined consequence of impaired respiration, Drp-driven fragmentation, and defective mitophagy is sustained oxidative stress. These mechanisms do not act independently of each other; in fact, they build on top of one another: respiratory-chain dysfunction increases ROS production, excessive fission produces fragmented mitochondria, and failed mitophagy allows the ROS-producing mitochondria to remain within neurons (Rhein et al., 2009; Manczak & Reddy, 2012; Pradeepkiran & Reddy, 2020).

This progression helps explain the transition from early mitochondrial abnormalities to later mitochondrial stress driven by Aβ/tau pathology. Therefore, Stage 2 demonstrates how Aβ and tau convert early mitochondrial vulnerability into sustained MD. The role of oxidative stress in this process is also important to note since mitochondrial damage increases ROS and ROS further damages mitochondria, creating a vicious cycle in which MD becomes self-sustaining.

Stage 3: Sustained Mitochondrial Stress Drives the Self-Sustaining Cycle of AD Pathology

As mitochondrial damage becomes prolonged, ROS are continuously produced, creating a persistent oxidative environment within neurons. This type of cellular environment provides a bridge into Stage 3, where mitochondrial stress leads to downstream consequences such as disrupted tau proteostasis and broader neuronal systems like synaptic function and inflammatory signaling. This review will especially focus on defective tau proteostasis as a central consequence in Stage 3 because tau pathology is one of the defining hallmarks of AD and recent research increasingly emphasizes tau degradation pathways as being therapeutically relevant (Wang et al., 2025; Samelson et al., 2026).

Persistent Mitochondrial ROS Promotes Tau Hyperphosphorylation

Under normal conditions, tau phosphorylation homeostasis is regulated by the balance between protein kinases, which add phosphate groups, and phosphatases (such as PP2A), which remove them. This phosphorylation balance is indispensable for microtubule stabilization and maintaining proper neuronal function. In AD, abnormal hyperphosphorylation weakens tau-microtubule binding and increases tau detachment, mislocalization, and aggregation (Dolan & Johnson, 2010; Basheer et al., 2023).

Melov et al. tested whether mitochondrial oxidative stress was a regulator of tau phosphorylation using mice deficient in mitochondrial superoxide dismutase 2 (SOD2), an antioxidant enzyme that limits mitochondrial superoxide accumulation. SOD2-null mice treated with a low-dose antioxidant had significantly elevated levels of tau phosphorylation, whereas hyperphosphorylation was prevented with an increased dose of the antioxidant, supporting the idea that mitochondrial oxidative stress actively promotes tau phosphorylation (Melov et al., 2007). The pathway by which oxidative stress contributes to tau phosphorylation involves protein phosphatase 2A (PP2A). PP2A is responsible for dephosphorylating tau at key sites and Sontag et al. explain that PP2A dysfunction is strongly associated with AD-related tau hyperphosphorylation (Sontag et al., 2014). A reduction in phosphatase activity allows kinase-driven phosphorylation to persist and tau to accumulate in abnormal forms. Mitochondrial ROS therefore disturbs the kinase-phosphatase balance that normally regulates tau and thus amplifies tau pathology.

Broadly, mitochondrial ROS is just one of several contributors to tau hyperphosphorylation. Abnormal post-translational tau processing is also influenced by several overlapping factors including Aβ toxicity, calcium dysregulation, kinase activation, and phosphatase suppression, many of which are affected by mitochondrial damage. Weidling and Swerdlow describe the relationship between mitochondria and other

AD-relevant proteins as reciprocal: Aβ and tau pathology trigger mitochondrial defects while mitochondrial dysfunction also influences tau physiology and AD proteostasis (Weidling & Swerdlow, 2020). This directionality component is crucial to note because Stage 3 does not suggest a linear pathway from mitochondrial dysfunction to downstream AD pathology. Instead, persistent mitochondrial stress and pathological tau reinforce one another in a cycle.

Mitochondrial Stress Disrupts Tau Proteostasis and Clearance Mechanisms

Tau hyperphosphorylation is a key initial event in tau pathology and further downstream processes like oligomerization, aggregation, and degradation explain how abnormal tau begins to accumulate. Tau proteostasis includes the cellular processes that maintain functional tau and remove tau species that are misfolded. In AD, tau accumulation results not only from pathological modification but also from defective degradation pathways, which this subsection examines.

Tau can be cleared through multiple protein quality-control systems, including the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway (ALP). In the UPS pathway, under normal cell conditions, soluble and unmodified tau can be degraded directly by the ATP- and ubiquitin-independent 20S proteasome; however, hyperphosphorylated tau is typically ubiquitinated and directed to the ATP-dependent 26S proteasome. In the ALP, soluble tau monomers may be removed through chaperone-mediated autophagy (CMA) or endosomal microautophagy, while larger aggregates are enclosed within autophagosomes and degraded through macroautophagy (Wang et al., 2025). Poppek et al. provide experimental evidence that tau phosphorylation can interfere with these tau degradation pathways. Their study found that a combination of oxidative stress and treatment with OA (okadaic acid, an inhibitor of PP1 and PP2A) in HT22 neuronal cells led to significant tau hyperphosphorylation and inhibition of tau degradation (Poppek et al., 2006). Interestingly, oxidative stress alone caused little or no increase in tau phosphorylation until paired with inhibition of protein phosphatases, suggesting that oxidative stress drives tau pathology most strongly when phosphatase activity is already impaired.

Recent CRISPR-based work in human iPSC-derived neurons further supports the link between mitochondrial dysfunction and unbalanced tau proteostasis. Using iPSC-derived neurons, Samelson et al. found acute oxidative stress leading to the generation of a 25 kD tau fragment similar to the NTA tau biomarker. Specifically, since ETC Complexes I and III are considered major sources of mitochondrial ROS, the researchers concluded that ROS accumulation generated the 25 kD fragment (Samelson et al., 2026). This finding shows that mitochondrial stress in tau pathology can not only increase tau phosphorylation but also alter tau protein processing by promoting abnormal fragmentation. The same study also found that disruption of mitochondrial ETC-related genes was associated with altered proteasome-mediated tau handling and identified CRL5/SOCS4 as an E3 ligase complex capable of ubiquitinating tau (Samelson et al., 2026). ETC dysfunction likely contributes to a mitochondrial stress state which increases ROS accumulation and reduces proteasome function, changing how tau is both processed and cleared.

Synaptic Bioenergetic Failure and Impaired Axonal Transport

Outside of disrupting tau proteostasis and contributing to tau pathology, sustained mitochondrial stress also damages neuronal systems directly dependent on mitochondrial function. Mitochondria serve key roles in regulating and carrying out specific functions in neurons, with specific subtypes known as synaptic mitochondria being crucial to synaptic activity (Guo et al., 2017). Given the importance of mitochondria in ATP production, calcium buffering, and redox balance, mitochondrial stress can greatly impair neuronal communication, resulting in broader neuronal consequences.

As mentioned above, synaptic dysfunction is one of the major downstream consequences because synapses depend heavily on local mitochondrial support. The bioenergetic deficit in synapses manifests in an inability to sustain local ATP concentrations at presynaptic terminals. Under normal physiological conditions, kinesin and cytoplasmic dynein motors shuttle mitochondria along microtubule tracks to areas of high energy demand. However, Aβ- and tau-induced mitochondrial fragmentation, combined with tau-mediated microtubule destabilization, severely impairs mitochondrial trafficking (Cai et al., 2017). Damaged mitochondria fail to buffer calcium adequately and this dyshomeostasis, combined with the opening of the mitochondrial permeability transition pore (mPTP) and cytochrome c release, triggers local synaptic depression (Cai et al., 2017). This synaptic bioenergetic failure initiates a degenerative feedback loop. As synapses degenerate, the failure to adequately transport neurotransmitters and other molecular signals across neurons disrupts cellular communication, accelerating neuronal deterioration. This cellular stress then feeds back into the mitochondrial and proteostatic collapse mentioned above by increasing oxidative stress, disrupting axonal transport of mitochondria, and impairing clearance of damaged mitochondria and tau.

Mitochondrial DAMPs and Neuroinflammatory Amplification

As mitochondrial integrity further deteriorates in Stage 3, stressed mitochondria release internal molecular signals into the cytosol and extracellular space. These molecules are known as mitochondrial damage-associated molecular patterns (DAMPs); they include mitochondrial reactive oxygen species (mtROS) and mitochondrial double-stranded DNA (mtDNA) (Lin et al., 2022). DAMPs are released as endogenous triggers of innate immune signaling, linking MD with neuroinflammation.

There are two primary immune-activation pathways engaged by mitochondrial DAMPs. In the first pathway, cytosolic mtDNA activates the cyclic GMP-AMP synthase (cGAS), which produces the second messenger cGAMP that activates STING, a protein located on the ER (Kim et al., 2023). Recent studies found neuronal and microglial cGAS-STING signaling to be significantly upregulated in AD brains and transgenic models (Chung et al., 2024). Aβ- and tau-associated mitochondrial stress can promote mtDNA leakage into the cytoplasm, where it is then detected by cGAS, activating STING-dependent type I interferon responses and downstream pro-inflammatory transcription (Xie et al., 2023).

In the second pathway, mitochondrial ROS acts as a primary upstream signal for activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome in microglia. Aβ- and tau-induced mitochondrial dysfunction increases mtROS production, which then promotes the assembly of the NLRP3 inflammasome complex. This leads to caspase-1 activation and the cleavage of pro-inflammatory cytokines like pro-IL-1β into mature interleukin-1β (IL-1β) which then amplifies neuroinflammation (Parajuli et al., 2013). Sheng et al. reported increased IL-1 expression in AD brains, which correlated with elevated levels of phosphorylated tau. This suggests a feedback cascade in which IL-1 overexpression leads to tau hyperphosphorylation in AD pathogenesis (Sheng et al., 2001). As pro-inflammatory cytokines worsen mitochondrial respiration, they can also upregulate kinases that promote tau hyperphosphorylation, meaning that mtDAMP-mediated neuroinflammation reinforces both MD and tau pathology in a self-reinforcing manner.

Stage-Specific Therapeutic Implications

Based on the stage-dependent role of MD proposed in this review, this section will suggest important therapeutic implications that target each stage. Since mitochondrial dysfunction changes from early bioenergetic vulnerability to Aβ- and tau-driven decompensation then later to a driver of downstream AD pathology, optimal therapeutic targets are likely to change across disease progression.

Stage 1: Preserve Mitochondrial Resilience

Therapies during Stage 1 may aim to preserve the ability of mitochondria to maintain ATP production, regulate mtROS, and replace damaged mitochondria. As shown in Section 1, early mitochondrial abnormalities do not necessarily reflect complete energetic failure. Because some models display reduced ATP production in early AD pathogenesis while others show temporarily elevated ATP levels, early treatment should focus on supporting mitochondrial adaptability.

One potential target is the PGC-1α-NRF-TFAM pathway that controls mitochondrial biogenesis. Sheng et al. found reduced expression of PGC-1α, NRF1, NRF2, and TFAM in AD hippocampal tissues, meaning that reduced mitochondrial biogenesis may contribute to the transition from mitochondrial compensation to dysfunction (Sheng et al., 2011). Therapeutic activation of upstream regulators such as AMPK and SIRT1 could increase PGC-1α activity and maintain mitochondrial biogenesis. However, generation of new mitochondria without clearance of defective ones may be ineffective. Therefore, the therapeutic goal should be balanced mitochondrial turnover in which biogenesis is coordinated with mitophagy.

Reducing excessive oxidative stress is also key in preserving early mitochondrial function. ROS are already naturally generated as by-products of normal cellular metabolism; therefore, several mitochondria-targeted antioxidants and other compounds have been investigated for their potential to reduce ETC-related oxidative damage. Since ROS are not exclusively pathological, broad antioxidant treatments may interfere with physiological redox responses. Therefore, Stage 1 treatments should aim to limit persistent oxidative damage while preserving intracellular redox processes.

A central difficulty in proposing treatments for Stage 1 is that early mitochondrial abnormalities are not necessarily specific to AD. Altered ATP production, excessive ROS generation, or reduced biogenesis may also arise due to aging, vascular disease, or metabolic disorders. Stage 1 intervention will therefore require biomarkers capable of distinguishing general mitochondrial aging from AD-specific mitochondrial vulnerability. Without biomarkers specific to AD progression, mitochondrial-targeted therapies may risk being too broad and applied to patients whose mitochondrial abnormalities reflect non-AD causes.

Stage 2: Interrupting Aβ- and Tau-Driven Mitochondrial Decompensation

Stage 2 examines how Aβ and pathological tau directly impair mitochondrial respiration, increase fragmentation, and reduce mitophagic clearance (Reddy & Oliver, 2019). Therapeutic interventions in this stage should therefore focus on these three mechanisms: limiting Aβ and tau interactions with the ETC, normalizing Drp1-mediated mitochondrial fission, and restoring mitophagic clearance.

A potential target for therapies could be the direct interaction of Aβ and tau with mitochondrial complexes. Aβ peptides bind to TOM40 and Cytochrome c Oxidase (Complex IV), impairing electron transport and increasing ROS production (D'Alessandro et al., 2025); similarly, hyperphosphorylated tau targets Complex I, depressing NADH dehydrogenase activity and disrupting membrane potential (Rhein et al., 2009). While most anti-amyloid treatments have focused on plaque clearance, upstream mitochondrial-protective strategies such as preventing Aβ from entering mitochondria or blocking Aβ interactions within mitochondria can decouple amyloid and tau accumulation from respiratory-chain dysfunction.

Within mitochondria, both Aβ and tau abnormally recruit hyperactive Drp1 to drive excessive fission (Reddy & Oliver, 2019). Normalizing Drp1-mediated mitochondrial fragmentation may preserve mitochondrial network integrity as well as prevent the accumulation of damaged mitochondria. Pharmacological inhibition of Drp1 or targeted disruption of the Drp1-Fis1 interaction has shown significant preclinical efficacy. For example, Baek et al. showed that inhibiting Drp1 suppressed mitochondrial fragmentation, reduced ROS production, and alleviated cognitive deficits in APP/PS1 transgenic mice (Baek et al., 2017) while Joshi et al. used the P110 peptide to selectively inhibit Drp1-Fis1 interaction which reduced Aβ-mediated oxidative stress and energetic failure (Joshi et al., 2017). Together these studies suggest that Drp1-based interventions show strong potential in ameliorating Stage 2 mitochondrial decompensation.

Finally, restoring mitophagy as a means to clear defective mitochondria is critical in Stage 2. Since Aβ and tau pathology suppress PINK1/Parkin-dependent mitophagy, damaged mitochondria are able to accumulate and continuously generate ROS (Reddy & Oliver, 2019). Fang et al. stimulated mitophagy using urolithin A, NAD+ supplementation, and actinonin which reduced insoluble Aβ and tau hyperphosphorylation (Fang et al., 2019). More recently, Hou et al. showed that long-term urolithin A

treatment improved learning and memory in AD mouse models while restoring mitophagy and lysosomal function (Hou et al., 2024).

Stage 3: Breaking the Feedback Cycle

By Stage 3, evidence supports a reciprocal cycle between mitochondrial dysfunction and tau pathology in which mitochondrial stress promotes abnormal tau processing while pathological tau further damages mitochondrial respiration, dynamics, and quality control. The first direction of this cycle – mitochondrial dysfunction driving tau pathology – was established in Section 3. Mitochondrial oxidative stress promotes tau hyperphosphorylation through impairment of the kinase-phosphatase balance necessary for normal tau phosphorylation (Melov et al., 2007; Poppek et al., 2006). The reverse direction is also supported by various experimental studies. Tau and Aβ pathology act synergistically to reduce OXPHOS as well as ATP synthesis by impairing complexes I and IV of the ETC, respectively (Rhein et al., 2009). Additionally, in primary cortical neurons, expression of Asp421-cleaved tau induced significant mitochondrial fragmentation and truncated tau combined with Aβ led to increases in levels of oxidative stress along with mitochondrial potential loss (Quintanilla et al., 2012). Both of these studies display the combined effects of classic AD pathology on mitochondrial processes and how one drives another in a feedback loop.

To address this vicious cycle, the first therapeutic priority should be to remove damaged mitochondria before they continuously generate ROS and interfere with downstream tau clearance. Rather than using general antioxidants, therapeutics addressing specific mitophagic pathways can target the source of persistent oxidative stress rather than neutralizing ROS after they have been produced. PINK1-dependent mitophagy provides strong experimental support for this approach. Du et al. demonstrated an association between reduced PINK1 expression and AD pathology and found that restoring neuronal PINK1 function reduced Aβ accumulation, oxidative stress, and mitochondrial abnormalities in mAPP mice. Conversely, PINK1 deficiency – loss of PINK1 activity or blockage of PINK1-mediated signalling (OPTN or NDP52) – accelerated mitochondrial and amyloid pathology (Du et al., 2017). Restoring mitochondrial quality control may also improve tau clearance because of the shared lysosomal systems used in both mitophagy and autophagy. A recent study using human neurons containing NFT pathology found that activation of adiponectin-receptor signaling with AdipoRon (AR) reduced phosphorylated tau while restoring mitochondrial metabolism and lysosomal pathways (McGregor et al., 2024). These effects involved LC3 and p62 activation, linking mitochondrial function and tau clearance and offering the connected mitochondrial-lysosomal pathway as a therapeutic target to address tau accumulation.

Once pathological tau begins to accumulate, a second therapeutic priority is to reduce its contribution to mitochondrial injury. Tau-directed therapies can be divided into two main approaches: inhibiting tau hyperphosphorylation in the first place or improving degradation of pathological tau. The first approach targets tau hyperphosphorylation by inhibiting tau kinases or restoring phosphatase activity. In tau-transgenic mice, sodium selenate increased PP2A and reduced tau phosphorylation and neurofibrillary pathology by stabilizing PP2A-tau complexes (van Eersel et al., 2010). Given the major role of PP2A as a

phosphatase in tau proteostasis, the ability of sodium selenate to improve the effects of PP2A makes it a promising target for future tau-directed AD treatments. Further, clinical studies demonstrated CNS penetration of sodium selenate, reporting that treatment was well-tolerated and possibly disease-modifying (Cardoso et al., 2019; Vivash et al., 2021). This could represent a key focus for future tau-targeted AD therapies as most current treatments are symptomatic rather than disease-modifying. A second approach is to improve the degradation and clearance of pathological tau that has already formed. As discussed above in the section on tau proteostasis, tau is typically degraded through the ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP); therefore, therapeutic strategies could selectively direct pathological tau toward these pathways. Recent CRISPR screening in human iPSC-derived neurons identified $CRL5^{SOCS4}$ as an E3 ubiquitin-ligase complex capable of clearing tau. CUL5 expression was also associated with neuronal resilience in human tauopathies, making it a valuable target to support selective tau ubiquitination (Samelson et al., 2026). However, since this pathway is newly identified, further studies are needed to determine whether $CRL5^{SOCS4}$ activity can be safely enhanced without disturbing the degradation of other cellular proteins. Another method to target tau clearance is through autophagic degraders. A recent study developed TauAutac-3 (TA-3), a molecule designed to bind tau and direct it toward lysosomal degradation. Yoon et al. found that TA-3 reduced tau monomers and oligomers *in vitro*. In 6xTg AD mouse models, TA-3 reduced phosphorylated tau and Aβ accumulation, thereby ameliorating lysosomal stress (Yoon et al., 2025). Together, these studies suggest that tau-directed strategies can take two forms: activation of phosphatases such as PP2A to prevent hyperphosphorylation or UPS- and ALP-directed degradation to remove accumulated pathological tau. Since tau phosphorylation can interfere with tau turnover, combining both approaches may be more effective in countering tau pathology in AD.

DISCUSSION

This review proposes that mitochondrial dysfunction plays a changing, stage-dependent role in Alzheimer's disease. In Stage 1, early mitochondrial abnormalities may appear before the development of substantial Aβ and tau pathology as bioenergetic vulnerability in cells. In Stage 2, accumulating Aβ and tau directly worsen mitochondrial processes such as respiration, dynamics, and mitophagy. In Stage 3, sustained mitochondrial stress then amplifies AD pathology by impairing tau proteostasis, which further drives mitochondrial dysfunction and produces a self-reinforcing feedback loop.

The primary usefulness of this model is that it responds to conflicting evidence on whether mitochondrial dysfunction occurs upstream or downstream of classical AD pathology and emphasizes its relative importance as a hypothesis for explaining AD. The model integrates the current mitochondrial, amyloid, and tau-centered explanations instead of treating them as competing hypotheses. This stage-dependent interpretation also has therapeutic value. It proposes that treatments should target the dominant mechanisms present at different stages of disease progression. For example, Stage 2 therapies may aim to limit Aβ- and tau-induced mitochondrial injury while restoring mitochondrial dynamics and mitophagy. The transition between Stages 2 and 3 may also serve as an important therapeutic window as MD and tau

pathology have begun to reinforce each other but cellular quality-control systems still remain partially functional.

However, the proposed model should only be taken as a conceptual framework rather than a clinically validated disease progression system. Its sequence is mainly assembled from studies on postmortem tissue, transgenic animal models, cultured cells, and human iPSC-derived neurons rather than a single longitudinal human study. Most experimental models also best reflect familial forms of AD rather than sporadic late-onset disease, which accounts for the majority of AD cases. Additionally, the stages proposed are overlapping mechanistic states rather than fixed chronological periods and may vary across both brain regions and individuals. Mitochondrial abnormalities are also not AD-specific and occur in normal aging or in other neurological and metabolic conditions. This lack of specificity is particularly important in preclinical AD, where mitochondrial dysfunction may be detectable before substantial Aβ and tau pathology, but its underlying cause remains difficult to determine. Single-cell RNA sequencing (scRNA-seq) could help identify cell-type-specific transcriptional changes associated with mitochondrial dysfunction in pre-AD and potentially distinguish between AD-related mitochondrial vulnerability and broader age- or disease-associated mitochondrial changes.

More broadly, the stage-dependent model proposed requires experimental validation. Future studies should test whether mitochondrial, amyloid, and tau alterations emerge in the predicted sequence through longitudinal studies with the same experimental systems and human cohorts. Single-cell RNA sequencing and spatial transcriptomics could characterize cell-type- and region-specific mitochondrial changes over disease progression. These approaches may also help identify the molecular mechanisms behind pre-AD mitochondrial vulnerability. Since current biomarkers cannot distinguish which mitochondrial abnormalities are indicative of AD, future research should focus on finding biomarkers that can identify declining mitochondrial function specific to AD. Future studies should also aim to test mitochondrial, amyloid, and tau changes longitudinally within the same model and in human cohorts. Validation in sporadic AD models and multicellular human systems will be necessary to determine how broadly the proposed model applies.

Overall, mitochondrial dysfunction in Alzheimer's disease appears to change from an early state of vulnerability or compensation to a consequence of Aβ and tau pathology and ultimately to an amplifier of tau pathology and neuronal degeneration. In this way, the model aims to provide not a fixed explanation of AD pathogenesis, but a framework for generating and evaluating future hypotheses on how mitochondrial dysfunction interacts with classical pathology over time.

CONCLUSION

Mitochondrial dysfunction (MD) is increasingly recognized as an important component of Alzheimer's disease, yet its relationship with classical AD pathology remains complex. This review examined current evidence to propose a stage-dependent model of MD in AD in which MD begins as an early bioenergetic

vulnerability, then is amplified by accumulating Aβ and tau pathology, ultimately becoming a driver of abnormal protein aggregation. Across the proposed stages, impaired mitochondrial biogenesis, respiration, dynamics, mitophagy, and oxidative stress all contribute to a self-reinforcing cycle of neuronal degeneration. This framework also suggests therapeutic targets based on the dominant mitochondrial mechanisms present at each stage of disease progression. Although further longitudinal and experimental validation is needed, viewing mitochondrial dysfunction as an evolving feature of AD helps reconcile existing hypotheses and guides further research to produce more precise disease models.

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