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REVIEW

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Molecular and cellular mechanisms underlying Alzheimer's disease: an integrated review

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Abstract

Alzheimer's disease (AD) is a multi-event neurodegenerative disease, typified by the development of cognitive deficits in conjunction with a range of genetic, molecular, cellular, and environmental processes. This review integrates evidence from more than 90 peer-reviewed publications across major domains of AD pathogenesis, including genetic risk factors (*APOE*, *APP*, *PSEN1*, and *PSEN2*); amyloid-β (Aβ) production, aggregation, and neurotoxicity; tau hyperphosphorylation and neurofibrillary tangle (NFT) formation; synaptic dysfunction; mitochondrial impairment and oxidative stress; neuroinflammation; and vascular dysfunction. Lifestyle and environmental modulators, such as sleep, nutrition, physical activity, and epigenetic influences, are also considered. By integrating these mechanisms, we provide a systems-level view in which interacting pathological pathways act in concert rather than independently to promote disease progression, and we discuss the therapeutic implications of this holistic model, including biomarker-based, multi-target precision approaches.

Keywords: Alzheimer's disease, neurodegenerative disease, blood–brain barrier, pathological pathways, neuroinflammation, mitochondrial dysfunction, tau pathology, precision medicine

Introduction

Alzheimer's disease (AD) is a progressive and complex neurodegenerative disorder that is recognized as the leading cause of dementia worldwide. AD is the most common cause of dementia, accounting for an estimated 60–70% of all dementia cases. Globally, approximately 57 million people were living with dementia in 2021, with nearly 10 million new cases each year, and this number is projected to rise to 139 million by 2050. In the United States, an estimated 7.2 million people aged 65 years and older currently live with Alzheimer's dementia, a figure projected to grow to 13.8 million by 2060 [1, 2]. At the organismal level, AD begins with a gradual loss of memories, problem-solving skills, and mental flexibility; in later stages, it is characterized by significant impairments in daily functioning and reduced quality of life. At the molecular level, AD involves the presence of extracellular deposits called amyloid-β (Aβ) peptides and intracellular accumulations known as hyperphosphorylated tau protein that form neurofibrillary tangles; these lesions are thought to disrupt neuron function [3]. Recent advances in molecular neuroscience suggest that these lesions are part of more complex processes, including synaptic dysfunction, mitochondrial damage, oxidative stress, neuroinflammation, and vascular issues [4, 5]. Genetic susceptibility factors, including variants and mutations in *APOE*, *APP*, *PSEN1*, and *PSEN2* influence amyloid processing and other disease-related pathways [4, 6]. AD is more complex in its etiological processes since it does not result from one pathway but arises from the culmination of various molecular, cellular, and systemic components that result in neurodegenerative processes over time. Rather than attributing AD simplistically to inherited genes or mutations, it is important to understand the underlying molecular processes, which are essential for identifying potential biomarkers [7]. Despite the breadth of this literature, most prior reviews have addressed individual pathogenic cascades in isolation. The present review addresses this gap by providing an integrated, systems-level synthesis of how genetic, molecular, cellular, vascular, and environmental pathways interact dynamically to drive AD, and

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by translating this integrated model into a framework for biomarker-based, multi-target therapeutic strategies.

Methods

To synthesize current knowledge on the molecular and cellular mechanisms of AD, a structured and comprehensive literature search was conducted. Primary searches were performed in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar using a combination of Medical Subject Headings (MeSH) and keywords related to AD pathogenesis, including "amyloid-beta," "tau," "neuroinflammation," "mitochondrial dysfunction," "blood–brain barrier," and "genetic risk factors," with an emphasis on literature from the past decade (2014–2025). The search strategy prioritized peer-reviewed original research, systematic reviews, meta-analyses, and key clinical trials. Additional relevant studies were identified through backward and forward citation tracking. Selected literature was evaluated for methodological quality and integrated to construct a coherent, systems-level overview of interacting pathogenic pathways in AD.

Genetic risk factors and molecular susceptibility

An important role in molecular susceptibility to AD, as well as its progression, is attributed to genetic propensity. Among many identified genes, the *APOE ε4* allele, a gene encoding APOE, remains the strongest genetic risk factor for late-onset AD. A recent multi-omics study suggests *APOE ε4*, an Alzheimer's risk factor, causes perturbation in lipid homeostasis, affects Aβ regulation, and impacts microglial reactions, leading to the development of neuroinflammatory and synaptic deregulatory alterations, respectively [8, 9]. The *APOE ε2* allele is generally associated with reduced AD risk and influences lipid transport and Aβ homeostasis, which are reduced by amyloidogenic pathways, respectively.

Familial, early-onset AD is mainly due to dominantly inherited mutations in *APP, PSEN1*, and *PSEN2* genes, which code for the components of the gamma-secretase complex involved in Aβ production. The mutations result in an elevated $A\beta_{42}/A\beta_{40}$ ratio, favoring the assembly of Aβ oligomers that trigger tau pathology as a sequela [10, 11]. It is worth noting, however, that even in sporadic AD, various low-penetrance risk modifiers have been unraveled by genome-wide association studies, influencing molecular susceptibility patterns related to endosomal trafficking, autophagy, mitochondrial dynamics, and the regulation of the innate immune response [6]. These genetic risk factors and their associated molecular pathways are summarized in Table 1.

Moreover, novel epigenetic and transcriptomic research has indicated that the interactions between genetic predispositions and the influence of environmental factors, including aging, dietary components, and metabolism, dynamically regulate gene expression related to AD, establishing a continuum between genetically and sporadically related AD types. The intersection between risk factors and commonly shared molecular pathways represents a fruitful approach toward biomarker identification and targeted therapies focusing on the primary molecular alterations established during the pathogenesis of AD.

Table 1. Key genetic risk factors and molecular susceptibility pathways in AD.

Gene/variant	Role in AD	Effect (risk/protective)	Associated pathways/molecular mechanisms
APOE ε4	Strongest genetic risk factor for late-onset AD	Risk	Perturbation in lipid homeostasis; affects Aβ regulation; impacts microglial reactions → neuroinflammatory and synaptic dysregulatory alterations
APOE ε2	Protective component in late-onset AD	Protective	Affects lipid transfer and Aβ homeostasis (these processes are reduced by amyloidogenic pathways)
APP (mutations)	Autosomal dominant early-onset familial AD	High-penetrance risk	Elevated $A\beta_{42}/A\beta_{40}$ ratio; favors Aβ oligomer assembly → triggers tau pathology
PSEN1 (mutations)	Autosomal dominant early-onset familial AD	High-penetrance risk	Component of γ-secretase complex; mutations result in elevated $A\beta_{42}/A\beta_{40}$ ratio
PSEN2 (mutations)	Autosomal dominant early-onset familial AD (rarer form)	High-penetrance risk	Component of γ-secretase complex; mutations result in elevated $A\beta_{42}/A\beta_{40}$ ratio
Low-penetrance GWAS variants	Genetic susceptibility modifiers in sporadic AD	Risk modifiers	Influence endosomal trafficking, autophagy, mitochondrial dynamics, and regulation of innate immune response

Notes: AD, Alzheimer's disease; Aβ, amyloid-β; APOE, apolipoprotein E; APP, amyloid precursor protein; PSEN1, presenilin 1; PSEN2, presenilin 2; GWAS, genome-wide association study.

Aβ pathology and aggregation dynamics

The amyloid hypothesis continues to be a prominent theory among those explaining the molecular mechanisms leading to the development of AD. The hallmark component of this theory involves the misfolding and over-accumulation of Aβ peptides, leading to a series of molecular events that ultimately end with neuronal cell death and neuronal dysfunction. Aβ peptides are generated through sequential proteolytic processing of amyloid precursor protein (APP) by β-secretase 1 and γ-secretases. Out of all the fragments, $Aβ_{42}$, being two amino acids longer than $Aβ_{40}$, has a significantly greater hydrophobic core and a higher potential to form toxic oligomers and fibrils compared to $Aβ_{40}$ [12, 13]. Under physiological circumstances, monomeric soluble Aβ is involved in synaptic functions and antimicrobial activities, while under pathological circumstances, an imbalance between the production and clearance levels leads to self-aggregation via β-sheets, resulting in oligomers that are rich in β-sheets. It has been proposed that the soluble oligomers are the most toxic species to neurons as they perturb lipid membranes, disrupt calcium homeostasis, disrupt synaptic functions, and prevent long-term potentiation (LTP) [14, 15]. Experimental studies have indicated that Aβ oligomers bind to postsynaptic receptors, including the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leading to glutamatergic excitotoxicity and synaptic loss, a process that may occur before plaque formation and may better correlate with dementia severity than plaque burden itself [16]. Structurally, Aβ aggregation occurs via a nucleation-dependent polymerization mechanism, whereby Aβ monomers accumulate as low-order oligomers, protofibrils, and finally as mature fibrils, which make up the extracellular amyloid plaques characteristic of AD brains [17]. However, recent cryo-electron microscopy studies have identified various fibrillar polymorphs of Aβ, implying that structural variability may influence the variability seen in Aβ-related disease phenotypes among patients [18, 19]. Additionally, modifications, including pyroglutamylation and oxidative modifications, accelerate both Aβ aggregation and toxicity [20]. The spatiotemporal distribution of Aβ pathology varies considerably among individuals. Longitudinal positron emission tomography (PET) scan studies have found two patterns: "amyloid-first" patterns, whereby Aβ pathologies manifest before tau, and "tau-first" patterns, marked by early tau accumulation within the medial temporal lobe, antedating extensive cortical Aβ deposition [21]. Worth noting is recent evidence that Aβ pathologies interact synergistically with tau pathologies by inducing tau hyperphosphorylation via kinase activation, including glycogen synthase kinase-3 beta (GSK-3β) and cyclin-dependent kinase 5 (CDK5) [22, 23]. Additionally, Aβ has been found to provoke microglial activation and the release of cytokines, creating a milieu conducive to persistent neuronal injury [24, 25]. From a therapeutic perspective, Aβ targeting has remained one of the primary approaches to disease modification. The use of monoclonal antibodies, including aducanumab and lecanemab, has appeared promising in lowering amyloid levels and arresting disease progression, although the degree of clinical response has remained moderate and largely contingent upon disease stage [26]. The significance of examining Aβ aggregation kinetics and pathways involving the *APOE* allele, glymphatic currents, and proteolytic enzyme action by neprilysin and insulin-degrading enzyme, respectively, has thus remained paramount among researchers seeking ideal windows for therapeutic targeting to slow or halt disease progression due to its molecular underpinnings.

Tau hyperphosphorylation and neurofibrillary tangle formation

An important event in the molecular pathogenesis of AD is the hyperphosphorylation of the microtubule-associated protein tau, which leads to its dissociation from microtubules and subsequent mislocalization to neuronal soma and dendrites, where it aggregates into paired helical filaments and neurofibrillary tangles. Under physiological conditions, tau stabilizes microtubules; it supports axonal transport; nevertheless, when aberrantly hyperphosphorylated by kinases such as GSK-3β, CDK5, and c-Jun N-terminal kinase, it loses its tight affinity to microtubules, leading to cytoskeleton destabilization and damage to neurons [27]. The subsequent assembly of tau into oligomeric seeds and fibrils drives a prion-like spread of pathology throughout functionally connected brain networks, which is strongly associated with neurodegeneration and clinical severity of AD [28]. Compounding this, upstream inducers like Aβ deposition, oxidative stress, mitochondrial injury, and glial activation come together to elevate tau kinase activity while depressing phosphatases, collectively accelerating tau phosphorylation [27, 29]. Crucially, tau pathology evolves in a stereotyped anatomical distribution; it initially emerges in the entorhinal cortex and hippocampus before distributing to neocortical areas [30, 31], thus associating molecular features with structural brain alterations and cognitive deterioration. Therefore, investigating detailed molecular mechanisms of tau dysregulation, especially in terms of the balance between kinase and phosphatase activities, post-translational modifications in tau protein, aggregation kinetics, and trans-neuronal spreading is crucial to identify novel diagnostic and therapeutic strategies targeting tau pathology in AD.

Synaptic dysfunction and neuronal network disruption

Synaptic dysfunction is one of the earliest functional changes observed in AD and is closely associated with cognitive impairment [32]. Several different but convergent lines of evidence at the molecular, cellular, and imaging levels suggest that both the soluble oligomeric forms of Aβ and tau proteins impair synaptic functions and connectivity. The soluble form of Aβ oligomers impairs the excitatory synapse through alterations of glutamatergic

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receptor homeostasis, including the endocytosis and subsequent destabilization of both NMDA and AMPA receptors, resulting in the failure of LTP, enhanced calcium influx, and the reorganization of the dendritic spine structure [33]. Tau protein misfolding and further localization to the dendrite and the synapse also impair the homeostasis of microtubule and vesicle functions through the impairment of the cytoplasmic and vesicle trafficking pathway of the neurons. Recent studies in humans have revealed the presence of tau oligomers within the synaptic terminals that are selectively taken up by microglia and astrocytes. Interestingly, the glial cell uptake of tau oligomers appears to be significantly enhanced within individuals with dementia, and such uptake is much lower within individuals who are mentally intact and share similar levels of AD pathology [34]. These data indicate that the accumulation of tau pathology and the uptake of these proteins by glial cells coincide within the synaptic interface, leading to regional synaptic loss. Moreover, astrocyte transcriptional programs are reprogrammed in AD models, and such reprogramming contributes to reduced synaptic maintenance and changes within the inflammatory pathway [35]. Further studies indicate that the enhancement of autophagy within astrocytes could lead to the degradation of Aβ and synaptic robustness [36, 37]. Microglia play a bifunctional role during synaptic remodeling in the AD brain: whereas during normal conditions, microglia participate positively in the process of synaptic pruning and maintenance, deregulation of microglial reactivity and the consequent overactivation of the complement system lead to synaptic loss. In AD models, dysregulated complement signaling promotes excessive microglial pruning of excitatory synapses, contributing to synaptic dysfunction and cognitive impairment [38]. PET imaging and single-cell transcriptome studies in humans have also revealed the deregulation of microglial networks within the AD brain, and that desynchronization of microglial networks within the AD brain shows a very high positive relationship to the degradation of synaptic proteins and impaired cognition [39]. Microglia-astrocyte interaction also regulates the vulnerability of the synaptic membrane. Elevation of the cerebrospinal fluid protein β_2-microglobulin, for instance, has been found to trigger tau-induced synapse destruction through the synchronized activation of glial inflammatory pathways [40]. Further evidence also suggests the role of the cellular prion protein (PrP^c) in the degeneration of the synapse itself. Deletion of the *Prnp* gene attenuates synapse destruction and tau phosphorylation, but does not affect the level of Aβ accumulation and the gliosis in the knock-in model of AD [41]. This suggests that PrP^c may function as a ligand for the Aβ oligomers at the synapse. Disruptions at the network level are the direct result of the early vulnerability of synapses. Longitudinal multimodal imaging analyses indicate that the degeneration of synapses within medial temporal lobe structures occurs before large-scale network desynchronization, such that connectivity within the default mode network and hippocampal-cortical networks is impaired [42]. At the level of the networks, interneurons and pyramidal neurons demonstrate a selective vulnerability to the toxicity of both Aβ and tau, such that pyramidal neurons within the hippocampus's field CA1 demonstrate spine instability, and parvalbumin interneurons display abnormalities in oscillatory firing rhythms, each of which collectively remodels network coherence [43].

Mitochondrial dysfunction and oxidative stress

Mitochondria are the major bioenergetic centers of neurons, serving to produce ATP, buffer calcium, regulate reactive oxygen species (ROS), and trigger apoptotic signaling. Recent findings raise the possibility that mitochondrial impairment is not simply a downstream event, but a central mediator of AD pathogenesis [44, 45]. Studies of AD brain and animal models have consistently reported reduced activity of electron transport chain complexes, especially those of complexes I and IV, resulting in ATP depletion due to diminished energy generation, together with elevated electron leakage that further augments ROS production [46, 47]. Several studies have demonstrated that neurons at early-stage AD present high mitochondrial superoxide production, depolarized mitochondrial membrane potential ($\Delta\Psi_m$), and increased markers of mitochondrial damage associated with a compensatory proliferation [46]. Meanwhile, the protective antioxidant apparatus (such as SOD2, glutathione peroxidase, and peroxiredoxins) is overloaded, leading to ROS-induced damage to mitochondrial DNA, lipids, and proteins [48]. This oxidative load triggers a feed-forward loop: ROS causes the accumulation of both Aβ and hyperphosphorylated tau, which in turn leads to the enhancement of mitochondrial dysfunction [47]. Mitochondrial dynamics, the balance of fission and fusion regulated by proteins such as Drp1, Mfn1/2, and Opa1, are profoundly disrupted in AD. Evidence from transgenic mouse models (*e.g.*, 5×FAD) demonstrates early downregulation of fusion mediators (Mfn2, Opa1) and upregulation or hyper-activation of Drp1 and Fis1, leading to fragmented and swollen mitochondria, impaired motility, and reduced trafficking to synaptic terminals [46]. These morphological abnormalities coincide with decreased mitochondrial distribution in dendrites and axons, underpinning synaptic vulnerability. Moreover, mitophagy, the selective autophagic removal of damaged mitochondria via PINK1/Parkin and BNIP3 pathways, is impaired in AD, leading to accumulation of dysfunctional organelles and sustained oxidative stress (Figure 1) [47]. An additional dimension involves calcium dysregulation: mitochondria unable to buffer cytosolic Ca^{2+} overload trigger opening of the mitochondrial permeability transition pore, loss of mitochondrial membrane potential, release of cytochrome c, and initiation of apoptosis [44]. Concomitantly, structural perturbations of mitochondria-endoplasmic-reticulum contacts (MERCs) alter lipid and Ca^{2+} exchanges, and in AD models, shortening of MERCs distances has been documented, further impairing bioenergetics and Ca^{2+} homeostasis [46]. Beyond neurons, mitochondrial dysfunction extends to glial and peripheral

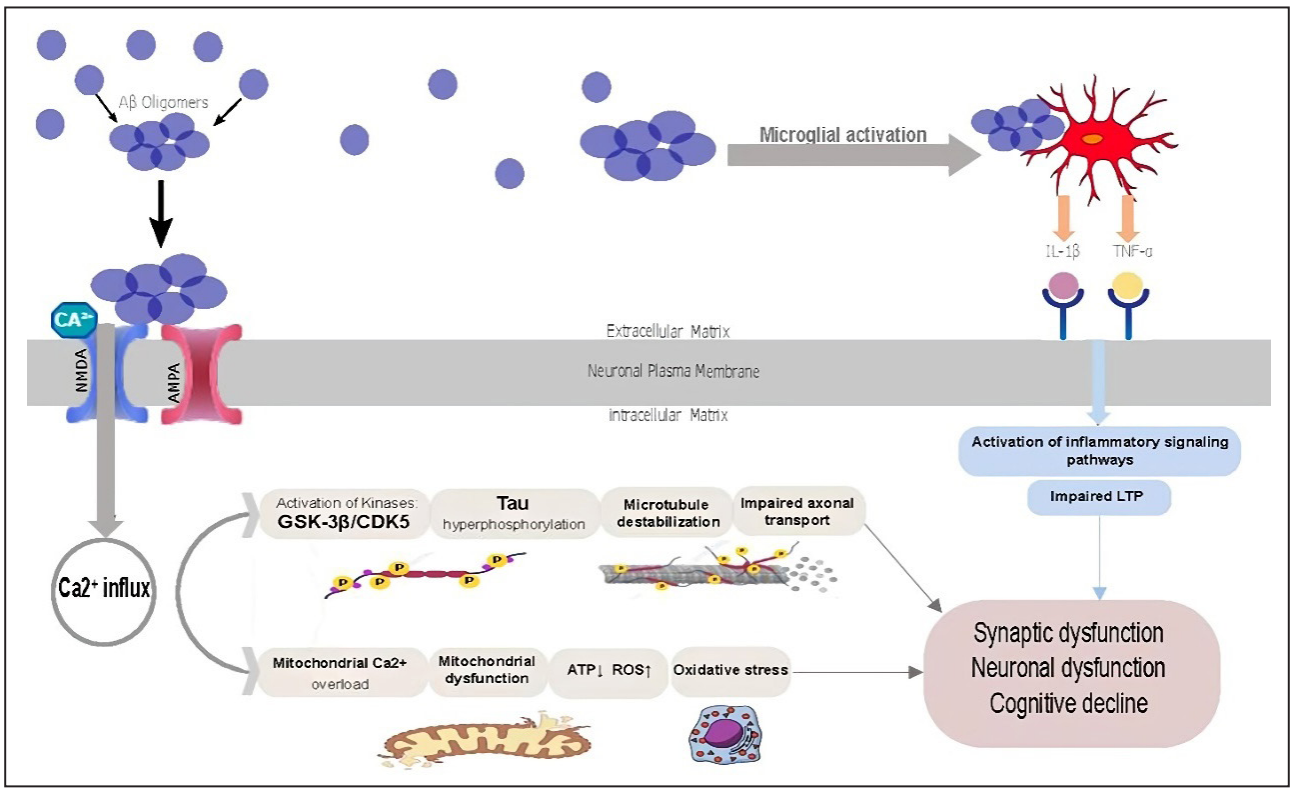


Figure 1. Schematic illustration of amyloid-β oligomer-induced synaptic and mitochondrial dysfunction, neuroinflammation, and convergent pathways leading to cognitive decline. Soluble Aβ oligomers bind to postsynaptic receptors (NMDAR, AMPAR), triggering excessive Ca^{2+} influx and mitochondrial Ca^{2+} overload, which in turn impairs oxidative phosphorylation (ATP↓), elevates reactive oxygen species (ROS), and induces oxidative stress. Concurrently, Aβ oligomers activate microglia, leading to release of pro-inflammatory cytokines (IL-1β, TNF-α) and subsequent activation of neuronal kinases such as GSK-3β and CDK5. These kinases promote tau hyperphosphorylation, microtubule destabilization, and impaired axonal transport. Both Ca^{2+}-mediated mitochondrial dysfunction and tau pathology converge on synaptic failure (impaired LTP, receptor loss) and ultimately neuronal dysfunction and cognitive decline. Solid arrows indicate direct or established pathways; crosstalk between inflammatory and intracellular cascades further amplifies neurotoxicity.

cells: recent work identifies mitochondrial defects in microglia that precede overt neuroinflammation, suggesting that immune cell bioenergetic failure may contribute to the inflammatory component of AD [49]. Collectively, mitochondrial collapse in multiple cell types underscores its systemic contribution to AD neuropathological mechanisms.

From a therapeutic standpoint, mitochondria-targeted strategies are gaining traction. Approaches such as mitochondrial-targeted antioxidants (*e.g.*, mitoquinone), peptides stabilizing mitochondrial membranes (SS-31), small-molecule inhibitors of Drp1, and agents enhancing mitophagy (*e.g.*, PINK1 agonists) have shown efficacy in preclinical AD models by reducing ROS, restoring mitochondrial respiration, and preserving synaptic function [50]. Moreover, the concept of "mitochondrial rejuvenation" via mitochondrial transplantation or exosome-mediated mitochondrial delivery is emerging, though clinical translation remains nascent [45].

Neuroinflammation and immune system activation

Neuroinflammation is a fundamental molecular feature of AD, occurring early in the pathogenic process and increasing as neuronal and synaptic injury accumulate. The brain's major innate immune cells—microglial cells—exhibit dramatic phenotypic changes from a surveillant homeostatic state to a chronically activated, pro-inflammatory state. This transition is defined by the release of cytokines (IL-1β, TNF-α, IL-6), compromised phagocytic function, metabolic reprogramming, and a unique transcriptional profile linked with disease severity [25]. Genetic data also emphasize the role of microglial pathways in AD, with risk-modifying variants found in genes related to the innate immune system: *TREM2, CD33*, and *CR1*. Functional data demonstrate that loss of *TREM2* impairs the ability of microglia to aggregate around amyloid plaques and heightens plaque-associated neurotoxicity, thus worsening amyloid-driven pathology [51]. Reactive astrocytes also serve as a major determinant of the inflammatory landscape in AD. These cells are associated with astrogliosis (increase in glial fibrillary acidic protein, changes in calcium signaling, inflammatory mediator production). Recent transcriptomic and morphological studies have identified multiple reactive astrocyte states in AD. Although the A1/A2 framework has been experimentally useful, current evidence indicates that reactive astrocytes exist along a spectrum of context-dependent and region-specific transcriptional states rather than as two strictly discrete populations [36, 52]. A seminal discovery revealed that microglial cytokines, including IL-1α, TNF-α, and C1q, are able to polarize astrocytes to an A1-

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neurotoxic phenotype that features the loss of homeostatic functions and production of factors injurious to neurons and oligodendrocytes [52]. This bidirectional signaling between microglia and astrocytes is involved in the enhancement of neuroinflammation during AD and in the molecular instability that occurs in at-risk brain regions.

The growing evidence indicates that AD-associated immune dysregulation is not confined to the central nervous system (CNS). Blood–brain barrier (BBB) disruption, which is predicated on vascular degeneration, inflammation, and endothelial dysfunction, allows the entry of circulating immune cells and pro-inflammatory mediators into the CNS [53]. Single-cell sequencing and postmortem analyses of brains from patients with AD have reported infiltration of peripheral $CD8^+$ T cells into the hippocampus as well as into cerebrospinal fluid in AD patients, and imply that adaptive immunity might be playing a previously underappreciated role in promoting neuronal stress or cytotoxicity [54].

Vascular contributions to neurodegeneration

Vascular dysfunction is an important factor in the pathogenesis of AD that influences early vulnerability and progression of neurodegeneration. Disruption of the BBB, a characteristic feature of cerebrovascular decline, has increasingly been reported in AD, including at relatively early stages of the disease before conspicuous accumulation of amyloid or tau. BBB breakdown leads to loss of endothelial tight-junction integrity, altered pericyte coverage, and increased transcytosis, thereby permitting plasma proteins and inflammatory mediators to enter the brain parenchyma [55-57]. These vascular changes provide a permissive substrate for neuronal stress and promote molecular cascades paralleled by synaptic dysfunction, neuroinflammation, and oxidative injury. One of the main vascular mechanisms contributing to neuronal susceptibility in AD is chronic cerebral hypoperfusion. A decrease in cerebral blood flow leads to the attenuation of mitochondrial energy production, elevation of ROS, and perturbation of metabolic homeostasis in highly active neural circuits. Preclinical models indicate that continuous hypoperfusion results in white matter degeneration, synaptic loss, and decreased neurovascular coupling, processes similar to early AD pathology. Human neuroimaging results also indicate that reductions of perfusion in areas like the hippocampus and posterior cingulate cortex are associated with cognitive decline, predicting the conversion from mild cognitive impairment to AD [58]. These findings suggest that vascular dysfunction interacts with the amyloid and tau pathways, modulating spatial (site-dependent) and temporal (age-dependent) dimensions of neurodegeneration.

Aβ itself is associated with strong cerebrovascular toxicity. Deposition of Aβ in the walls of cerebral arteries and arterioles, referred to as cerebral amyloid angiopathy, results in vessel stiffening, microhemorrhages, reduced vasodilation, and endothelial dysfunction. Vascular Aβ compromises smooth muscle cell contractility and clearance of interstitial fluid (ISF) via perivascular pathways, in addition to inducing the inflammatory activation of perivascular macrophages [59]. In preclinical models, *APOE ε4* is associated with increased cerebral amyloid angiopathy burden, whereas impaired glymphatic clearance may promote parenchymal Aβ accumulation and tau pathology [60-62]. These results demonstrate a relationship of mutual influence between vascular Aβ deposition and brain amyloid dynamics. Neurovascular coupling, the collective term for the coordinated link between neuronal activity and local blood flow, is also disrupted by endothelial dysfunction. Endothelial nitric oxide synthase signaling is impaired in AD models, resulting in decreased nitric oxide bioavailability and decreased vasodilatory responses during cognitively demanding conditions [63]. These deficiencies lead to impaired synaptic plasticity and information processing within susceptible cortical and hippocampal networks. In addition, capillary stalling, mediated by leukocytes, was also observed in AD patients and mouse models, leading to microvascular hypoperfusion and local hypoxia [64]. These alterations in microvascular dynamics increase metabolic stress on neurons and glial cells. Taken together, vascular injury in AD encompasses BBB degradation, chronic hypoperfusion, microbleeds, endothelial dysfunction, and glymphatic clearance deficits, and these processes interact with amyloid, tau, inflammatory, and metabolic pathways to shape the molecular landscape of neurodegeneration.

Lifestyle and environmental modulators of molecular pathways

Lifestyle and environmental exposures have now been recognized as powerful modulators of molecular pathways that underlie AD, affecting not only susceptibility but also the rate of progression of the disease. Good sleep, especially slow-wave sleep, is at the heart of clearing neurotoxic proteins, including Aβ and tau, by facilitating glymphatic circulation. Experimental and human evidence reveal that sleep fragmentation and disruption of circadian rhythm hinder ISF exchange, increase extracellular concentrations of Aβ, and influence the pattern of tau phosphorylation in a way that causes early molecular changes observed in AD [65, 66]. These disruptions also interfere with synaptic homeostasis, mitochondrial energetics and inflammatory signaling, indicating that the organization of sleep serves as a sensitive integrator for multiple intertwined disease pathways. Diet and metabolic status significantly affect neurodegenerative processes by modulating oxidative stress, insulin signaling, lipid metabolism, and neuroinflammation. High-fat and high-sugar diets can promote peripheral and brain insulin resistance, impair neuronal glucose metabolism, and alter insulin-degrading enzyme activity, thereby potentially influencing Aβ clearance [67, 68]. Likewise, adherence to diet patterns such as Mediterranean or Mediterranean-DASH intervention for neurodegenerative delay has been associated with lower cortical atrophy, reduced inflammatory profiles, and enhanced mitochondrial function [69]. Experimental studies

further suggest that bioactive constituents of diet, including polyphenolic compounds, omega-3 fatty acids, and ketone body intermediates, can modify synaptic plasticity as well as mitochondrial function and autophagy signaling cascade, again indicating the biochemical relationships involved in dietary factors for cellular resistance.

One of the most powerful lifestyle modifiers of molecular AD pathways is physical activity. Neurovascular coupling is improved, cerebral blood flow increases, and physical activity also increases brain-derived neurotrophic factor, which supports synaptic maintenance and hippocampal neurogenesis [70, 71]. Physical activity also ameliorates microglial activation, decreases pro-inflammatory cytokine levels and increases mitochondrial turnover through the PGC-1α signaling pathway. Animal studies suggest that voluntary exercise reduces Aβ plaque deposition and alters tau phosphorylation, at least in part by improving cerebrovascular clearance pathways and reducing oxidative stress [72]. These results are indicative of the association between physical activity and metabolic, vascular and inflammatory systems that are important in AD pathogenesis. Environmental exposures (such as air pollution, heavy metals, and endocrine-disrupting chemicals) also influence AD-relevant molecular pathways. Long-term exposure to fine particulate matter has been associated with increased dementia risk and may contribute to cerebrovascular dysfunction, neuroinflammation, oxidative stress, and AD-related protein pathology [73]. Some metals, such as lead and cadmium, have the potential to induce oxidative stress, disturb calcium homeostasis and increase tau hyperphosphorylation, whereas exposure to pesticides has been linked with mitochondrial dysfunction and perturbation of lipid metabolism [74]. These environmental challenges emphasize the vulnerability of neuronal and glial molecular networks at all ages to exogenous toxicants. Epigenetic regulation is another mechanistic link between lifestyle factors and AD-relevant molecular pathways. DNA-methylation, histone-modifications and microRNA expression profiles are subject to dietary habits, physical activity levels, sleep habits, environmental exposure and psychosocial stress. Emerging evidence indicates that lifestyle-associated epigenomic changes in genes related to synaptic plasticity, immune activation, mitochondrial metabolism, and APP processing may also be influenced by lifestyle behaviors [75]. These results establish a dynamic system of change, in which environmental and behavioural components have sustained molecular consequences that can affect susceptibility to AD (Figure 2). Genetic risk, aging-related cellular decline, vascular dysfunction, and lifestyle influences collectively promote Aβ accumulation and tau dysregulation. These interacting processes initiate downstream synaptic dysfunction and cognitive decline (Figure 1).

Converging pathways and therapeutic implications

AD is increasingly understood as an interconnected network in which Aβ, tau, neuroinflammation, mitochondrial dysfunction, vascular impairment, and systemic influences interact rather than act as isolated pathways. Multiomic and network-based studies indicate that these processes form dynamic regulatory modules, including cell-type-specific interactions between Aβ and tau [76, 77]. Aβ-driven inflammatory and oxidative responses can promote tau phosphorylation and aggregation, while tau pathology can worsen mitochondrial dysfunction and innate immune activation, creating self-reinforcing feedback loops involving NOD-like receptor family pyrin domain-containing 3 (NLRP3) signaling [28, 78, 79]. Vascular dysfunction, BBB impairment, hypoperfusion, and mitochondrial

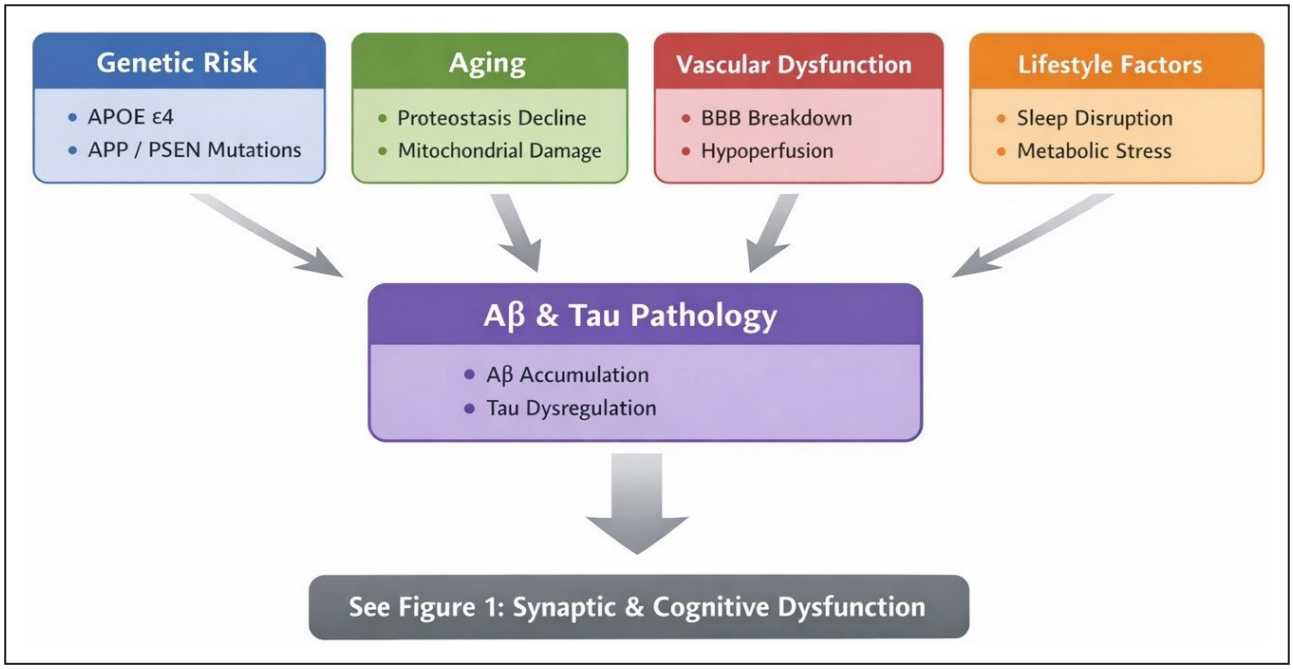


Figure 2. Converging upstream factors driving Alzheimer's disease pathology.

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stress further amplify neuroinflammation, synaptic loss, impaired protein clearance, and neurovascular dysfunction [80, 81]. Patient-specific network analyses also reveal molecularly heterogeneous AD subtypes shaped by genetic and environmental factors, supporting a systems-level rationale for biomarker-guided, multi-target therapeutic strategies [82, 83].

Building on this integrated disease model, therapeutic development is increasingly focused on molecular nodes that can be targeted within these interacting pathways. Aβ-directed therapies remain the cornerstone of disease-modifying interventions, and reducing amyloid burden modestly slowed cognitive decline in early AD (Table 2) [84]. Monoclonal antibodies such as lecanemab and donanemab have been reported to decrease amyloid burden with improved plaque clearance through fragment crystallizable-mediated microglial phagocytosis. With its ability to stabilize $A\beta_{42}$ monomers and inhibit oligomerization [85], ALZ-801, an oral prodrug of tramiprosate, is also being tested in patients with *APOE ε4* risk alleles in small-molecule approaches. Concomitantly, clinical-development pipeline analyses show that amyloid-directed modalities continue to broaden and now include multivalent antibodies, bispecific molecules, as well as prophylactic vaccines aimed at generating endogenous immune responses against toxic Aβ forms [86]. Likewise, tau-targeted therapies have advanced to approaches that interfere with hyperphosphorylation, aggregation, or dysfunctional propagation of tau. Such antibodies, including posdinemab (JNJ-63733657), selectively bind abnormal forms of phospho-tau, reducing seeding and spreading [87]. Similarly, antisense oligonucleotides and kinase inhibitors that modify tau expression and phosphorylation kinetics are currently under investigation, with recent reviews discussing intracellular availability and immunogenicity as dose-limiting factors [88]. Tau immunotherapies are increasingly paired with biomarker-based patient stratification, enabling direct-to-target treatment for molecular subgroups. Table 2 summarizes selected molecularly targeted therapies currently under investigation or approved for AD.

Neuroinflammation has also been recently identified as a major therapeutic axis on the basis of the importance of microglial activation and inflammasome signaling in AD. In the fully symptomatic stage, NLRP3 inflammasome inhibition, including clinically emerging CNS-penetrant agents, has recently been shown to limit caspase-1 activation, reduce pro-inflammatory cytokine release, and limit tau pathology in preclinical models [90]. These data reinforce increasing attention to immune-modulating targets that drive microglia from pro-inflammatory toward neuroprotective, disease-resolving directions. Cellular

Table 2. Therapeutic targets and candidate drugs for Alzheimer's disease.

Therapeutic target	Example drug/agent	Mechanism of action	Current stage (research/clinical)
Amyloid-β	Lecanemab, Donanemab	Monoclonal antibodies promoting fragment crystallizable-mediated microglial phagocytosis and clearance of amyloid plaque	FDA-approved/Phase 3 [26, 89]
Tau pathology	JNJ-63733657 (Posdinemab)	Anti-tau monoclonal antibody inhibiting pathological tau seeding and trans-neural propagation	Phase 1 [87]
Neuroinflammation	NLRP3 inflammasome inhibitors	Inhibition of NLRP3 inflammasome activation reducing caspase-1 activity and IL-1β/IL-18 release	Preclinical [90]
Mitochondrial dysfunction	Mitoquinone, elamipretide (SS-31)	Mitochondria-targeted antioxidant activity and stabilization of mitochondrial membranes, improving bioenergetics and reducing reactive oxygen species	Preclinical [50]
Aβ oligomerization in *APOE ε4* carriers	ALZ-801 (Tramiprosate prodrug)	Stabilizes $A\beta_{42}$ monomer and inhibits toxic Aβ oligomer formation, evaluated in *APOE ε4* carriers	Phase 3 trial [91]

senescence has also emerged as a promising therapeutic target: senescent cells accumulate in the aging brain and contribute to neuroinflammation and cognitive decline, and senescence-targeted approaches (senolytics and senomorphics) are being evaluated to counteract aging-driven AD pathology [92]. In addition, this review also investigates modulation of the complement pathway, colony-stimulating factor 1 receptor inhibitors, and TREM2-mediated microglial signaling to tailor immune responses in a controlled manner. In light of the close relationship between mitochondrial impairment and early neuronal vulnerability, mitochondria-targeted therapies are emerging. Compounds targeting protection or cell biology pathways, including restoration of mitochondrial energy production, reduction of ROS, and stimulation of mitophagy, are beneficial in cellular and animal models. The mitochondria-targeted antioxidants and bioenergetic modulators are among the most developed drug classes (*e.g.*, ATP-deficit rescue agents or mitochondrial membrane potential stabilizers) [47]. For instance, Ebselen has been reported to improve mitochondrial membrane potential, respiratory capacity, and ATP production in AD cybrid cells [93], underlining potential benefit of pharmacological intervention at the level

of bioenergetic impairment itself. Natural polyphenols with combined antioxidant and inflammasome-regulating activity, such as malvidin, have also been considered as adjunct approaches [50]. The clinical perspective is also shifting toward personalized and multimodal precision medicine paradigms. Novel computational approaches now combine genomics, proteomics, and biomarker data to determine patient-specific molecular subtypes and treatment responsiveness. These paradigms imply that a stratification approach according to tau burden, pro-inflammatory signatures, mitochondrial read-outs, or *APOE* genotype could significantly enhance treatment effects. Furthermore, machine-learning algorithms (including adaptive Bayesian controllers) are being refined and used for treatment scheduling and dosing of tau-directed therapies, with the potential to deliver increased therapeutic efficacy and reduce adverse effects [94]. Personalized and multimodal precision-medicine approaches are transforming the therapeutic landscape for AD. Current multi-omics approaches, such as genomic, proteomic, transcriptomic, and metabolomic analyses, integrated into large cohorts of well-characterized populations, have led to the identification of molecular signature-based subtypes of AD with the possibility for targeted therapeutic intervention according to subtype [95, 96]. In addition, computational models and machine learning (ML) pipelines are being developed to take advantage of this deluge of multi-modal data; sophisticated algorithms can analyze proteomic, genomic, biomarker, and clinical data to predict individual disease trajectories and to predict which treatment strategies are most likely to be beneficial. These ML-based strategies support not only diagnosis and subtype definition, but also dynamic treatment personalization (*i.e.*, optimal administration of therapy, adaptive response monitoring, stratifying to plan the next intervention), allowing redesigned treatments as precision-guided rather than an empirical trial-and-error design process [97].

Herbal and alternative medicine approaches

Beyond conventional molecularly targeted therapies, herbal and alternative medicines have attracted growing interest as adjunct strategies in AD management. Bioactive plant-derived compounds exert pleiotropic effects relevant to AD pathogenesis, including antioxidant, anti-inflammatory, anti-amyloid, and pro-cognitive activities. For example, extracts of *Ginkgo biloba*, *Curcuma longa* (curcumin), *Withania somnifera*, and *Bacopa monnieri* have been reported to modulate Aβ aggregation, tau phosphorylation, mitochondrial function, and neuroinflammation in experimental models, with some supportive clinical evidence [98]. Plant sterols such as β-sitosterol have been proposed as nutrient-derived steroidal scaffolds with neuroprotective and anti-aging properties, acting through modulation of cholesterol homeostasis, oxidative stress, and inflammatory signaling [99]. Likewise, phytosterols have been proposed to modulate the gut–brain axis and attenuate neuroinflammation through effects on gut microbiota, lipid metabolism, and farnesoid X receptor/G protein-coupled bile acid receptor 1-mediated signaling, representing a potential adjunctive avenue in AD research [100]. Although most herbal candidates remain at the preclinical or early clinical stage, and issues of bioavailability, standardization, and drug–herb interactions persist, their multi-target profiles align well with the systems-level, multi-pathway view of AD advocated in this review. Future well-designed randomized controlled trials are warranted to establish their efficacy and safety.

Conclusions

Throughout this review, evidence supports the view that AD can no longer be linked to a single pathological cascade: Aβ dysregulation, tau pathology, synaptic and mitochondrial dysfunction, neuroinflammation, vascular damage, and environmental modulators crosstalk dynamically in the AD brain and self-perpetuate. The intricate nature of this intertwined network calls for sophisticated disease models that account for the non-linear and heterogeneous process of AD pathogenesis. At the same time, breakthroughs in genomics, proteomics, neuroimaging, and computational modeling have transformed our understanding of AD from a monolithic disease into a spectrum of molecularly defined subtypes. The recognition of this complexity has created new opportunities for precision medicine, directing therapeutic strategies toward biomarker-based stratification and multi-target interventions rather than single-pathway treatments. Emerging molecular therapeutics, from amyloid- and tau-directed therapies to agents targeting neuroinflammation, mitochondrial resilience, and vascular health, exemplify this transformation toward more comprehensive and personalized paradigms of care.

Declarations

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