

Review

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Targeting glial dysfunction in Alzheimer's disease: insights into pathogenesis and emerging therapeutics

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, amyloid- β (A β) plaques, and neurofibrillary tangles. Despite extensive research, its pathogenesis remains incompletely understood and no disease-modifying therapies are currently available. While early studies focused on neuronal dysfunction, growing evidence implicates glial cells - including microglia, astrocytes, and oligodendrocytes - in driving AD pathogenesis. Microglia initially clear A β and cellular debris; however, chronic activation triggers the release of proinflammatory cytokines that worsen A β and tau pathology and induce neurotoxic astrocytes. Reactive astrocytes compromise blood-brain barrier integrity, secrete inflammatory mediators, and impair synaptic transmission. Oligodendrocytes and their progenitors, beyond their role in myelination, can adopt disease-



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associated states that alter metabolic support and immune signaling, yielding both protective and detrimental effects. Recent multi-omics studies have identified critical regulatory pathways, including NF- κ B, the NLRP3 inflammasome, and the cGAS-STING axis, that govern glial phenotype transitions. Therapeutic strategies targeting these pathways, such as small-molecule inhibitors, immunomodulators, and NAD⁺ precursors, have shown promise in preclinical AD models by reducing neuroinflammation, restoring glial homeostasis, and improving cognition. In this review, we summarize glial cell functions in health and disease, dissect molecular mechanisms of glial dysfunction in AD, and evaluate emerging glia-directed therapies. Finally, we discuss translational challenges and outline future directions for leveraging glial biology in the development of effective AD therapies.

Keywords: Alzheimer's disease, glia cells, microglia, astrocytes, oligodendrocytes, neuroinflammation, cGAS-STING, therapeutics

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia worldwide, accounting for approximately 70% of all cases, and poses a substantial healthcare burden due to its progressive and inexorable decline in cognitive function^[1,2]. Clinically, AD manifests as deficits in memory, language, executive function, and visuospatial skills, ultimately compromising the ability to perform routine daily activities. Neuropathologically, AD is defined by the extracellular accumulation of misfolded β -amyloid (A β) peptides into senile plaques and the intraneuronal formation of neurofibrillary tangles composed of hyperphosphorylated tau (p-tau). A β is generated through the sequential cleavage of amyloid precursor protein (APP) by β -secretase (BACE1) and γ -secretase, contributing to synaptic dysfunction and neuronal loss, alongside p-tau-driven tangle assembly, particularly in familial AD variants^[1,3]. Despite decades of intensive investigation into these hallmark pathways, current pharmacological interventions offer only symptomatic relief or modest delays in cognitive decline; no treatments or medications have been shown to cure or stop AD pathology.

In recent years, research attention has shifted toward the non-neuronal milieu, where glial cells, including microglia, astrocytes, and oligodendrocytes, maintain central nervous system (CNS) homeostasis and support neuronal integrity through immune surveillance, synaptic modulation, blood-brain barrier (BBB) maintenance, and myelin preservation^[4-6]. Dysregulation of glial cells has been shown to profoundly influence AD progression.

In AD, microglia initially confer neuroprotection by phagocytosing A β and clearing debris, yet chronic activation triggers a proinflammatory phenotype that amplifies A β and tau pathology and induces neurotoxic "A1" astrocytes^[7]. Reactive astrocytes compromise BBB integrity and secrete cytokines that exacerbate neuroinflammation and synaptic loss. Emerging evidence also implicates oligodendrocyte dysfunction and altered progenitor cell dynamics in myelin disruption and metabolic insufficiency within AD brains. Mechanistically, these glial responses are orchestrated by key signaling cascades, such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), the NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome, and the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) axis, offering novel molecular targets for therapeutic intervention^[6,8].

In this review, we first outline the physiological functions of microglia, astrocytes, and oligodendrocytes in the healthy CNS. We then critically summarize their dynamic phenotypic shifts and associated regulatory mechanisms in AD pathogenesis. Finally, we discuss emerging glia-targeted strategies aimed at restoring neuron homeostasis, mitigating neuroinflammation, and preserving synaptic function, and we highlight translational challenges and future directions for glia-based therapies in AD.

GLIAL CELLS IN THE NERVOUS SYSTEM

Microglia

Microglia are the resident innate immune cells and specialized macrophages of the CNS, originating from primitive yolk sac macrophages during embryogenesis and persisting throughout life as vigilant sentinels^[9,10]. Beyond immune surveillance, microglia engage in dynamic crosstalk with other CNS cell types to orchestrate critical developmental processes^[11-13]. During neurogenesis, they guide the migration of inhibitory cortical interneurons, modulate axonal growth trajectories, and support the survival of layer V pyramidal neurons^[14,15]. A defining function of microglia is activity-dependent synaptic refinement, whereby they selectively prune redundant synapses to optimize neural network efficiency^[16,17]. In the mature brain, microglia maintain homeostasis by monitoring the neurovascular unit, regulating cerebral blood flow, and supporting metabolic demands^[18,19]. Emerging evidence also implicates microglia in clearing apoptotic debris and dysfunctional synapses through interactions with astrocytes, oligodendrocytes, and vascular cells^[20,21]. Their capacity to release both neurotrophic factors and proinflammatory mediators underscores their dual role in maintaining physiological function and mediating pathological responses in the CNS [Figure 1].

Astrocytes

Astrocytes are the most abundant glial population in the CNS and exhibit structural and functional diversity essential for neural circuit optimization. They are classified into protoplasmic and fibrous subtypes based on their localization in gray and white matter, respectively, and extend processes that contact synapses, blood vessels, and nodes of Ranvier^[22]. Regional astrocyte subpopulations are further shaped by local microenvironmental cues and epigenetic programming^[23-25]. Astrocytes far surpass their historical role as mere “glial glue”^[26]. They actively regulate synaptogenesis through thrombospondin and SPARC secretion^[27,28], modulate neurotransmitter homeostasis via glutamate and gamma-aminobutyric acid (GABA) recycling^[29,30], and preserve BBB integrity through AQP4-enriched endfeet^[31]. Under inflammatory conditions, astrocytes can also clear cellular debris and upregulate MHC-II expression^[32,33], highlighting their neuroimmunological duality [Figure 1].

Oligodendrocytes

Oligodendrocytes and oligodendrocyte progenitor cells (OPCs) provide electrical insulation and metabolic support to CNS axons^[34]. OPCs persist throughout life and differentiate into myelinating oligodendrocytes, forming lipid-rich sheaths that facilitate saltatory conduction^[35,36]. Myelination exhibits activity-dependent plasticity, allowing adaptive refinement of neural circuits^[37,38]. Beyond insulation, oligodendrocytes transfer lactate to axons and buffer extracellular potassium, thereby sustaining axonal integrity and preventing degeneration^[39-41]. Through lifelong myelin remodeling and supporting mechanisms, oligodendrocytes maintain CNS resilience during development, adulthood, and nerve repair following injury^[42] [Figure 1].

ALZHEIMER'S DISEASE PATHOLOGY

AD is driven by multiple neuropathological processes. A β is widely distributed in AD brains. Extracellular A β plaques result from aberrant proteolysis of APP by BACE1 and the γ -secretase complex, yielding aggregation-prone A β_{42} peptides that form insoluble fibrils^[43-45], particularly in the neocortex and hippocampus^[45,46]. Intracellular neurofibrillary tangles (NFTs), composed of p-tau aggregates, disrupt microtubule stability and axonal transport^[47-49]. The Braak staging system correlates the stereotypical spread of tau pathology with clinical symptom severity^[50,51], and emerging evidence supports a prion-like, trans-synaptic propagation of misfolded tau species^[52] [Figure 2].

Synaptic dysfunction precedes neuronal loss in AD, with affected regions showing an estimated 30%-40% reduction in synaptic density^[53,54]. The basal forebrain cholinergic system is particularly vulnerable, exhibiting decreased choline acetyltransferase activity and cortical acetylcholine depletion, both of which

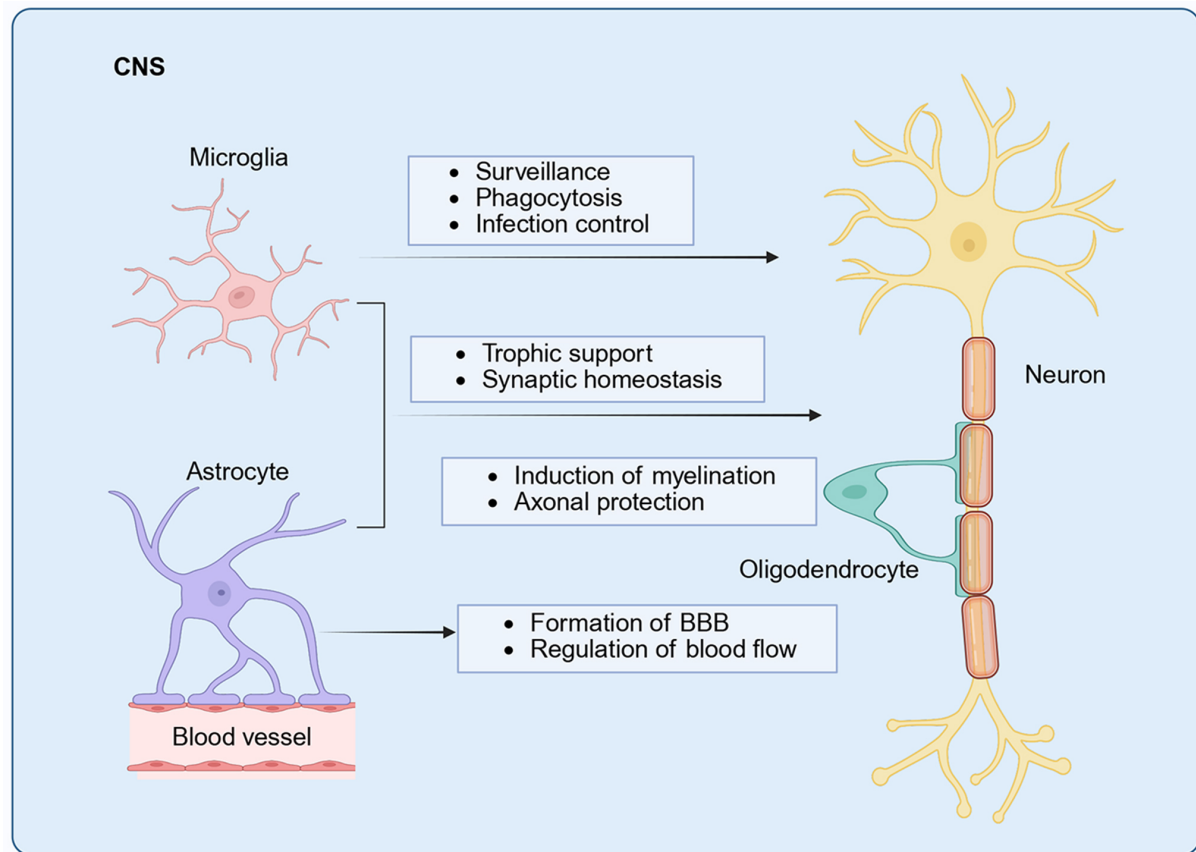


Figure 1. Functions of glial cells in the CNS. Under physiological conditions, microglia act as resident immune cells, engaging in immune surveillance, phagocytosis of cellular debris, and infection control. Astrocytes contribute to the formation of the BBB, regulate cerebral blood flow, and maintain synaptic homeostasis and neurotrophic support. Oligodendrocytes facilitate myelin formation and support the efficient propagation of bioelectrical signals through saltatory conduction, thereby safeguarding normal neuronal function. [Created in BioRender. 2, 1. (2025) <https://BioRender.com/5gn4zwwg>]. CNS: Central nervous system; BBB: blood-brain barrier.

contribute to memory impairment^[55,56]. Hippocampal atrophy observed on magnetic resonance imaging (MRI) reflects advanced neurodegeneration^[57,58]. Concurrently, cerebral amyloid angiopathy (CAA), present in up to 95% of AD cases, deposits A β in leptomeningeal and cortical vessels, impairing cerebrovascular regulation and increasing the risk of hemorrhage^[59,60].

Chronic neuroinflammation in AD is mediated by activated microglia and astrocytes responding to A β and tau pathology^[61]. While initially protective, sustained release of proinflammatory cytokines (IL-1 β , TNF- α , IL-6, IL-18) and complement factors creates a neurotoxic milieu that exacerbates neuronal damage^[62-64]. Astrocytic upregulation of glial fibrillary acidic protein (GFAP) marks astrogliosis and has prognostic significance in disease progression^[65,66]. Reactive microglia colocalize with amyloid plaques, underscoring their role in plaque-associated inflammation^[67,68].

Aging remains the dominant risk factor for AD, with cellular senescence contributing to disease through the senescence-associated secretory phenotype (SASP), characterized by the release of proinflammatory and matrix-degrading molecules^[69-71]. In AD, accumulation of senescent cells is accompanied by increased oxidative stress, mitochondrial dysfunction, and activation of inflammatory cascades^[72,73], which in turn accelerate A β deposition and tau phosphorylation via a deleterious feedback loop. Additional drivers of

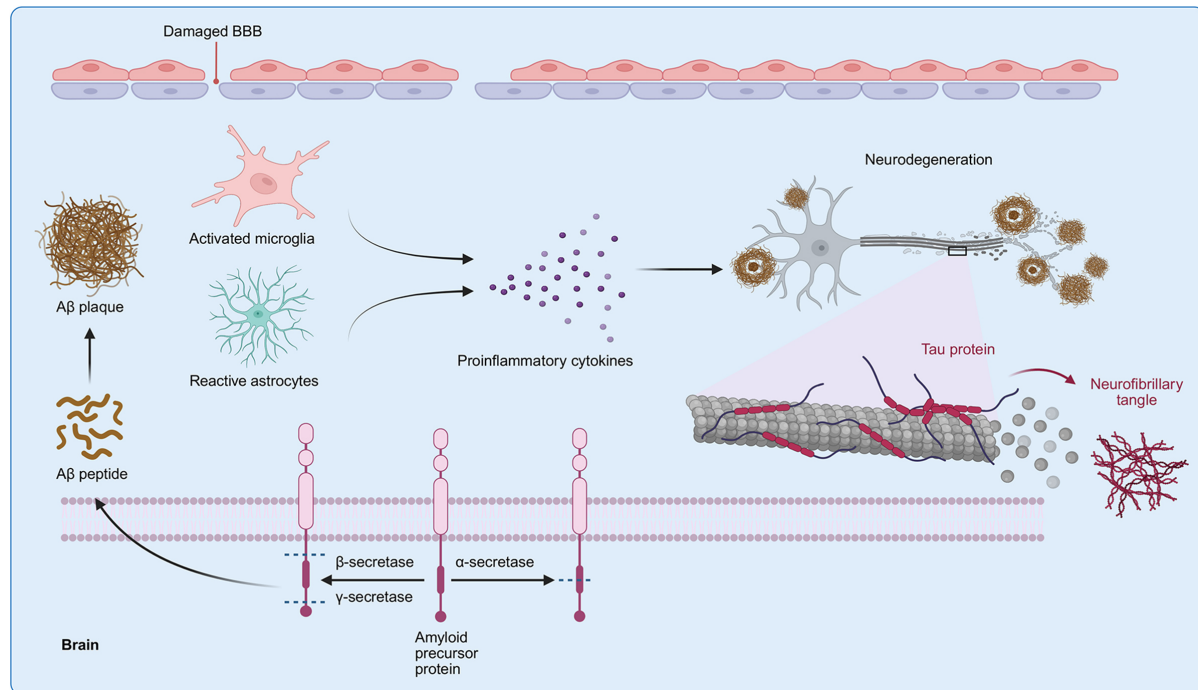


Figure 2. Pathological cascade of AD. Aberrant proteolytic cleavage of APP generates A β peptides with strong aggregation propensity. These peptides accumulate extracellularly to form insoluble A β plaques, which trigger microglial activation and astrocytic reactivity. Activated glial cells release proinflammatory cytokines, creating a neurotoxic microenvironment. Meanwhile, intracellular tau undergoes pathological hyperphosphorylation, leading to NFT formation. The synergy of A β -driven neuroinflammation, tau pathology, and glial activation ultimately disrupts BBB integrity and drives progressive neurodegeneration in the brain parenchyma. [Created in BioRender. Y, S. (2025) <https://BioRender.com/4lv920b>]. AD: Alzheimer's disease; APP: amyloid precursor protein; A β : amyloid- β ; NFT: neurofibrillary tangle; BBB: blood-brain barrier.

senescence include impaired proteostasis, DNA damage, telomerase deficiency, and telomere shortening^[74,75]. Collectively, AD pathogenesis reflects intricate interactions among protein misfolding, cellular stress responses, and impaired homeostatic mechanisms, highlighting the need for therapies that target these interconnected pathways.

GLIAL CELLS IN AD PATHOGENESIS

Microglia in AD

Microglial proliferation is a hallmark of AD-related neuroinflammation and correlates with cognitive decline^[76]. Increased microglial density, driven by upregulation of colony-stimulating factor 1 receptor (CSF1R), has been observed in APP/PS1, 3 $\times$ TgAD, and 5 $\times$ FAD mouse models, where it is associated with plaque load and behavioral deficits^[77-82]. Pharmacological or genetic inhibition of CSF1R reduces microglial numbers, synaptic loss, and cognitive impairment without markedly altering A β burden^[79].

Microglial phagocytosis modulates disease progression by engulfing A β plaques, synapses, and even entire neurons^[83]. This process is orchestrated by receptors and risk genes including *TREM2* and *APOE*^[84]. APOE opsonizes A β to facilitate uptake^[85], while TREM2 engagement promotes plaque compaction and restricts new seeding^[85-88]. Early-stage phagocytosis may confer neuroprotection, but excessive or misdirected engulfment in later stages contributes to synaptic loss and neuronal death, underscoring the therapeutic complexity of modulating this function^[89-91].

Under homeostatic conditions, microglia exhibit a ramified morphology and secrete minimal inflammatory mediators^[92]. In AD, however, A β and p-tau activate and polarize microglia into diverse functional states. The classical M1 phenotype produces IL-1 β , TNF- α , and IL-6, driving neuroinflammation and neuronal damage, whereas the M2 phenotype releases IL-4, IL-10, and TGF- β , supporting tissue repair and neuroprotection^[93-96]. Recent single-cell and single-nucleus RNA sequencing (scRNA-seq and snRNA-seq) studies have revealed spatial and temporal heterogeneity beyond the M1/M2 paradigm, identifying disease-associated microglia (DAM) localized near A β plaques. DAM exhibit activated TREM2 signaling and enrichment of genes related to lipid metabolism and phagocytosis^[97-100], indicating the therapeutic potential of targeting TREM2 or other DAM regulators. Microglia can thus transition from protective guardians to drivers of neurodegeneration^[101].

In early AD, microglia clear A β via phagocytosis, a process enhanced by peripheral anti-A β antibodies that cross the blood-brain barrier and opsonize plaques^[102]. However, chronic exposure to A β oligomers and phosphorylated tau drives a sustained proinflammatory state. A β binds TLR4, activating MyD88-dependent NF- κ B signaling, while scavenger receptors (e.g., CD36) amplify cytokine release and oxidative burst^[103]. Early TLR3 stimulation with poly(I:C) paradoxically suppresses this cycle, reducing plaques and inflammation in APP/PS1 mice^[104]. Downstream, NF- κ B upregulates TNF- α and IL-6, while apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC)-dependent NLRP3 inflammasome activation triggers caspase-1-mediated cleavage of pro-IL-1 β into mature IL-1 β ^[105,106]. These cytokines recruit astrocytes, which secrete additional inflammatory mediators, establishing a feed-forward loop of glial hyperactivation that undermines synaptic integrity and accelerates neuronal loss. Activated microglia also generate reactive oxygen species (ROS) and nitric oxide (NO), causing oxidative damage to lipids, proteins, and DNA, thereby contributing to synaptic dysfunction^[107,108] and accelerating neuronal injury and loss^[109,110]. Neuronal apoptosis is closely linked to this inflammatory milieu^[111]. TNF- α engages neuronal death receptors to activate caspase-8 and downstream executioner caspases, while ROS/NO disrupt mitochondrial integrity, promote cytochrome c release, and activate intrinsic apoptotic pathways^[107,112,113].

Microglial energy metabolism mirrors their activation state. Under physiological conditions, microglia predominantly rely on mitochondrial oxidative phosphorylation (OXPHOS) to meet energy needs and support surveillance functions^[114]. Upon activation, they undergo metabolic reprogramming toward aerobic glycolysis, which provides rapid ATP and biosynthetic precursors for inflammation. In AD, this glycolytic shift becomes constitutive, persisting even in the absence of acute stimuli^[115,116]. AD microglia exhibit elevated lactate production and acidification of the microenvironment, further impairing mitochondrial respiration^[117,118]. Lipid droplet accumulation, commonly observed in AD microglia, also disrupts mitochondrial function and fosters a proinflammatory phenotype^[119]. Several molecular mechanisms link mitochondrial dysfunction to altered microglial metabolism^[120]. A key regulator is hypoxia-inducible factor 1- α (HIF-1 α), stabilized under oxidative stress and promoting transcription of glycolytic enzymes^[121]. Conversely, peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α), a master regulator of mitochondrial biogenesis and function, is downregulated in APP/PS1 and 3 $\times$ TgAD mouse models, correlating with impaired mitochondrial biogenesis and reduced respiratory capacity^[122-124].

Cellular senescence, a state of irreversible cell-cycle arrest accompanied by the SASP, is increasingly implicated in AD^[69,125]. In aged and APP/PS1 mouse brains, microglia exhibit DNA damage and telomere attrition caused by A β -induced oxidative stress and prolonged cytokine exposure^[71]. These stressors activate the p53-p21 and p16^{INK4a}-Rb pathways, driving microglial senescence^[126]. Senescent microglia secrete SASP factors that perpetuate chronic neuroinflammation; elevated levels of these proteins have been detected in

the brains, cerebrospinal fluid, and serum of AD patients^[127-131]. Moreover, replicative senescence in A β -laden APP/PS1 mice exacerbates plaque deposition and synaptic deficits^[132]. While senolytic approaches targeting p16^{INK4a}-positive microglia have demonstrated efficacy in reducing neuroinflammation and improving cognition in other neurodegenerative models^[70], a standardized set of microglial senescence markers remains undefined. Future studies should integrate longitudinal analyses of human brain tissue with single-cell profiling to establish robust senescence signatures and assess the therapeutic potential of senolytics in AD [Figure 3].

Astrocytes in AD

Astrocytes are a heterogeneous glial population with diverse morphologies and functions that are essential for CNS homeostasis^[133]. Under physiological conditions, they provide structural and metabolic support to neurons, regulate BBB integrity, modulate synaptic activity, recycle neurotransmitters, and maintain ion balance^[133,134].

In AD, astrocytes undergo morphological, transcriptional, and functional remodeling, termed “reactive astrogliosis”, in response to A β and tau pathology^[135]. Although reactive astrocytes were first described more than a century ago, their precise roles in CNS pathology, regeneration, and aging remain unresolved and continue to be debated. Reactive astrocytes are often categorized into two broad phenotypes: proinflammatory A1 and neuroprotective A2^[136]. A1 astrocytes secrete neurotoxic factors (e.g., IL-1 β , TNF- α , and IFN- γ) that worsen neuroinflammation and synaptic loss, whereas A2 astrocytes release anti-inflammatory cytokines (e.g., IL-4, IL-10, and TGF- β) that support neuronal survival and promote A β clearance^[137,138].

In AD, reactive astrocytes exhibit hypertrophy of the soma and processes, increased expression of cytoskeletal proteins such as GFAP and vimentin, and retraction of fine processes^[139]. Transcriptomic studies show upregulation of innate immune genes, including lipocalin 2 (*LCN2*) and serpin peptidase inhibitor alpha-1-antichymotrypsin (*SERPINA3N*), as well as enzymes in the cholesterol biosynthesis pathway. These alterations precede overt cognitive decline and correlate with amyloid plaque and neurofibrillary tangle burden^[140,141].

Astrocytes also secrete proinflammatory mediators that amplify microglial activation and recruit peripheral immune cells^[142,143]. Furthermore, they express complement proteins and pattern-recognition receptors (PRRs) such as TLR4, which facilitate A β recognition and inflammasome activation^[144]. Crosstalk between astrocytes and microglia establishes a feed-forward loop: astrocyte-derived cytokines prime microglia for heightened inflammatory responses, while microglial factors reinforce astrocytic reactivity^[145,146].

Astrocyte endfeet enwrap cerebral vessels, supporting tight junctions and BBB integrity through polarized aquaporin-4 (AQP4) localization and secretion of vascular-stabilizing factors^[147]. In AD, reactive astrocytes release matrix metalloproteinases (MMPs) and proinflammatory cytokines that degrade basement membrane components and disrupt tight junction proteins, thereby increasing BBB permeability and promoting leukocyte infiltration^[7,148]. Loss of AQP4 polarization further impairs glymphatic clearance of A β and tau, facilitating their extracellular accumulation^[149].

Perisynaptic astrocytes play a key role in neurotransmitter clearance and synaptic plasticity^[150]. In AD, reactive astrocytes exhibit increased expression of monoamine oxidase-B (MAO-B), leading to elevated GABA synthesis and enhanced tonic inhibition, which contributes to cognitive impairment^[151]. Additionally, astrocytic secretion of ceramides and other lipid mediators can directly damage synapses^[152].

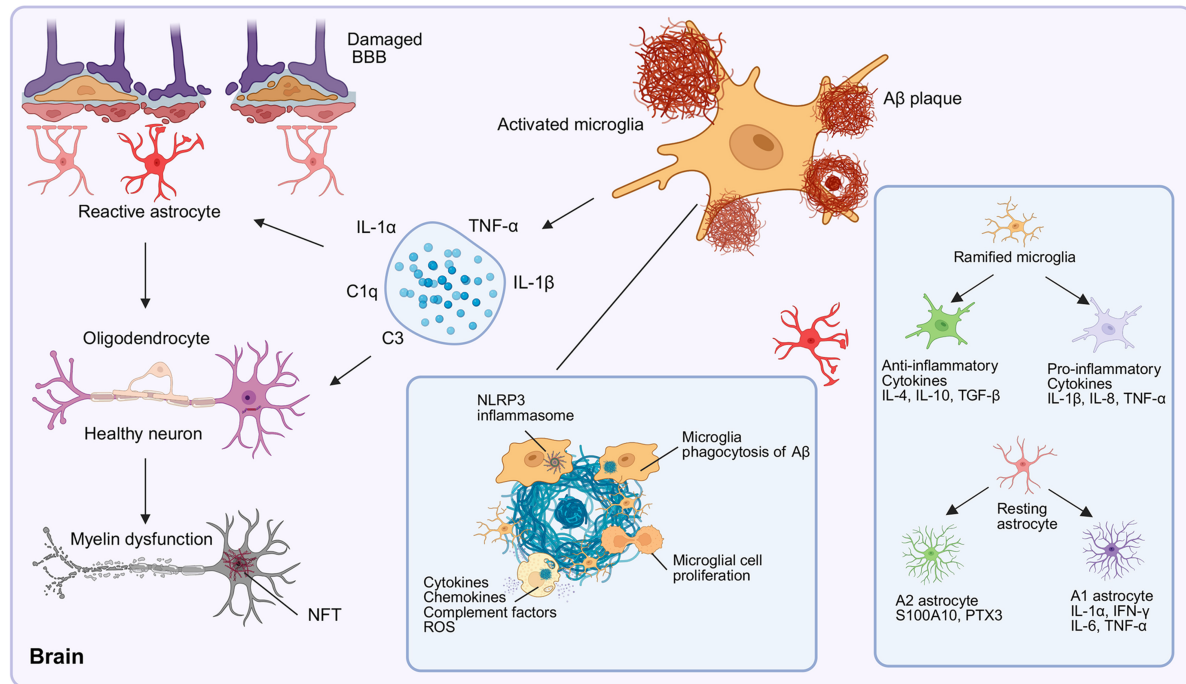


Figure 3. Role of glial cells in AD pathogenesis. Microglia transition from a ramified morphology to an activated state in an attempt to phagocytose A β . Chronic activation prompts microglia to release proinflammatory cytokines, ROS, and complement factors. This neuroinflammation promotes astrocytic reactivity, driving their polarization into proinflammatory A1 or potentially anti-inflammatory A2 subtypes, thereby contributing to astrogliosis. The interplay among activated glia, A β plaques, NFTs, BBB disruption, and inflammatory mediators (including those derived from the NLRP3 inflammasome) drives neuronal damage and disease progression, highlighting the dual neuroprotective and neurotoxic roles of glial cells in AD pathogenesis. [Created in BioRender. 1, 1. (2025) <https://BioRender.com/w3zqhfhf>]. AD: Alzheimer's disease; A β : amyloid- β ; ROS: reactive oxygen species; NFT: neurofibrillary tangle; NFTs: neurofibrillary tangles; BBB: blood-brain barrier; NLR: NOD-like receptor; NLRP3: the NLR family pyrin domain containing 3.

In contrast, A2-like astrocytes release neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), and help maintain extracellular potassium homeostasis, thereby supporting neuronal viability^[153-155]. The overall impact of astrocytes on synaptic health in AD reflects the dynamic balance between these opposing phenotypic states.

The widely used binary classification of reactive astrocytes into “A1” (neurotoxic) and “A2” (neuroprotective) subtypes has provided a useful framework for studying astrocyte heterogeneity. However, subsequent studies, including recent reviews, emphasize that this dichotomy oversimplifies the diverse and context-dependent phenotypes of reactive astrocytes, particularly in chronic neurodegenerative conditions such as AD^[138,156]. For example, single-cell and single-nucleus RNA sequencing of mouse models and human AD brains has revealed a continuum of stage-dependent transcriptomic states that do not align neatly with the classical A1-A2 model. We therefore recommend that studies on reactive astrocytes integrate multiple molecular and functional readouts - ideally obtained *in vivo* - together with multivariate analyses and direct evaluation of their effects on disease-defining hallmarks in AD models [Figure 3].

Oligodendrocytes in AD

Oligodendrocytes, once considered passive bystanders in AD, are now recognized as active participants in neurodegeneration. scRNA-seq of the oligodendrocyte lineage in mice has revealed a developmental continuum from OPCs through immature to mature oligodendrocytes^[157]. Both OPCs and mature oligodendrocytes interact closely with the neuroinflammatory milieu and A β -mediated toxicity,

underscoring their active involvement in AD pathogenesis^[158]. Before proliferating, OPCs must migrate toward lesion sites^[159]. In AD, however, the OPC pool becomes progressively depleted. Their migration along blood-vessel scaffolds is impeded by extracellular matrix stiffening and amyloid-plaque barriers, leading OPCs to cluster rather than infiltrate lesions^[160]. As a reservoir for new oligodendrocytes, OPCs are indispensable for myelin formation and repair^[161]. In AD, A β peptides induce dysfunction and death of both OPCs and mature oligodendrocytes *in vitro* and *in vivo*^[162]. Transcriptomic profiling of post-mortem dementia brains has revealed disrupted signaling cascades that drive progressive loss of OPC differentiation^[163]. Furthermore, myelin debris shed by damaged oligodendrocytes accumulates extracellularly and strongly inhibits OPC differentiation^[164]. The loss of myelin sheaths during demyelination compromises synaptic transmission and disrupts learning and memory^[164,165]. Interestingly, a recent mouse study demonstrated concurrent myelin degeneration and repair, showing a robust loss of pre-existing myelin alongside increased oligodendrogenesis and remyelination during disease progression^[166]. Mechanistically, myelin dysfunction exacerbates A β pathology by trapping β -secretase within axonal swellings, thereby enhancing cortical APP cleavage^[167].

Emerging evidence identifies OPC senescence as a key driver of demyelination in AD. Post-mortem analysis revealed significantly higher numbers of senescent OPCs in the inferior parietal cortex of late-onset AD brains compared with MCI brains^[70]. In an AD mouse model, Olig2- and NG2-expressing OPCs exhibited an aging-like phenotype, with elevated p21 and p16^{INK4a} expression and increased senescence-associated β -galactosidase activity^[70]. Senescent OPCs adopt a SASP rich in IL-6 and ROS, thereby amplifying neuroinflammation and secondary microglial activation^[168,169]. Notably, in APP/PS1 mice, intermittent senolytic treatment (Dasatinib plus Quercetin) reduced plaque-associated senescent OPCs, attenuated neuroinflammation and A β burden, and improved hippocampus-dependent memory, supporting the therapeutic potential of targeting OPC senescence in AD^[70].

In response to injury or amyloid and tau pathology, oligodendrocytes acquire a distinct disease-associated transcriptional signature marked by upregulation of immune-related genes (e.g., *Serpina3n* and *C4b*), suggesting engagement in protease inhibition and complement-mediated clearance^[170-172]. Additional enriched pathways include TNF receptor signaling (Tnfrsf1a), interleukins (Il1 β , Il33), heme oxygenase-1 (Hmox1), tumor necrosis factor (Tnf), and MHC class I molecules (H2-D1, H2-K1, B2m), indicating a shift toward immune surveillance and antigen presentation^[172,173]. These oligodendrocyte states emerge in parallel with plaque deposition and may reflect a reactive adaptation to chronic injury and aging. *Serpina3n* encodes a serine protease inhibitor that can neutralize granzyme B, potentially protecting oligodendrocytes from CD8⁺ T cell-mediated cytotoxicity^[170]. Similarly, *C4b* may facilitate cellular debris clearance but can also drive complement-dependent synaptic pruning and neurodegeneration^[170].

Oligodendrocytes are crucial for neuronal health by providing metabolic support and ensuring efficient myelination. Reactive oligodendrocytes may relinquish these canonical roles, leading to impaired axonal conduction and neuronal energy deficits. As AD progresses, glial cells may undergo further functional changes, possibly shifting from protective states toward exhaustion or dysfunction. For instance, OPCs adjacent to A β plaques can undergo senescence and secrete proinflammatory mediators, worsening tissue damage^[70]. Motif enrichment analysis of disease-associated oligodendrocyte transcripts has identified nuclear factor κ B (NF- κ B), signal transducer and activator of transcription (STAT), and interferon regulatory factor (IRF) family transcription factors as key regulators of this reactive state^[171]. Notably, oligodendrocytes express high levels of amyloid processing genes - including *APP*, *BACE1*, *PSEN1*, and *PSEN2* - in both mouse and human RNA-sequencing datasets^[174,175]. Conditional deletion of *BACE1* in oligodendrocytes reduces the amyloid plaque burden, underscoring their contribution to A β

production^[176,177]. However, oligodendrocyte states in human AD brains diverge from those in mouse models, emphasizing the need for species-specific mechanistic studies^[100] [Figure 3].

MOLECULAR MECHANISMS AND SIGNALING PATHWAYS OF GLIAL CELLS IN AD

Glial cells in AD orchestrate a multilayered immune response that begins with the recognition of endogenous danger signals and culminates in chronic neuroinflammation, synaptic dysfunction, and neuronal loss. The following sections expand on each major axis - recognition, signaling hubs, effector release, pathological states, and modulatory receptors - highlighting mechanistic details, temporal dynamics, and therapeutic implications [Figure 4].

Recognition of damage and DAMPs

Neurons and glia experiencing proteotoxic and metabolic stress release a spectrum of damage-associated molecular patterns (DAMPs), including oligomeric A β , misfolded tau, extracellular ATP, oxidized phospholipids, mitochondrial DNA (mtDNA), nuclear chromatin fragments, HMGB1, and S100 proteins^[178,179]. Each DAMP engages specific PRRs on microglia and astrocytes.

Within minutes of exposure, A β oligomers induce the formation of the TLR2-TLR6-MyD88 complex, leading to NF- κ B activation^[178]. Simultaneously, fibrillar A β acts as an opsonin, providing a secondary activation signal for NLRP3 inflammasome assembly^[64]. Extracellular tau species bind to TLR4, activating p38 and ERK1/2-MAPKs, which further amplify NF- κ B signaling^[179]. Microglial P2X7 receptors detect extracellular ATP released from dying cells or dysfunctional astrocytes, inducing K⁺ efflux, a potent trigger for NLRP3 inflammasome assembly^[180]. In AD brains, cytosolic mtDNA and nuclear fragments accumulate due to impaired mitophagy and genotoxic stress. cGAS binds to this DNA, producing cGAMP, which activates STING and initiates its downstream signaling cascade^[181]. Complement activation further amplifies danger signals: C1q and C3 are upregulated in the AD cortex and cluster around plaques and tangles, tagging synapses for microglial elimination^[182,183]. The cleavage products C3a and C5a act as anaphylatoxins, and their receptors (C3aR and C5aR1) synergize with TLRs to enhance microglial inflammatory responses^[184,185]. Experimental studies underscore the pathological role of complement. Genetic knockout of C3 in APP/PS1 mice preserves dendritic spines and reduces synaptic pruning^[186], while pharmacological inhibition of C5aR1 (e.g., PMX205) decreases astrocytic GFAP expression and mitigates neuronal loss^[187].

Core signaling pathways

Recognition signals converge on several central hubs, including NF- κ B, cGAS-STING, the NLRP3 inflammasome, and JAK-STAT pathways, that coordinate the neuroinflammatory response in AD. NF- κ B serves as a master regulator of proinflammatory gene expression. Downstream of MyD88, STING, or cytokine receptors, NF- κ B is released from I κ B α inhibition, translocates into the nucleus, and promotes transcription of numerous proinflammatory genes, including TNF- α , IL-6, pro-IL-1 β , pro-IL-18, NLRP3, and iNOS^[178]. Sustained NF- κ B activity correlates with worsened cognitive performance in AD models.

The cGAS-STING pathway acts as a critical sensor of cytosolic DNA. Upon binding DNA, cGAS generates the second messenger cGAMP, which binds STING and triggers its translocation from the ER to the Golgi apparatus. Activated STING recruits TBK1, which phosphorylates the transcription factor IRF3, promoting its dimerization, nuclear translocation, and transcription of type I interferons (IFN-I), primarily IFN- β . Concurrently, STING activates the IKK complex, particularly IKK β , resulting in NF- κ B activation. The resulting IFN- β orchestrates an antiviral-like glial response by upregulating interferon-stimulated genes (ISGs) that modulate phagocytosis and antigen presentation^[188]. While IFN-I signaling can initially enhance A β clearance, chronic activation contributes to synaptic dysfunction and memory deficits, indicating a

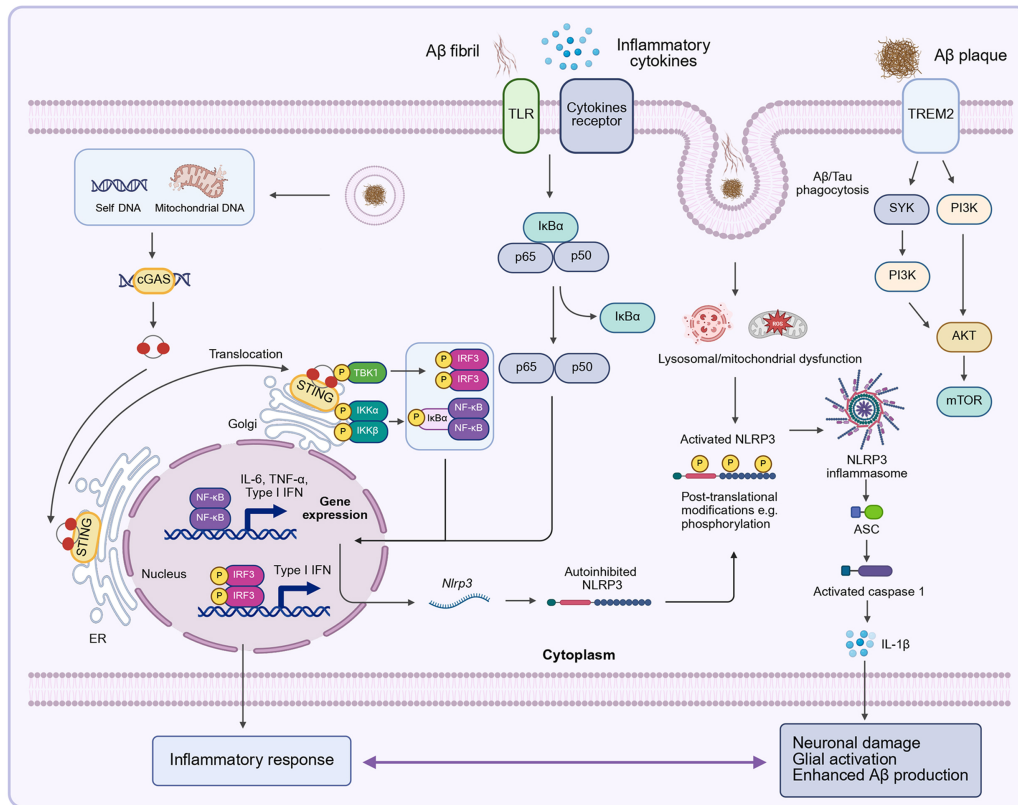


Figure 4. Molecular mechanisms and signaling pathways in AD. Multiple signaling pathways contribute to AD pathology, particularly those linked to neuroinflammation, neuronal death, and A β deposition. (1) cGAS-STING pathway: Cytosolic leakage of mtDNA or self-DNA activates cGAS, generating cGAMP that binds STING. This triggers TBK1-mediated IRF3 phosphorylation and NF- κ B activation (via I κ B α degradation and p65/p50 nuclear translocation), inducing type I interferons and proinflammatory cytokines (e.g., TNF- α , IL-6); (2) NLRP3 inflammasome pathway: DAMPs (e.g., A β fibrils) activate NLRP3, promoting ASC speck formation and caspase-1 cleavage. Activated caspase-1 converts pro-IL-1 β into its mature form, amplifying neuroinflammation. This process is influenced by mitochondrial and lysosomal dysfunction and regulated by post-translational modifications; (3) TREM2 signaling: A β plaques engage TREM2 receptors on microglia, initiating SYK/PI3K/AKT phosphorylation cascades that enhance phagocytosis (A β /tau clearance) and support microglial survival. Dysregulated TREM2 impairs these functions, exacerbating plaque accumulation. Crosstalk among these pathways creates feed-forward loops that reinforce glial activation, neuronal damage, and further A β production. [Created in BioRender. 1, 1. (2025) <https://BioRender.com/x4z0nw6>]. AD: Alzheimer's disease; A β : amyloid- β ; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon genes; mtDNA: mitochondrial DNA; cGAMP: 2',3'-cyclic GMP-AMP; NF- κ B: nuclear factor- κ B; NLR: NOD-like receptor; NLRP3: NLR family pyrin domain containing 3.

narrow therapeutic window for targeting this pathway.

The NLRP3 inflammasome requires a two-step activation: priming by NF- κ B and a secondary trigger such as K⁺ efflux, ROS, or lysosomal damage. Assembly of the NLRP3/ASC/caspase-1 complex initiates the autocatalytic activation of caspase-1. Active caspase-1 cleaves pro-IL-1 β and pro-IL-18 into their mature, secreted forms (IL-1 β and IL-18). Released ASC specks can further seed A β aggregation, perpetuating a vicious cycle of inflammation and proteopathy^[64]. Pharmacological inhibition with compounds such as MCC950 has been shown to attenuate neuronal loss and cognitive decline in AD models.

The JAK-STAT pathway translates cytokine signaling into transcriptional programs. Activation of IFNAR phosphorylates STAT1/2, forming ISGF3 complexes that regulate hundreds of genes involved in antigen processing and phagocytosis. IL-6R-STAT3 signaling promotes acute-phase responses, while IL-10R-STAT3 drives glial cells toward suppression of proinflammatory programs^[189]. Dysregulation of JAK-STAT

signaling in AD contributes both to impaired resolution of inflammation and to inappropriate immunosuppression^[190].

Effector mediators

Glial activation generates a complex cytokine and chemokine milieu that critically shapes the neuroinflammatory environment in AD. Among these mediators, proinflammatory cytokines - including TNF- α , IL-1 β , IL-6, IL-18, and IFN- β - can reach nanomolar concentrations in AD brains^[191]. These cytokines impair synaptic plasticity (by inhibiting LTP), disrupt BBB tight junctions, and recruit peripheral monocytes. In contrast, anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and TGF- β are secreted by A2 astrocytes and regulatory T cells. Notably, IL-10 reduces microglial TNF- α production and enhances phagocytic clearance of A β , highlighting its therapeutic potential^[191,192].

Chemokines also play crucial roles in leukocyte trafficking and microglial function. For instance, CCL2 (MCP-1) expression is elevated around amyloid plaques, recruiting CCR2⁺ monocytes that differentiate into CNS macrophages. The CX3CL1/CX3CR1 axis maintains homeostatic microglial motility and neuron-glia communication; its dysregulation correlates with excessive synaptic pruning^[193].

Pathological cellular states

Chronic exposure to DAMPs and cytokines drives glia into maladaptive states characterized by oxidative stress, mitochondrial dysfunction, and defective autophagy. A β upregulates NOX2/4 and iNOS, generating ROS and RNS that oxidize mitochondrial proteins and lipids, impair electron transport, and trigger mtDNA release, thereby activating cGAS and NLRP3 signaling^[120,194]. Impaired PINK1/Parkin-dependent mitophagy limits clearance of dysfunctional mitochondria, sustaining ROS production and inflammasome activation^[194].

AD-linked mutations in PSEN1/2 elevate lysosomal pH, blocking autophagosome-lysosome fusion and causing A β /tau accumulation^[195,196]. GWAS variants in *PICALM* and *CLU* impair vesicle trafficking and enzyme activity, leading to enlarged endolysosomal compartments in glia^[197,198]. Hyperactive mTORC1 (via phosphorylated S6K1) suppresses ULK1/BECN1, while TFEB downregulation reduces lysosomal biogenesis. Pharmacological TFEB activation restores lysosomal hydrolase activity and promotes clearance of intracellular A β and tau in cell models^[199,200].

Modulatory receptors and phagocytic pathways

Glial responses are further modulated by receptors that balance clearance and inflammation. TREM2 binds APOE and A β , activating DAP12/SYK-PI3K/AKT signaling to support microglial survival, proliferation, and phagocytosis^[201]. TREM2 R47H variants diminish these functions, leading to greater plaque burden and neuronal damage^[90]. GWAS have identified TREM2 variants (particularly R47H) that increase late-onset Alzheimer's disease (LOAD) risk by impairing microglial activity^[202,203]. In early AD, TREM2 promotes microglial clustering around amyloid plaques and enhances A β clearance, whereas in later stages, TREM2 deficiency or mutation (e.g., R47H) compromises plaque compaction, leading to larger deposits and increased neuronal injury^[204].

CD33/Siglec receptors recruit SHP phosphatases to intracellular ITIM motifs, attenuating Src kinase activation downstream of DAMP receptors. In AD cortex, CD33 overexpression is associated with reduced microglial A β clearance^[205]. Scavenger receptors (CD36, SR-A1) mediate uptake of oxidized lipids and A β fibrils^[206]. However, chronic stimulation promotes lipid droplet accumulation in microglia, skewing them toward a proinflammatory, glycolytic phenotype.

TARGETING GLIAL CELLS TO TREAT AD

NAD⁺ precursors

NAD⁺ is an essential coenzyme in redox reactions, regulating mitochondrial energy metabolism and DNA repair. Its levels decline with age and in neurodegenerative diseases, including AD. The NAD⁺ precursor nicotinamide riboside (NR) is converted to nicotinamide mononucleotide (NMN) by nicotinamide phosphoribosyltransferase (NAMPT), after which NMN is converted to NAD⁺ by nicotinamide mononucleotide adenylyltransferase (NMNAT)^[207,208]. Recent studies have highlighted the therapeutic potential of NR and NMN in ameliorating AD pathology^[69,209].

Supplementation with NR has been shown to restore NAD⁺ levels, reduce neuroinflammation and DNA damage through NAD⁺-dependent activation of sirtuins (e.g., SIRT3, SIRT6), and thereby decrease tau phosphorylation and improve memory in AD mouse models^[75]. Mitochondrial dysfunction, a hallmark of AD, is associated with impaired energy production, oxidative damage, and neuronal apoptosis^[210]. NMN administration enhances mitochondrial biogenesis and activity through NAD⁺-dependent activation of sirtuins, leading to reduced tau phosphorylation in human neuronal cells and improved memory in tauopathy models, including transgenic nematodes and mice^[194]. Furthermore, NR promotes mitophagy through the PINK1-Parkin pathway, suppresses the cGAS-STING pathway, reduces cellular senescence and SASP, and thereby decreases neuroinflammation and improves motor function in neurodegeneration-prone AD and *Atm*^{-/-} mice^[71,211] [Table 1].

Natural compounds and metabolites

Mounting evidence supports the pivotal role of chronic neuroinflammation in AD progression. This recognition has driven increased interest in plant-derived natural compounds and microbiome-derived metabolites as potential modulators of glial activation and neuroinflammatory responses^[212-215] [Table 1].

Resveratrol, a polyphenol abundant in red grapes, peanuts, and various berries, has been shown to reduce cerebrospinal fluid (CSF) levels of matrix metalloproteinase-9 (MMP9) while exerting potent anti-inflammatory effects. Mechanistically, resveratrol activates SIRT1, inhibits NF-κB signaling, and enhances mitochondrial function. Collectively, these actions contribute to its neuroprotective effects, promote adaptive immune activation, and modestly improve cognition in AD patients^[216-218].

Quercetin, a flavonoid present in apples, onions, and many vegetables, also demonstrates potent anti-inflammatory activity. It inhibits microglial NF-κB and MAPK signaling, thereby reducing the production of proinflammatory cytokines such as IL-1β and TNF-α^[219]. In addition, quercetin enhances microglial phagocytosis and promotes neuronal survival by reducing oxidative stress and preserving mitochondrial integrity^[220,221].

Melatonin, a pineal-derived indoleamine, has also been implicated in AD therapy^[222]. In rodent models, melatonin administration suppresses IL-1β-induced astrocyte and microglial activation, decreases proinflammatory cytokine expression, and improves learning and memory performance^[223]. Accumulating evidence indicates that melatonin enhances Aβ clearance by upregulating neprilysin and insulin-degrading enzyme, while also promoting synaptic plasticity via BDNF and CREB signaling pathways^[224,225]. Furthermore, melatonin stabilizes mitochondrial membrane potential, reduces cytochrome c release, and prevents neuronal apoptosis, underscoring its multifaceted neuroprotective potential in AD^[226].

Urolithin A (UA), a gut microbiota-derived metabolite of ellagitannins, has recently emerged as a promising therapeutic candidate in AD models^[227,228]. Owing to its phenolic hydroxyl groups, UA exhibits strong antioxidant properties that neutralize ROS and reduce oxidative stress. Beyond its antioxidant

Table 1. Therapeutic approaches and compounds in AD treatment

Therapeutic approach	Agent/compound	Mechanism of action	References
NAD ⁺ precursors	NR, NMN	Elevate NAD ⁺ levels; reduce oxidative stress; restore hippocampal synaptic plasticity; decrease tau phosphorylation; enhance mitochondrial function; improve cognitive performance	[75,194,211]
Natural compounds & metabolites	Curcumin	Inhibits NF-κB and MAPK signaling, attenuating neuroinflammation; acts as a potent antioxidant, reducing lipid/protein oxidation; inhibits Aβ and tau aggregation	[214,215]
	Resveratrol	Activates SIRT1 and suppresses NF-κB signaling; downregulates MMP-9; inhibits Aβ aggregation; promotes mitochondrial biogenesis	[217,218]
	Quercetin	Blocks NF-κB/MAPK signaling, reducing proinflammatory cytokines; enhances microglial phagocytosis of Aβ; reduces oxidative stress	[219–221]
	Melatonin	Suppresses IL-1β-mediated glial activation; upregulates Aβ-degrading enzymes; enhances BDNF/CREB-dependent synaptic plasticity; protects mitochondria integrity	[222,224, 225]
	Urolithin A (UA)	Scavenges ROS; promotes mitochondrial quality control (mitophagy); reduces Aβ aggregation; enhances lysosomal function; improves learning and memory	[194,229,230]
NSAIDs	Ibuprofen	Inhibits COX activity, reducing prostaglandin levels; suppresses microglial activation; reduces Aβ plaque load; improves cognitive performance in APP models	[237,238]
AChE inhibitors	Donepezil	Inhibits AChE, increasing synaptic acetylcholine, which improves cognition and ADL scores	[243,245]
	Rivastigmine	Inhibits both AChE and BuChE, increasing acetylcholine; improves cognition and daily function	[246,247]
	Galantamine	Inhibits AChE and allosterically modulates α7-nAChR, increasing acetylcholine; slows cognitive and functional decline	[244,248]
NLRP3 inflammasome inhibitors	MCC950	Directly blocks NLRP3, inhibiting IL-1β/IL-18 release; reduces microgliosis and synaptic loss	[256]
cGAS-STING inhibitors	H-151	Covalently antagonizes STING, suppressing type I IFN and NF-κB signaling; attenuates neuroinflammation and Aβ pathology	[258]
Immunotherapeutic strategies	CAD106	Aβ _{1–6} peptide conjugated to a Qβ carrier; induces anti-Aβ antibodies, associated with reduced amyloid burden on PET	[264,265]
	AADvac1	Tau-derived peptide vaccine that elicits anti-tau antibodies, reducing tau aggregation and improving cognition	[266,267]
	Aducanumab	Human IgG1 monoclonal antibody targeting aggregated Aβ N-terminus; reduces amyloid plaque burden	[268,269]
	Lecanemab	Human monoclonal antibody against soluble Aβ protofibrils; reduces plaque burden and slows cognitive decline	[268,272]
	AL002c	Agonistic anti-TREM2 monoclonal antibody enhances microglial phagocytosis of Aβ; improves synaptic markers	[277,279]

AD: Alzheimer's disease; NAD⁺: nicotinamide adenine dinucleotide; Aβ: amyloid-β; ADL: activities of daily living; AChE: acetylcholinesterase; BuChE: butyrylcholinesterase; COX: cyclooxygenase; IFN: interferon; mAb: monoclonal antibody; NF-κB: nuclear factor-κB; NMN: nicotinamide mononucleotide; NR: nicotinamide riboside; PET: positron emission tomography; ROS: reactive oxygen species; SASP: senescence-associated secretory phenotype; NSAIDs: nonsteroidal anti-inflammatory drugs; APP: amyloid precursor protein.

activity, UA exerts immunomodulatory effects by enhancing microglial phagocytosis and reducing neuroinflammation in APP/PS1 mice^[194,229]. Mechanistically, UA promotes mitophagy through the PINK1/Parkin pathway and induces the expression of lysosomal histone proteases, particularly CTSZ, which is frequently disrupted in AD brains. Long-term UA treatment has been shown to improve learning, memory, and olfactory function in transgenic AD mice while concurrently reducing Aβ deposition and tau pathology^[230]. Additionally, UA activates SIRT1 and inhibits mTOR, thereby enhancing neuronal resilience to aging-related stressors, including D-galactose-induced senescence^[231]. In 3×TgAD mice, UA not only reduced amyloid burden but also significantly enhanced spatial memory performance. *In vitro*, UA stimulates mitophagy and promotes Aβ clearance in neuronal cultures. Notably, in normal aging wild-type mice, UA supplementation has been associated with lifespan extension and improved mitochondrial

function^[232].

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated for their neuroprotective potential in AD due to their ability to inhibit cyclooxygenase (COX) enzymes and thus reduce prostaglandin-mediated neuroinflammation^[233]. Prostaglandins, produced by COX-1 and COX-2, contribute to glial activation, cytokine release, and BBB permeability^[234,235]. In APP-overexpressing mouse models, chronic ibuprofen treatment reduces A β plaque deposition and attenuates microglial activation^[236-238]. Similarly, other NSAIDs, such as indomethacin and celecoxib, decrease γ -secretase activity and lower brain A β_{42} levels in the Tg2576 mouse model^[239]. Early small-scale clinical studies suggested that indomethacin might slow cognitive decline in mild-to-moderate AD^[240]. However, subsequent large, double-blind, randomized, placebo-controlled trials of nonselective NSAIDs (e.g., naproxen, diclofenac) and COX-2 selective inhibitors (e.g., celecoxib, rofecoxib) failed to demonstrate significant cognitive benefits in AD patients^[241]. These disappointing outcomes may reflect the importance of timing: anti-inflammatory interventions may be more effective if initiated during preclinical or prodromal stages of AD, before extensive pathology has developed^[242] [Table 1].

Acetylcholinesterase inhibitors

Cholinergic hypofunction led to the development of acetylcholinesterase inhibitors (AChEIs) to increase synaptic acetylcholine levels. Donepezil, rivastigmine, and galantamine are FDA-approved AChEIs that modestly improve cognition, activities of daily living, and global clinical status in mild-to-moderate AD^[243,244]. Donepezil (5-10 mg/day) inhibits acetylcholinesterase (AChE), elevating cortical acetylcholine and producing small but consistent improvements on the ADAS-Cog and ADCS-ADL scales over 12-24 weeks; higher doses (23 mg/day) do not confer additional efficacy and are associated with more adverse events^[243,245]. Rivastigmine (6-12 mg/day), which inhibits both AChE and butyrylcholinesterase, improves cognitive and functional measures in international placebo-controlled trials^[246,247]. Galantamine (16-24 mg/day), which also modulates nicotinic receptors, slows cognitive and behavioral decline over six months^[244,248]. Meta-analyses indicate broadly comparable efficacy among these agents, though donepezil may exhibit a more favorable tolerability profile than rivastigmine^[249] [Table 1].

NMDA receptor antagonists

Overactivation of N-methyl-D-aspartate (NMDA) receptors contributes to excitotoxicity and glial activation in AD^[250]. Memantine, an uncompetitive NMDA receptor antagonist, reduces pathological calcium influx, thereby protecting neurons and modulating microglial and astrocytic responses^[251]. In moderate-to-severe AD, memantine (10-20 mg/day) produces modest improvements in cognitive, functional, and behavioral outcomes compared with placebo, as demonstrated in meta-analyses of randomized trials^[252,253]. By normalizing glutamatergic neurotransmission and reducing excitotoxic drive, memantine complements cholinergic therapies and represents one of the few currently licensed adjunctive agents for AD management^[254] [Table 1].

NLRP3 inflammasome inhibitors

Preclinical studies demonstrate that pharmacological inhibition of NLRP3 reduces A β deposition, attenuates glial activation, and preserves cognitive function in animal models of AD^[255]. For example, the small-molecule inhibitor MCC950 blocks NLRP3 assembly and has shown efficacy in both streptozotocin-induced and transgenic AD mouse models by lowering IL-1 β levels, reducing microgliosis, and improving memory performance^[256]. These findings support NLRP3 as a promising therapeutic target for disrupting the cycle of inflammation and neurodegeneration in AD [Table 1].

cGAS-STING antagonists

Inhibitors of the cGAS-STING pathway show significant therapeutic potential in neurodegenerative disorders. Pharmacological blockade with brain-penetrant cGAS inhibitors or the covalent STING antagonist H-151 suppresses IFN-I and NF- κ B signaling, decreases expression of *Tnfa*, *C1q*, *C3*, and *Il1a*, and preserves synaptic integrity in both amyloid and tauopathy models^[257,258]. Mechanistically, H-151 covalently targets Cys91 on STING, preventing dimerization and subsequent TBK1-IRF3 signaling^[259], while novel cGAS inhibitors (e.g., acetaldehyde derivatives) prevent cGAS-DNA binding and phase separation^[260]. Notably, mTORC2-mediated phosphorylation of cGAS at Ser37 regulates its chromatin localization, suggesting that epigenetic modulation may represent an alternative strategy^[261]. Refining selective cGAS-STING inhibitors with favorable CNS pharmacokinetics, particularly enhancing BBB penetration and minimizing off-target effects, remains critical for clinical translation. Future directions include developing dual inhibitors that block both cGAS enzymatic activity and STING activation, as well as exploring combination therapies with immunomodulatory agents [Table 1].

Immunotherapeutic strategies

Glial cells play both pathogenic and protective roles in AD pathology, driving the development of active and passive immunotherapies targeting A β , tau, or immune receptors on microglia^[262,263] [Table 1].

Active immunization employs antigenic peptides to stimulate endogenous antibody production. CAD106, which displays multiple copies of A β ₁₋₆ on a bacteriophage Q β carrier, demonstrated safety and a correlation between antibody tiers and PET imaging in a 90-week Phase 2 trial in patients with mild AD, with reduced amyloid load on PET scans^[264,265]. AADvac1 targets pathological tau epitopes, and its ongoing Phase 2 trial is evaluating effects on cognitive measures and tau biomarkers in mild-to-moderate AD^[266,267].

Passive immunization involves the administration of monoclonal antibodies that directly clear toxic proteins. Aducanumab, approved by the FDA in 2021, selectively binds aggregated A β and reduces plaque burden^[268,269]. In Phase 3 trials, EMERGE showed a significant reduction in clinical decline, whereas ENGAGE did not replicate this effect^[270,271]. In January 2024, the manufacturer announced the global discontinuation of aducanumab development and commercialization. Lecanemab, a monoclonal antibody targeting soluble A β protofibrils, received accelerated approval in 2023 after demonstrating both plaque reduction and slower cognitive decline^[272]. Across multiple clinical trials, lecanemab was generally well tolerated^[272-274]; the most common adverse events were infusion-related reactions, amyloid-related imaging abnormalities (ARIA), and headache. ARIA is subdivided into ARIA-E (edema) and ARIA-H (hemosiderin deposition, including microhemorrhage and superficial siderosis), both of which are associated with cerebral amyloid angiopathy (CAA) and ApoE ϵ 4, and may also occur spontaneously in AD^[275]. ARIA-E was more frequent in the lecanemab group than in placebo, but was generally mild to moderate on imaging and typically occurred within the first 3-6 months of treatment^[276]. Awareness of incidence, monitoring, and management strategies is therefore critical for clinicians, patients, and caregivers to ensure optimal patient care.

Antibodies against receptors such as TREM2 have also shown promise in preclinical models by enhancing microglial phagocytosis, reducing A β plaques, and improving synaptic markers^[201,277]. Anti-TREM2 antibodies such as AL002c are designed to enhance microglial clearance of A β but face unique translational challenges^[277]. Chronic TREM2 agonism may drive microglia toward a neurotoxic DAM stage, as observed in mouse models. Highaffinity AL002c mimetics have been reported to increase peri-plaque neuritic tau pathology and neuritic dystrophy without reducing A β plaque burden, and to exacerbate synapse loss in an amyloidosis mouse model where AD-tau was injected to induce A β -dependent tau seeding and spreading^[278,279]. These findings highlight the context- and disease stage-dependent nature of microglial

function: administration that is too early (when microglia remain largely quiescent) or too late (when they are already proinflammatory) may tip the balance toward detrimental rather than beneficial effects. It is also important to note that not all TREM2 agonist antibodies are equivalent, and whether similar outcomes would be observed with other antibodies remains uncertain. By modulating glial immune functions and directly clearing pathogenic aggregates, these immunotherapeutic modalities offer complementary strategies to attenuate neuroinflammation and slow disease progression in AD.

CONCLUSION

Glial cells, including microglia, astrocytes, and oligodendrocytes, have emerged as central regulators of AD pathogenesis, wielding both neuroprotective and neurotoxic influences that influence disease onset and progression^[5,280]. Microglia orchestrate innate immune responses: in early stages, they clear A β and secrete neurotrophic factors, but chronic activation promotes the release of IL-1 β , TNF- α , and reactive oxygen species, exacerbating synaptic loss and neuronal death^[4,281]. Astrocytes support BBB integrity, neurotransmitter recycling, and metabolic function; however, the “A1” reactive subtype contributes to neuroinflammation and impairs A β clearance^[138,280]. Oligodendrocytes, once overlooked, can adopt disease-associated states that modulate immune signaling and myelin homeostasis, thereby affecting neuronal network stability^[157].

Therapeutic strategies must reflect the complexity of glial biology, moving beyond amyloid- and tau-centric monotherapies toward integrated combination regimens. These regimens should incorporate inflammasome and innate immune modulators, such as small-molecule inhibitors targeting NLRP3 or cGAS-STING pathways, which have demonstrated preclinical efficacy in reducing glial inflammation and preserving cognition^[282,283]. Metabolic and senescence-targeted agents, including NAD⁺ precursors like NR or NMN, combined with senolytics, also hold promise for restoring glial energy metabolism, reducing SASP burden, and restoring phagocytic capacity^[71,194]. Additionally, immune-modulatory antibodies and vaccines, encompassing both passive and active immunotherapies directed at A β , tau, or glial receptors such as TREM2 and CD33, offer opportunities to recalibrate microglial states toward enhanced debris clearance and repair^[283,284].

Precision medicine approaches may further optimize therapy by stratifying patients based on glial biomarkers, such as CSF or plasma cytokine panels, PET imaging of TSPO or MAO-B, and single-cell transcriptomic profiles of microglial and astrocyte states^[139,285]. Longitudinal monitoring of glial activation with emerging PET ligands may also help determine treatment timing and dosage.

Next-generation experimental models are critical for translating these insights. Patient-derived iPSC systems, ranging from simple glial monocultures to complex 3D neural tissues, reproduce AD-related A β /tau pathology and glial activation while linking cellular phenotypes to donor cognitive traits, despite inherent heterogeneity^[139,286]. Human-mouse chimeric brains, in which iPSC-derived microglia colonize immunodeficient rodents, replicate human-specific glial responses to A β and reveal time-dependent disease-associated states^[287,288]. Future hybrid platforms - such as organ-on-chip systems incorporating perfused microvessels and adaptive immune cells - combined with high-resolution single-cell and spatial omics, will enable precise mapping of glial state dynamics and temporally controlled perturbations^[289]. Such models will help identify intercellular nodes whose modulation can shift glial communities from pathogenic to protective states.

Nevertheless, significant challenges remain. Robust glial biomarkers that predict treatment response, improved *in vitro* and *in vivo* models that better recapitulate human glial diversity, and delivery platforms

(e.g., nanoparticles, viral vectors) with high glial specificity are urgently needed. Moreover, the interplay between central and peripheral immunity in AD remains underexplored; modulating systemic myeloid cells may synergize with CNS-focused glial therapies.

In summary, a glia-centric paradigm for AD - one that acknowledges the dual roles of microglia, astrocytes, and oligodendrocytes - offers the potential for durable disease modification. Continued investment in glial biology, coupled with advances in biomarker development and drug delivery, may transform AD from an inexorable decline into a manageable condition with preserved cognition and quality of life.

DECLARATIONS

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Authors' contributions

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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