THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 14 Issue 2

NARRATIVE REVIEW

Glial Dysfunction in Alzheimer's Disease: Contributions to Disease Progression, Pathomechanism and Therapeutic Opportunities

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OPEN ACCESS

PUBLISHED
28 February 2026

CITATION
Dreschnack, I., Dreschnack, P.A., 2026. Glial Dysfunction in Alzheimer's Disease: Contributions to Disease Progression, Pathomechanism and Therapeutic Opportunities. Medical Research Archives, [online] 14(2).

https://doi.org/10.18103/mra.v14i2.XXXX

DOI
https://doi.org/10.18103/mra.v14i2.XXXX

ISSN
2375-1924

ABSTRACT

Alzheimer's disease (AD), the most common cause of dementia, remains a major neurodegenerative disorder with an incompletely understood etiology despite decades of research. While beta-amyloid plaques and neurofibrillary tau tangles represent the defining pathological hallmarks of AD, growing evidence indicates that the disease's progression is profoundly influenced by chronic neuroinflammation. Microglia and astrocytes, which are essential for maintaining neuronal homeostasis, clear plaques, support vascular and synaptic function, undergo a pathological shift in AD from protective regulators to dysfunctional, proinflammatory mediators. This transition is characterized by impaired plaque phagocytosis, excessive cytokine release, oxidative stress, and blood-brain barrier (BBB) disruption, all of which contribute to synaptic loss and neurodegeneration. However, the mechanisms driving glial failure remain poorly defined, leaving unresolved questions about whether neuroinflammation in AD acts as an amplifier of existing pathology or a downstream consequence. This literature review examines recent evidence on microglial and astrocytic dysfunction in AD, evaluates proposed cellular and molecular mechanisms underlying their pathological transformation, and explores the potential for glial-targeted interventions. Emerging research suggests that restoring glial function, rather than solely targeting plaques or tau tangles, may offer a promising strategy to slow or delay AD progression by enhancing plaque clearance, maintaining metabolic and vascular stability, and reducing inflammatory neurotoxicity.

Keywords: Alzheimer's disease, microglia, astrocytes, beta-amyloid plaques, neurofibrillary tangles, neuroinflammation, cytokine dysregulation, blood-brain barrier, vascular pathology, therapeutic targets.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease known to be the most common cause of dementia, accounting for approximately 70% of cases[1]. Aging is considered the strongest risk factor for AD development[2]. Currently, 1 in 8 people over the age of 65 in the USA is diagnosed with AD[3]. Despite extensive research, the exact etiology and pathomechanism of AD remain incompletely understood[1].

Beta-amyloid (senile) plaque accumulation and neurofibrillary tangles are the two cardinal lesions of AD pathology[4]. However, AD pathogenesis is complex and multifactorial[1]. Genetic and epigenetic factors, along with alterations in the immune system, contribute to the development and progression of the disease[1,5,6].

Recent research highlights the critical role of glial cells, particularly microglia and astrocytes, in neuroinflammation and AD progression[2]. In early stages, microglia and astrocytes play a protective role, supporting neuronal tissue and maintaining brain homeostasis, but eventually fail to maintain this function[2]. As the disease progresses, over-activated glial cells produce excessive pro-inflammatory cytokines, which, together with oxidative stress, promote neurotoxicity and accelerate neurodegeneration[2].

Numerous studies have documented glial dysfunction, cytokine dysregulation, and vascular impairment in AD, although many remain descriptive rather than mechanistic[7,8]. Microglia and astrocytes normally regulate brain homeostasis, promote amyloid clearance, and maintain vascular integrity, yet the mechanisms that drive their transition into dysfunctional, pro-inflammatory states remain poorly defined. Key questions include why microglia lose their phagocytic capacity and fail to clear beta-amyloid plaques, why astrocytes become excessively reactive and contribute to BBB breakdown, and how these glial changes interact with the plaque/tau tangle pathomechanism. These gaps leave it uncertain whether neuroinflammation in AD is an amplifier of existing pathology or is merely a downstream consequence.

This review analyzes recent evidence regarding microglia and astrocyte dysfunction in AD, critically examines proposed cellular and molecular mechanisms underlying glial failure, and suggests that maintaining glial function may help prevent or delay AD progression. Although no current therapy effectively slows AD progression, recent evidence targeting neuroinflammation presents a promising potential solution[3].

Building on this evidence, we propose that restoring microglia and astrocytes to their full protective capacities, enabling efficient plaque clearance, metabolic support, and maintenance of vascular and synaptic homeostasis, may represent a viable strategy for preventing or delaying AD progression. While such an approach cannot reverse genetic predispositions to plaque production, stabilizing glial function could reduce the impact of downstream pathology and ultimately slow cognitive decline.

Evidence strongly supports a key role for inflammation in disease progression[9]. Studies on both mouse models of AD and post-mortem human tissue highlight the role of inflammation in excessive synaptic pruning, which correlates with memory loss and cognitive deficits[9]. Nevertheless, the two primary lesions required for of AD diagnosis are beta-amyloid plaques and neurofibrillary tau tangles[3,4]. Other neuropathological changes, such as vascular amyloid deposition or granulovacuolar degeneration, may also occur, but AD is defined by these two cardinal lesion[4].

Macroscopically, AD brains show significant hippocampal and cortical atrophy, often resulting in symmetrical dilation of the lateral ventricles[4]. However, these gross changes are not diagnostic, as similar findings may occur in elderly individuals without AD[4]. While beta-amyloid aggregates and neurofibrillary tau tangles are the defining lesions, increasing evidence emphasizes the importance of persistent neuroinflammation in AD pathogenesis and progression[4,10].

2. AD Pathology

2.1 BETA-AMYLOID PATHOLOGY

Briefly, beta-amyloid (senile) plaques are extracellular structures formed from amyloid precursor protein (APP) in the brain's extracellular space[1]. APP is a transmembrane neuronal protein that plays a critical role in signaling pathways[1,11].

This large, complex protein is cleaved into peptide fragments of varying lengths by enzymes such as alpha- and gamma-secretases[2,13].

In AD pathophysiology, beta-secretase (BACE1), rather than alpha-secretase, cleaves APP at alternative sites to generate amyloid-β peptides after subsequent gamma-secretase cleavage, forming beta-amyloid monomers[13]. These monomers aggregate into insoluble polymers and larger plaques, known as beta-amyloid (senile) plaques[1].

This process occur is influenced by the Swedish mutation (KM670/671NL), located immediately N-terminal to the β-site of APP, which alters the amino-acid sequence near the cleavage site[12,14,15,16]. This mutation increases APP's susceptibility to BACE1, modifies intracellular trafficking, and collectively enhances β-cleavage and Aβ production[12,14,15,16]. BACE1 cleaves APP because the APP sequence precisely fits its active site, and BACE1 is localized in neuronal compartments, such as the Golgi and endosomes, where it can access APP[13,17,18].

These changes disrupt neuronal communication, particularly synaptic function, eventually leading to neuronal death[4]. Soluble plaque oligomers, rather than large insoluble amyloid plaques, are increasingly recognized as the primary neurotoxic species in AD, as they more potently impair neuronal communication, synaptic function, and induce neurodegeneration than fibrillar plaque[12,19]. At the synapse, oligomers bind postsynaptic structures, interfere with glutamate receptor function (especially NMDA receptors), and trigger aberrant calcium influx, leading to mitochondrial dysfunction, oxidative stress, and AMPA receptors[20,21]. Ultimately causing synaptic loss and impaired long-term potentiation[20,21].

Beyond direct neuronal toxicity, oligomers also affect glial cells: they bind microglial receptors such as TREM2, disrupting phagocytosis and triggering maladaptive pro-inflammatory activation[22,23]. In mouse models, oligomer burden correlates more strongly with microglial activation and synaptic loss than dense plaque deposits, emphasizing oligomers as critical drivers of early neurodegeneration in AD[8].

Thus, through direct synaptic/neuron damage and indirect glial-mediated inflammatory pathways, Aβ oligomers emerge as central mediators of early neurotoxicity in AD, highlighting the need to focus on oligomer-specific mechanisms. Beta-amyloid aggregates are found not only in the brain parenchyma but also in cerebral and leptomeningeal blood vessels, a condition known as cerebral amyloid angiopathy (CAA)[3,24]. Although CAA can occur in some individuals without significant parenchymal plaques, it frequently accompanies AD pathology and may cause lobar hemorrhage (bleeding into cortical areas rather than deeper structures)[w]. CAA also contributes to ischemic brain damage[3].

2.2 TAU PATHOLOGY

In addition to the accumulation of beta-amyloid plaques in AD pathology, nerve cell bodies in specific brain areas develop neurofibrillary tangles, neuropil threads and neuritic dystrophy[3]. NFTs are abnormal fibrous inclusions within neuronal cytoplasm and are considered cardinal microscopic lesions of AD pathology3[3,4].

Both neuropil threads (present in neuronal processes) and NFTs are primarily composed of hyperphosphorylated, aggregated tau, a microtubule-binding protein[3]. Tau, synthesized in all neurons and glia, stabilizes microtubules in the cytoskeleton[3]. In AD, tau hyperphosphorylation causes detachment from microtubules, misfolding, and aggregation into NFTs within neuronal cell bodies, contributing to neuronal dysfunction, synaptic loss, and cognitive decline[3,25].

Recent genetic studies on tau protein have clarified its connection with beta-amyloid plaque accumulation and tangle formation[3]. While the initial events in plaque and tangle formation can occur independently, evidence suggests that plaque aggregation accelerates NFT formation[3]. Tau aggregates can spread across synapses to connected neurons, facilitating the transfer of misfolded tau and amplifying network-level neurodegeneration[26,27].

Importantly, Aβ burden promotes tau hyperphosphorylation and NFT formation, demonstrating a synergistic effect in driving disease progression[3,28]. Experimental models indicate that increased plaque deposition promotes tau misfolding, NFT propagation, and synaptic dysfunction, suggesting plaque acts as an upstream amplifier of tau pathology rather than the sole driver of neurodegeneration[3,11].

Animal models genetically modified to overproduce plaque show neuritic plaques, microglial/astrocytic activation, oxidative damage, changes in cytoskeletal proteins including tau, and behavioral impairment[3]. The extent of these toxic events is still under investigation. Currently, no human evidence indicates that therapies targeting both plaques and NFTs significantly affect disease progression or the biochemical interplay between these lesions[3].

Despite extensive efforts, anti-plaque and anti-tau therapies have shown limited efficacy in halting AD progression. Clinical trials targeting plaque aggregation or tau phosphorylation have largely failed to produce meaningful cognitive improvement, highlighting the limitations of a purely amyloid–tau-focused approach[29,30]. This underscores the need to integrate additional factors, such as glial dysfunction and neuroinflammation, into AD pathogenesis models[6,31].

3. Glial Cell Dysfunction in Alzheimer's Disease.

3.1 MICROGLIAL DYSFUNCTION

Over the past decade, attention has increasingly focused on the role of immune cell activity and inflammation in neurodegenerative diseases. Emerging evidence indicates that dysregulated inflammation is not merely a byproduct of Alzheimer's disease (AD) but a significant contributor to its development and progression. Several neuroinflammatory pathways directly involve overactivation and alteration of microglia and astrocytes, the two primary immune cells residing in brain tissue[1].

Recent studies confirm that chronic microglial activation contributes to synaptic dysfunction and cognitive decline in AD, independent of amyloid and tau burden[32,33]. Microglia serve as the brain's primary immune cells, maintaining homeostasis and protecting against pathogens and cellular debris via phagocytosis and cytokine release[1]. Traditionally, people believe microglia protect the brain by clearing amyloid and damaged neurons[33].

Microglial cells exist in two morphological forms: inactive and active[34]. The active form is further classified into two functional states: M1 and M2[34]. The M1 state exhibits pro-inflammatory features, secreting cytokines such as interleukin-1β (IL-1β), interleukin-1 (IL-1), tumor necrosis factor (TNF-α), interferon-γ (IFN-γ), reactive oxygen species (ROS), and nitric oxide (NO). In contrast, the M2 state is anti-inflammatory and promotes tissue repair[34]. M1/M2 polarization is fundamental for plaque clearance[34,35].

In early AD, activated microglia positively clear Aβ through phagocytosis[2]. However, chronic exposure reduces their phagocytic efficiency, leading to Aβ accumulation and extracellular plaque formation, which perpetuates microglial activation[2]. Over-activated microglia adopt reactive phenotypes with pronounced morphological changes and elevated expression of pro-inflammatory cytokines TNF-α, IL-6, IL-1β, and NO[2]. This persistent activation fosters a chronic neuroinflammatory environment, exacerbating neuronal and synaptic loss[2,35]. It also fuels a self-perpetuating cycle of inflammation and synaptic injury, as illustrated in Figure 1[35].

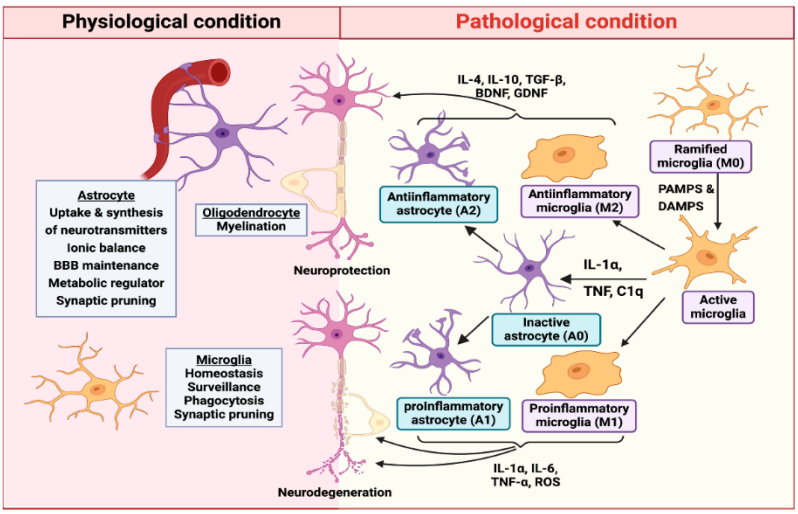

Figure 1: Glial dysfunction mechanisms in Alzheimer's disease. Microglia transition from protective (M2) to pro-inflammatory (M1) states, contributing to impaired amyloid clearance, synaptic loss, and neuronal injury. Astrocytes also shift from neuroprotective (A2) to neurotoxic (A1) phenotypes, further amplifying neuroinflammation[350].

Moreover, single-cell RNA sequencing has revealed heterogeneous microglial populations in AD brains, including disease-associated microglia (DAM) that correlate with plaque burden and neurodegeneration[36]. Mutations in the microglial receptor TREM2, a transmembrane protein, link to AD progression1. TREM2 signaling is critical for phagocytosis and the clearance of Aβ aggregates[34]. Reduced TREM2 levels impair microglial Aβ clearance, increasing plaque burden[2]. Experimental studies demonstrate that enhancing TREM2 signaling improves microglial phagocytic activity, attenuates early amyloid deposition, and reduces neuroinflammation, suggesting therapeutic potential, especially in early disease stages[37,38].

The presence of beta-amyloid oligomers and tau pathology activates a cytosolic protein complex known as the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) inflammasome in microglia and astrocytes, which serves as a key molecular link in AD neuroinflammatory[2,10,38]. Upon stimulation by Aβ oligomers or tau aggregates, NLRP3 activation induces secretion of pro-inflammatory cytokines such as IL-1β, which is overexpressed in the hippocampus of AD patients[2,10]. Pharmacological inhibition of NLRP3 in preclinical models reduces IL-1β levels, attenuates microglial activation, and improves cognition[38,39]. In rodent studies, hippocampal IL-1β injections impair memory by activating microglia[2].

Pro-inflammatory cytokines released by activated microglia contribute to neuronal damage and synaptic pruning deficits, which are directly implicated in AD clinical manifestations[34,40]. Under physiological conditions, resting microglia monitor their microenvironment and regulate synaptic pruning, a process essential for synapse formation, neuronal activity regulation, memory, and learning[9,40]. Chronic microglial overactivation, however, leads to excessive synaptic elimination, contributing to cognitive deficits observed in AD[9,40]. PET imaging studies in humans confirm that microglial activation occurs early in AD and is associated with amyloid and tau pathology, as well as longitudinal cognitive decline[41,42,43].

3.2 ASTROCYTE REACTIVITY AND DYSFUNCTION

Scientists widely observe reactive astrocytes in AD, often considering them a secondary response to neuronal injury[44]. Pro-inflammatory cytokines released from microglia1 directly activated them. Astrocytes normally support blood–brain barrier (BBB) integrity, neurogenesis, fluid homeostasis, and clearance of neurotoxic molecules, including plaques and NFTs[2].

Astrocytes undergo a functional transformation, becoming "reactive astrocytes" in response to injury or disease[44]. They adopt either a neurotoxic A1 phenotype, releasing pro-inflammatory cytokines that induce neuronal apoptosis, or a neuroprotective A2 phenotype, secreting anti-inflammatory factors[1]. Post-mortem analyzes of AD brains show abundant A1 astrocytes[1]. Mouse models indicate that A1 astrocytes are induced by activated microglia and acquire neurotoxic functions, killing neurons and mature oligodendrocytes[44].

Astrocytes are also the main source of glutathione, the brain's primary antioxidant, for neurons and microglia[2]. In AD, reduced astrocytic glutathione contributes to neurodegeneration as astrocytes become inflammatory rather than neuroprotective[2]. Emerging evidence from in vitro and in vivo studies demonstrates that enhancing astrocytic antioxidant capacity via nuclear factor erythroid-2 related factor-2 (NRF2) activation or glutathione analogs restores glutathione levels, reduces amyloid-β and pro-inflammatory cytokines, mitigates oxidative stress, and limits neurodegeneration[45,46]. These findings highlight the therapeutic potential of targeting astrocytic redox pathways in AD.

3.3. BLOOD-BRAIN BARRIER AND VASCULAR PATHOLOGY

Besides their neuroprotective function, astrocytes play a crucial role in maintaining the integrity of the blood–brain barrier (BBB). The BBB acts as a selective barrier that regulates the movement of molecules into the brain, preventing entry of red blood cells, leukocytes, neurotoxic plasma components, and pathogens or toxins into the CNS[2]. Structurally, the BBB consists of brain microvessels composed of endothelial cells (ECs), pericytes, basement membrane, and astrocytic endfeet, where ECs are connected by tight junction proteins and junction adhesion molecules (JAMs)[2].

Disruption of the BBB is associated with abnormal vessel regression, brain hypoperfusion, and activation of inflammatory responses[2]. Reactive astrocytes (A1 type) can alter normal endothelial

function by releasing inflammatory mediators[1]. While astrocyte reactivity is widely recognized, the specific molecular mechanisms and signaling pathways that drive the transition from neuroprotective to neurotoxic phenotypes remain poorly defined. Understanding these mechanisms is critical, as modulating astrocyte reactivity may represent a viable therapeutic approach.

Emerging evidence suggests that astrocyte-derived factors regulate BBB integrity, and dysregulation of astrocyte vascular signaling is associated with BBB breakdown in AD. This indicates that interventions targeting astrocyte-mediated inflammation may have therapeutic potential, though direct evidence in AD models remains limited.

According to data from the US National Alzheimer's Coordinating Center, 80% of AD patients exhibit vascular pathology, including arteriosclerosis, hemorrhage, and cerebral amyloid angiopathy[47]. Cerebral angiopathy is a significant contributor to BBB disruption, increasing permeability and allowing toxins and pathogens to enter the brain[47]. In preclinical AD, alterations in vascular biomarkers occur before cognitive impairment and before detectable increases in classical AD biomarkers such as amyloid deposition and elevated CSF tau levels[47].

A study examining BBB disruption in the hippocampus of individuals with mild cognitive impairment found that increased hippocampal permeability preceded hippocampal atrophy, suggesting that BBB breakdown may occur before neurodegeneration[47]. Post-mortem analyses further demonstrate BBB disruption through accumulation of thrombin, blood-derived fibrinogen, IgG, and albumin, as well as loss of pericytes in the cortex and hippocampus[47].

The two-hit vascular hypothesis of AD proposes that vascular injury is an initial insult causing BBB dysfunction and diminished brain perfusion, which in turn leads to neuronal injury and Aβ accumulation[47]. These findings suggest that cerebrovascular disruption is influenced by lifestyle and may act independently or synergistically with Aβ formation to drive AD pathology, which is further exacerbated by genetic predisposition and epigenetic (environmental) risk factors[47].

Maintaining BBB integrity is therefore critical for regulating the chemical composition of brain fluid. Breakdown of the BBB permits entry of toxic blood-derived molecules, peripheral immune cells, and pathogens, triggering further neuroinflammation and initiating neurodegeneration[47]. Evidence implicates peripheral inflammation as another contributor to AD development[48]. Peripheral immune cells such as neutrophils, T lymphocytes, B lymphocytes, and NK cells can infiltrate the brain through a compromised BBB and release inflammatory cytokines, affecting glial cell behavior[48].

Although clinical evidence linking systemic inflammation and AD risk remains limited and sometimes controversial, several observational studies indicate that elevated peripheral inflammatory markers are associated with increased risk of AD dementia, suggesting a positive correlation between systemic inflammation and neurodegeneration[49].

4. Discussion

4.1 NEUROINFLAMMATION IS AN AMPLIFIER AND A DOWNSTREAM CONSEQUENCE OF ALZHEIMER'S DISEASE.

Prior research shows that Alzheimer's disease (AD) is primarily defined by the accumulation of beta-amyloid plaques and neurofibrillary tau tangles, which impair synaptic function, disrupt neuronal signaling, and drive cognitive decline[3,10]. Prior research also shows that microglia and astrocytes initially serve protective roles, clearing plaques, maintaining synaptic homeostasis, supporting blood-brain barrier (BBB) integrity, and modulating neuroinflammatory responses[2]. However, these glial cells eventually become over-activated, shifting toward pro-inflammatory phenotypes that exacerbate neuronal injury through cytokine release, reactive oxygen species, and impaired synaptic pruning[2,40,44].

Our analysis suggests that neuroinflammation is not merely a downstream consequence of protein aggregation but a dynamic contributor to disease progression. Chronic microglial activation, including disease-associated microglia (DAM) and TREM2 dysfunction, reduces the phagocytic clearance of plaques, perpetuating extracellular plaque accumulation and reinforcing neurotoxic signaling pathways[34,36,37]. At the synapse, soluble Aβ

oligomers disrupt neurotransmission and trigger maladaptive microglial responses, including excessive synaptic pruning, which directly correlates with memory loss and cognitive deficits[20,40]. These events suggest that microglial dysfunction may act not only as a downstream effect of Aβ deposition but also as a driver of early neurodegeneration. Additionally, prior research demonstrates that astrocytes play a complementary role in maintaining neuronal metabolism, glutathione levels, and BBB function[2]. Reactive astrocytes can adopt either neuroprotective (A2) or neurotoxic (A1) phenotypes, with A1 astrocytes releasing pro-inflammatory cytokines and contributing to neuronal apoptosis[1,44]. In AD, the predominance of A1 astrocytes, coupled with glutathione depletion and oxidative stress, suggests a loss of neuroprotective capacity, amplifying both neuronal dysfunction and microglial activation[45,46].

Furthermore, our analysis suggests that the interplay between microglia and astrocytes forms a neuroinflammatory network that both responds to and drives plaque/tau pathology. Activation of NLRP3 inflammasomes in microglia and astrocytes by plaque oligomers and tau aggregates provides a molecular mechanism linking abnormal protein aggregation to chronic inflammation, while promoting the release of IL-1β and other pro-inflammatory cytokines that exacerbate synaptic loss[11,38]. This dual role of glial cells, protective under physiological conditions but detrimental when chronically activated, supports the concept that neuroinflammation is both an amplifier and a consequence of AD pathomechanism.

Vascular and BBB dysfunction also play a critical role in disease progression. Disruption of the BBB allows peripheral immune cells, blood-derived toxins, and pathogens to enter the CNS, further exacerbating glial activation and neuroinflammation[47,48]. Evidence also shows that cerebrovascular changes can precede detectable amyloid deposition and hippocampal atrophy, suggesting that BBB breakdown may act as an early contributor rather than a mere consequence of neuronal injury[47].

4.2 THERAPEUTIC IMPLICATIONS

Understanding glial dysfunction and blood–brain barrier (BBB) disruption provides a critical framework for developing novel therapeutic interventions in Alzheimer's disease (AD). Glial cells, including microglia and astrocytes, play essential roles in maintaining neuronal homeostasis, modulating immune responses, and clearing toxic protein aggregates. Dysfunction in these cells contributes to chronic neuroinflammation, oxidative stress, and impaired clearance of amyloid-β and tau, all of which exacerbate neurodegenerative cascades. Enhancing microglial phagocytosis through TREM2 signaling, inhibiting NLRP3 inflammasome activation, and restoring astrocytic antioxidant capacity via NRF2 activation or glutathione analogs represent promising glial-targeted strategies to counteract these pathological processes[52].

In parallel, maintaining BBB integrity and limiting peripheral immune cell infiltration may reduce neuroimmune activation and prevent the amplification of central inflammation. Strategies that stabilize endothelial and pericyte function can help preserve selective barrier properties, thereby mitigating the deleterious effects of systemic inflammatory mediators on the CNS. Collectively, these approaches highlight neuroinflammation as a critical and complementary therapeutic target alongside traditional amyloid- and tau-focused interventions (Table 1), emphasizing the importance of a multi-faceted approach that addresses both central and systemic contributors to disease progression.

Table 1: Therapeutic strategies targeting neuroinflammation.

Target	Mechanism	Expected Effect	Reference
Microglia/TREM2	Enhance phagocytic activity	Increase Aβ clearance	[2]
NLRP3 inflammasome	Inhibit inflammasome activation	Reduce pro-inflammatory cytokine release	[17]
Astrocytes/NRF2	Boost antioxidant response	Attenuate oxidative stress	[29]
BBB integrity	Stabilize endothelial and pericyte function	Limit peripheral immune cell infiltration	[39]

Our analysis suggests that integrating glial-targeted interventions with systemic anti-inflammatory approaches offers a multi-pronged therapeutic strategy for AD. By restoring microglial and astrocytic homeostasis, enhancing clearance of toxic proteins, reducing chronic neuroinflammation, and maintaining BBB integrity, it may be possible to slow or prevent downstream neurodegenerative

cascades, preserve synaptic function, and maintain cognitive performance. This integrated approach acknowledges the interconnected nature of central and peripheral immune pathways and underscores the potential of integrated therapies that address multiple aspects of disease pathology simultaneously.

In conclusion, while amyloid and tau accumulation remain defining pathological features of AD, growing evidence supports neuroinflammation as both an amplifier and a consequence of disease progression. Targeting glial function, maintaining BBB integrity, and modulating chronic inflammatory pathways may represent critical strategies for slowing or preventing cognitive decline. Incorporating these mechanisms into therapeutic development and mechanistic models of AD emphasizes the need for comprehensive approaches that go beyond traditional amyloid and tau paradigms. Such strategies may improve the efficacy of future disease-modifying interventions.

5. Conclusion

Alzheimer's disease is a multifactorial neurodegenerative disorder in which beta-amyloid plaques, tau tangles, glial dysfunction, neuroinflammation, and cerebrovascular pathology interact to drive cognitive decline. Evidence indicates that glial cells, particularly microglia and astrocytes, transition from protective to pro-inflammatory phenotypes, exacerbating synaptic loss, neuronal death, and blood-brain barrier dysfunction. Current therapies targeting plaques and tau have shown limited efficacy, highlighting the need to integrate glial-mediated neuroinflammation into disease models.

Maintaining or restoring microglial and astrocytic function offers a potential avenue to delay disease progression, complementing efforts to reduce amyloid and tau pathology. Future research should elucidate the molecular triggers of glial dysfunction, the mechanisms underlying BBB breakdown, and the interplay between systemic inflammation and central pathology. Addressing these gaps may provide novel strategies to mitigate cognitive decline and improve patient outcomes in Alzheimer's disease.

Evidence suggests that neuroinflammation may not only follow plaque and tau accumulation but also actively drive disease progression. The persistent pro-inflammatory environment contributes directly to neuronal and synaptic damage, making neuroinflammation a rational and critical therapeutic target. We argue that, whether neuroinflammation functions as an amplifier or a consequence, targeting inflammatory pathways may offer a promising strategy to slow or inhibit AD progression and associated cognitive decline.

Conflict of Interest Statement:

None.

Funding Statement:

None.

Acknowledgements:

None.

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