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Neuroinflammatory mechanisms and immunomodulatory therapies in Alzheimer's disease

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Abstract. Alzheimer's Disease (AD) is a multifactorial neurodegenerative disorder affecting over 55 million individuals worldwide, characterised by Amyloid beta (Aβ) plaques, neurofibrillary tangles, and sustained neuroinflammation. While amyloid- and tau-targeted therapies have dominated therapeutic research, their limited clinical efficacy has intensified focus on neuroinflammation as a central and modifiable disease mechanism. This review synthesises current understanding of neuroinflammatory pathogenesis in AD, with emphasis on Microglial polarisation (M1/M2), Disease-Associated Microglia (DAM), TREM2 signalling, and reactive astrocyte conversion. This paper further evaluates pharmacological strategies targeting these pathways, including cytokine inhibitors (TNF-α and IL-6 blockade), microglial modulators (CSF-1R inhibitors, TREM2 agonistic antibodies), and emerging innate immune targets (cGAS-STING pathway inhibitors, and S-palmitoylation inhibitors). Despite strong preclinical rationale, clinical translation has been impeded by Blood-Brain Barrier (BBB) penetration challenges, intervention timing, peripheral immunosuppression risks, and the biological redundancy of neuroimmune networks. Future therapeutic success will likely require combination approaches, CNS-targeted delivery systems, and biomarker-guided patient stratification to fully exploit the therapeutic potential of neuroinflammation-directed strategies in AD.

Keywords: Alzheimer's disease, neuroinflammation, microglia, immunomodulatory therapy

1. Introduction

Alzheimer's Disease (AD) is the leading cause of dementia, accounting for approximately 60–70% of cases worldwide and affecting more than 55 million individuals globally [1]. With the rapid expansion of ageing populations, AD has emerged as a major contributor to morbidity and mortality, especially in developed countries [1]. Coupled with progressive cognitive decline and functional impairment, AD represents a growing global health concern.

Neuropathologically, AD is characterised by the extracellular accumulation of Amyloid beta (Aβ) plaques and intracellular deposits of Neurofibrillary Tangles (NFTs) composed of hyperphosphorylated tau proteins, as well as brain atrophy and neuroinflammation within the Central Nervous System (CNS) [2, 3]. Although Aβ plaques and tau have long been established as the primary pathological drivers of AD, increasing evidence indicates that additional co-pathogenic mechanisms play critical roles in disease initiation and progression.

AD is now widely recognised as a multifactorial disorder involving oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity, and sustained neuroinflammation. Importantly, the limited clinical

efficacy of therapies targeting Aβ and tau has intensified interest in alternative and complementary pathogenic pathways, particularly neuroinflammatory mechanisms [4].

Neuroinflammation was first described by Alois Alzheimer, who observed glial abnormalities surrounding amyloid plaques; however, it was historically regarded as a secondary or epiphenomenal feature of the disease [2]. Recent studies have redefined neuroinflammation as a dynamic, stage-dependent process with both protective and detrimental roles.

In early AD, glial activation can facilitate Aβ clearance and initiate antioxidant responses to mitigate reactive oxygen species. As disease progresses, chronic exposure to misfolded proteins and oxidative stress drives sustained activation of CNS-resident immune cells, particularly microglia, leading to excessive production of pro-inflammatory cytokines, synaptic dysfunction, and neuronal loss [5].

In this review, we summarise the current understanding of neuroinflammatory mechanisms in AD, focusing on key cellular and molecular interactions that contribute to inflammatory pathogenesis. We further evaluate pharmacological strategies targeting neuroinflammation, including both approved therapies and investigational agents, highlighting their mechanisms of action, clinical outcomes, and translational challenges.

2. Methods

2.1. Literature search strategy

A comprehensive literature search was conducted between October 2025 and November 2025 to identify studies published from 2015 onward. The databases used included PubMed, Google Scholar, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov. Search terms included Alzheimer's disease, Alzheimer dementia, astrocytes, amyloid plaque, Amyloid-beta (Aβ), Neurofibrillary Tangles (NFTs), microglia, neuroinflammatory disease, gliosis, cytokines, chemokines, inflammasomes, drug therapy, pharmaceuticals, drugs, anti-inflammatory agents, clinical trials, and randomised control trials. Boolean operators ("AND", "OR") were applied to refine search queries and identify relevant mechanistic and therapeutic studies. This framework (Table 1) was designed to specifically prioritize high-quality, empirically validated pharmacological interventions targeting neuroinflammatory cascades in Alzheimer's disease.

2.2. Inclusion and exclusion criteria

Table 1. Eligibility criteria for study selection.

Inclusion Criteria	Exclusion Criteria	Reasoning
English	Other languages	English is the primary language employed in scientific literature, and this paper is written in English
Human participants with AD or in vivo/in vitro models of AD	Other diseases without AD comparator or using suboptimal AD models	The focus of this paper is solely on AD pathology
Neuroinflammation mechanisms in the context of AD	Papers that are mechanistically irrelevant to NI in AD	Only complementary neuroinflammation pathways that are relevant to AD are preferred

Table 1. Continued

Pharmaceutical therapies for neuroinflammation, their efficacy, outcomes and indications	Non-pharmacological interventions (such as exercise or diet)	This review focuses on pharmacological therapies
Original research with concrete data and conclusions, systematic reviews and meta-analyses (used only for background information)	Preliminary data that yield unclear conclusions and papers that do not provide data (case reports, non-systematic reviews)	Ensures inclusion of high-quality primary data

Eligibility criteria applied during the title/abstract and full-text screening stages. Studies were required to meet all inclusion criteria to be selected for data extraction and synthesis.

3. Results

3.1. Neuroinflammatory mechanisms in Alzheimer's disease

Neuroinflammation in AD is initially triggered by Aβ deposition and mediated by glial cells, particularly microglia and astrocytes, through a process commonly referred to as gliosis [4] (Figure 1). Resting (M0) microglia become activated upon binding soluble Aβ oligomers, fibrils, and Amyloid Precursor Protein (APP) via multiple receptors, including class A and B scavenger receptors, CD36, Toll-Like Receptors (TLR2 and TLR4) with the co-receptor CD14, and the Receptor for Advanced Glycation End products (RAGE) [4, 6].

Classically activated M1 microglia produce pro-inflammatory cytokines such as Tumour Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6), as well as reactive oxygen and nitrogen species, including nitric oxide and superoxide [6, 7]. These responses activate downstream inflammatory pathways, including NF-κB signalling, inducible Nitric Oxide Synthase (iNOS), and complement cascades, while simultaneously suppressing anti-inflammatory microglial phenotypes.

Microglial activation has historically been categorised into pro-inflammatory M1 and anti-inflammatory M2 phenotypes. M2 microglia can be induced by cytokines such as IL-4 and IL-13 or through deactivation pathways mediated by IL-10 and Transforming Growth Factor-β (TGF-β) [6]. In AD, M2 microglia localise near Aβ plaques and contribute to plaque clearance through enhanced phagocytosis. These cells also promote tissue repair by releasing Insulin-like Growth Factor-1 (IGF-1) and expressing genes such as Arg1 and Chil3 [4, 7].

However, recent transcriptomic analyses suggest that microglial activation states exist along a continuum rather than as discrete M1/M2 phenotypes. Disease-Associated Microglia (DAM) represent a distinct microglial state closely linked to AD pathology [7]. DAM activation is largely dependent on Triggering Receptors Expressed on Myeloid cells 2 (TREM2), with variants such as R47H and R62H conferring increased AD risk [8]. Binding to TREM2 enhances microglial proliferation, lipid metabolism, and phagocytic capacity, thereby enhancing plaque clearance [8, 9]. Conversely, loss-of-function mutations in TREM2 impair these protective responses and exacerbate inflammatory signalling, underscoring TREM2 as both a genetic risk factor and a potential therapeutic target in AD [9].

Astrocytes also contribute to neuroinflammatory processes in AD by internalising and degrading Aβ [4]. However, chronic neuroinflammation promotes astrocytic conversion into neurotoxic A1 reactive astrocytes, driven by pro-inflammatory signals such as IL-1α, TNF-α, and complement components C1q and C3 released from M1 microglia [2, 10]. A1 astrocytes exhibit reduced Aβ-clearing capacity and secrete factors that induce

neuronal and oligodendrocyte death, thereby exacerbating neurodegeneration [10]. This maladaptive astrocyte–microglia feedback loop represents a key driver of chronic neuroinflammation in AD.

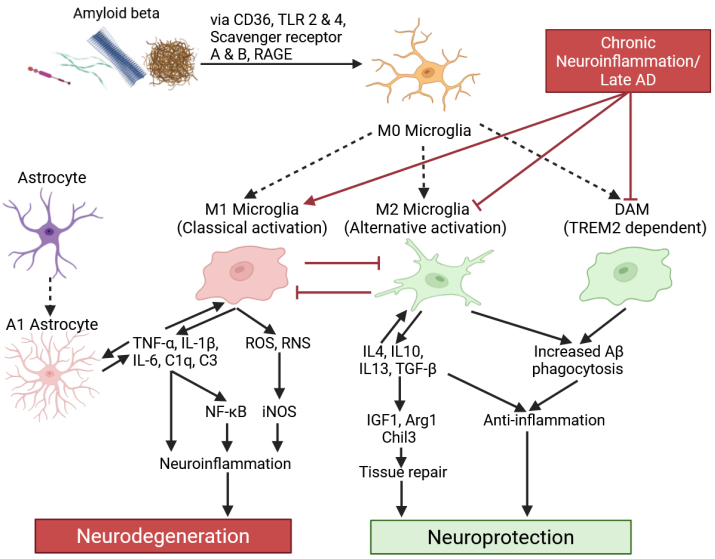

Figure 1. Glial induced neuroinflammation mechanism in AD

Aβ activates M0 microglia via CD36, TLR2/4, scavenger receptors A & B, and RAGE, driving their differentiation into M1 or M2 phenotypes, or DAM. M1 microglia release TNF-α, IL-1β, IL-6, C1q, and ROS/RNS, activating NF-κB and iNOS to drive neuroinflammation and neurodegeneration. M1-derived signals also convert resting astrocytes into neurotoxic A1 reactive astrocytes. M1 and M2 microglia mutually inhibit one another while promoting their respective phenotypic programmes. M2 microglia release IL-4, IL-10, IL-13, and TGF-β, promoting tissue repair via IGF-1, Arg1, and Chil3, while DAM enhances Aβ phagocytosis and anti-inflammatory responses, collectively driving neuroprotection. Chronic neuroinflammation perpetuates M1 dominance in late AD.

3.2. Pharmaceutical targeting strategies for neuroinflammation

Growing recognition of neuroinflammation as a major contributor to AD pathogenesis has stimulated the development of therapeutic strategies aimed at modulating inflammatory pathways. These approaches include cytokine inhibition, modulation of microglial activation states, and targeting innate immune signalling cascades.

3.2.1. Cytokine-based therapeutic strategies

Pro-inflammatory cytokines such as TNF-α and IL-6 are central mediators of chronic neuroinflammation in AD [6]. Accordingly, biologic inhibitors targeting these cytokines have been investigated as potential therapeutic interventions.

TNF-α inhibitors, including etanercept, infliximab, and adalimumab, originally developed for autoimmune diseases, have been evaluated for their ability to suppress CNS inflammation. However, clinical trials have yielded limited success, largely due to poor blood–brain barrier penetration and inconsistent effects on cognitive outcomes [10]. XPro1595 (pegipanermin), a dominant-negative soluble TNF inhibitor that selectively neutralises soluble TNF while sparing transmembrane TNF signalling, entered clinical trials based

on data suggesting attenuation of neuroinflammation and neuronal injury in AD mouse models that was superior to previous biologic TNF-α inhibitors [11].

However, results from the Phase II MINDful trial in 2025 revealed a statistically insignificant change in cognitive function when compared with a placebo [12]. Overall, TNF-α inhibitors suffer from poor Blood–Brain Barrier (BBB) penetration, requiring high systemic doses to achieve modest CNS exposure, and have not demonstrated robust cognitive benefit in late-stage trials. Plasma and Cerebrospinal Fluid (CSF) biomarker changes have been inconsistent, and peripheral immune suppression poses additional safety concerns in elderly AD populations [13]. Similarly, monoclonal antibodies targeting IL-6 signalling pathways have been explored for their ability to attenuate inflammatory cascades. Although preclinical studies demonstrated reductions in glial activation and inflammatory cytokine production, clinical evidence supporting their efficacy in AD remains limited [14].

Additionally, blockades of IL-6 receptors can paradoxically increase circulating IL-6 levels and may interfere with physiological immune responses [15]. Collectively, these findings suggest that broad cytokine inhibition may disrupt both protective and pathological immune responses, thereby limiting therapeutic benefits.

3.2.2. Microglia-modulating therapies

Given the central role of microglia in AD pathology, therapeutic strategies aimed at modulating microglial function have received increasing attention. One approach involves inhibition of the Colony-Stimulating Factor-1 Receptor (CSF1R) pathway, which regulates microglial survival and proliferation [16]. Small-molecule CSF1R inhibitors such as PLX3397 and PLX5622 have been shown to reduce microglial populations and attenuate plaque-associated inflammation in preclinical models [17].

However, complete microglial depletion may impair beneficial homeostatic functions, raising concerns regarding long-term therapeutic viability. More recently, therapeutic efforts have focused on enhancing protective microglial states. Agonistic antibodies targeting TREM2 aim to stimulate disease-associated microglial responses that promote Aβ clearance and tissue repair [18-20].

AL002, a humanised monoclonal antibody developed by Alector, demonstrated encouraging preclinical results, including increased microglial proliferation and reduced neuritic dystrophy in AD mouse models [21]. However, despite promising biomarker responses, the Phase II INVOKE-2 trial failed to meet its primary efficacy endpoint in early 2025, leading to discontinuation of development [22].

Another candidate, VHB937, has shown promising preclinical activity by enhancing TREM2 signalling, promoting protective microglial phenotypes, and reducing neuroinflammation in animal models [20]. A Phase II clinical trial evaluating VHB937 in early AD is currently ongoing and is expected to conclude in 2030 [23].

3.2.3. Innate immune pathway inhibitors

Recent studies have identified the cGAS–STING signalling pathway as an important mediator linking mitochondrial dysfunction, DNA damage, and inflammatory signalling in AD. Activation of cGAS by cytosolic DNA triggers STING-dependent interferon responses that promote chronic neuroinflammation [24]. Pharmacological inhibitors targeting cGAS–STING signalling, including small-molecule STING inhibitors such as H-151 and C-176, have demonstrated reductions in inflammatory markers and improvements in synaptic function in preclinical AD models [24–27]. However, because this pathway is essential for antiviral immunity, therapeutic inhibition must carefully balance anti-inflammatory benefits against potential immune suppression.

Another emerging target involves protein S-palmitoylation, a post-translational modification regulating the trafficking and stability of several proteins implicated in AD pathology, including APP and BACE1 [28-30]. Increased palmitoylation levels have been observed in AD models and patient brain tissue. Pharmacological

inhibition of palmitoylation enzymes such as zDHHC7 has been shown to reduce Aβ accumulation and improve cognitive performance in experimental models [30]. Although still in the early stages of investigation, targeting protein palmitoylation represents a novel approach for modulating inflammatory and amyloidogenic pathways in AD.

4. Mechanistic limitations underlying clinical failure and future directions

Although the mechanistic rationale for targeting neuroinflammation in AD is robust and supported by extensive preclinical investigation, clinical translation has been limited by several interconnected challenges. First, therapeutic timing remains a critical barrier, as neuroinflammatory processes are highly dynamic and evolve across disease stages; early innate immune responses may aid Aβ clearance and limit oxidative damage, whereas chronic glial cell activation in later stages drives synaptic dysfunction and neurodegeneration, making late intervention less effective or even detrimental [31, 32].

Furthermore, BBB dysfunction not only contributes to AD pathogenesis but also impairs CNS delivery of many therapeutic agents, particularly large biologics such as monoclonal antibodies and cytokine modulators [33, 34]. Moreover, a CNS-peripheral immune mismatch complicates immunomodulation, as peripheral immune modulation does not necessarily translate to effective regulation of CNS-resident microglia and astrocytes within the compartmentalised neuroimmune environment that characterises AD [31, 35].

Additionally, issues of model translatability undermine predictive validity; while transgenic animal models replicate aspects of amyloid deposition and immune activation, they fail to recapitulate the full heterogeneity, chronic progression, and CNS-peripheral immune interactions seen in human AD, leading to discrepancies between promising preclinical results and disappointing clinical outcomes [32, 35]. Finally, redundancy within inflammatory signalling networks limits the effectiveness of targeting individual cytokines or receptors. Neuroimmune pathways exhibit compensatory mechanisms and context-dependent functions, meaning that inhibition of a single pathway may not sufficiently reset the broader inflammatory landscape [31, 36].

Future therapeutic strategies will likely require precision immunomodulation that accounts for disease stage, cellular context, and patient-specific genetic factors. Combining immunomodulatory agents with therapies targeting amyloid, tau, and metabolic dysfunction may provide synergistic effects. Advances in biomarker development and single-cell profiling of human brain tissue will further facilitate patient stratification and the identification of optimal therapeutic windows.

5. Conclusion

This review synthesizes the current evidence establishing neuroinflammation as a central and dynamic driver of Alzheimer's disease pathogenesis, mediated through gliosis via a continuum of Microglial states (M1/M2, DAM), TREM2-dependent signaling, and maladaptive A1 astrocytic conversion. The evaluated pharmacological landscape, encompassing cytokine inhibitors, CSF-1R modulators, TREM2 agonistic antibodies, and emerging cGAS-STING or palmitoylation inhibitors, demonstrates robust preclinical activity but has consistently struggled to translate into meaningful clinical cognitive benefit. Cumulative evidence indicates that broad or single-target suppression is insufficient; rather, the field must reconcile the protective versus pathogenic duality of neuroinflammation across disease stages. Translational hurdles, including CNS bioavailability across BBB, immune redundancy, and model limitations, are substantial, yet they do not invalidate the therapeutic premise. Looking forward, the reviewed literature supports a strategic reorientation towards precision immunomodulation: combination regimens that pair neuroimmune agents with anti-amyloid or anti-tau therapies, advanced BBB-penetrant delivery platforms, and biomarker-guided treatment

personalization (e.g., TREM2 genotype, CSF glial signatures). While the path to regulatory approval remains challenging, the integration of immunomodulatory strategies into multi-target AD regimens represents a scientifically grounded and clinically necessary evolution in the pursuit of disease-modifying therapies.

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