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Interleukins in Alzheimer's Disease: Mechanisms, Biomarkers, and Therapies

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Abstract. Alzheimer's disease (AD) is a complex neurodegenerative disorder in which long-term brain inflammation interacts with amyloid-β (Aβ) and tau abnormalities, leading to synaptic damage and cognitive decline. Interleukins are important in this process because they connect glial activation, harmful protein accumulation, and neuronal injury. Although recent studies have identified inflammatory pathways and blood cytokine patterns associated with AD, their roles at different stages and their clinical value remain unclear. This review discusses interleukin-related inflammation, inflammatory biomarkers, and developing immune-regulating treatments for AD. It describes how microglia change from protective cells that clear harmful substances into overactivated cells that may increase damage; the NLRP3–caspase-1 pathway is also presented as a link between Aβ or tau stress and IL-1β/IL-18 release. IL-6, IL-17A, IL-7, and IL-15 are examined within wider immune networks, as combined inflammatory patterns may be more closely related to cognition and nerve fiber injury than single cytokines. Treatments involving NLRP3, TREM2, CD33, TNF-related pathways, natural products, diet, gut microbiota, and lifestyle are also reviewed; combination therapy may be suitable because AD varies among patients. Current findings support a move from general anti-inflammatory treatment toward stage-based, biomarker-guided immune regulation, which may reduce cytokine damage while maintaining microglial clearance and repair. However, causal links, suitable treatment periods, and reliable brain-specific inflammatory markers remain uncertain; future studies should use long-term multimodal cohorts, human-relevant models, and grouped clinical trials combining cytokine patterns with Aβ, tau, NfL, GFAP, genetics, and neuroinflammatory imaging.

Keywords: Alzheimer's disease, Neuroinflammation, Interleukins, Microglia, NLRP3 inflammasome

1. Introduction

Alzheimer's disease (AD) is the main cause of dementia among older adults, and its clinical features include progressive memory loss, cognitive decline, and reduced ability to perform daily activities [1]. For many years, AD research has mainly focused on two pathological features: extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles formed by hyperphosphorylated tau [2]. These abnormal protein changes remain important for AD diagnosis and treatment development,

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but the limited clinical benefits of several amyloid-targeting treatments have led to a broader understanding of AD pathogenesis [3]. Growing evidence indicates that AD should not be viewed only as a disease of protein accumulation; instead, it is a complex degenerative process involving glial cell dysfunction, oxidative stress, mitochondrial damage, poor protein clearance, vascular changes, and long-term neuroinflammation [2].

Neuroinflammation has become an important area of AD research because it links common protein abnormalities with continuing neuronal damage [4]. As resident immune cells of the central nervous system, microglia support immune monitoring, synaptic remodeling, and the removal of cellular waste; in early AD, these cells may provide some protection by clearing Aβ and limiting the spread of harmful aggregates [5]. However, continued exposure to Aβ oligomers, abnormal tau, damaged neurons, and metabolic stress may push microglia into long-term activation [6]. Recent models show that prolonged Aβ stimulation may change microglia from cells mainly responsible for clearance into excessively activated inflammatory cells; these cells release cytokines and contribute to oxidative damage and neuronal injury [5]. Astrocytes may further increase this response by activating complement, releasing cytokines, damaging the blood-brain barrier, and reducing metabolic support [7].

Among inflammatory factors, interleukins (ILs) are closely related to AD progression [1]. IL-1β and IL-18 are mainly produced after activation of the NLRP3 inflammasome–caspase-1 pathway; Aβ aggregates, lysosomal injury, mitochondrial dysfunction, and reactive oxygen species can activate this pathway [6]. These cytokines can increase inflammation and contribute to pyroptosis, tau-related changes, and synaptic damage [3]. IL-6 is usually linked to long-term inflammation and neurodegenerative changes; meanwhile, IL-17A, IL-7, and IL-15 indicate that T-cell-related immune responses may also participate in AD-related cognitive decline [8]. Recent plasma inflammatory studies show that AD-related inflammation does not involve an equal increase in all cytokines; some inflammatory groups, including ILs and TNF-α, appear more closely related to poorer cognitive performance, while other factors may affect cognition indirectly through neuronal degeneration, as reflected by neurofilament light chain levels. These findings suggest that IL-related inflammation in AD works as a varied and connected network with clinical importance [8].

Current approaches include NLRP3 inflammasome inhibitors, regulation of microglial receptors such as TREM2 and CD33, control of TNF-related pathways, natural anti-inflammatory compounds, diet- and microbiota-based methods, and combinations with anti-amyloid treatments [5]. However, inflammation changes across AD stages; excessive suppression may weaken protective clearance, while inadequate control may allow long-term cytokine damage to continue [6]. Therefore, this review summarizes the role of IL-related neuroinflammation in AD development, discusses its possible use as a biomarker network, and reviews recent treatment progress and remaining challenges in targeted immune regulation.

2. Interleukin-mediated neuroinflammation in AD pathogenesis

2.1. Microglial activation and the transition from protection to neurotoxicity

Microglia continuously monitor the central nervous system, and they also participate in removing cellular waste, reshaping synapses, and repairing damaged tissue. In Alzheimer's disease (AD), however, microglial behavior gradually changes as amyloid-β (Aβ), abnormal tau, damaged nerve fibers, and metabolic stress continue to accumulate. During the early stage of amyloid deposition, microglia move toward plaques and take up Aβ; they also change loose deposits into more compact structures, and this barrier-like response may reduce the exposure of nearby nerve fibers to soluble

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Aβ. Recent experimental findings also indicate that microglia in their normal state may participate in the early formation of plaques, which means that their early effects are not always protective; therefore, microglial activity is better understood as a process that changes over time rather than a simple change between two fixed states [6].

Continued stimulation can change microglial gene expression, lipid metabolism, mitochondrial activity, and lysosomal function. Microglia associated with disease commonly show lower expression of genes related to normal cell functions, while genes involved in phagocytosis and lipid handling show increased expression. Microglial survival, metabolic adjustment, movement toward plaques, and interaction with plaques are supported by TREM2; by contrast, CD33 reduces phagocytic activity. However, these pathways do not produce the same effects at every stage, because TREM2-related responses may help contain plaques during one stage but may occur together with inflammatory or aged cell states after long-term activation [7]. As AD progresses, cytokines may still be released by microglia, although these cells become less effective at removing Aβ and cellular waste; the continued production of IL-1β, IL-6, IL-18, TNF-α, reactive oxygen species, and complement components may damage synapses and maintain glial activation. For this reason, treatment should not broadly suppress all microglial activity; instead, it should preserve the clearance and tissue-supporting roles of microglia while controlling long-term inflammatory signals [3].

2.2. NLRP3 inflammasome and IL-1β/IL-18 signaling

The NLRP3 inflammasome connects harmful protein stress with the release of interleukins. Its activation usually involves two main steps; first, an NF-κB-related priming signal increases the expression of NLRP3 and pro-IL-1β, then a second signal is produced through potassium loss, lysosomal rupture, cathepsin release, mitochondrial reactive oxygen species, or oxidized mitochondrial DNA. After fibrillar Aβ is taken up by microglia, several of these changes may occur at the same time [9]. Once activated, NLRP3 recruits the adaptor protein ASC and pro-caspase-1; caspase-1 then changes pro-IL-1β and pro-IL-18 into their mature forms and breaks down gasdermin D, which allows cytokines to be released and may cause pyroptotic cell death during continued activation. IL-1β may weaken synaptic plasticity and activate enzymes related to tau phosphorylation, while IL-18 may strengthen communication between innate and adaptive immune cells; therefore, NLRP3 signaling is involved in the disease process itself rather than acting only as a late response to neuronal injury [6].

Inflammasome activation may also worsen abnormal protein changes. Extracellular ASC specks released from activated microglia can bind to Aβ and promote its aggregation; at the same time, abnormal tau may activate NLRP3, while cytokines produced through inflammasome activation can increase tau phosphorylation and spread. This two-way relationship provides a possible explanation for how a local inflammatory response gradually becomes self-sustaining [3]. However, much of the direct evidence about this mechanism has come from cell and animal studies; human research supports the involvement of this pathway, but it has not yet identified the most suitable disease stage, patient group, or level of inhibition needed to produce clinical benefits. Overall, the NLRP3 inflammasome acts as an important center in AD-related inflammation; it changes danger signals from Aβ and tau into IL-1β and IL-18 production, and these cytokines maintain microglial activation, increase tau phosphorylation and spread, and connect innate immune responses with possible adaptive immune activity. These functions make inflammasome signaling a possible treatment target within the wider inflammatory network.

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2.3. ILs in chronic inflammation and cognitive decline

Inflammation related to AD is not limited to cytokines produced by inflammasomes. Among the wider interleukin family, IL-6, IL-17A, IL-7, and IL-15 are discussed here because they represent different immune processes; IL-6 is related to long-term glial activation, while IL-17A, IL-7, and IL-15 are more closely connected with adaptive immunity, and recent clinical studies have repeatedly linked these interleukins with cognitive decline. IL-6 is produced by microglia, astrocytes, endothelial cells, and peripheral white blood cells; continued IL-6 signaling may activate JAK/STAT3 and related pathways, maintain glial reactivity, and interfere with synaptic function. However, short-term IL-6 activity also contributes to immune defense and tissue repair; its effect therefore depends on the cell producing it, its concentration, receptor conditions, and disease stage [7].

The Bio-Hermes study provides clinical evidence for a wider interleukin network. Among amyloid-positive participants with AD or mild cognitive impairment (MCI), a plasma inflammatory component containing IL-17A, IL-7, IL-15, TNF-α, and interferon-related signals was higher than that in controls; this component was also related to poorer cognitive performance [8]. IL-17A is associated with Th17-cell activity and may increase inflammation in endothelial and glial cells; IL-7 supports T-cell survival, while IL-15 regulates natural killer cells and memory T cells. The coordinated changes in these cytokines are more reasonably understood as a combined state of cell-related immune activation, rather than proof that a single cytokine independently causes cognitive decline [8]. This difference is important because cytokines function through connected networks; a small change in one cytokine may have limited value, whereas changes across several inflammatory factors may represent a more consistent immune state. Current evidence therefore supports the analysis of groups of inflammatory factors, but it does not confirm IL-17A, IL-7, or IL-15 as independent diagnostic markers or established treatment targets for AD.

2.4. Crosstalk among Aβ, tau, glial cells, and interleukin networks

Aβ, tau, glial cells, and interleukins interact through several connected feedback processes. Aβ activates receptors that recognize harmful signals, as well as NF-κB/NLRP3 signaling; this response increases the production of IL-1β, IL-6, IL-18, and TNF-α. These inflammatory factors may weaken lysosomal clearance, increase oxidative and mitochondrial stress, and promote amyloid-related protein processing, which then produces additional signals that activate microglia [9].

Activated microglia also affect astrocytes through IL-1α, TNF-α, and complement C1q. Reactive astrocytes may gradually lose some of their normal functions, including glutamate uptake, metabolic support, potassium balance, and maintenance of the blood-brain barrier; meanwhile, these cells may produce more cytokines and complement components. Tau abnormalities are also included in this network, because inflammatory signaling increases tau phosphorylation, while extracellular vesicles released by microglia may help tau spread; damaged neurons then release danger-related molecules, and glial cells are activated again [7]. A small postmortem study reported greater glial activation and a higher synaptic tau burden in individuals with dementia than in cognitively resilient individuals who had similar plaque and tangle levels. However, this evidence came from a conference report with a small sample, so it should be treated as support for a possible explanation rather than as a final conclusion [10]. Together, these interactions form a multidirectional process; Aβ and tau increase interleukin production by activating glial cells, while interleukins further promote abnormal protein changes and neuronal injury. In this network, interleukins are not only later markers of inflammation; they also act as active factors that connect protein accumulation, glial dysfunction,

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and synaptic damage, creating a disease cycle that continues to strengthen itself. Overall, neuroinflammation can be understood as an amplifying process that links abnormal protein changes with synaptic and neuronal injury.

3. ILs as biomarkers and inflammatory signatures

3.1. Peripheral cytokine profiles in AD and MCI

Peripheral cytokines have potential value as biomarkers because blood samples can be collected repeatedly with limited physical burden. However, their interpretation remains difficult because cytokine levels may change with age, infection, vascular and metabolic diseases, medication use, sleep conditions, and sample handling before testing; these differences may partly explain why studies examining individual factors, such as IL-1β and IL-6, have produced inconsistent findings. Profiles containing several cytokines may provide more useful information because they reflect coordinated immune activity rather than a temporary change in one cytokine [8].

The Bio-Hermes analysis initially included 349 participants, and 337 remained after multivariable outliers were removed; the final group included 171 participants with amyloid-positive AD or MCI and 166 controls. Principal component analysis identified two inflammatory components, which together explained about 34% of the differences in cytokine levels. Component 1 mainly included CCL11, CXCL10, macrophage migration inhibitory factor, IL-16, and TNF receptor II; Component 2 was mainly formed by IL-17A, TNF-α, IL-7, IL-15, and interferon-related signals. Only Component 2 was significantly higher in the AD/MCI group, suggesting that AD is related to certain inflammatory patterns rather than an equal increase in all circulating cytokines [8]. Component 2 also differed among self-reported ethnic groups, although the non-White subgroups were small; this result should not be understood as evidence of fixed biological differences between racial groups. Genetic background, environmental exposure, vascular risk, long-term illness, medication use, and social conditions may all affect basic inflammatory levels; therefore, larger and more diverse groups are needed to confirm this finding [8].

3.2. Links between IL-related inflammation, cognition, and neurodegeneration

The two Bio-Hermes components showed different clinical associations. Component 2 was associated with lower Mini-Mental State Examination scores, and the relationship remained significant after adjustment for age, sex, neurofilament light chain (NfL), phosphorylated tau 217, and glial fibrillary acidic protein. Component 1 was associated with NfL but not directly with cognition. In the researchers' reduced path model, the relationship between Component 1 and cognitive performance was indirectly mediated by NfL [8]. These results suggest that different inflammatory patterns may relate to clinical impairment through partly distinct routes. Component 2, enriched in T-cell-related cytokines (IL-17A, IL-7, IL-15) and TNF-α, may reflect adaptive immune activation that directly impairs synaptic plasticity and network efficiency through receptor-mediated signaling at the neurovascular unit. Component 1, associated with chemokines and soluble TNF receptors, may instead mark a chronic state in which blood-brain barrier disruption and sustained microglial metabolic stress lead to progressive axonal degeneration, indirectly affecting cognition through structural damage reflected by NfL elevation. One profile may track immune processes associated with synaptic or network dysfunction, whereas another may accompany cumulative neuroaxonal injury. However, mediation analysis of cross-sectional data does not establish temporal sequence or biological causality. It remains possible that inflammation precedes

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neuronal injury, arises in response to neurodegeneration, or participates in a bidirectional process. Neither component showed a significant association with plasma p-tau217 or GFAP. This does not demonstrate independence from tau pathology or astrocytic activation. Peripheral cytokines and central pathological events occupy different biological compartments and may evolve over different timescales. Regional interactions visible with cerebrospinal fluid analysis or molecular imaging may therefore be absent from a single blood measurement [8].

3.3. Limitations of peripheral inflammatory markers

Peripheral inflammatory markers lack specificity for AD. Cytokine concentrations may be altered by infection, obesity, diabetes, cardiovascular disease, psychological stress, sleep disruption, and medication. Blood cytokines can influence the brain through endothelial signaling, blood-brain barrier changes, and immune-cell trafficking, but their circulating concentrations do not directly measure cytokine production within the central nervous system. Analytical limitations are equally important. Many cytokines circulate near assay detection limits, and results are sensitive to collection time, processing delay, storage, freeze-thaw cycles, and assay platform. In Bio-Hermes, 28 of 65 analytes were excluded because more than 75% of values were missing; missing observations among retained analytes were statistically imputed. These procedures were methodologically defensible, but they show how measurement constraints can influence the inflammatory signatures produced by multivariate analysis [8]. The cross-sectional design of most studies further limits clinical interpretation. Longitudinal cohorts should combine repeated cytokine measurements with amyloid and tau biomarkers, NfL, GFAP, cerebrospinal fluid markers, and neuroinflammatory imaging. Peripheral interleukin panels are therefore unlikely to replace established AD biomarkers. Their more plausible near-term role is patient stratification: identifying immune-active subgroups, enriching immunomodulatory trials, and monitoring pharmacodynamic responses. This application is consistent with the heterogeneous and stage-dependent biology of neuroinflammation [8].

4. Therapeutic advances targeting IL-related neuroinflammation

4.1. NLRP3 inflammasome inhibitors and IL-1β/IL-18 suppression

The NLRP3 inflammasome lies at a critical intersection between proteotoxic stress and inflammatory cytokine release. Following the uptake of Aβ, microglial lysosomal damage, mitochondrial dysfunction, reactive oxygen species accumulation, and potassium efflux can promote NLRP3 assembly. The activated inflammasome subsequently cleaves pro-caspase-1, leading to the maturation of IL-1β and IL-18 and, under sustained stimulation, gasdermin D-mediated pyroptosis. Inhibiting this pathway may therefore reduce cytokine release while interrupting the positive feedback loop connecting Aβ accumulation, tau pathology, and persistent microglial activation. In cellular and animal models of AD, genetic or pharmacological inhibition of NLRP3 has reduced microgliosis and Aβ deposition, enhanced microglial clearance, and improved cognitive performance [2]. MCC950 is among the most extensively studied selective NLRP3 inhibitors. In preclinical AD models, it suppresses IL-1β maturation and reduces amyloid-related pathology; nevertheless, its long-term safety, brain penetration, and optimal therapeutic window in humans remain uncertain [5]. Downstream approaches, including caspase-1 inhibition, IL-1 receptor antagonism, and blockade of gasdermin D-mediated pyroptosis, may provide alternative means of limiting inflammatory amplification. However, NLRP3 also contributes to host defense and the

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recognition of cellular damage. Continuous systemic inhibition could therefore compromise necessary innate immune functions. Brain-selective, partial, or disease-stage-specific modulation may be more appropriate than complete and prolonged suppression.

4.2. Microglia-targeted approaches: TREM2, CD33, and immune checkpoint modulation

Compared with broad anti-inflammatory treatment, methods aimed at microglial receptors may control harmful inflammation while preserving waste removal and tissue repair. TREM2 recognizes lipids, dying cells, and molecules released after damage; through the DAP12/SYK and PI3K–AKT pathways, it supports microglial survival, metabolic adjustment, lysosomal function, and movement toward Aβ plaques. In preclinical models, antibodies that activate TREM2 have increased microglial responses around plaques and reduced pathological changes; AL002 has also entered clinical evaluation, and early studies have shown target engagement and acceptable short-term tolerability, although lasting cognitive benefits remain unconfirmed [2].

However, TREM2 should not be treated as a molecular switch that is protective in every situation. During early amyloid accumulation, stronger TREM2 signaling may help compact plaques and maintain microglial metabolism; at later stages, continued stimulation of aged or metabolically exhausted microglia may increase antigen presentation and cytokine release. Therefore, the clinical effect of TREM2-targeted treatment may depend on treatment time, dose, genotype, and the existing condition of microglia, rather than receptor activation alone. CD33 is another possible target because its full-length form acts as an inhibitory immune checkpoint; through intracellular inhibitory motifs, CD33 recruits SHP-1 and SHP-2 phosphatases, then reduces signals needed for phagocytosis and Aβ clearance. Blocking CD33 or changing its splicing toward forms with weaker inhibitory effects may restore microglial clearance [5]. Neither TREM2 activation nor CD33 inhibition should increase microglial activity without control; a more suitable method would restore phagocytic, metabolic, and lysosomal functions while limiting continued NF-κB and NLRP3 signaling.

4.3. TNF-related and broader cytokine pathway regulation

TNF signaling shows why cytokine-targeted treatments need to consider receptor differences. Soluble TNF mainly activates inflammatory and cell-death pathways related to TNFR1; by contrast, transmembrane TNF and TNFR2 signaling may support immune control, neuronal survival, and tissue repair. Complete TNF neutralization could therefore reduce both harmful and protective functions; selectively blocking soluble TNF or TNFR1, while preserving TNFR2 signaling, may be a more suitable method. Although studies have reported benefits from TNF inhibition, clinical and observational results remain inconsistent, so a disease-modifying effect in AD has not been established [1].

Other targets include IL-6/JAK–STAT, IL-17-related signaling, and the IL-10–STAT3 pathway. Continued IL-6 signaling may increase glial reactivity and synaptic dysfunction, while blocking JAK/STAT signaling has reduced microglial activation in experimental models [5]. STAT3 activated by IL-10 can selectively bind to regulatory areas of inflammatory genes, reducing the transcription of Il1b, Tnf, Il6, and Nlrp3; this process is linked to lower binding of NF-κB and RNA polymerase II, changes in enhancer acetylation, and recruitment of factors that regulate chromatin. IL-10–STAT3 signaling may also increase genes involved in phagocytosis, lysosomal breakdown, and metabolic support [11].

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However, IL-10 does not always provide protection in amyloid-related disease. In some experimental conditions, excessive or poorly timed IL-10 signaling may weaken microglial clearance and increase Aβ accumulation [11]. These different findings show that cytokines cannot simply be divided into pro-inflammatory and anti-inflammatory groups; their effects vary according to cell source, receptor type, signaling period, disease conditions, and disease stage. Treatment development should therefore focus on regulating specific pathways and receptors, rather than broadly suppressing or increasing cytokines.

4.4. Natural products, nutrition, microbiota, and lifestyle interventions

Natural compounds have attracted interest because they can act simultaneously on several AD-related mechanisms. Curcumin, quercetin, apigenin, berberine, ginkgolides, and carnosic acid have been reported to regulate NF-κB, MAPK, NLRP3, Nrf2/HO-1, oxidative stress, autophagy, and microglial functional states. This multi-target activity is conceptually relevant to AD, in which protein aggregation, metabolic impairment, oxidative damage, and neuroinflammation reinforce one another [5]. However, most evidence remains preclinical. Poor water solubility, low oral bioavailability, rapid metabolism, limited blood–brain barrier penetration, variation in extract composition, and the absence of standardized dosing continue to restrict clinical translation [12]. Nanocarriers and prodrug approaches may improve stability and brain delivery, but their long-term safety, manufacturing reproducibility, and clinical advantages require further validation.

Nutrition and lifestyle interventions offer broader, although less pathway-specific, approaches to reducing inflammatory risk. Mediterranean, DASH, and MIND dietary patterns emphasize fruits, vegetables, whole grains, fish, unsaturated fats, and dietary fiber and have been associated with slower cognitive decline or reduced dementia risk [13]. Dietary fiber can be metabolized by intestinal bacteria into short-chain fatty acids, which help maintain intestinal barrier integrity and regulate peripheral and central immune responses. In contrast, gut microbial dysbiosis may increase the systemic availability of lipopolysaccharides and other inflammatory metabolites, promoting blood–brain barrier dysfunction and microglial activation [5]. Exercise, cognitive stimulation, social engagement, and management of vascular and metabolic risk factors may further complement these effects. Such interventions may reduce systemic inflammation, improve cerebral perfusion, and strengthen cognitive reserve. Nevertheless, they should be regarded as components of early prevention and multidomain risk management rather than substitutes for disease-modifying treatment, because current evidence does not demonstrate that they can reverse established AD pathology.

4.5. Combination therapy and precision immunomodulation

Because AD differs greatly among patients, one anti-inflammatory treatment is unlikely to benefit everyone or remain effective throughout the disease course. A more practical method may combine treatments acting on related disease processes; for example, anti-Aβ therapy may reduce harmful protein stimulation, selective NLRP3 inhibition may limit inflammasome activation, and methods targeting TREM2 or CD33 may restore microglial clearance. These combinations would address Aβ or tau accumulation while reducing the two-way reinforcement between poor protein control and neuroinflammation [2].

However, combination therapy needs careful design. Anti-Aβ antibodies may cause amyloid-related imaging abnormalities, while immune-regulating drugs may affect host defense, peripheral immune activity, or vascular inflammation; therefore, their doses, treatment order, and treatment

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windows cannot simply be combined without adjustment. Future trials should confirm that treatments affect their targets in the central nervous system; combinations should also be selected according to disease stage, inflammatory pattern, genetic background, including APOE and TREM2 variants, and related vascular or metabolic conditions.

Plasma cytokine profiles, NfL, GFAP, soluble TREM2, cerebrospinal fluid inflammatory markers, and molecular imaging of microglia may help identify patients with active inflammation-related injury. Recent studies indicate that inflammatory components have different relationships with cognition and neurodegeneration; one cytokine profile containing IL-17A, IL-7, IL-15, and TNF-α was directly related to poorer cognition, while another component was indirectly linked to cognition through NfL-related neuroaxonal injury [8]. These results support grouping patients according to inflammatory networks rather than individual cytokines; however, the stability, predictive value, and treatment response of these profiles still require confirmation in independent long-term cohorts.

5. Challenges and future perspectives

A main challenge in targeting neuroinflammation is that immune responses are not always harmful in Alzheimer's disease (AD). At first, microglia may protect neural tissue by helping remove Aβ and maintain tissue balance; however, continued activation can cause excessive cytokine release, oxidative stress, and neuronal damage [5]. The effects of anti-inflammatory treatment may therefore change across disease stages; early or excessive immune suppression may weaken useful clearance, while treatment started after major neuronal loss may have limited effects [6]. For this reason, treatment should match the disease stage; broad or long-term immune suppression during the early protective stage may disturb amyloid clearance, whereas treatment given after serious synaptic and neuronal loss may provide little clinical benefit.

Differences among patients create another difficulty. Peripheral cytokine levels can be affected by age, infection, metabolic and vascular diseases, medication, and sample handling; therefore, these levels cannot directly represent inflammatory activity in the central nervous system. The Bio-Hermes cohort shows this problem; among the 349 participants initially included, 337 remained after multivariable outliers were removed, and only one of the two inflammatory components was clearly higher in amyloid-positive AD or mild cognitive impairment and independently related to poorer cognition [8]. This result supports using combined inflammatory profiles rather than single interleukins; however, the cross-sectional design cannot confirm a causal relationship.

Future research should combine long-term cytokine measurements with amyloid, phosphorylated tau, NfL, GFAP, cerebrospinal fluid biomarkers, and brain inflammation imaging; these profiles may help identify patient groups with active immune responses, determine suitable treatment periods, and assess combined strategies involving immune-regulating and disease-modifying treatments.

6. Conclusion

This review has examined the contribution of interleukin-related neuroinflammation to the pathogenesis and progression of Alzheimer's disease. Current evidence indicates that neuroinflammation is not merely a secondary response to Aβ and tau accumulation, but an important biological interface linking protein aggregation, glial dysfunction, oxidative and mitochondrial stress, impaired proteostasis, synaptic damage, and neurodegeneration. The NLRP3 inflammasome converts Aβ-induced lysosomal and mitochondrial injury into IL-1β and IL-18 production, whereas IL-6, IL-17A, IL-7, and IL-15 reflect broader interactions among glial cells, peripheral immunity,

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and adaptive immune responses. At the same time, the relationship between inflammation and protein pathology is bidirectional: abnormal proteins activate glial cells, while persistent cytokine signaling weakens protein clearance, promotes tau-related pathology, and intensifies synaptic injury.

The principal implication of this analysis is that the clinical heterogeneity of AD may depend not only on the burden of Aβ and tau but also on the manner in which each patient's immune system responds to these pathological changes. Individuals with apparently similar classical neuropathology may experience different cognitive outcomes because their inflammatory networks, glial states, and levels of neuroaxonal injury are not equivalent. Interleukins and related inflammatory indicators are therefore unlikely to replace established Aβ and tau biomarkers. Their greater value may lie in identifying immune-active subgroups, guiding the selection of therapeutic targets, and determining whether an intervention has produced the intended immunological effect. This perspective extends the argument introduced at the beginning of the review: moving beyond an exclusively amyloid- and tau-centered model does not require abandoning protein pathology, but rather understanding how immune responses modify its clinical consequences.

Current evidence is limited by the reliance on preclinical models and cross-sectional human studies, while peripheral cytokine levels may not accurately reflect region-specific immune activity in the brain.Future longitudinal studies should integrate inflammatory profiles with established AD biomarkers to identify stage-specific treatment windows and develop precision therapies that suppress harmful inflammation while preserving the protective functions of microglia.

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