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The Role of Neuroinflammation in Alzheimer's Disease: Molecular Mechanisms and Emerging Therapeutic Approaches

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder traditionally characterized by amyloid-beta (Aβ) accumulation, tau pathology, synaptic dysfunction, and neuronal loss. Increasing evidence indicates that neuroinflammation is not merely a secondary consequence of neurodegeneration but an important component of AD pathogenesis. This review examines the molecular and cellular mechanisms through which neuroinflammation contributes to the progression of AD, with particular emphasis on microglial activation, TREM2 and soluble TREM2 (sTREM2) signaling, NLRP3 inflammasome activation, astrocyte–microglia interactions, and blood–brain barrier dysfunction. The review further evaluates emerging therapeutic strategies aimed at modulating these pathways, including NLRP3 inhibition, TREM2/sTREM2-targeted approaches, restoration of glial homeostasis, cytokine modulation, and pro-resolving strategies. Current evidence suggests that inflammatory responses may exert both protective and detrimental effects depending on disease stage, duration, and cellular context. Consequently, broad suppression of neuroinflammation may be insufficient and potentially counterproductive. Future therapeutic development may benefit from precision immunomodulation guided by disease-stage-specific biomarkers and molecular profiling. Understanding the complex interactions between neuroinflammation, pathological protein accumulation, glial dysfunction, and neurovascular abnormalities may therefore provide new opportunities for developing disease-modifying approaches to Alzheimer's disease.

Keywords: Alzheimer's disease; Neuroinflammation; Microglia; Astrocytes; TREM2; sTREM2; NLRP3 inflammasome

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, neuronal loss, synaptic dysfunction, and progressive brain atrophy. Its classical pathological features include extracellular accumulation of amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein [1, 2]. Although amyloid and tau pathology have traditionally formed the central framework for understanding AD, increasing evidence indicates that chronic neuroinflammation is closely associated with disease initiation and progression [1, 3].

Neuroinflammation refers to an immune response within the central nervous system (CNS) involving resident immune and glial cells. Under physiological conditions, inflammatory signaling contributes to

immune surveillance, tissue maintenance, synaptic remodeling, and removal of cellular debris. However, prolonged or dysregulated activation of inflammatory pathways can produce an environment that promotes neuronal dysfunction and degeneration [5]. In AD, microglia and astrocytes are considered major cellular mediators of this inflammatory response. Their interaction with Aβ, tau, neurons, and other components of the brain microenvironment can influence both disease pathology and cognitive outcomes [3, 5].

Importantly, neuroinflammation should not be regarded as an exclusively detrimental process. Microglial activation can initially facilitate the recognition and removal of abnormal proteins, cellular debris, and damaged tissue. However, persistent exposure to pathological stimuli may alter microglial function and promote the sustained production of pro-inflammatory mediators, reactive oxygen species, and other neurotoxic factors [3, 5]. Therefore, the transition from a potentially protective immune response to chronic, maladaptive inflammation represents an important area of investigation in AD.

The growing recognition of neuroinflammation has also expanded the potential therapeutic landscape of AD. Molecular pathways involving microglial receptors, inflammasomes, astrocytes, inflammatory cytokines, and the blood-brain barrier (BBB) are being investigated as possible therapeutic targets [1, 2, 4, 5]. A better understanding of these mechanisms may therefore contribute to the development of interventions aimed not only at reducing pathological protein accumulation but also at restoring appropriate immune regulation within the diseased brain.

2. Alzheimer's Disease and Its Pathological Basis

The neuropathology of AD is characterized principally by Aβ deposition, tau pathology, synaptic loss, gliosis, and neuronal degeneration [1, 3]. Aβ peptides are generated from amyloid precursor protein through sequential enzymatic processing and can aggregate into oligomers, fibrils, and plaques. Tau pathology involves abnormal phosphorylation and aggregation of tau protein, ultimately resulting in neurofibrillary tangles within neurons [5].

The relationship between these pathological features and neuroinflammation is increasingly understood to be bidirectional. Aβ aggregates can act as danger-associated molecular stimuli capable of activating innate immune receptors on microglia. Similarly, tau aggregates can stimulate inflammatory pathways and contribute to further microglial activation [3]. Thus, pathological protein accumulation does not merely represent a passive consequence of neurodegeneration; it can actively alter the immune environment of the brain.

Microglia are particularly important in this process because they are the principal resident immune cells of the CNS. In the healthy brain, microglia continuously survey their surrounding environment and participate in synaptic remodeling, neurogenesis, maintenance of homeostasis, and removal of cellular debris [3, 4]. Following detection of pathological stimuli, their morphology, gene expression, and functional state can change substantially. In AD, these changes include the emergence of disease-associated microglial states characterized by altered phagocytic, metabolic, and inflammatory functions [4].

The role of microglia is therefore complex. Effective microglial responses may facilitate Aβ clearance and containment of pathological lesions, whereas prolonged or dysregulated activation may contribute to synaptic injury and neuronal dysfunction [3, 4]. Evidence concerning the precise balance between protective and harmful microglial activity remains an important area of investigation.

3. Neuroinflammation in Alzheimer's Disease

Neuroinflammation in AD involves a complex network of interactions between microglia, astrocytes, neurons, vascular cells, and circulating immune components. Rather than representing a single inflammatory pathway, it consists of interconnected molecular and cellular processes that can influence Aβ metabolism, tau pathology, synaptic function, neuronal survival, and BBB integrity [1, 5].

Aβ aggregates can activate pattern-recognition receptors expressed by microglia, including Toll-like receptors and other innate immune receptors. This activation can initiate intracellular signaling pathways that promote the production of inflammatory cytokines and other mediators [3, 5]. Astrocytes can also respond to Aβ and participate in inflammatory signaling. Persistent activation of these glial cells may disrupt normal communication between microglia, astrocytes, and neurons, potentially affecting synaptic plasticity and neuronal survival [5].

One important consequence of chronic inflammatory signaling is the development of feed-forward interactions. Pathological Aβ can activate inflammatory pathways, while inflammatory mediators can impair the normal clearance of Aβ and contribute to additional tissue damage. This creates a potentially self-sustaining cycle in which protein aggregation and inflammation reinforce one another [5].

The BBB represents another important component of this process. It normally regulates the movement of substances and immune cells between the circulation and CNS. During AD, dysfunction of the BBB and the broader neurovascular unit can increase vascular inflammation and alter interactions between circulating immune cells and neural tissue [1]. Aβ deposition within cerebral vessels may contribute to vascular and endothelial dysfunction, while tau pathology has also been associated with deterioration of BBB integrity [1]. These changes may further amplify inflammatory responses within the brain.

Consequently, neuroinflammation should be considered in the broader context of the neurovascular and immune environment of AD rather than as an isolated response of microglial cells.

4. Microglial Activation and the Initiation of Inflammatory Signaling

Microglia are central to the initiation and regulation of neuroinflammatory responses in AD. In their homeostatic state, microglia continuously monitor the CNS and respond rapidly to alterations in the local environment. They possess multiple pattern-recognition receptors capable of detecting pathological or damaged-associated signals [3, 4].

Following exposure to Aβ or other pathological stimuli, microglia undergo substantial molecular and morphological changes. Activated microglia can release pro-inflammatory cytokines, chemokines, nitric oxide, and reactive oxygen species. Although these responses may initially contribute to the containment and clearance of pathological material, prolonged activation can produce an inflammatory environment that is detrimental to neuronal function [3, 5].

The microglial receptor TREM2 has emerged as an important regulator of this response. TREM2 influences microglial chemotaxis, phagocytosis, inflammatory signaling, metabolism, and interaction with pathological structures [4]. Loss-of-function variants of TREM2 have been associated with increased AD risk, highlighting the importance of appropriate microglial regulation in disease progression [4]. Recent evidence further indicates that TREM2 signaling may influence disease-associated microglial states and may represent a potential therapeutic target [2, 4].

Another major inflammatory mechanism is activation of the NLRP3 inflammasome. NLRP3 is a multiprotein inflammatory complex that can be activated following recognition of cellular danger signals. In microglia, activation of the NLRP3 inflammasome promotes caspase-1 activation and maturation of

inflammatory cytokines such as interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) [3]. Evidence from experimental models and human AD tissue has implicated NLRP3 signaling in both Aβ-associated and tau-associated pathology [3].

These findings demonstrate that microglial activation is not simply an accompanying feature of AD pathology. Instead, microglial signaling can participate directly in the interaction between pathological protein accumulation and chronic inflammation. The TREM2 and NLRP3 pathways therefore provide important mechanistic links between innate immune activation and neurodegeneration and represent potential targets for therapeutic intervention [2, 3, 4].

5. Molecular Mechanisms Linking Neuroinflammation to Alzheimer's Disease

Neuroinflammation in Alzheimer's disease is mediated through a complex interaction between pathological protein accumulation, innate immune signaling, glial dysfunction, and neurovascular abnormalities. Among the most extensively studied mechanisms are microglial TREM2 signaling, activation of the NLRP3 inflammasome, astrocyte–microglia interactions, and dysfunction of the blood–brain barrier (BBB) [1–5]. These pathways do not operate independently; rather, they form interconnected inflammatory networks that may reinforce amyloid-beta (Aβ) and tau pathology and contribute to progressive neuronal injury.

5.1 TREM2 Signaling and Microglial Dysfunction

Triggering receptor expressed on myeloid cells 2 (TREM2) is an innate immune receptor predominantly expressed by microglia in the brain. It has emerged as an important regulator of microglial survival, migration, phagocytosis, metabolism, and inflammatory responses [2, 4]. Genetic evidence has established a significant relationship between TREM2 dysfunction and Alzheimer's disease (AD), with loss-of-function variants associated with increased disease risk [4].

TREM2 does not possess an intrinsic intracellular signaling domain and therefore depends on adaptor proteins, particularly DNAX-activating protein of 12 Kad (DAP12) and DAP10, to transmit extracellular signals. Binding of ligands such as Aβ, phospholipids, and apolipoproteins initiates phosphorylation of the immunoreceptor tyrosine-based activation motif within DAP12, leading to recruitment and activation of spleen tyrosine kinase (SYK). Downstream signaling involves pathways including phospholipase C gamma 2 (PLCγ2), phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), and Rac1/Cdc42 [2]. These pathways collectively regulate phagocytosis, cytoskeletal remodeling, cell migration, survival, proliferation, and cellular metabolism.

The functional importance of TREM2 becomes particularly apparent during exposure to pathological Aβ. Microglia surrounding amyloid plaques require appropriate TREM2 signaling to respond to pathological material and maintain effective phagocytic activity [4]. Loss or impairment of TREM2 signaling can reduce microglial responses to plaques and compromise the containment and clearance of pathological material. TREM2-associated signaling is therefore not simply an inflammatory pathway; it represents a regulatory mechanism that can determine whether microglial activation remains protective or becomes dysfunctional.

The relationship between TREM2 and inflammation is nevertheless complex. TREM2 influences inflammatory responses, but its effects vary according to disease stage and cellular context. Recent evidence indicates that TREM2 signaling may have a more prominent protective role during early amyloid accumulation, when efficient microglial responses can facilitate the clearance or containment of amyloid seeds [2]. In later disease stages, however, prolonged microglial activation may become less effective and

increasingly associated with pathological inflammation. This stage-dependent behavior represents an important consideration for therapeutic strategies targeting TREM2.

5.2 Soluble TREM2 as a Potential Mediator and Biomarker

TREM2 can undergo proteolytic shedding, producing a soluble form known as soluble TREM2 (sTREM2). Alternative splicing can also contribute to the production of sTREM2 [2, 4]. The soluble receptor can be detected in cerebrospinal fluid (CSF) and plasma, making it particularly relevant to the study of neuroinflammation and disease progression.

sTREM2 appears to have biological effects in addition to its potential value as a biomarker. Experimental evidence has associated sTREM2 with microglial survival and inflammatory signaling, although its precise physiological functions remain incompletely characterized [4]. The 2025 review by Zhang et al. further highlights evidence linking sTREM2 with microglial activity, Aβ and tau pathology, and clinical disease stage [2].

An important feature of sTREM2 is its apparent stage-dependent behavior. Elevated CSF sTREM2 levels have been associated with early symptomatic stages of AD, while higher levels have also been linked in some studies with reduced Aβ accumulation and slower cognitive decline [2]. These observations suggest that sTREM2 may reflect an active microglial response rather than simply indicating the presence of neurodegeneration. Consequently, sTREM2 has potential applications in disease monitoring and patient stratification, although further research is required before it can be considered a definitive clinical biomarker.

5.3 NLRP3 Inflammasome Activation

The NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome represents another major molecular pathway connecting innate immune activation with AD pathology. NLRP3 is a multiprotein complex that generally consists of a sensor molecule, the adaptor apoptosis-associated speck-like protein containing a CARD (ASC), and the downstream effector caspase-1 [3].

Activation of the canonical NLRP3 pathway involves at least two major stages. The first is a priming signal, frequently mediated through pattern-recognition receptors and nuclear factor kappa B (NF-dB), which increases the expression of pro-IL-1β, pro-IL-18, and NLRP3 itself. The second involves recognition of intracellular danger-associated molecular signals, leading to NLRP3 oligomerization, recruitment of ASC and procaspase-1, and formation of the inflammasome complex [3].

Activated caspase-1 subsequently cleaves pro-IL-1β and pro-IL-18 into their mature inflammatory forms. Caspase-1 also cleaves adermin D (GSDMD), which can induce proptosis, a highly inflammatory form of programmed cell death [3]. The resulting release of inflammatory mediators can contribute to neuronal injury and further activation of microglia.

The relationship between NLRP3 activation and AD pathology appears to be bidirectional. Aβ and tau-associated pathological stimuli can activate the inflammasome, while inflammasome-derived inflammatory mediators may impair normal microglial functions and contribute to additional pathological protein accumulation. Experimental studies summarized by Hanslik and Ulland indicate that NLRP3 activation can restrict beneficial microglial plaque-clearance functions, whereas genetic deficiency of NLRP3 or caspase-1 increased plaque phagocytosis in experimental models [3].

This creates a potential positive feedback mechanism:

Aβ/tau pathology → microglial activation → NLRP3 activation → IL-1β/IL-18 release → neuronal injury → further microglial activation.

Such a feedback loop may help explain why inflammation can become self-sustaining during disease progression.

5.4 Microglia–Astrocyte Crosstalk

Although microglia represent the principal resident immune cells of the CNS, astrocytes are also important regulators of neuroinflammation. Under physiological conditions, astrocytes contribute to neuronal homeostasis, metabolic support, neurotransmitter regulation, and maintenance of the neural environment. During AD, however, exposure to Aβ and inflammatory signals can induce reactive astrocytic states [5].

Aβ aggregates can interact with inflammatory receptors expressed by both microglia and astrocytes. Activation of these pathways can stimulate the production of inflammatory mediators, including cytokines, chemokines, reactive oxygen species, and nitric oxide [5]. Consequently, astrocytes can participate in the amplification of inflammatory signaling rather than functioning solely as passive responders.

Importantly, microglia and astrocytes interact through reciprocal signaling. Persistent microglial activation can alter astrocytic responses, while reactive astrocytes can release mediators that influence microglial activity and neuronal survival. Singh describes this process as a disruption of normal immune crosstalk between microglia, astrocytes, and neurons, with potential consequences for synaptic plasticity, neuronal survival, and cognition [5].

This interaction provides another mechanism through which initially localized inflammatory responses may become persistent. When Aβ-induced inflammatory signaling establishes a feed-forward loop, the normal mechanisms responsible for resolving inflammatory responses may become insufficient. The resulting chronic inflammatory environment can impair the clearance of pathological aggregates and increase the likelihood of neuronal dysfunction [5].

5.5 Blood–Brain Barrier Dysfunction and Neurovascular Inflammation

The blood–brain barrier forms a highly selective interface between the circulation and the CNS. It is maintained by specialized endothelial cells together with pericytes, basement membrane components, astrocytic end feet, and other components of the neurovascular unit (NVU) [1]. In AD, dysfunction of the BBB can contribute to the development and persistence of neuroinflammation.

Aβ deposition within cerebral vessels can promote inflammatory and cytotoxic processes that compromise BBB integrity. In addition, vascular Aβ accumulation is associated with changes affecting endothelial cells and pericytes, potentially increasing vascular permeability [1]. Tau pathology has also been associated with BBB deterioration, suggesting that both major pathological proteins of AD may contribute to neurovascular dysfunction.

BBB dysfunction may additionally influence the movement of circulating immune cells into the CNS. Activated endothelial cells can express adhesion molecules that facilitate leukocyte interactions with the vascular wall. Pericytes can also respond to inflammatory stimuli by increasing expression of adhesion molecules and producing chemotactic factors, potentially contributing to leukocyte recruitment [1].

The resulting interaction between vascular inflammation and neural inflammation suggests that AD cannot be understood solely as a disorder of neurons and pathological protein aggregation. The BBB and NVU form an additional interface through which peripheral immune signals, vascular dysfunction, glial activation, and neuronal pathology may interact.

5.6 Interconnection of the Major Neuroinflammatory Pathways

The mechanisms described above form an interconnected network rather than independent pathological processes. Aβ and tau can activate microglia, while altered TREM2 signaling can modify microglial

phagocytosis, metabolism, and inflammatory responses [2–4]. Activated microglia can subsequently engage the NLRP3 inflammasome, resulting in the production of IL-1β and IL-18 and potentially promoting neuronal damage [3]. Reactive astrocytes can further amplify inflammatory signaling, while BBB and NVU dysfunction may facilitate vascular inflammation and immune-cell trafficking [1, 5].

6. Emerging Therapeutic Approaches Targeting Neuroinflammation

The recognition of neuroinflammation as an important component of Alzheimer's disease (AD) pathology has led to increasing interest in therapies that modulate immune and inflammatory pathways. However, the therapeutic objective is not necessarily complete suppression of inflammation. Because microglia and astrocytes perform essential physiological functions, broad inhibition of these cells may interfere with amyloid clearance, tissue maintenance, and neuronal homeostasis [2, 4, 5]. Consequently, current approaches increasingly focus on selectively modifying pathological inflammatory pathways while preserving beneficial immune functions.

6.1 Targeting the NLRP3 Inflammasome

The NLRP3 inflammasome has emerged as a promising target because its activation is associated with inflammatory cytokine production, impaired microglial clearance, and pathological changes in experimental models of AD [3]. Pharmacological inhibition can theoretically occur by suppressing upstream signals, preventing inflammasome assembly, or directly interfering with components of the inflammasome complex.

Several compounds have demonstrated NLRP3-inhibitory effects in experimental models. Ginsenoside Rg3, oridonin, and Trani last have been reported to interfere with different stages of NLRP3 activation, while compounds such as MCC950 and β-hydroxybutyrate have also demonstrated inhibitory effects through distinct mechanisms [3]. In experimental AD models, some NLRP3 inhibitors have reduced amyloid burden and microglial activation, suggesting that inflammasome modulation may influence both inflammation and pathological protein accumulation.

However, most of the evidence supporting NLRP3 inhibition remains preclinical. The available studies demonstrate biological plausibility, but the extent to which these findings translate into clinically meaningful improvements in human AD remains uncertain. Future clinical studies must therefore determine whether inhibition of NLRP3 can produce sustained improvements in cognition and disease progression rather than merely reducing inflammatory markers or pathological features in experimental models [3].

6.2 TREM2 and sTREM2-Directed Therapies

TREM2 represents a particularly attractive therapeutic target because it regulates several aspects of microglial function, including survival, phagocytosis, metabolism, and inflammatory signaling [2, 4]. Therapeutic strategies aimed at enhancing TREM2 activity may potentially improve microglial responses to pathological protein accumulation.

The therapeutic relevance of TREM2 is complicated by its context-dependent role. During early amyloid accumulation, TREM2 signaling may facilitate the containment and clearance of amyloid seeds. In later stages, however, the biological consequences of prolonged microglial activation may differ substantially [2]. This suggests that therapeutic activation of TREM2 may need to be carefully timed rather than continuously stimulated throughout disease progression.

sTREM2 provides an additional therapeutic and diagnostic possibility. Evidence summarized by Zhang et al. suggests that increased sTREM2 may be associated with reduced amyloid and tau pathology and

improved cognitive outcomes in certain disease stages [2]. Consequently, approaches designed to increase sTREM2 production or reproduce its potentially protective effects are being considered. Nevertheless, some TREM2 agonistic antibodies may interact with epitopes shared by membrane-bound TREM2 and sTREM2, potentially interfering with beneficial sTREM2 functions. This illustrates the complexity of developing therapies that selectively manipulate the TREM2 system.

6.3 Modulation of Microglial and Astrocytic States

Another therapeutic strategy involves restoring glial cells toward a more homeostatic functional state rather than simply eliminating or suppressing them. Microglia and astrocytes perform essential physiological functions, and their complete inhibition could therefore be counterproductive [5].

Experimental approaches have investigated pathways involved in microglial phagocytosis, inflammatory resolution, oxidative stress, and cellular metabolism. For example, modulation of sphingosine kinase-related pathways and pro-resolving mediators has been associated with improved microglial phagocytic activity and reduced neuroinflammation in experimental AD models [5]. Similarly, targeting astrocytic activation may reduce the production of neurotoxic inflammatory mediators. The interdependence of microglial and astrocytic responses suggests that therapies targeting both cell types may eventually prove more effective than interventions directed at a single inflammatory pathway.

6.4 Anti-Inflammatory Drugs and Cytokine Modulation

Conventional anti-inflammatory drugs have also been investigated as potential interventions for AD. However, clinical evidence has not consistently supported the effectiveness of broad anti-inflammatory treatment. Singh reports that many non-steroidal anti-inflammatory drugs (NSAIDs) failed to demonstrate meaningful efficacy in AD clinical trials, despite promising evidence from experimental studies [5].

This discrepancy illustrates an important challenge in translating neuroinflammatory mechanisms into therapeutic benefit. A drug may successfully suppress an inflammatory pathway without significantly altering the complex pathological processes responsible for cognitive decline. Consequently, future approaches may need to target specific inflammatory mediators or cellular states rather than broadly suppressing inflammation.

Several more selective approaches remain under investigation. Inflammation, an inhibitor of p38 mitogen-activated protein kinase alpha, has demonstrated beneficial effects in experimental models, including reductions in amyloid burden and improvements in synaptic and memory-related outcomes. The compound has also progressed through early clinical investigation, although further evidence is required to establish its long-term clinical efficacy [5].

6.5 Natural Compounds and Pro-Resolving Approaches

Natural compounds have attracted interest because of their potential anti-inflammatory and antioxidant properties. Compounds including curcumin, quercetin, resveratrol, and ginkgolides have been investigated for their effects on gliosis, oxidative stress, inflammatory signaling, and Aβ-associated pathology [5]. Experimental evidence summarized by Singh suggests that some of these compounds can reduce neuroinflammation and improve pathological or behavioral outcomes in disease models.

However, these findings should be interpreted cautiously. Evidence of benefit in experimental models does not establish clinical efficacy in humans. Factors such as bioavailability, blood–brain barrier penetration, pharmacokinetics, dosing, and reproducibility remain important considerations. Therefore, natural compounds may represent potential components of future therapeutic strategies, but their clinical value requires rigorous investigation.

An alternative approach is to promote the resolution of inflammation rather than simply blocking inflammatory signaling. Pro-resolving mediators have been investigated as a means of restoring microglial phagocytic function while limiting prolonged inflammatory activity [5]. Such strategies may be particularly relevant because they aim to preserve beneficial immune functions while reducing the pathological consequences of chronic inflammation.

7. Current Challenges and Limitations

Despite substantial evidence linking neuroinflammation with AD, several important challenges remain. First, the precise temporal relationship between neuroinflammation, Aβ accumulation, tau pathology, and neuronal degeneration remain incompletely resolved. Evidence suggests that inflammatory signaling can occur early in disease development, but it is unclear whether specific inflammatory changes initiate pathology, accelerate existing pathology, or represent responses to neuronal and protein-associated damage [3, 5].

Second, neuroinflammation is highly heterogeneous. Microglia and astrocytes do not exist in a single functional state, and their responses can vary according to disease stage, anatomical region, genetic background, and local environmental conditions. Evidence summarized in the literature indicates that microglial activation may be either neuroprotective or neurotoxic depending on its timing, duration, and magnitude [5].

Third, significant translational limitations exist between experimental models and human AD. Findings obtained from transgenic mouse models may not completely reproduce the cellular and molecular complexity of human disease. TREM2 studies have produced differing results depending on the model and experimental conditions, emphasizing the need for human cellular, organoid, and clinical validation [4].

Another major challenge is therapeutic timing. The effects of immune modulation may differ considerably between preclinical, early symptomatic, and advanced stages of disease. TREM2 and sTREM2 provide a clear example of this issue, as their apparent biological roles and associations with pathology vary across disease stages [2]. Therapeutic interventions may therefore need to be individualized according to disease stage and biomarkers of inflammatory activity.

Finally, the complexity of the inflammatory network raises concerns about single-target therapies. TREM2, NLRP3, astrocytic signaling, BBB dysfunction, cytokine signaling, and metabolic changes are interconnected. Modifying one pathway may therefore produce compensatory effects elsewhere in the system. A successful intervention may require selective combination therapy rather than inhibition of a single inflammatory molecule.

8. Future Directions

Future research should move beyond the concept of generalized anti-inflammatory treatment toward **precision immunomodulation**. The objective should be to identify which inflammatory pathways are harmful at a particular disease stage while preserving immune mechanisms necessary for tissue maintenance and pathological protein clearance.

TREM2 and sTREM2 represent promising examples of this approach. Their potential roles as biomarkers may allow inflammatory activity to be monitored alongside disease progression, potentially helping identify patients who are most likely to benefit from immune-modulating interventions [2]. CSF sTREM2 may also provide information about microglial activation and disease stage, although further validation is

necessary before routine clinical implementation.

Future studies should also investigate the relationship between neuroinflammation and cellular metabolism. Recent evidence indicates that Aβ exposure can induce metabolic reprogramming in microglia, including a shift toward glycolysis, while TREM2 signaling influences metabolic pathways through DAP12/DAP10 and downstream signaling networks [2]. Understanding how metabolism controls inflammatory cell states may provide additional therapeutic opportunities.

Another important direction is the development of therapies that simultaneously regulate multiple components of the neuroimmune environment. Combination strategies involving TREM2 modulation, inflammasome inhibition, restoration of glial homeostasis, and enhancement of pathological protein clearance may ultimately be more effective than broad anti-inflammatory treatment. However, such approaches will require careful consideration of treatment sequence, dosage, disease stage, and potential interactions between pathways.

Greater use of human-derived experimental systems will also be important. Human induced pluripotent stem cell-derived microglia, cerebral organoids, and patient-derived cellular models may help bridge the gap between animal studies and clinical disease. These models could allow researchers to examine how genetic factors such as TREM2 and APOE influence individual inflammatory responses and therapeutic sensitivity [4].

Finally, future research should integrate inflammatory biomarkers with imaging, molecular profiling, and clinical assessments. Such multimodal approaches could improve the identification of inflammatory subtypes of AD and support the development of more personalized therapeutic strategies.

9. Conclusion

Neuroinflammation has emerged as a major component of the biological complexity underlying Alzheimer's disease. Rather than functioning as an isolated consequence of neurodegeneration, inflammatory signaling interacts with amyloid-beta and tau pathology, microglial dysfunction, astrocytic activation, and blood–brain barrier abnormalities [1–5].

Microglia occupy a central position within this network. TREM2 signaling regulates their survival, phagocytosis, metabolism, and inflammatory responses, while dysregulation of the NLRP3 inflammasome can promote inflammatory cytokine production, impair pathological protein clearance, and contribute to neuronal injury [2–4]. At the same time, interactions between microglia and astrocytes can amplify inflammatory responses, while neurovascular dysfunction may further connect peripheral immune signaling with the CNS [1, 5].

The therapeutic implications are promising but remain uncertain. NLRP3 inhibition, TREM2/sTREM2 modulation, restoration of glial homeostasis, selective cytokine regulation, pro-resolving approaches, and metabolic interventions represent important areas of investigation. However, evidence from experimental models cannot yet be directly equated with established clinical efficacy. The failure of several broad anti-inflammatory approaches also demonstrates that simply suppressing inflammation is unlikely to provide a universal solution [5].

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