THE ROLE OF NEUROINFLAMMATION IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia worldwide. While amyloid-beta (Aβ) plaques and neurofibrillary tangles have long been considered the central pathological hallmarks of AD, increasing evidence highlights neuroinflammation as a critical contributor to disease onset and progression. Chronic activation of microglia and astrocytes leads to sustained inflammatory responses, synaptic dysfunction, neuronal loss, and cognitive decline. This article reviews the role of neuroinflammation in the pathogenesis of Alzheimer's disease, focusing on cellular and molecular mechanisms, inflammatory mediators, genetic risk factors, and interactions with classical AD pathology. Furthermore, the clinical significance of neuroinflammatory pathways as diagnostic biomarkers and therapeutic targets is discussed, along with future perspectives in Alzheimer's research.

Keywords: Alzheimer's disease, neuroinflammation, microglia, astrocytes, cytokines, neurodegeneration

Introduction

Alzheimer's disease (AD) is a chronic, irreversible neurodegenerative disorder characterized by progressive cognitive decline, memory impairment, and behavioral disturbances. It accounts for approximately 60–70% of all dementia cases and poses a growing global health challenge due to aging populations. Despite decades of research, the exact mechanisms underlying AD remain incompletely understood, and disease-modifying treatments are still lacking.

Traditionally, the amyloid cascade hypothesis has dominated AD research, proposing that accumulation of amyloid-beta peptides initiates a cascade leading to tau pathology, synaptic dysfunction, and neuronal death. However, therapeutic strategies targeting amyloid deposition alone have yielded limited clinical success. This has prompted a paradigm shift toward alternative and complementary mechanisms, including neuroinflammation.

Neuroinflammation refers to the inflammatory response within the central nervous system (CNS), primarily mediated by microglia and astrocytes. In Alzheimer's

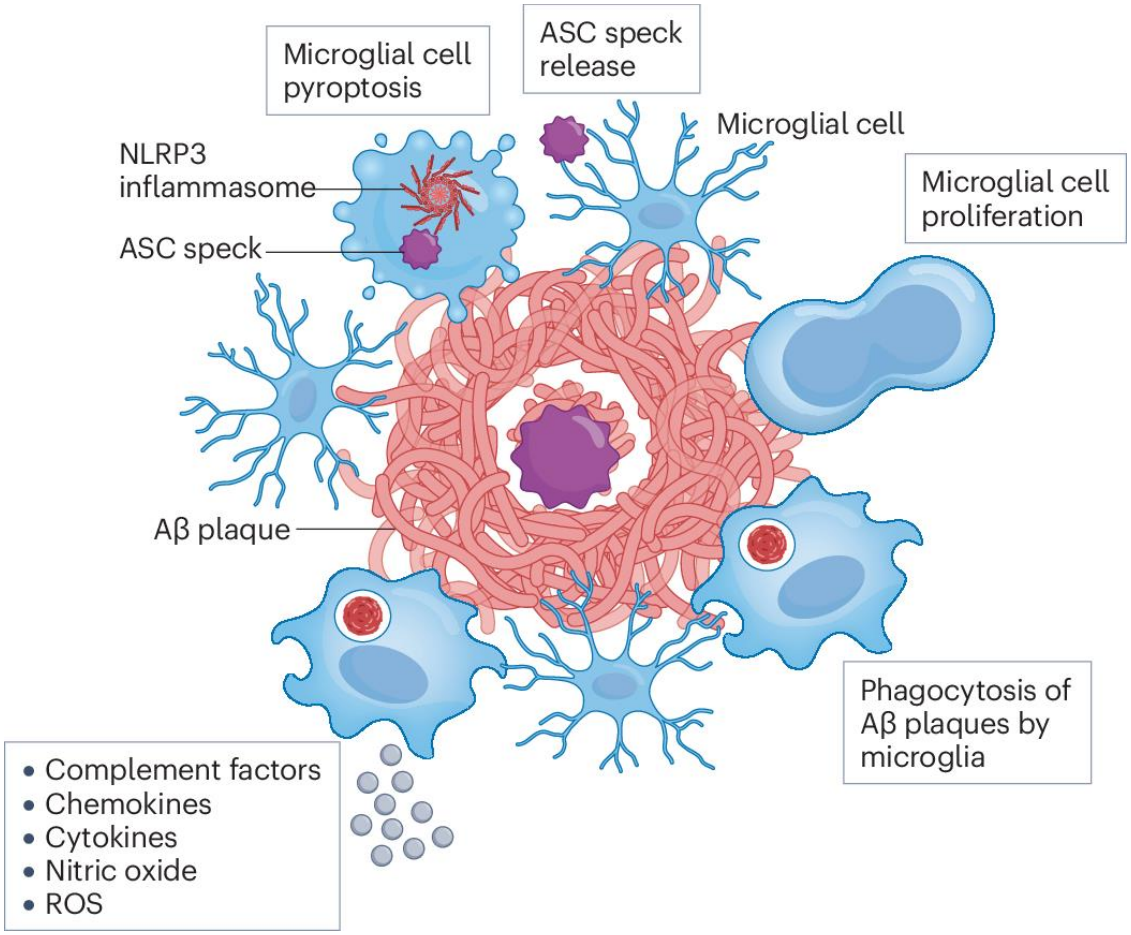
disease, neuroinflammation becomes chronic and maladaptive, contributing to neuronal injury rather than protection. Increasing evidence suggests that neuroinflammation is not merely a secondary response but an active driver of disease progression.

The aim of this article is to provide a comprehensive overview of the role of neuroinflammation in the pathogenesis of Alzheimer's disease and to discuss its implications for diagnosis, prognosis, and therapeutic intervention.

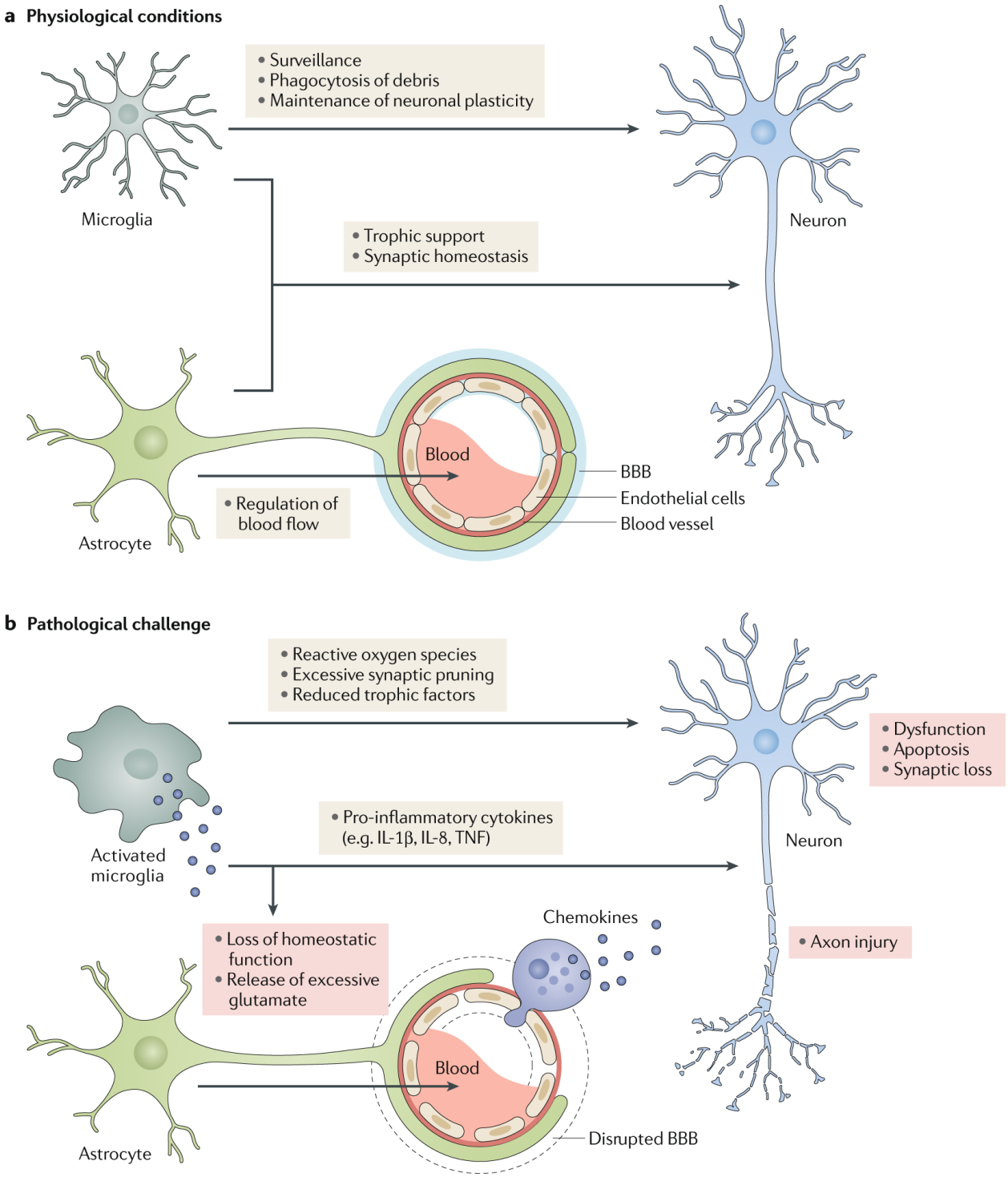
Materials and Methods

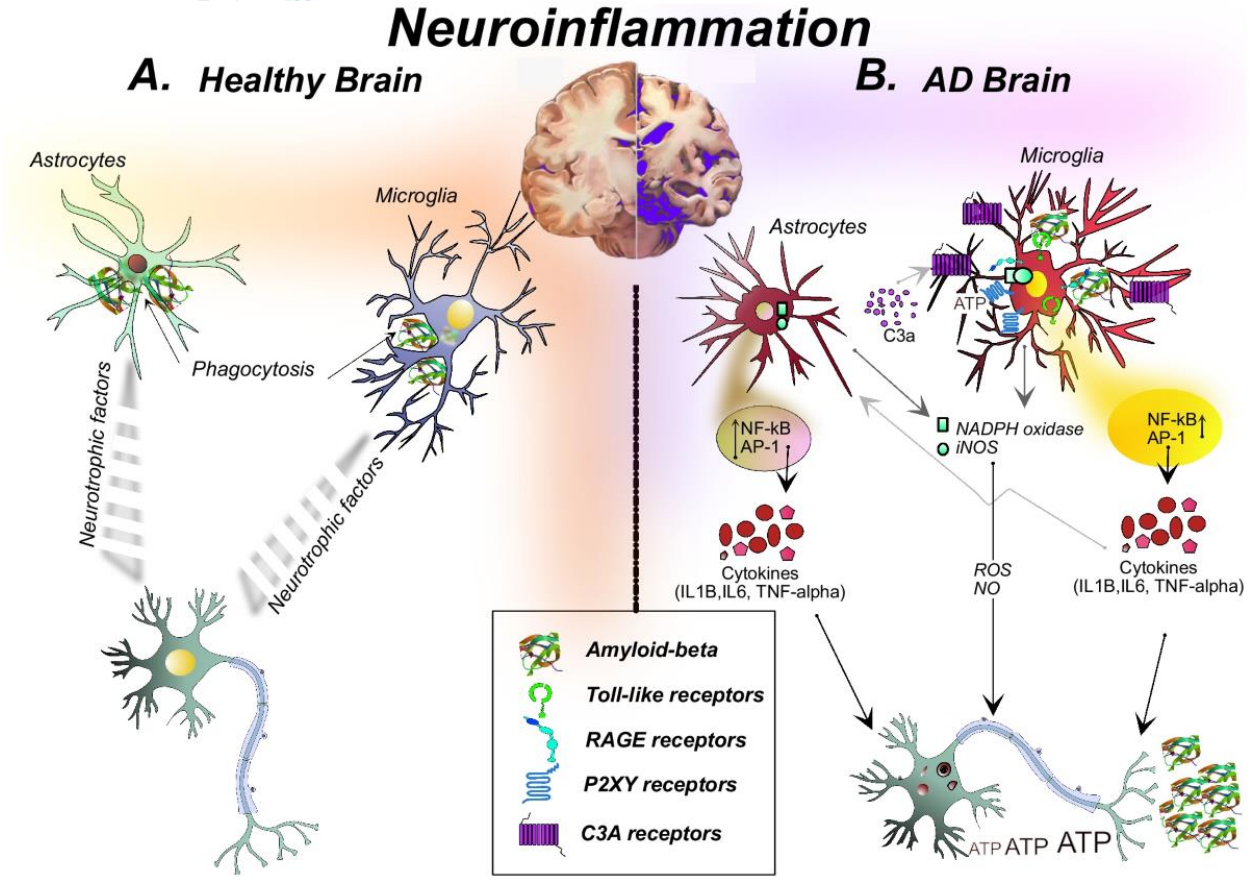
This narrative review is based on a comprehensive analysis of peer-reviewed literature published between 2000 and 2025. Scientific databases including PubMed, Scopus, Web of Science, and Google Scholar were searched using keywords such as *Alzheimer's disease*, *neuroinflammation*, *microglial activation*, *astrocytes*, *cytokines*, and *neurodegeneration*.

Original research articles, clinical studies, systematic reviews, and meta-analyses were included. Both human and animal model studies were analyzed to provide translational insights. Articles with insufficient methodological quality or limited relevance to neuroinflammatory mechanisms were excluded.



Pathophysiological Basis of Neuroinflammation in Alzheimer's Disease





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Neuroinflammation in Alzheimer's disease arises from persistent activation of innate immune responses in the brain. Under physiological conditions, microglia and astrocytes maintain homeostasis, clear debris, and support neuronal function. In AD, however, chronic exposure to amyloid-beta aggregates and tau pathology triggers sustained glial activation.

This prolonged inflammatory state results in excessive production of pro-inflammatory cytokines, chemokines, reactive oxygen species, and nitric oxide, leading to synaptic dysfunction and neuronal loss. Blood–brain barrier disruption further amplifies inflammation by allowing peripheral immune cells and mediators to enter the CNS.

Results

Microglial Activation and Alzheimer's Disease

Microglia are the resident immune cells of the CNS and play a central role in neuroinflammation. In Alzheimer's disease, microglia cluster around amyloid plaques, initially attempting to phagocytose amyloid-beta. However, chronic activation leads to a phenotypic shift toward a pro-inflammatory state.

Activated microglia release cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which exacerbate neuronal damage. Genetic studies have identified several AD risk genes related to microglial function, highlighting their importance in disease susceptibility.

Astrocytes and Inflammatory Signaling

Astrocytes are essential for maintaining synaptic homeostasis, regulating neurotransmitter levels, and supporting the blood–brain barrier. In Alzheimer's disease, astrocytes undergo reactive astrogliosis, characterized by morphological and functional changes.

Reactive astrocytes contribute to neuroinflammation by releasing inflammatory mediators, impairing glutamate clearance, and promoting oxidative stress. While astrocytes can exert neuroprotective effects in early disease stages, chronic activation contributes to neurodegeneration.

Cytokines and Chemokines

Elevated levels of pro-inflammatory cytokines have been consistently observed in the brains, cerebrospinal fluid, and blood of AD patients. IL-1β and TNF-α promote tau hyperphosphorylation and synaptic dysfunction, while IL-6 is associated with disease severity and cognitive decline.

Chemokines facilitate the recruitment and activation of immune cells, perpetuating inflammatory responses and neuronal injury.

Interaction Between Neuroinflammation and Amyloid-Beta

Neuroinflammation and amyloid-beta pathology are closely interconnected. Amyloid-beta aggregates activate microglia and astrocytes, while inflammatory mediators impair amyloid clearance and promote further deposition. This vicious cycle accelerates disease progression.

Oxidative Stress and Neuroinflammation

Inflammation-induced oxidative stress plays a crucial role in neuronal damage. Activated glial cells generate reactive oxygen and nitrogen species, leading to lipid peroxidation, mitochondrial dysfunction, and DNA damage in neurons.

Discussion

The evidence reviewed in this article supports the concept that neuroinflammation is a key driver of Alzheimer's disease pathogenesis rather than a mere bystander. Chronic glial activation contributes to synaptic loss, neuronal death, and cognitive impairment.

Targeting neuroinflammatory pathways offers promising therapeutic opportunities. Anti-inflammatory agents, immune-modulating therapies, and strategies

aimed at restoring glial homeostasis are currently under investigation. However, the dual role of inflammation—protective in early stages and harmful in later stages—poses significant challenges for therapeutic timing and specificity.

Integration of neuroinflammatory biomarkers with neuroimaging and clinical assessment may improve early diagnosis and disease monitoring.

Future Perspectives

Future research directions include:

- Identification of reliable neuroinflammatory biomarkers for early diagnosis
- Development of targeted therapies modulating microglial and astrocytic responses
- Application of precision medicine approaches based on individual inflammatory profiles
- Exploration of lifestyle and environmental factors influencing neuroinflammation

Advances in molecular biology and neuroimmunology are expected to transform Alzheimer's disease management.

Conclusion

Neuroinflammation plays a central and dynamic role in the pathogenesis of Alzheimer's disease. Persistent activation of microglia and astrocytes, coupled with excessive inflammatory mediator release, contributes significantly to neurodegeneration and cognitive decline. Understanding neuroinflammatory mechanisms provides new insights into disease progression and opens novel avenues for diagnosis and therapeutic intervention.

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