Article type: Editorial

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Neuroinflammation in neurodegenerative diseases: Friend or foe?

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Received: *02-Apr-2025, Manuscript No. AAICR-25-171200;* ***Editor assigned:*** *03-Apr-2025, Pre QC No. AAICR-25-171200(PQ);* ***Reviewed:*** *18-Apr-2025, QC No. AAICR-25-171200;* ***Revised:*** *24-Apr-2025, Manuscript No. AAICR-25-171200(R);* ***Published:*** *30-Apr-2025, DOI: 10.35841/aaicr-8.2.200*

Introduction

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) are characterized by progressive loss of neuronal structure and function. While the exact causes of these disorders remain elusive, neuroinflammation has emerged as a central player in their pathogenesis. Once considered a mere consequence of neuronal damage, neuroinflammation is now recognized as both a driver and modulator of disease progression. This duality—protective in some contexts, destructive in others—raises a critical question: is neuroinflammation a friend or foe in neurodegeneration? Given its central role, neuroinflammation is an attractive target for therapeutic intervention. Anti-inflammatory drugs, immunomodulators, and biologics are being explored to modulate glial activity and cytokine production. For example, monoclonal antibodies targeting IL-1β and TNF-α have shown promise in preclinical models of AD and PD. Minocycline, a tetracycline antibiotic with anti-inflammatory properties, has demonstrated neuroprotective effects in ALS and MS trials. However, clinical translation remains challenging due to the complexity and context-dependent nature of neuroinflammation [1].

Moreover, systemic infections and chronic inflammatory conditions can exacerbate neurodegeneration by priming microglia and increasing CNS cytokine levels. This bidirectional communication underscores the need to consider whole-body inflammation in managing neurodegenerative diseases. Neuroinflammation refers to the activation of the brain's innate immune system, primarily involving microglia and astrocytes. These glial cells respond to injury, infection, or abnormal protein accumulation by releasing cytokines, chemokines, and reactive oxygen species (ROS). While acute neuroinflammation can be beneficial—clearing debris and promoting repair—chronic activation often leads to sustained tissue damage and neuronal loss [2].

The CNS is not isolated from systemic immunity. Peripheral immune cells can infiltrate the brain through a compromised blood-brain barrier (BBB), further fueling neuroinflammation. In MS, autoreactive T cells cross the BBB and attack myelin, initiating a cascade of inflammatory damage. Microglia are the brain's resident macrophages and first responders to pathological stimuli. In early stages of neurodegeneration, microglia can adopt a neuroprotective phenotype, clearing misfolded proteins and secreting anti-inflammatory cytokines. However, prolonged activation shifts microglia toward a pro-inflammatory state, characterized by the release of TNF-α, IL-1β, and IL-6, which exacerbate neuronal injury. In AD, for instance, microglia initially help clear amyloid-beta (Aβ) plaques. Over time, however, they become dysfunctional, contributing to plaque accumulation and synaptic loss. Similarly, in PD, microglial activation around dopaminergic neurons in the substantia nigra correlates with disease severity [3].

Understanding the molecular switches that govern glial phenotypes and cytokine profiles is essential. Personalized approaches that consider genetic background, disease stage, and comorbidities may help harness the protective aspects of neuroinflammation while minimizing its deleterious effects. Astrocytes, traditionally viewed as support cells, also play a pivotal role in neuroinflammation. Reactive astrocytes can release inflammatory mediators and form glial scars that impede neuronal regeneration. In MS, astrocytes contribute to demyelination and axonal damage by

amplifying immune responses. Recent studies have identified distinct astrocyte phenotypes—A1 (neurotoxic) and A2 (neuroprotective)—highlighting the complexity of their role in neurodegeneration. The balance between these phenotypes may determine whether astrocytes act as friends or foes [4].

Cytokines and chemokines orchestrate the neuroinflammatory response. In ALS, increased IL-6 and TNF-α levels in cerebrospinal fluid are associated with faster motor decline. In AD, IL-1β promotes tau phosphorylation and Aβ aggregation, linking inflammation to hallmark pathological features. While some, like IL-10 and TGF-β, are anti-inflammatory and promote healing, others, such as IL-1β and TNF-α, drive neurotoxicity. Elevated levels of pro-inflammatory cytokines are consistently observed in neurodegenerative diseases and correlate with disease progression [5].

Conclusion

Neuroinflammation is a complex and dynamic process that plays both protective and pathogenic roles in neurodegenerative diseases. It is neither inherently good nor bad—but rather a biological response that can tip the balance toward recovery or decline. As research advances, the goal is not to eliminate neuroinflammation, but to modulate it intelligently. By decoding its dual nature, we can develop therapies that transform neuroinflammation from a foe into a powerful ally in the fight against neurodegeneration. The answer to whether neuroinflammation is beneficial or harmful lies in its timing, intensity, and cellular context. Acute, regulated inflammation can support tissue repair and pathogen clearance. Chronic, dysregulated inflammation, however, perpetuates neuronal damage and accelerates disease progression.

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Citation: Taher N. Neuroinflammation in neurodegenerative diseases: Friend or foe?. Immunol Case Rep. 2025;8(2):200.