

# From Chronic Inflammation to Neurodegeneration: Mechanistic Convergence and Therapeutic Opportunities at the Neuroimmune Interface

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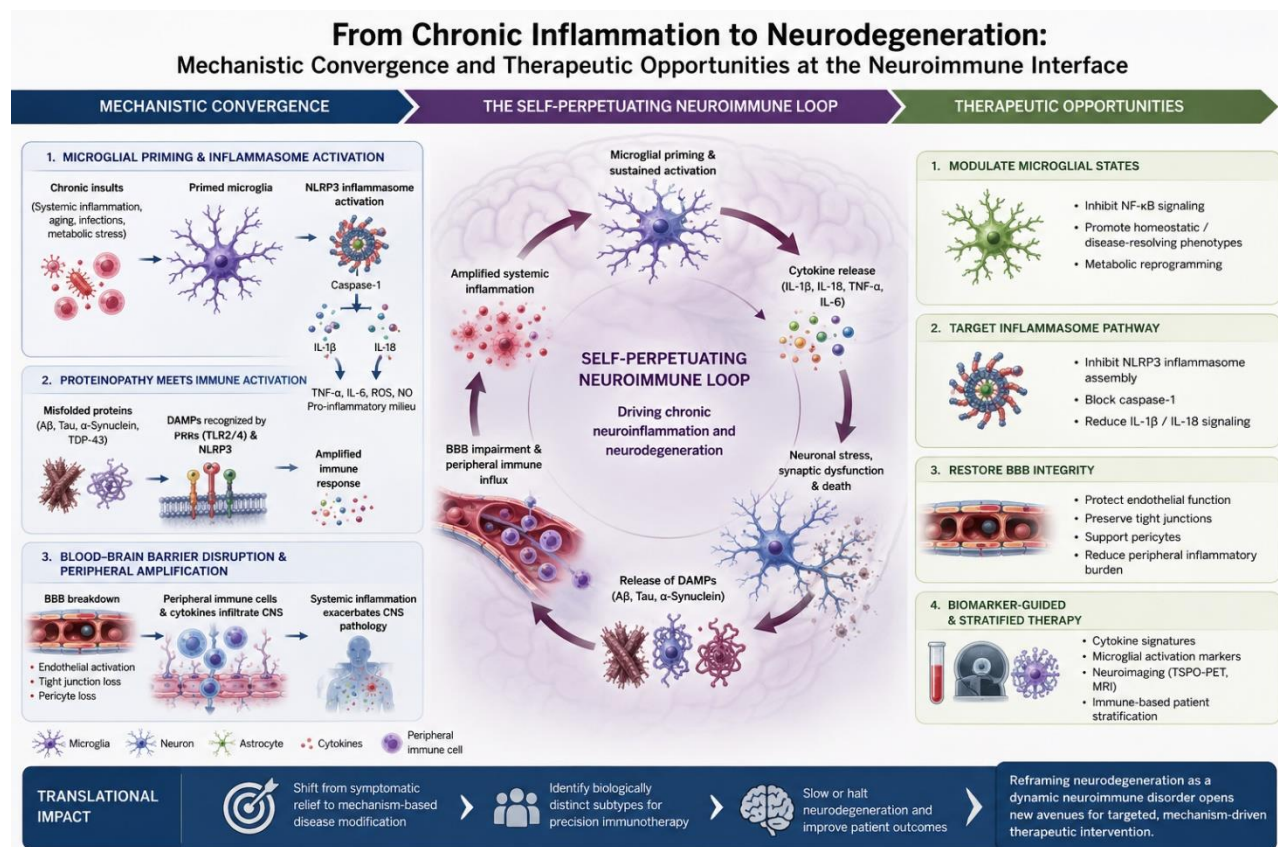
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## Abstract:

Neurodegenerative disorders, including Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis, are increasingly recognized as complex neuroimmune conditions rather than purely neuron-centric diseases. Although classical frameworks have emphasized protein aggregation, synaptic dysfunction, and progressive neuronal loss, these mechanisms alone do not fully explain disease heterogeneity or the limited efficacy of current disease-modifying therapies. Emerging evidence suggests that chronic neuroinflammation represents a central and sustained driver of neurodegeneration, acting through tightly interconnected neuronal, glial, and vascular pathways. At the mechanistic level, persistent activation of innate immune signaling—particularly microglial priming and NLRP3 inflammasome activation with downstream IL-1 $\beta$  and IL-18 signaling—establishes a chronic pro-inflammatory milieu within the central nervous system. Misfolded protein species, including amyloid- $\beta$  and tau, further amplify immune activation by functioning as damage-associated molecular patterns, thereby linking proteinopathy with innate immune responses. Concurrently, progressive disruption of the blood–brain barrier facilitates bidirectional communication between the central and peripheral immune systems, enabling systemic inflammation to exacerbate ongoing neurodegenerative processes. Together, these mechanisms form a self-reinforcing neuroimmune loop that may contribute to disease initiation and progression. From a translational perspective, this integrated framework highlights the limitations of therapeutic strategies that primarily target neurotransmitter imbalance or protein aggregation. Instead, disease modification may require interventions that directly modulate neuroimmune pathways, including regulation of microglial activation states, inhibition of inflammasome signaling, and restoration of blood–brain barrier integrity. Importantly, such approaches necessitate a shift toward mechanism-guided clinical development supported by biomarkers reflecting immune activation, glial reactivity, and neurovascular dysfunction. This may enable improved patient stratification and identification of biologically distinct disease subtypes with differential therapeutic responsiveness. Overall, reframing neurodegeneration as a dynamic and interconnected neuroimmune process provides a more comprehensive understanding of disease pathogenesis and offers a rational foundation for developing mechanism-based therapeutic strategies aimed at modifying disease progression rather than merely alleviating symptoms.

**Keywords:** Neuroinflammation; Neurodegeneration; Microglia; Inflammasome; Blood–brain barrier



**Graphical Abstract. From Chronic Inflammation to Neurodegeneration: A Self-Perpetuating Neuroimmune Loop Driving Disease Progression and Therapeutic Opportunities.** This graphical abstract illustrates the mechanistic convergence between chronic neuroinflammation and neurodegeneration, highlighting the role of microglial priming, inflammasome activation, protein aggregation, and blood–brain barrier disruption in sustaining a self-reinforcing neuroimmune loop. It further summarizes key therapeutic strategies targeting these pathways, including modulation of microglial states, inhibition of inflammasome signaling, and restoration of neurovascular integrity, offering a framework for mechanism-driven intervention in neurodegenerative disease.

## Introduction

Neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis are now generally understood to involve more than just neuron-specific pathology. Over the past decades, research has identified several key features of these disorders, including protein aggregation, synaptic dysfunction, and progressive neuronal loss (1). However, despite these advances, current treatment approaches have had limited success in significantly slowing or altering disease progression in patients (2). One important issue in many existing models is that they often focus mainly on describing structural and cellular changes, without fully explaining how different disease processes are connected in a causal

way. In particular, the role of neuroinflammation has sometimes been considered a secondary response rather than a driving factor in disease development (3). More recent studies suggest that this view may be too narrow.

There is growing evidence supporting the idea that the nervous system and immune system interact in a two-way manner during neurodegenerative disease. In this context, chronic inflammation may not only occur as a result of neuronal damage, but could also contribute to initiating and sustaining disease progression over time (4).

## Microglial Priming and the Shift Toward Chronic Neuroinflammation

At the cellular level, microglia are the main immune-related cells in the central nervous system and play an important role in maintaining brain homeostasis (5). Under normal physiological conditions, they help regulate synaptic remodeling, remove cellular debris, and provide support for neurons through different trophic functions (6).

However, when the brain is exposed for a prolonged period to systemic inflammatory signals or to abnormal protein species, microglia can shift into what is often described as a “primed” state (7). In this condition, they do not necessarily become fully activated all the time, but they tend to respond more strongly than usual when they encounter a second stimulus.

From a mechanistic perspective, this change is associated with sustained activation of innate immune signaling pathways, particularly the NLRP3 inflammasome. Pattern-recognition receptors (PRRs) sense harmful stimuli and trigger downstream inflammatory cascades, including inflammasome assembly and activation of caspase-1, which in turn matures IL-1 $\beta$  and IL-18 to mediate pro-inflammatory responses (8). As a result, primed microglia may show a more persistent release of pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 (9). These mediators can contribute to ongoing neuronal stress and functional impairment. Over time, this pattern may support a cycle in which inflammatory signaling is not fully resolved and instead continues to be reinforced by glial dysfunction. This may contribute to the maintenance of chronic neuroinflammation as a self-perpetuating process within the CNS, supported by the persistent pro-inflammatory and maladaptive responses of glial cells (10).

### **Molecular Convergence: Proteinopathy Meets Immune Activation**

A key point where different mechanisms seem to meet in neurodegenerative diseases is the

interaction between misfolded protein aggregates and the innate immune system (11). Proteins such as amyloid- $\beta$  are considered damage-associated molecular patterns (DAMPs) that can be recognized by pattern recognition receptors, including TLR2, TLR4, and components of the NLRP3 inflammasome (12). This interaction provides a link between classical protein aggregation pathology and immune system activation. In this way, what was previously viewed mainly as a neuronal protein accumulation problem is now often considered to have a meaningful inflammatory and immune component as well (13). Activation of the inflammasome pathway can lead to caspase-1-dependent processing of cytokines such as IL-1 $\beta$  and IL-18 (14). These cytokines may contribute to local neuronal stress and can also influence broader inflammatory signaling within the nervous system. Overall, these findings suggest that protein aggregation and neuroinflammatory processes may not be completely separate events. Instead, they may be more closely connected and potentially part of a shared disease network, although the exact causal relationships are still being clarified (15).

### **Systems-Level Dysregulation: Blood–Brain Barrier and Peripheral Amplification**

At the tissue level, chronic neuroinflammation has been associated with gradual impairment of the blood–brain barrier (BBB) (16). Changes such as endothelial cell activation, disruption of tight junction proteins, and loss of pericytes can all contribute to increased barrier permeability (17). As this barrier becomes more compromised, peripheral immune cells and circulating inflammatory mediators may gain easier access to the central nervous system (18).

This type of disruption suggests that neurodegenerative diseases may not be limited to processes within the brain alone, but can also involve interactions between the central nervous

system and the peripheral immune system. In this context, Systemic inflammation—such as that associated with metabolic disorders, aging, or infections—may contribute to the exacerbation of ongoing CNS pathology (19). Overall, these interactions may form a bidirectional relationship, where signals from the brain and the periphery influence each other and possibly contribute to the persistence or progression of disease over time (20).

### **Therapeutic Implications: From Symptomatic Treatment to Mechanism-Driven Intervention**

Collectively, the mechanistic framework described above suggests that integrative therapeutic approaches may be required beyond traditional strategies focused primarily on neurotransmitter modulation or protein clearance (15). One possible direction is targeting microglial activation states, for example by modulating NF- $\kappa$ B signaling, inhibiting inflammasome activity, or shifting immune cell metabolism toward a more homeostatic profile (21). In a similar way, direct inhibition of NLRP3 inflammasome assembly has been proposed as a possible strategy to reduce IL-1 $\beta$ -related neuroinflammatory effects (22). Alongside this, improving or restoring blood–brain barrier integrity may also be relevant, especially in cases where systemic inflammation or comorbid conditions are present (23).

Taken together, these approaches highlight the importance of designing clinical studies that are guided by mechanistic understanding rather than only clinical outcomes. This approach would likely rely on pharmacodynamic biomarkers such as peripheral cytokine signatures, markers of microglial activation, and neuroimaging techniques that enable *in vivo* assessment of neuroinflammatory processes (24).

**Future Directions: Toward Mechanistically Stratified Neurotherapeutics**

Future research may benefit from classifying neurodegenerative diseases not only based on

anatomical location or clinical presentation, but also according to patterns of immune activation. For example, distinct microglial subtypes associated with Alzheimer’s disease, such as A $\beta$ -associated AD1 microglia and tau-associated AD2 microglia, as well as disease-stage-specific states like EADAM and LADAM, exhibit markedly different gene expression profiles and immune responses during disease progression (25). This kind of stratification could help identify subgroups of patients who might respond better to immunomodulatory treatments.

In addition, longer-term mechanistic studies that combine omics-based approaches, neuroimaging, and functional immune assays are likely to be important. Such integrated approaches may help clarify which inflammatory changes are driving disease processes and which are more likely to be secondary responses (26).

### **Conclusion**

Neurodegenerative disorders are increasingly difficult to explain as purely neuron-based diseases. Many studies suggest that they may instead reflect broader system-level dysfunction that involves ongoing interaction between the nervous system and immune responses. In this view, long-lasting neuroimmune imbalance could play a role in how these diseases develop and progress over time.

Understanding chronic inflammation as a contributing factor to neurodegeneration may help refine current disease models and also point to new therapeutic directions. However, the strength of this relationship and the exact causal pathways are still being actively investigated. Overall, bringing together insights from neurobiology and immunology in a more integrated way may be important for moving beyond mainly symptomatic treatments toward approaches that are better informed by underlying disease mechanisms.

### **Mechanistic and Translational Relevance**

The evidence discussed in this review supports the concept that neurodegenerative diseases involve interconnected neuroimmune mechanisms rather than isolated neuronal dysfunction alone. Processes such as microglial priming, inflammasome activation, protein aggregation, and blood–brain barrier disruption appear to interact in a self-reinforcing manner that may contribute to chronic neuronal injury and disease progression.

From a translational perspective, these findings suggest that therapies targeting neuroinflammatory pathways could complement traditional approaches focused on neurotransmission or protein clearance. In addition, integrating mechanistic biomarkers such as cytokine profiles, markers of microglial activation, and neuroimaging measures may improve patient stratification and support the development of more mechanism-driven therapeutic strategies in neurodegenerative disease.

#### **Data Availability Statement**

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

#### **Conflict of Interests**

The author declares that there is no conflict of interest.

#### **Ethics Statement**

All ethical considerations, including plagiarism, data fabrication, and duplicate publication, have been fully observed by the author.

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