ACCSCIENCE PUBLISHING

Advanced Neurology

EDITORIAL

Neuroinflammation and neurodegeneration: Linking mechanisms, biomarkers, and therapeutic opportunity

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Neuroinflammation has emerged as a central and dynamic regulator of neurological disease progression. Beyond acting as a response to neuronal loss, it can actively steer the course of a wide range of neurological disorders, particularly chronic neurodegenerative diseases. Acute and subacute brain injuries provide complementary contexts in which inflammatory signaling intersects with ionic imbalance, oxidative stress, mitochondrial dysfunction, vascular injury, and regulated cell death.[1–3] The central immune response is inherently double-edged. In some situations, microglia and astrocytes support synaptic remodeling, remove protein aggregates, limit injury spread, and help restore homeostasis. However, under conditions of persistent or dysregulated activation, these cells may adopt maladaptive phenotypes that amplify cytokine signaling, excitotoxicity, vascular dysfunction, and tissue damage.[1,2,4,5] For this reason, neuroinflammation should not be viewed solely as a marker of pathology, but as a biologically consequential process that can either buffer or accelerate neurodegeneration depending on timing, cell state, and disease context.[1,2,4]

This duality is especially important across diseases. In Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), sustained immune activation increasingly appears to contribute directly to disease progression rather than simply following it.[1,2,6,7] In AD, inflammatory signaling intersects with amyloid and tau pathology, synaptic dysfunction, vascular injury, and aging-related vulnerability.[1,2] In PD, it interacts with α-synuclein aggregation, mitochondrial dysfunction, lysosomal impairment, and dopaminergic neuronal loss.[2,6] In ALS, glial and peripheral immune mechanisms may contribute to motor neuron vulnerability and disease propagation.[2,7] These examples highlight that neurodegeneration is not solely neuron-centric but reflects sustained crosstalk among neurons, glia, vascular components, and systemic immune signals. Similar principles apply in time-defined injury settings, such as stroke, where inflammatory cascades evolve over hours to days.[8] These models provide valuable translational insight, allowing investigation of how protective responses shift toward secondary injury, how neurovascular dysfunction recruits peripheral immune signals,

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Citation: Zhang X, Ho HL, Fu Y, Yuan Z, Sun H-S. Neuroinflammation and neurodegeneration: Linking mechanisms, biomarkers, and therapeutic opportunity. *Adv Neurol*. doi: 10.36922/AN026250026

Received: June 18, 2026

Published online: July 20, 2026

and how early inflammatory events influence long-term neurological outcomes.[2,8] Figure 1 summarizes these context- and stage-dependent relationships.

At the mechanistic level, several interlocking pathways now define the neuroinflammation–neurodegeneration interface. Microglia are not confined to "activated" or "resting" states but instead exist across diverse functional phenotypes shaped by regional identity, aging, proteinopathy, vascular stress, and systemic cues.[2,5] Astrocytes also exhibit context-specific roles. They maintain metabolic and ionic homeostasis, limit damage propagation, and support blood–brain barrier (BBB) repair; however, they can also contribute to neurotoxicity, scar formation, and chronic inflammatory signaling.[4] The neurovascular unit plays a central role in this balance.[9] BBB dysfunction alters molecular trafficking, permits entry of peripheral immune mediators, and reinforces feed-forward loops linking vascular injury, glial activation, and neuronal vulnerability.[10] In parallel, inflammasome pathways, particularly NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)-associated signaling, intersect with oxidative stress, mitochondrial dysfunction, and danger-associated molecular patterns to sustain cytokine release and pyroptotic injury.[11] Growing evidence also identifies systemic immune crosstalk as an integral component of disease biology, with peripheral immune signatures and lymphocyte-associated mechanisms contributing to central nervous system (CNS) pathology in at least some patient subsets.[7,12]

Clinical translation of these insights requires biomarker strategies that connect inflammatory mechanisms with patient stratification and therapeutic design. Fluid biomarkers, neuroinflammatory positron emission tomography (PET), spatial multi-omics, single-cell approaches, and computational modeling collectively provide scalable, spatially resolved, and quantitative readouts of glial activation, neuroaxonal injury, inflammatory tone, disease stage, and regional inflammatory niches.[13–19] Therapeutically, this framework points toward context- and stage-informed modulation

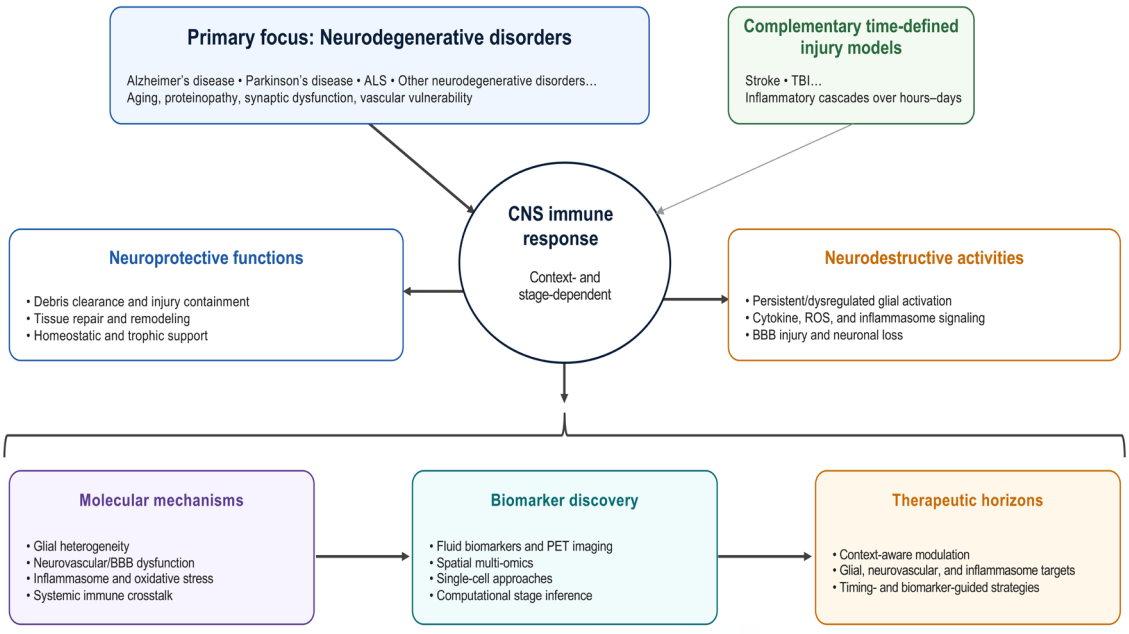

Figure 1. Conceptual framework linking neuroinflammation and neurodegeneration. Chronic neurodegenerative disorders are shaped by dynamic interactions among neuronal, glial, vascular, and immune mechanisms, with AD, PD, ALS, and other neurodegenerative disorders characterized by aging-related vulnerability, proteinopathy, synaptic dysfunction, and vascular contributions. Complementary time-defined diseases, such as stroke and TBI, provide additional platforms to study inflammatory cascades over defined temporary windows. CNS immune responses remain context- and stage-dependent, encompassing both neuroprotective functions, such as debris clearance, injury containment, tissue repair, and homeostatic support, and neurotoxic effects, including persistent or dysregulated glial activation, cytokine, ROS, and inflammasome signaling, BBB disruption, and neuronal loss. Integrating molecular mechanisms, biomarker development, and therapeutic innovation will be critical for identifying the transition from adaptive inflammation to pathological injury, enabling more precise, stage-informed therapeutic strategies.
Abbreviations: AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; BBB: Blood–brain barrier; CNS: Central nervous system; PD: Parkinson's disease; PET: Positron emission tomography; ROS: Reactive oxygen species; TBI: Traumatic brain injury.

of glial states, neurovascular integrity, inflammasome-associated signaling, and oxidative or mitochondrial injury, rather than broad immunosuppression.[4,10,11,20–23] In chronic neurodegenerative diseases, effective strategies will likely require alignment between target selection, disease stage, cellular context, and dominant injury pathways, rather than treating neuroinflammation as uniform.[1–3,6,22] Acute injury models provide proof-of-concept for such approaches. For example, in neonatal hypoxic-ischemic brain injury, inhibition of transient receptor potential melastatin 7 (TRPM7) kinase with TG100-115 reduced brain injury and suppressed NLRP3-associated neuroinflammatory signaling.[20] Although these findings are not directly generalizable to chronic neurodegenerative diseases, they illustrate the potential of mechanism-based, stage-specific modulation of neuroinflammatory pathways.[3,20]

Despite progress, major translational challenges remain. Disease heterogeneity is a central issue. Inflammatory programs can differ across disorders, between individuals, and over time. Timing is equally critical, as pathways that are protective early may become detrimental during chronic activation. The model-to-human gap further limits translation, as animal models do not fully capture aging, disease duration, comorbidities, or the molecular heterogeneity observed in patients. Biomarker-guided patient stratification will therefore be essential to identify individuals with active inflammatory endophenotypes and avoid dilution of therapeutic effects in biologically heterogeneous cohorts.[7,15–17] Equally, target specificity and safety must be prioritized, as excessive suppression of CNS immunity may impair physiological surveillance, debris clearance, and tissue repair, especially if therapies are deployed without stage-specific considerations.[2,4,24]

This Special Issue welcomes original research and authoritative reviews on neuroinflammation across scales and disease contexts, with particular emphasis on neurodegenerative disease initiation, progression, biomarker evolution, and therapeutic response. Topics of interest include microglial and astrocyte heterogeneity, neurovascular dysfunction, systemic immune crosstalk, oxidative and mitochondrial stress, inflammasome biology, fluid and PET biomarkers, spatial multi-omics, single-cell analysis, computational modeling, and translational therapeutic strategies. We particularly encourage contributions that bridge mechanistic insight with measurement and intervention, clarifying how inflammatory processes drive, modify, or reflect chronic neurodegenerative disorders, and drawing on acute brain injury models, where useful, to illuminate shared inflammatory pathways. Progress will depend on moving beyond simplistic binaries that frame neuroinflammation and glial responses as solely protective or harmful, and on treating biomarkers not merely as descriptive, but as potentially targetable.[2,4,5,24] The central challenge is to define when, where, and in whom inflammatory responses shift from compensation to pathology. Aligning molecular mechanisms, biomarker resolution, disease stage, and therapeutic timing will be essential to advance truly disease-modifying strategies.[13,18,19]

Funding

This work was financially supported by the following grants: Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grants (RGPIN-2022-04589) and Heart and Stroke Foundation of Canada (HSFC) grant (G-23-0035032) to HSS; Ontario Graduate Scholarship International (OGS-PhD Int), Heart & Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research (HSRLCE) Studentship Award, and China Scholarship Council (CSC) Doctoral Scholarship to XZ.

Conflict of interest

Yuhong Fu, Zengqiang Yuan, and Hong-Shuo Sun serve as Editorial Board Members of this journal. All authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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