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Commentary
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Neuroinflammation: Cause, Consequence, or Therapeutic Target in Chronic Neurodegeneration - A Perspective

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ABSTRACT

Neuroinflammation, the sustained activation of central nervous system (CNS) innate and adaptive immune responses, is increasingly recognized as a central, yet complex, component of chronic neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Rather than being purely reactive, inflammatory processes can precede clinical symptoms, interact bidirectionally with disease-specific proteinopathies (pathological aggregation of proteins such as amyloid-β, tau, α-synuclein, TDP-43, or mutant huntingtin), and alter disease trajectories.

This Perspective synthesizes mechanistic and translational evidence supporting three non-mutually exclusive roles for neuroinflammation: (1) an upstream contributor to disease initiation; (2) an amplifier/consequence of ongoing neurodegeneration; and (3) a mutable therapeutic target whose success depends on timing, cellular specificity, and patient stratification. We highlight key molecular mediators (NLRP3 inflammasome, complement cascade, microglial and astrocytic transcriptional states, innate immune receptors such as TREM2), discuss the evolving understanding beyond binary M1/M2 polarization frameworks, summarize advances in imaging and fluid biomarkers, and propose a pragmatic roadmap for translating immunomodulatory strategies including NLRP3 inhibitors, complement modulators, and TREM2-targeted therapies into precision biomarker-guided trials.

Keywords: *Neuroinflammation; microglia; astrocytes; NLRP3; inflammasome; TREM2; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; Huntington's disease; therapeutic target; biomarkers; innate immunity; neurodegeneration*

1. INTRODUCTION

Neuroinflammation encompasses dynamic immune responses in the CNS involving microglia, astrocytes, endothelial cells, and infiltrating peripheral immune cells. Traditionally viewed as secondary to neuronal injury, emerging evidence now positions immune mechanisms as active contributors to disease susceptibility and progression (1,2).

Genetic studies in Alzheimer's disease have identified immune-related risk loci, particularly variants in TREM2 (5), implicating innate immunity in disease pathogenesis. Microglial dysfunction and chronic activation are also increasingly documented in PD, ALS, and HD (6,8). These converging data suggest that inflammation is not merely reactive but may actively shape neurodegenerative cascades.

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2. METHODS

This Perspective synthesizes high-impact mechanistic, genetic, and translational studies published over the past decade. Studies were selected based on conceptual relevance to immune mechanisms in neurodegeneration, including inflammasome activation, complement-mediated synaptic pruning, microglial and astrocytic state transitions, and translational biomarker research (1–10).

No formal systematic review or meta-analysis was conducted; rather, representative and influential studies were integrated to develop a conceptual framework.

3. RESULTS

3.1 Mechanistic Spectrum: From Protective to Pathogenic

Acute inflammatory responses are host protective; however, chronic or dysregulated activation engages maladaptive programs. Core pathways implicated include:

- NLRP3 inflammasome activation (2,9)
- Persistent NF-κB signaling (2)
- Complement-mediated synapse elimination (6)
- Maladaptive glial transcriptional states (4,8)

Complement components C1q and C3, physiologically involved in developmental synaptic pruning, become aberrantly reactivated in neurodegeneration, contributing to synapse loss (6).

Experimental studies demonstrate that NLRP3 activation links amyloid pathology to IL-1β release and cognitive decline (2,9), establishing a mechanistic bridge between protein aggregation and inflammatory damage.

3.2 Temporal and Genetic Evidence: Cause or Consequence?

Several lines of evidence support a contributory role for neuroinflammation:

1. Genetic association of TREM2 variants with increased AD risk (5).
2. Early microglial activation is detectable in preclinical disease stages (7).
3. Experimental inflammatory stimulation accelerates protein aggregation and neuronal dysfunction (2).

Single-cell transcriptomic analyses have identified disease-associated microglia (DAM), demonstrating that microglial states are dynamic and context-dependent rather than strictly M1/M2 polarized (4,8). These findings support a feed-forward model wherein inflammation both precedes and amplifies pathology.

3.3 Cellular Actors: Microglia and Astrocytes

Microglia

Microglia adopt diverse transcriptional states in neurodegenerative contexts (4,8). Their impact is stage-specific, contributing to both plaque containment and inflammatory injury.

Astrocytes

Activated microglia induce neurotoxic reactive astrocytes through cytokines such as IL-1α, TNF, and C1q (3). While the A1/A2 framework provided early insight, astrocyte activation is now recognized as a spectrum rather than a binary classification (3,6).

3.4 Molecular Nodes of Interest

Central mediators include:

- NLRP3 inflammasome (2,9)
- Complement cascade (6)

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- TREM2 signaling (5,10)
- Glial metabolic and epigenetic reprogramming (6)

TREM2 regulates microglial metabolic fitness and plaque containment. Variants impairing this pathway increase susceptibility to AD (5,10), underscoring the importance of appropriate immune resolution. Adaptive immune components have also been observed in neurodegenerative brains, adding complexity to innate immune-driven models (8).

3.5 Biomarkers and Measurement

Advances in biomarker development include:

- PET imaging of microglial activation (7)
- CSF and plasma cytokines (7)
- Soluble TREM2 measurements (10)
- Complement fragments (6)

Such biomarkers enable staging of inflammatory activity and may define optimal therapeutic windows.

3.6 Therapeutic Opportunities

Epidemiological observations linking NSAID use with reduced dementia risk prompted clinical trials; however, large studies in symptomatic populations largely failed (7). These findings highlight two principles:

1. Timing of intervention is critical.
2. Broad immunosuppression may disrupt beneficial immune functions.

Contemporary approaches emphasize targeted modulation:

- NLRP3 inhibitors (2,9)
- Complement inhibitors (6)
- TREM2 agonistic antibodies (10)

These strategies aim to recalibrate rather than silence immune responses.

4. DISCUSSION

Evidence across neurodegenerative diseases supports a dynamic, bidirectional model of neuroinflammation.

Neuroinflammation can:

- Precede pathology via genetic and early immune activation signals (5,7)
- Amplify protein aggregation and neuronal injury (2,9)
- Serve as a potentially modifiable therapeutic axis (7,10)

Failures of broad anti-inflammatory strategies underscore the importance of precision targeting, biomarker-guided stratification, and stage-specific intervention.

Translational Challenges

- Inter-individual inflammatory heterogeneity
- Stage-dependent immune roles
- Systemic immune side effects
- Cross-disease variability

Adaptive, biomarker-rich clinical trial designs will be essential.

5. CONCLUSION

Neuroinflammation is neither purely causal nor purely reactive; it represents a dynamic and context-dependent dimension of neurodegenerative biology. Evidence from genetic, mechanistic, and translational studies (1–10) supports a feed-forward model in which immune processes initiate, amplify, and potentially modify disease trajectories.

Precision biomarker-guided targeting of inflammatory pathways offers a plausible strategy to alter the course of chronic neurodegenerative disorders.

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AI Use Statement

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Conflict of Interest

None declared.

Ethical Statement

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REFERENCES

1. Heppner, F. L., Ransohoff, R. M., & Becher, B. (2015). Immune attack: the role of inflammation in Alzheimer's disease. *Nature Reviews Neuroscience*, *16*(6), 358-372.
2. Heneka, M. T., Golenbock, D. T., & Latz, E. (2015). Innate immunity in Alzheimer's disease. *Nature immunology*, *16*(3), 229-236.
3. Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., ... & Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*, *541*(7638), 481-487.
4. Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T. K., ... & Amit, I. (2017). A unique microglia type associated with restricting the development of Alzheimer's disease. *Cell*, *169*(7), 1276-1290.
5. Jonsson, T., Stefansson, H., Steinberg, S., Jonsdottir, I., Jonsson, P. V., Snaedal, J., ... & Stefansson, K. (2013). A variant of TREM2 is associated with the risk of Alzheimer's disease. *New England journal of medicine*, *368*(2), 107-116.
6. Hansen, D. V., Hanson, J. E., & Sheng, M. (2018). Microglia in Alzheimer's disease. *Journal of Cell Biology*, *217*(2), 459-472.
7. Van Eldik LJ, Carrillo MC, Cole PE, et al. The roles of inflammation and immune mechanisms in Alzheimer's disease: a perspective for translational research. *Alzheimer's Dement (N Y)*. 2016;2(2):99–109.
8. Hickman, S., Izzy, S., Sen, P., Morsett, L., & El Khoury, J. (2018). Microglia in neurodegeneration. *Nature neuroscience*, *21*(10), 1359-1369.
9. Venegas, C., & Heneka, M. T. (2019). Inflammasome-mediated innate immunity in Alzheimer's disease. *The FASEB Journal*, *33*(12), 13075-13084.
10. Yeh, F. L., Hansen, D. V., & Sheng, M. (2017). TREM2, microglia, and neurodegenerative diseases. *Trends in molecular medicine*, *23*(6), 512-533.