Short Communication
Volume 11: 02, 2025

Immunochemistry and Immunopathology

ISSN: 2469-9756

Open Access

Immunopathology in Neurodegeneration: The Immune System's Role in Brain Health

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Introduction

For decades, the Central Nervous System (CNS) was considered an immune-privileged site, largely protected from peripheral immune responses by the Blood-Brain Barrier (BBB). This long-standing belief has been transformed by accumulating evidence demonstrating that the immune system plays a crucial role in maintaining brain health and, paradoxically, in driving neurodegenerative diseases. Immunopathology-the study of immune system dysfunction-has become essential in understanding the mechanisms underlying neurodegeneration, a category of diseases including Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), multiple sclerosis (MS) and Huntington's Disease (HD) [1].

Immune responses in the CNS involve a complex interplay between resident immune cells, such as microglia and astrocytes and peripheral immune cells that infiltrate under pathological conditions. While these responses can be protective, excessive or chronic immune activation can contribute to neuronal damage, synaptic loss and disease progression. This article explores how immunopathological processes influence neurodegeneration, the mechanisms involved and emerging therapeutic strategies aimed at modulating neuroinflammation to preserve brain health [2].

Description

Microglia are innate immune cells responsible for surveillance, phagocytosis and synaptic pruning. Under pathological stimuli, microglia transition from a homeostatic to an activated phenotype, releasing pro-inflammatory cytokines (e.g., IL-1β, TNF-α, IL-6), ROS and complement proteins. Astrocytes maintain the BBB, regulate neurotransmitter levels and support neuronal metabolism. Reactive astrocytes can adopt neurotoxic (A1) or neuroprotective (A2) phenotypes in response to inflammation. Oligodendrocytes myelinate axons, essential for rapid signal transmission. Immune-mediated demyelination, as in MS, leads to neuronal dysfunction and degeneration. Disruption of the BBB allows T cells, B cells and monocytes to enter the CNS. These cells can recognize CNS antigens and sustain chronic inflammation. Chronic activation of glial cells contributes to sustained release of inflammatory mediators. Cytokines such as IL-1β, TNF-α and IL-6 promote neurotoxicity and synaptic dysfunction. The complement cascade, especially C1q and C3, mediates synapse pruning. Excessive activation contributes to synapse loss in AD and other neurodegenerative diseases. In MS, autoreactive T cells target myelin basic protein (MBP), resulting in demyelination. Autoantibodies against neuronal antigens are implicated in autoimmune encephalitis and paraneoplastic syndromes. Immune cells produce ROS and nitric oxide (NO), which damage cellular components. Mitochondrial dysfunction exacerbates oxidative injury in neurons [3].

Misfolded proteins (e.g., Aβ in AD, α-synuclein in PD, TDP-43 in ALS) trigger immune responses. Microglia attempt to clear aggregates but may become dysregulated and neurotoxic. Gut microbiota influence systemic and CNS immunity via microbial metabolites and endotoxins. Dysbiosis is linked to altered immune profiles and may exacerbate neurodegeneration. Microglial activation around amyloid plaques leads to chronic inflammation. Genetic variants in TREM2 and CD33 influence microglial response and disease risk. Complement-mediated synapse loss occurs early in disease. α-synuclein aggregates activate microglia and inflammasomes. Activated microglia and astrocytes contribute to motor neuron death. Elevated cytokines in CSF and serum reflect systemic inflammation. Autoimmune attack on CNS myelin causes inflammation, demyelination and neurodegeneration. Remyelination is impaired by chronic inflammation. Mutant huntingtin protein triggers microglial activation. Systemic immune abnormalities observed, including increased IL-6 and TNF-α [4].

Anti-inflammatory Agents: NSAIDs, corticosteroids and specific cytokine inhibitors. Natalizumab (anti-integrin) in MS; emerging anti-TREM2 and anti-C1q therapies in AD. Regulatory T cells (Tregs), mesenchymal stem cells (MSCs). Targeting Aβ, tau and α-synuclein to reduce aggregate burden. Genetic and transcriptomic profiling to identify immune-related risk factors. Personalized therapies based on immune signatures and biomarker levels. Diet, exercise and microbiome-targeted interventions modulate systemic inflammation. Reduction of risk factors like infections and pollutants may delay disease onset. Defines immune cell heterogeneity and disease-associated microglial (DAM) phenotypes. Reveals dynamic immune responses across disease stages. Maps immune activity in brain regions with high resolution. Correlates immune signatures with histopathology. Recapitulate human neural-immune interactions in vitro. Used for drug screening and mechanistic studies. Integrates multimodal data to predict progression and treatment response. Aids in early diagnosis based on neuroinflammatory patterns. Need for better understanding of context-specific immune responses. Therapeutics should preserve beneficial immunity while curbing pathology. Therapies must distinguish between disease-promoting and homeostatic microglial/astrocyte states. Multimodal approaches addressing inflammation, aggregation and neuroprotection are likely more effective. Ensure access to diagnostics and advanced therapies [5].

Conclusion

Immunopathology has transformed our understanding of neurodegenerative diseases by highlighting the central role of the immune system in brain health and disease. Rather than mere bystanders, immune cells are active participants in neurodegeneration-capable of both protecting and harming neurons. By dissecting the complex immune landscape of the CNS, researchers are uncovering novel biomarkers and therapeutic targets that offer hope for earlier diagnosis and more effective interventions. As we move toward an era of precision neuroimmunology, the integration of immunopathological insights with cutting-edge technologies will be key to developing strategies that not only slow neurodegeneration but also preserve cognitive and motor function, ultimately improving the lives of millions affected by these debilitating conditions.

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Received: 03 April, 2025, Manuscript No. icoa-25-167414; **Editor assigned:** 05 April, 2025, PreQC No. P-167414; **Reviewed:** 17 April, 2025, QC No. Q-167414, **Revised:** 22 April, 2025, Manuscript No. R-167414; **Published:** 29 April, 2025, DOI: 10.37421/2469-9756.2025.11.296

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Francischini, Tommasino. "Immunopathology in Neurodegeneration: The Immune System's Role in Brain Health." *Immunochem Immunopathol* 11 (2025): 296.