Neuroinflammation as a Double-Edged Sword in the Central Nervous System: Cellular, Molecular, and Temporal Determinants of Neurodegeneration

Oriare A. K.*& Ajiboye R. F.

Department of Human Physiology, KolaDaisi University, Ibadan, Nigeria

**Corresponding Author:* ayomide.oriare@koladaisiuniversity.edu.ng; ayomidekarimat@gmail.com;

Abstract

Background: Neuroinflammation is a tightly regulated biological response in the central nervous system (CNS), serving as both a protective mechanism and a driver of pathological progression. Under physiological conditions, it supports immune surveillance, synaptic remodelling, and tissue repair. However, when dysregulated or chronically sustained, it disrupts neuronal homeostasis and accelerates neurodegenerative cascades. **Objective**: This review examines the cellular, molecular, and temporal frameworks that dictate inflammatory outcomes in the CNS and delineates the mechanistic boundaries between acute resolution and chronic neurotoxicity. **Methodology**: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for narrative reviews, the review synthesised peer-reviewed literature on glial biology, cytokine signalling, phase-specific immune dynamics, and biomarker strategies. Thematic analysis was used to integrate findings across cellular, molecular, and temporal domains. **Results**: Resident glia, particularly microglia and astrocytes, coordinate dynamic cross-talk with neurons, vascular elements, and peripherally derived immune cells. Their activation states are governed by pattern-recognition receptors, intracellular signalling cascades, and cytokine networks that shift between reparative and destructive phenotypes depending on contextual cues and exposure duration. Neuroinflammation is a dynamic, context-dependent process. Precision immunomodulation guided by cellular specificity, temporal staging, and molecular profiling offers a more viable therapeutic pathway than broad immunosuppression. **Conclusion**: This review outlines actionable research priorities for next-generation CNS therapeutics. **Recommendations:** Prioritise phase-specific immunomodulation over broad immunosuppression to preserve protective clearance mechanisms; and integrate multi-omics and fluid biomarker profiling for precise patient stratification in clinical trials.

Keywords: Neuroinflammation; Microglia; Astrocytes; Cytokines; Neurodegeneration; Immunomodulation

Introduction

Evolution of the neuroinflammation concept

Inflammation within the central nervous system has transitioned from being viewed as a secondary pathological event to a recognised hallmark and active driver of neurological and neurodegenerative disorders. Rather than operating as a uniform disease process, CNS inflammation follows a highly contextual, spatiotemporally regulated trajectory: acute, well-coordinated responses maintain tissue integrity, facilitate debris clearance, and promote

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functional recovery, whereas persistent activation disrupts synaptic function, compromises the blood–brain barrier (BBB), and accelerates neuronal loss (Nosi et al., 2021; Di Benedetto et al., 2017; Chitnis & Weiner, 2017; Profaci et al., 2020). The CNS immune landscape is shaped by resident glial populations, endothelial networks, and controlled peripheral immune surveillance (Li et al., 2023; Müller et al., 2025; Silvin et al., 2023). These cells continuously sample their microenvironment via pattern-recognition receptors and respond to diverse stimuli, including pathogens, misfolded proteins, mechanical trauma, and metabolic stress. Their downstream signalling cascades ultimately determine whether inflammation resolves, remains protective, or transitions into a maladaptive state (Chitnis & Weiner, 2017; Nosi et al., 2021; Silbereis et al., 2016).

The dual nature of CNS inflammation

During acute phases, resident microglia rapidly adopt phagocytic and reparative phenotypes, coordinating with astrocytes to clear cellular debris, restore ionic homeostasis, and contain tissue damage (Butovsky & Weiner, 2018; Morganti et al., 2021). Concurrently, transient BBB permeability facilitates controlled leukocyte trafficking for pathogen clearance and wound healing (Profaci et al., 2020). However, when inflammatory triggers persist or resolution pathways fail, chronic neuroinflammation emerges as a self-sustaining process characterised by sustained cytokine release, microglial priming, astrocyte reactivity, and progressive BBB breakdown (Zhang et al., 2023). This maladaptive state drives excitotoxicity, aberrant synaptic pruning, oxidative stress, and impaired neurogenesis, ultimately culminating in circuit disintegration and neurodegeneration (Mathys et al., 2019; Schafer & Stevens, 2015). Critically, the transition from protective surveillance to chronic pathology is not governed by a single molecular switch but by dynamic feedback loops involving glial–neuronal–vascular crosstalk, metabolic reprogramming, and epigenetic remodelling (Paolicelli et al., 2022; Haney et al., 2024).

Knowledge gaps and review objectives

Despite extensive research, a persistent gap exists in the synthesis of how cellular heterogeneity, molecular crosstalk, and temporal progression collectively dictate neuroinflammatory outcomes. Historically, glial activation was oversimplified into binary paradigms (e.g., M1/M2 microglia, A1/A2 astrocytes), which have since been refined by single-cell and spatial transcriptomics, revealing continuous phenotypic spectra and context-dependent functional states (Hammond et al., 2019; Masuda et al., 2020). This review addresses that gap by integrating recent advances in glial biology, cytokine signalling, and phase-specific immune dynamics. We critically evaluate how simplified activation paradigms have been refined by single-cell omics, delineate the dual roles of key molecular mediators, and map the transition from acute resolution to chronic neurodegeneration. By framing neuroinflammation as a temporally and contextually regulated process, this review provides a mechanistic foundation for precision therapeutic development and outlines priority research directions for the field.

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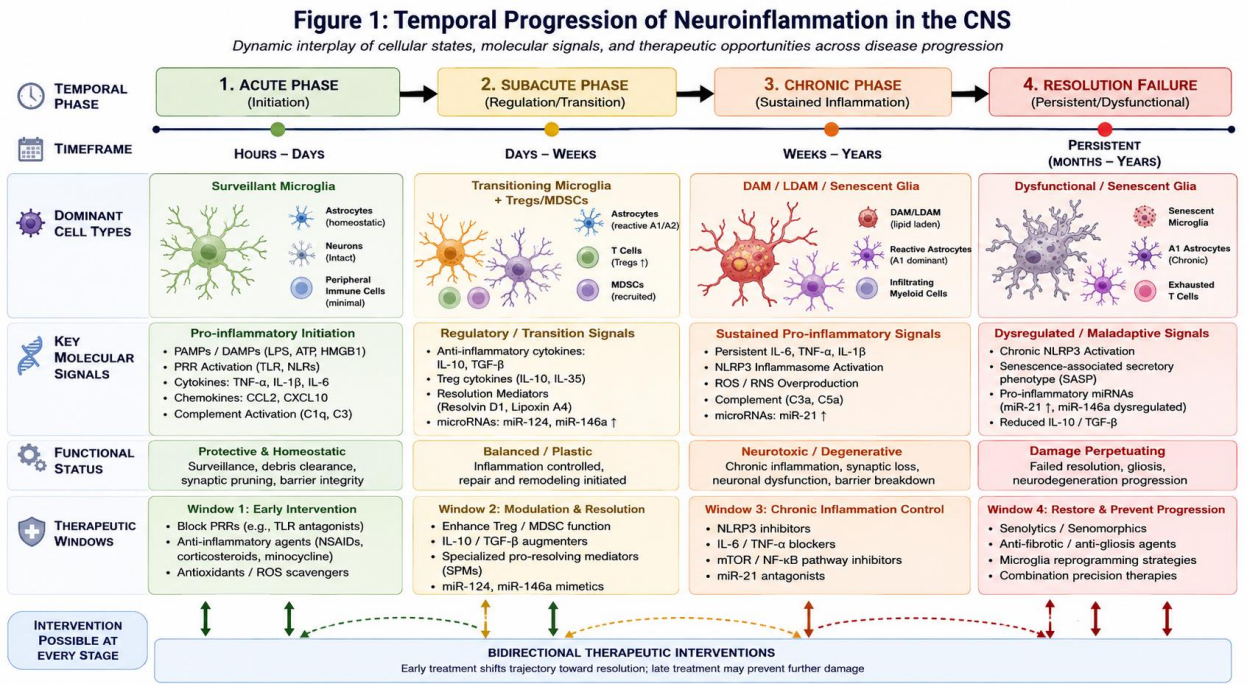

Figure 1. Temporal Progression of Neuroinflammation in the Central Nervous System. This schematic illustrates the dynamic interplay of cellular states, molecular signals, and therapeutic opportunities across the four distinct phases of neuroinflammatory progression. Phase 1 (Acute; Hours–Days): Initiated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), surveillant microglia rapidly activate alongside homeostatic astrocytes, releasing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines (CCL2, CXCL10) to clear debris and contain injury. This protective phase is characterised by intact neurons and minimal peripheral immune infiltration. Phase 2 (Subacute; Days–Weeks): A critical transition window where microglia shift towards reparative phenotypes, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) are recruited, and anti-inflammatory cytokines (IL-10, TGF-β) promote resolution. Reactive astrocytes (A1/A2 balance) support tissue remodelling. Phase 3 (Chronic; Weeks–Years): Failure to resolve inflammation leads to sustained activation of disease-associated microglia (DAM), lipid-droplet-accumulating microglia (LDAM), and senescent glia. Persistent NLRP3 inflammasome activation, ROS/RNS overproduction, and complement cascade engagement (C3a, C5a) drive synaptic loss, BBB breakdown, and neurodegeneration. Phase 4 (Resolution Failure; Persistent Months–Years): Dysfunctional, senescent glia exhibit a senescence-associated secretory phenotype (SASP) with chronically elevated pro-inflammatory miRNAs (miR-21↑, miR-146a dysregulated) and reduced resolution mediators (IL-10/TGF-β), perpetuating gliosis and neurodegenerative progression. Therapeutic Windows: Four distinct intervention opportunities are highlighted: (1) Early PRR blockade and antioxidant support; (2) Enhancement of Treg/MDSC function and specialised pro-resolving mediator (SPM) administration; (3) NLRP3 inhibition and cytokine pathway blockade; (4) Senolytics and microglial reprogramming strategies. Bidirectional interventions (bottom

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arrows) emphasise that early treatment can shift trajectory towards resolution, while late interventions may prevent further damage but cannot reverse established neurodegeneration. This framework underscores the necessity of phase-matched, biomarker-guided precision immunomodulation rather than uniform immunosuppression. Abbreviations: DAM = disease-associated microglia; LDAM = lipid-droplet-accumulating microglia; MDSC = myeloid-derived suppressor cell; PAMP = pathogen-associated molecular pattern; DAMP = damage-associated molecular pattern; PRR = pattern recognition receptor; TLR = toll-like receptor; NLR = NOD-like receptor; Treg = regulatory T cell; SPM = specialised pro-resolving mediator; NLRP3 = NOD-like receptor family pyrin domain-containing 3; ROS = reactive oxygen species; RNS = reactive nitrogen species; BBB = blood–brain barrier; SASP = senescence-associated secretory phenotype.

Note: Image generated using Alibaba Cloud (Qwen) on July 20, 2026. Prompt: "Temporal progression of neuroinflammation in the central nervous system". Created by A.K Oriare.

Materials and Methods

This narrative review was guided by PRISMA-informed reporting principles for narrative syntheses to enhance transparency, reproducibility, and methodological rigour in literature identification, screening, and thematic integration. A comprehensive, reproducible literature search was performed across PubMed, Scopus, and Web of Science from database inception to 2025, using a structured keyword strategy combining Medical Subject Headings (MeSH) terms and free-text terms related to neuroinflammation, microglia, astrocytes, cytokines, neurodegeneration, immunomodulation, single-cell transcriptomics, and resolution pharmacology. Boolean operators were applied to maximise sensitivity and specificity (e.g., ("neuroinflammation" OR "glial activation") AND ("microglia" OR "astrocytes") AND ("cytokine signalling" OR "NLRP3" OR "TREM2")). Articles were screened for relevance based on title, abstract, and full-text review by two independent reviewers; disagreements were resolved through consensus or consultation with a third reviewer.

Inclusion criteria prioritised peer-reviewed primary research articles, high-impact systematic/narrative reviews, and methodological papers published in English, with emphasis on studies employing single-cell/spatial omics, longitudinal biomarker approaches, human xenograft models, or CNS-penetrant therapeutic strategies.

Exclusion criteria encompassed non-peer-reviewed sources, studies lacking experimental validation, and publications focused exclusively on non-CNS inflammatory conditions. Data were synthesised thematically using a structured analytical framework to address cellular heterogeneity, molecular signalling networks, temporal progression, spatial compartmentalisation, and translational implications of neuroinflammatory responses in the CNS. No meta-analysis was performed due to the narrative scope, methodological heterogeneity, and evolving nature of the included evidence. All references cited are peer-reviewed and publicly accessible via DOI or PMID.

Results and Discussion

Cellular Determinants of Neuroinflammation

Neuroinflammatory responses are orchestrated by a highly integrated network of CNS-resident and peripherally derived cells that interact dynamically to maintain or disrupt neural homeostasis. While historically characterised as passive support cells, glia and infiltrating immune populations actively shape inflammatory

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trajectories through phenotypic plasticity, metabolic reprogramming, and intercellular signalling. Understanding the contextual triggers that govern their functional transitions is essential for deciphering when neuroinflammation serves protective versus pathogenic roles.

Microglial Heterogeneity and Functional States

Microglia originate from yolk sac progenitors and establish residence in the CNS prior to blood–brain barrier formation, maintaining a ramified, surveillant phenotype under physiological conditions characterised by continuous environmental monitoring, synaptic pruning, and debris clearance (Nosi et al., 2021; Tay et al., 2017). Upon detection of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), microglia transition to activated states that release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), reactive oxygen species (ROS), and nitric oxide (NO) via NF-κB, MAPK, and NLRP3 inflammasome pathways (Figuera-Losada et al., 2014; Gülke et al., 2018; Chen et al., 2023). Historically, microglial activation was simplified into pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. However, recent single-cell transcriptomic and proteomic studies reveal a far more heterogeneous landscape. Disease-associated microglia (DAM), for instance, emerge in neurodegenerative contexts and are regulated by TREM2 and APOE signalling, exhibiting enhanced phagocytic capacity alongside context-dependent inflammatory output (Colonna & Butovsky, 2017; Paolicelli et al., 2022; Haney et al., 2024). Similarly, lipid-droplet-accumulating microglia (LDAM) arise during ageing and metabolic stress, demonstrating impaired clearance and heightened oxidative stress (Paolicelli et al., 2022). These findings underscore that microglial function exists along a continuum shaped by microenvironmental cues rather than fixed binary states. Table 1 summarises the key cellular phenotypes in CNS neuroinflammation, including their activation markers, primary functions, context-dependent outcomes, and representative references. This phenotypic plasticity is further modulated by brain macrophage heterogeneity and region-specific transcriptional programmes, which collectively dictate the functional output of the innate immune response in the CNS (Silvin et al., 2023; Wang et al., 2023).

Astrocyte Reactivity Spectrum

Astrocytes maintain neuronal homeostasis through neurotransmitter recycling, metabolic support, ion buffering, and BBB integrity (Kunchok et al., 2019; Hol & Pekny, 2015). During neuroinflammation, they adopt reactive phenotypes historically classified as neurotoxic (A1) or neuroprotective (A2). A1 astrocytes, induced by microglial-derived IL-1α, TNF-α, and C1q, upregulate complement factors and release neurotoxic mediators, exacerbating synaptic loss (Lian et al., 2016). Conversely, A2 astrocytes, driven by IL-4 or IL-10, secrete neurotrophic factors (BDNF, GDNF) and support tissue repair (Henneberger et al., 2010; Albini et al., 2023). Like microglia, this dichotomy oversimplifies astrocytic diversity. Regional transcriptomic profiling identifies multiple astrocyte subtypes with distinct marker expression and functional specialisations across brain regions (John Lin et al., 2017). Reactive astrocytes also contribute to glial scar formation, which initially isolates injury and restricts leukocyte infiltration but may later impede axonal regeneration if resolution fails (Wanner et al., 2013; Patani et al., 2023). Consequently, the astrocyte reactivity spectrum is

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now understood as a multidimensional continuum influenced by local metabolic demands, epigenetic modifications, and specific neurotoxic environments, rather than a simple binary switch (Müller et al., 2025; Patani et al., 2023).

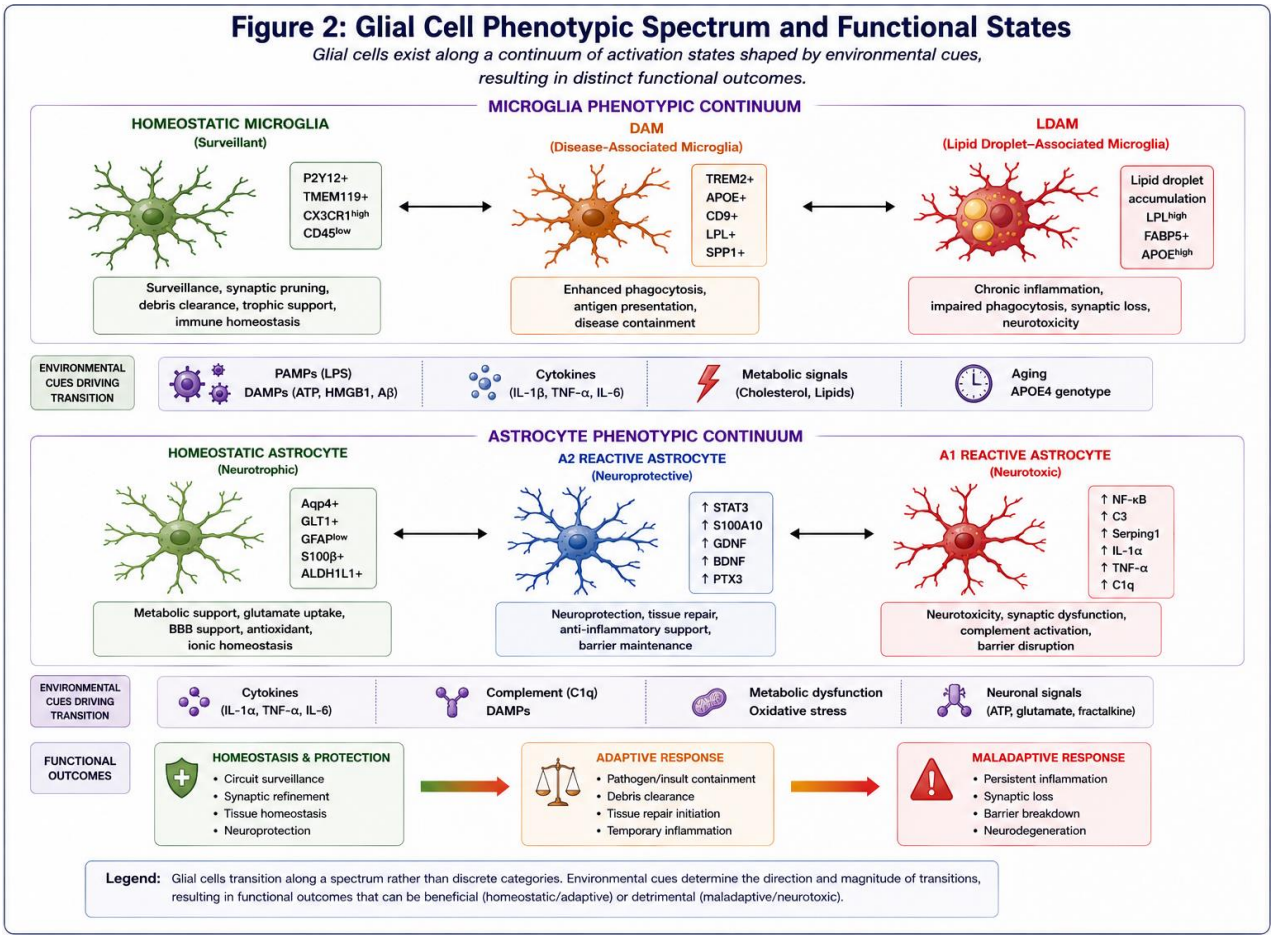

Figure 2. Glial Cell Phenotypic Spectrum and Functional States. Homeostatic glial cells undergo dynamic phenotypic transitions in response to environmental cues such as cytokines, damage-associated molecular patterns (DAMPs), metabolic stress, and lipid accumulation. Microglia transition from homeostatic P2Y12⁺/TMEM119⁺ states to disease-associated microglia (DAM; TREM2⁺/APOE⁺) and ultimately lipid droplet–accumulating microglia (LDAM) during persistent neuroinflammation. Astrocytes similarly shift from homeostatic phenotypes to neuroprotective A2 reactive astrocytes or neurotoxic A1 reactive astrocytes depending on inflammatory signalling. Each phenotype contributes distinct functional outcomes ranging from immune surveillance and tissue repair to chronic inflammation, synaptic dysfunction, and neuronal degeneration.
Note: Image generated using Alibaba Cloud (Qwen) on July 20, 2026. Prompt: "Microglial heterogeneity and functional states and astrocyte reactivity spectrum". Created by A.K Oriare.

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Oligodendrocyte-Immune Interactions

Oligodendrocytes, once considered passive bystanders, actively participate in neuroimmune signalling by expressing cytokine receptors and secreting chemokines that modulate microglial recruitment and myelin repair (Peferoen et al., 2014). During inflammation, they become vulnerable to cytotoxic T-cell-mediated lysis, NK cell activity, and cytokine-induced stress, particularly in demyelinating conditions (Omari et al., 2005; Cannella & Raine, 2004; Jurewicz et al., 1998). Furthermore, the vulnerability of the oligodendrocyte lineage highlights the critical need for myelin-directed immunomodulatory strategies that protect these cells from bystander immune damage while preserving their reparative functions (Adamu et al., 2024; Zhang et al., 2023).

Peripheral Immune Cell Infiltration

Peripheral immune cells, including T cells, monocytes, and macrophages, gain CNS access following BBB disruption or meningeal immune surveillance. Regulatory T cells (Tregs) and Th2 populations generally exert anti-inflammatory effects via IL-10 and TGF-β, whereas Th1 and Th17 subsets amplify neuroinflammation through IFN-γ and IL-17 (Xie et al., 2015; Matejuk et al., 2021). Bidirectional crosstalk between infiltrating immune cells, microglia, and astrocytes establishes feedback loops that can either resolve injury or perpetuate chronic activation (Sierra et al., 2013; Leng & Edison, 2021). The precise orchestration of this peripheral-central immune interface remains a major therapeutic frontier, as controlling leukocyte trafficking without abolishing essential CNS immune surveillance could prevent the transition from acute resolution to chronic neurodegeneration (Silvin et al., 2023).

Table 1. Cellular phenotypes in CNS neuroinflammation: markers, functions, and context-dependent roles

Cell Type	Key Activation Markers	Primary Functions	Context-Dependent Outcome	Representative References
Homeostatic Microglia	P2Y12, TMEM119, CX3CR1	Synaptic pruning, debris clearance, immune surveillance	Protective maintenance of CNS homeostasis	Nosi et al., 2021; Paolicelli et al., 2022
Disease-Associated Microglia (DAM)	TREM2, APOE, CD9, Lipid droplets	Enhanced phagocytosis, amyloid/tau clearance, context-dependent cytokine release	Early protective clearance → late pro-inflammatory neurotoxicity	Colonna & Butovsky, 2017; Haney et al., 2024

ISSN: 1595-1693

A1 Reactive Astrocytes	C3, GFAP↑, Vimentin, NF-κB	Complement activation, cytokine release, BBB modulation	Synaptic loss, neuronal toxicity, impaired plasticity	Lian et al., 2016; Patani et al., 2023
A2 Reactive Astrocytes	Arg1, S100A10, GDNF, BDNF	Neurotrophic support, glutamate clearance, inflammation resolution	Tissue repair, metabolic support, neuroprotection	Henneberger et al., 2010; Albini et al., 2023
Peripheral Macrophages/Monocytes	CD68, CCR2, Ly6C	Phagocytosis, cytokine production, ECM remodelling	Acute debris clearance → chronic fibrosis if unresolved	Silvin et al., 2023; Li & Barres, 2018

Note: Collectively, Table 1 illustrates that glial and immune phenotypes exist along functional continua rather than fixed binary states, with neuroprotective or neurotoxic outcomes dictated by microenvironmental cues and resolution capacity. This cellular plasticity directly supports our central thesis that therapeutic efficacy depends on targeting specific glial subsets rather than applying broad immunosuppression.

Molecular Mediators: Protective vs Pathogenic Signalling

The functional outcome of neuroinflammation depends on the balance and timing of molecular mediators, including cytokines, chemokines, reactive species, and pattern recognition pathways.

Cytokine Signalling Networks

Cytokines operate within complex, pleiotropic networks where dose, duration, and receptor availability dictate biological outcomes. IL-6 exhibits dual roles: classical signalling through membrane-bound IL-6R supports tissue repair and barrier integrity, whereas trans-signalling via soluble IL-6R drives chronic inflammation and neuronal stress (Heinrich et al., 2003; Schaper & Rose-John, 2015; Tanaka et al., 2014; Shan, 2024). IL-1α functions as an alarmin released during necrosis, while IL-1β requires caspase-1-dependent inflammasome cleavage for activation (Dinarello, 2009; Cullen et al., 2015). Persistent IL-1β signalling is linked to synaptic dysfunction and neurodegeneration, whereas acute pulses facilitate clearance and repair. IL-10 serves as a critical resolution cytokine, suppressing pro-inflammatory mediator release and promoting immune quiescence via STAT3 signalling (Sabat et al., 2010; Saraiva & O'Garra, 2010). TNF-α further illustrates duality: membrane-bound TNF-α supports synaptic plasticity and oligodendrocyte survival, whereas soluble TNF-α drives excitotoxicity and BBB disruption (Probert, 2015; Brambilla et al., 2015). The clinical failure of broad TNF-α blockade in neurodegeneration underscores the necessity of pathway-specific targeting. The regulation of these cytokine networks is increasingly recognised to be modulated by non-coding RNAs, which fine-tune microglial activation and

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neuroinflammatory cascades in conditions such as Alzheimer's disease (He et al., 2023).

Chemokine-Mediated Cell Recruitment

Chemokines (e.g., CCL2, CXCL8, CX3CL1) direct immune cell trafficking and amplify glial activation, with GPCR-mediated signalling modulating adhesion, migration, and secondary mediator release (Rot & von Andrian, 2004; Zlotnik & Yoshie, 2012; Wang et al., 2024). The precise spatial distribution of these chemokine gradients not only dictates the volume of immune infiltration but also determines the specific phenotypic composition of the recruited leukocytes, thereby influencing whether the local microenvironment shifts towards resolution or chronic pathology (Adamu et al., 2024; Zhang et al., 2023).

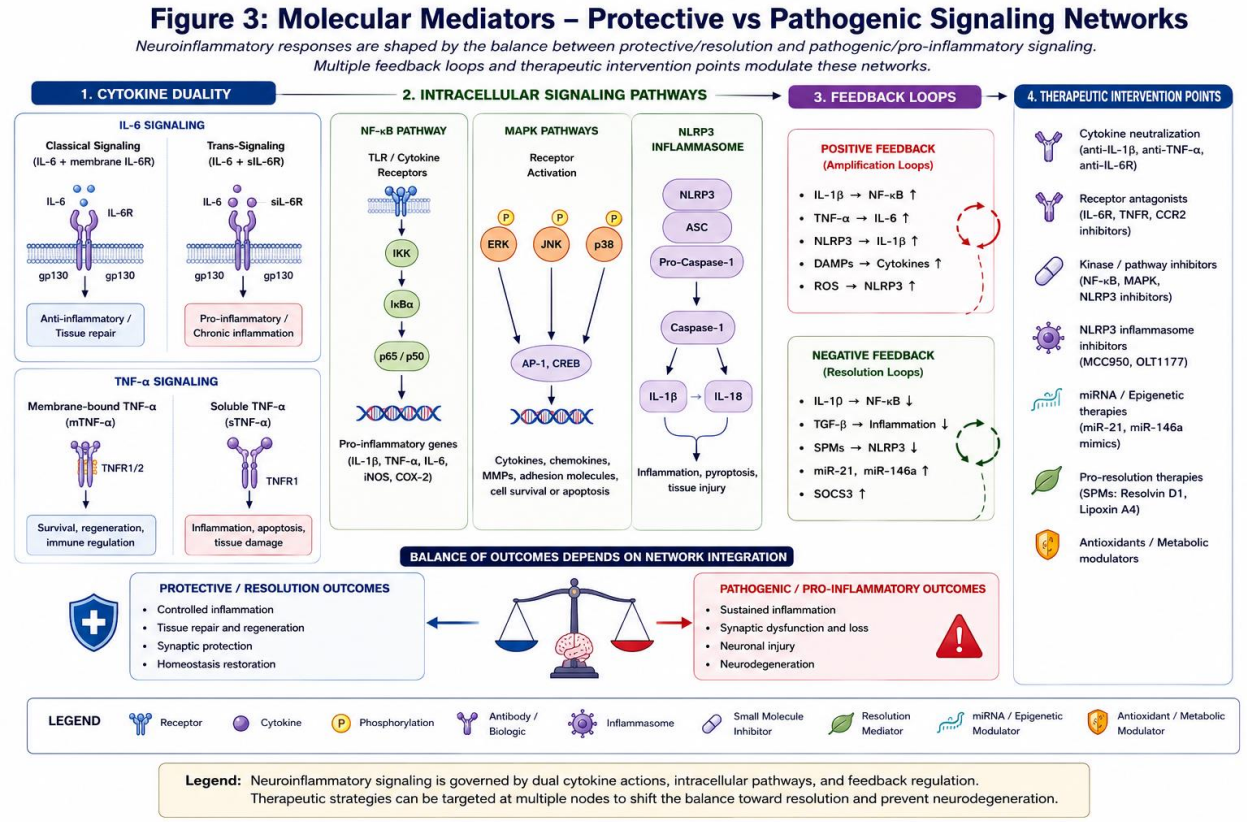

Figure 3. Molecular Mediators: Protective and Pathogenic Signalling Network in Neuroinflammation. Neuroinflammatory signalling is governed by a balance between protective and pathogenic molecular pathways. Cytokines such as IL-6 and TNF-α exert context-dependent effects through classical versus trans-signalling and membrane-bound versus soluble receptor pathways, respectively. These signals converge on intracellular regulators including NF-κB, MAPK, and the NLRP3 inflammasome, which coordinate inflammatory gene expression, cytokine production, and inflammasome activation. Positive feedback loops amplify inflammatory responses, whereas anti-inflammatory mediators promote resolution. Therapeutic intervention points targeting cytokine signalling, inflammasome activation, and intracellular pathways are highlighted.

ISSN: 1595-1693

Note: Image generated using Alibaba Cloud (Qwen) on July 20, 2026. Prompt: "Molecular mediators: protective vs pathogenic signalling explaining how the balance and timing of cytokines, chemokines, reactive species, and pattern-recognition pathways determine whether neuroinflammation is protective or pathogenic". Created by A.K Oriare.

Oxidative and Nitrosative Stress Pathways

ROS and RNS function as both signalling molecules and cytotoxic effectors. Controlled production facilitates pathogen clearance and redox signalling, whereas chronic overproduction damages lipids, proteins, and DNA, activating NF-κB and sustaining inflammatory loops (Mittal et al., 2014; Nathan & Cunningham-Bussel, 2013; Scarian et al., 2024). Targeting these oxidative and nitrosative stress pathways, particularly through the modulation of mitochondrial dysfunction and metabolic reprogramming, represents a critical frontier in halting the transition from acute neuroinflammation to chronic neurodegeneration (Müller et al., 2025).

Pattern Recognition Receptor Activation

PRR activation (TLRs, NLRs, RLRs) bridges innate sensing to chemokine transcription, establishing feed-forward cycles that determine whether inflammation resolves or escalates (Kawai & Akira, 2010; Takeuchi & Akira, 2010; Anilkumar & Wright-Jin, 2024). Recent single-cell transcriptomic advances have further elucidated how specific PRR activation thresholds dictate microglial phenotypic transitions, highlighting the NLRP3 inflammasome and TREM2-dependent pathways as pivotal checkpoints in disease-associated microglial states (Paolicelli et al., 2022; Haney et al., 2024; Xu et al., 2025).

Table 2. Key cytokines and molecular mediators in CNS inflammation: signalling pathways and functional duality

Mediator	Primary Signalling Pathway	Protective/Acute Role	Pathogenic/Chronic Role	Clinical/Experimental Evidence
IL-6	Classical (mbIL6R/gp130) & Trans (sIL6R/gp130)	Tissue repair, leukocyte switching, barrier maintenance	Chronic trans-signalling drives synaptic loss, BBB disruption	Schaper & Rose-John, 2015; Tanaka et al., 2014
IL-1α/β	MyD88/NF-κB, NLRP3/Caspase-1	Acute DAMP clearance, inflammasome activation, repair initiation	Sustained release promotes excitotoxicity, tau/Aβ accumulation	Dinarello, 2009; Heneka et al., 2018
IL-10	JAK1/Tyk2 → STAT3	Suppresses TNF-α/IL-1β, promotes microglial quiescence	Excessive suppression impairs pathogen clearance, delays repair	Saraiva & O'Garra, 2010; Sabat et al., 2010

 ISSN: 1595-1693

TNF-α	TNFR1 (NF-κB/caspase) & TNFR2 (PI3K/Akt)	Synaptic plasticity, oligodendrocyte survival, acute defence	Soluble TNF-α drives BBB breakdown, neuronal apoptosis	Probert, 2015; Tracey et al., 2008
ROS/RNS	NOX, iNOS, mitochondrial ETC	Microbial killing, redox signalling, acute pathogen clearance	Lipid peroxidation, nitrotyrosine formation, chronic NF-κB activation	Mittal et al., 2014; Nathan & Cunningham-Bussel, 2013

Note: Table 2 outlines key cytokines and molecular mediators implicated in neuroinflammatory signalling pathways within the CNS. It demonstrates the dual protective and pathogenic roles of inflammatory mediators depending on signalling context, duration of activation, and disease stage, thereby underscoring the complexity of therapeutic targeting in neurodegenerative disorders.

Temporal Dynamics of Neuroinflammation

Neuroinflammation progresses through distinct temporal phases, each characterised by shifting cellular phenotypes and molecular priorities.

Acute Phase: Immediate Response Mechanisms

Acute neuroinflammation, triggered by infection, trauma, or ischaemia, initiates rapid microglial activation and cytokine release to clear debris, restrict pathogen spread, and initiate repair (Crutcher et al., 2006; Popovich & Longbrake, 2008). This phase is typically self-limiting and neuroprotective. During this critical window, pattern-recognition receptor signalling ensures that the inflammatory response is tightly contained, prioritising rapid pathogen neutralisation and debris clearance without inducing collateral neuronal damage (Morganti et al., 2021).

Subacute Phase: Transition and Resolution

During days to weeks post-injury, immune cells shift from pro-inflammatory to reparative functions. DAMP clearance, trophic factor release, and regulatory T-cell infiltration support tissue remodelling and circuit reorganisation (Shichita et al., 2017; Mastorakos et al., 2021). Premature immunosuppression during this window impairs functional recovery, highlighting the necessity of phase-aware intervention (Ito et al., 2019). Consequently, this transitional period represents a fragile equilibrium where the successful recruitment of regulatory T cells (Tregs) and the secretion of anti-inflammatory cytokines are paramount for preventing the escalation into chronic pathology (Adamu et al., 2024).

Chronic Phase: Sustained Inflammation

Persistent activation leads to BBB compromise, peripheral immune infiltration, and sustained cytokine release, driving progressive neurodegeneration (Tansey et al., 2007). In ageing, low-grade systemic inflammation ("inflammageing") exacerbates CNS vulnerability through cellular senescence, mitochondrial dysfunction, and miRNA-mediated NF-κB activation (Franceschi & Campisi, 2014; Ferrucci & Fabbri, 2018; Olivieri et al., 2012). Chronic neuroinflammation thus represents a failure of resolution rather than an exaggerated acute response. This maladaptive state is further perpetuated by metabolic reprogramming within glial cells, such as lipid

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droplet accumulation in microglia, which locks them into a self-sustaining, neurotoxic feedback loop (Haney et al., 2024; Müller et al., 2025).

Resolution Failure and Pathological Consequences

Successful resolution depends on specialised pro-resolving mediators (SPMs; e.g., resolvins, protectins, maresins), IL-10/TGF-β signalling, and metabolic reprogramming of glia (Ponce et al., 2022; Valente et al., 2022). Failure to engage these pathways results in maladaptive scarring, persistent oxidative stress, and neurodegeneration.

Clinical Significance of the Protective to Maladaptive Transition:

Understanding this temporal shift is of paramount clinical significance. Therapeutic interventions that broadly suppress inflammation during the acute phase may inadvertently impair debris clearance and tissue repair, worsening long-term outcomes (Zhang et al., 2023). Conversely, failing to intervene during the subacute-to-chronic transition allows self-sustaining neurotoxic loops to become established, rendering later treatments less effective. Thus, clinical trial designs must incorporate temporal staging to ensure that immunomodulatory therapies are administered during the optimal therapeutic window, shifting the paradigm from blanket immunosuppression to phase-matched precision medicine (Adamu et al., 2024). Ultimately, leveraging fluid biomarkers and advanced neuroimaging to identify a patient's specific inflammatory phase will be the cornerstone of deploying SPMs and targeted immunomodulators to restore homeostatic balance rather than merely suppressing the immune response (Zhang et al., 2023; Ponce et al., 2022).

Neuroinflammation Across CNS Disorders

Chronic neuroinflammation is a unifying feature across neurodegenerative and neurovascular disorders, albeit with disease-specific triggers and cellular emphases.

Table 3. Temporal phases of neuroinflammation: cellular/molecular drivers and therapeutic windows (Ponce et al., 2022; Valente et al., 2022)

Phase	Duration	Dominant Cellular Players	Key Molecular Signals	Therapeutic Strategy Window
Acute	Hours–Days	Surveillant microglia, resident astrocytes	PAMP/DAMP sensing, NF-κB, IL-1β, TNF-α	Support clearance; avoid broad immunosuppression
Subacute	Days–Weeks	Transitioning microglia, infiltrating monocytes, Tregs	IL-10, TGF-β, trophic factors (BDNF, GDNF)	Promote phenotypic shift; enhance SPM production
Chronic	Weeks–Years	DAM/LDAM microglia, reactive	Sustained IL-6, NLRP3, ROS/RNS, complement	Precision immunomodulation; biomarker-guided targeting

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Failure of Resolution	Persistent	astrocytes, fibroblasts Senescent glia, fibrotic stromal cells, peripheral macrophages	miR-21/146a, NF-κB, TGF-β, ECM deposition	Target resolution pathways; restore metabolic homeostasis

Note: Table 3 maps the dynamic progression of neuroinflammation across distinct temporal phases, revealing how shifting cellular dominance and molecular priorities create narrow, phase-specific therapeutic windows. These findings validate our central thesis that clinical interventions must be timed to inflammatory stage rather than deployed uniformly, positioning biomarker-guided, phase-matched immunomodulation as the cornerstone of next-generation CNS therapeutics.

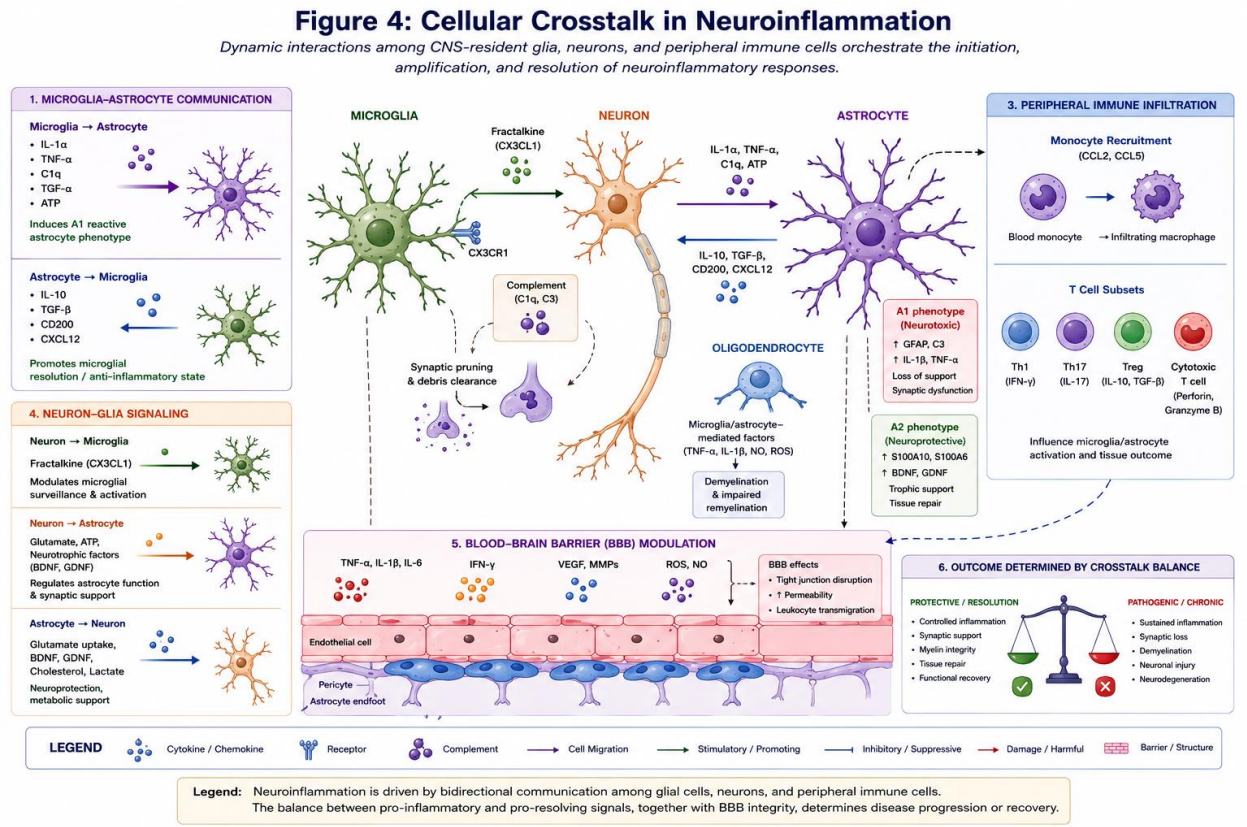

Figure 4. Cellular Crosstalk in Neuroinflammation. Bidirectional communication among microglia, astrocytes, neurons, infiltrating immune cells, and the blood–brain barrier orchestrates the progression of neuroinflammation. Activated microglia release IL-1α, TNF-α, and C1q to induce neurotoxic A1 astrocytes, while neuron–microglia signalling through the CX3CL1–CX3CR1 axis and complement pathways regulates synaptic remodelling and immune surveillance. Peripheral T cells and monocytes infiltrate the CNS following blood–brain barrier disruption, further amplifying inflammatory signalling. These interconnected cellular networks collectively determine whether neuroinflammation resolves or progresses towards chronic neurodegeneration.

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Note: Image generated using Alibaba Cloud (Qwen) on July 20, 2026. Prompt: "Cellular crosstalk in neuroinflammation". Created by A.K Oriare.

Alzheimer's Disease (AD)

Aβ and tau pathology activate microglial TLR/RAGE signalling, driving chronic cytokine release and oxidative stress that impair amyloid clearance and accelerate synaptic loss (Akiyama et al., 2000; Reed-Geaghan et al., 2009). Furthermore, the failure of microglial phagocytosis is closely linked to genetic risk factors such as APOE4, which promotes the accumulation of toxic lipid droplets in disease-associated microglia (DAM), locking them into a neurotoxic state (Haney et al., 2024). Concurrently, reactive astrocytes, induced by microglial-derived cytokines, upregulate complement cascade components (e.g., C1q, C3) that tag viable synapses for aberrant phagocytosis, directly linking neuroinflammation to early cognitive decline (Lian et al., 2016; Patani et al., 2023). This chronic state is further exacerbated by "inflammageing," where peripheral systemic inflammation primes central microglial responses, lowering the threshold for neurotoxic activation (Müller et al., 2025).

Parkinson's Disease (PD)

α-Synuclein aggregates trigger TLR2/4-mediated NF-κB activation in microglia, amplifying dopaminergic neurotoxicity through ROS and pro-inflammatory cytokines (Béraud & Maguire-Zeiss, 2012; Pajares et al., 2020). The vulnerability of dopaminergic neurons in the substantia nigra is compounded by their high metabolic demand, low antioxidant capacity, and iron accumulation, making them highly susceptible to microglial-derived oxidative stress (Zhang et al., 2023). Additionally, the activation of the NLRP3 inflammasome by misfolded α-synuclein establishes a feed-forward loop of IL-1β release, driving progressive neuronal death (Adamu et al., 2024). Emerging evidence also highlights the gut-brain axis, suggesting that peripheral intestinal inflammation may initiate α-synuclein misfolding and propagate neuroinflammation to the CNS via the vagus nerve, underscoring the need for systemic immunomodulatory approaches (Wang et al., 2024).

Multiple Sclerosis (MS)

Autoimmune T-cell infiltration drives demyelination, with microglia/macrophages and reactive astrocytes contributing to lesion progression and failed remyelination (Lassmann, 2018; Brosnan & Raine, 2013). The infiltration of autoreactive Th1 and Th17 cells across a compromised blood-brain barrier (BBB) initiates focal demyelination, while the failure of regulatory T cell (Treg) recruitment prevents the resolution of the inflammatory cascade (Matejuk et al., 2021). In chronic progressive MS, "smouldering" lesions characterised by iron-rimmed, chronically activated microglia at the lesion edge drive slow neurodegeneration independent of acute relapses (Silvin et al., 2023). Furthermore, the transition of astrocytes into a neurotoxic A1 phenotype within these lesions secretes factors that inhibit oligodendrocyte precursor cell (OPC) differentiation, thereby creating a microenvironment that actively prevents remyelination and circuit repair (Patani et al., 2023).

Stroke and Traumatic Brain Injury (TBI)

Ischaemic and traumatic insults initiate acute neuroinflammation that, if unresolved, transitions to chronic glial activation, BBB breakdown, and secondary neuronal death (Iadecola & Anrather, 2011; Johnson et al., 2013; Campbell et al., 2019). In the acute phase, the massive release of damage-associated molecular patterns (DAMPs) such as HMGB1 and ATP

 ISSN: 1595-1693

triggers sterile inflammation, recruiting peripheral monocytes that exacerbate tissue damage through excessive ROS production (Scarian et al., 2024). As the injury transitions to the subacute and chronic phases, the formation of a dense glial scar composed of reactive astrocytes and extracellular matrix proteins attempts to isolate the lesion but physically and chemically inhibits axonal regeneration (Morganti et al., 2021). The persistent presence of these chronic inflammatory niches, driven by unresolved oxidative stress and sustained NLRP3 activation, ultimately leads to progressive post-stroke dementia and chronic traumatic encephalopathy (Anilkumar & Wright-Jin, 2024; Xu et al., 2025). These conditions share a common trajectory: initial protective inflammation followed by maladaptive chronic activation when resolution mechanisms fail.

Current Controversies and Debates in Neuroinflammation Research

Despite significant advances, several controversies persist in the field that warrant critical examination.

The M1/M2 and A1/A2 Dichotomy Debate

The historical classification of microglia into pro-inflammatory M1 and anti-inflammatory M2 phenotypes, and astrocytes into neurotoxic A1 and neuroprotective A2 states, remains intensely debated. While these binary frameworks provided heuristic value for early research, contemporary single-cell transcriptomic studies reveal that glial cells exist along continuous, multidimensional spectra rather than discrete categories (Wang et al., 2023; Masuda et al., 2020). Proponents of refined classification argue that regional heterogeneity, disease context, and temporal dynamics generate hundreds of distinct glial states that cannot be captured by simplistic binary labels (Hammond et al., 2019; Paolicelli et al., 2022). For instance, disease-associated microglia (DAM) exhibit both phagocytic (traditionally M2) and inflammatory (traditionally M1) characteristics simultaneously, challenging the utility of the dichotomy. Opponents caution that abandoning these frameworks entirely may impede communication and therapeutic development, as they provide accessible conceptual anchors for clinical translation (Butovsky & Weiner, 2018). A middle ground suggests using these terms as descriptive shorthand while acknowledging their limitations and emphasising the underlying continuum.

Peripheral Immune Cell Infiltration: Friend or Foe?

The role of peripheral immune cells (T cells, monocytes, macrophages) in CNS pathology generates substantial controversy. The neurotoxic perspective emphasises that peripheral immune infiltration following BBB disruption amplifies neuroinflammation through Th1 and Th17 cell production of IFN-γ and IL-17, Ly6C-high monocyte differentiation into pro-inflammatory macrophages, and CD8+ cytotoxic T-cell-mediated neuronal lysis (Xie et al., 2015; Matejuk et al., 2021). Conversely, recent evidence suggests that these apparently opposing observations are not mutually exclusive; the neuroprotective perspective highlights evidence that specific peripheral immune subsets are essential for resolution. Regulatory T cells (Tregs) suppress microglial activation via IL-10 and TGF-β, promoting functional recovery (Ito et al., 2019), while alternatively activated macrophages facilitate debris clearance, and Th2 cells secrete IL-4 and IL-13 to drive reparative glial phenotypes. The emerging consensus suggests that the net effect depends on timing, subset composition, and disease context rather than representing an absolute dichotomy.

Therapeutic Target Selection: Global Suppression vs. Precision Modulation

The field remains divided regarding the most effective therapeutic approach for managing neuroinflammation. One strategy has focused on the broad suppression of inflammatory pathways, based on the premise that chronic neuroinflammation represents a predominantly pathological process driven by multiple

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interconnected and redundant inflammatory cascades. This approach aims to attenuate widespread inflammatory signalling using established anti-inflammatory agents that target common mediators of the immune response. However, growing evidence suggests that indiscriminate suppression of inflammation may inadvertently impair essential physiological functions of glial cells, including debris clearance, synaptic remodelling, and tissue repair, which may partly explain the limited success of several clinical trials evaluating broad anti-inflammatory therapies (Heneka et al., 2015; Ransohoff, 2016).

In contrast, precision immunomodulation has emerged as a more targeted therapeutic paradigm that seeks to selectively regulate disease-promoting inflammatory pathways while preserving the homeostatic and neuroprotective functions of resident glial cells. Proponents argue that cell-type-specific interventions, such as TREM2 agonism to modulate disease-associated microglia (DAM), together with phase-specific therapeutic strategies aligned with the temporal dynamics of neuroinflammation, may provide greater efficacy while minimising unintended disruption of beneficial immune responses. This evolving perspective reflects a broader shift towards precision medicine approaches tailored to the cellular, molecular, and temporal complexity of neuroinflammatory diseases.

Biomarker Validation and Standardisation

Significant controversy surrounds biomarker selection and interpretation. Regarding TSPO-PET imaging, while widely used to detect glial activation, TSPO expression varies with genetic polymorphisms and may not distinguish between protective and pathogenic states (Fan et al., 2017). For CSF cytokine profiling, a lack of standardised thresholds and inter-laboratory variability impedes clinical implementation. Furthermore, while neurofilament light chain (NfL) is highly sensitive for neurodegeneration, it lacks specificity for inflammatory versus other pathological processes.

Translational Gap: Rodent Models vs. Human Pathology

The reliance on rodent models generates ongoing debate. Limitations include the fact that murine microglia exhibit different lifespans, receptor expression profiles, and BBB permeability compared with humans. However, advantages such as genetic manipulability and experimental control enable mechanistic insights impossible in human studies. Emerging solutions like human iPSC-derived microglia, brain organoids, and xenograft models offer complementary approaches, though they introduce their own distinct limitations.

Collectively, these controversies underscore that neuroinflammation is a highly dynamic and context-dependent biological process that cannot be adequately explained by simplified binary models. Recent advances in single-cell transcriptomics, spatial multi-omics, longitudinal neuroimaging, and precision immunology have substantially refined our understanding of glial heterogeneity, inflammatory signalling, and cellular interactions within the central nervous system. These emerging technologies are redefining traditional concepts of microglial and astrocyte activation while facilitating the identification of disease-specific molecular signatures and therapeutic targets. Future investigations integrating these high-resolution approaches with robust clinical studies, biomarker validation, and precision medicine strategies will be essential for resolving current controversies and accelerating the development of personalised therapeutic interventions for neurodegenerative diseases (Paolicelli et al., 2022; Silvin et al., 2023; Zhang et al., 2023; Haney et al., 2024; Xu et al., 2025).

Therapeutic Implications and Future Directions

Limitations of Broad Immunosuppression

ISSN: 1595-1693

Historical trials targeting systemic inflammation in CNS diseases have largely failed due to the context-dependent nature of neuroinflammation. Non-specific inhibition disrupts protective clearance mechanisms, impairs repair, and compromises peripheral immunity (Calsolaro & Edison, 2016; Heneka et al., 2015; Ransohoff, 2016).

Precision Immunomodulation

Therapeutic success requires cell-specific, phase-targeted strategies. Selective modulation of DAM phenotypes, astrocyte reprogramming, and timed cytokine receptor blockade show greater preclinical efficacy than global suppression (Cherry et al., 2014; Hammond et al., 2019). NLRP3 inhibition, microglial metabolic reprogramming, and SPM administration exemplify approaches that restore immune balance without compromising host defence (Heneka et al., 2018; Butovsky et al., 2014).

Biomarker-Driven Personalisation

Integrating fluid biomarkers (CSF cytokines, NfL, complement proteins), PET imaging (TSPO, P2Y12), and transcriptomic profiling enables precise staging of neuroinflammatory phases (Fan et al., 2017; Sala Frigerio et al., 2019). Biomarker-guided timing of intervention will be critical for transitioning from blanket anti-inflammatories to adaptive immunomodulation.

Conclusion and Future Perspectives

Neuroinflammation operates as a highly regulated, dynamic process that can either preserve CNS integrity or accelerate neurodegenerative pathology. Acute, well-coordinated responses facilitate debris clearance, synaptic remodelling, and tissue repair, whereas chronic activation disrupts neuronal networks through sustained cytokine release, oxidative stress, and glial–immune feedback loops. This review demonstrates that inflammatory outcomes are not predetermined but are shaped by cellular heterogeneity, molecular signalling balance, and temporal progression.

Future research must prioritise the identification of regulatory checkpoints that govern phenotypic transitions, particularly within microglial and astrocytic populations, and develop biomarker-guided therapeutic strategies that align with the inflammatory phase. Shifting from non-specific immunosuppression to precision immunomodulation will enable clinicians to harness the protective potential of neuroinflammation while mitigating its pathological trajectory. Integrating single-cell omics, spatial transcriptomics, and longitudinal biomarker tracking will be essential for translating these insights into clinically effective interventions.

Recommendations

Based on the synthesised evidence, we propose the following actionable recommendations for research and clinical translation:

- Adopt phase-aware therapeutic design: Interventions should be timed to align with specific neuroinflammatory phases (acute, subacute, chronic) to avoid disrupting protective immune functions while targeting maladaptive pathways.
- Prioritise cell-specific targeting: Develop therapeutics that selectively modulate disease-associated microglia (DAM), reactive astrocyte subtypes, or peripheral immune subsets rather than applying global immunosuppression.
- Integrate multi-omics and spatial profiling: Leverage single-cell RNA sequencing, spatial transcriptomics, and proteomics to resolve glial heterogeneity and identify novel regulatory checkpoints for intervention.
- Validate biomarker panels for clinical staging: Establish standardised, cross-disorder biomarker thresholds (e.g., CSF cytokine signatures, neurofilament light chain, TSPO-PET ligands) to enable patient

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stratification and phase-matched trial enrolment.

- ❖ Advance resolution-focused therapeutics: Investigate specialised pro-resolving mediators (SPMs), metabolic reprogramming agents, and NLRP3 inflammasome inhibitors as strategies to restore immune balance without compromising host defence.
- ❖ Bridge translational gaps: Design preclinical studies with enhanced human relevance by incorporating humanised models, longitudinal biomarker tracking, and cross-species validation of inflammatory phenotypes.
- ❖ Foster interdisciplinary collaboration: Encourage integration of immunology, neuroscience, bioinformatics, and clinical neurology to accelerate the development of precision immunomodulatory therapies for CNS disorders.

Professional Implications of the Study

This review synthesises current evidence to reframe neuroinflammation not as a uniformly pathological process, but as a temporally and contextually regulated biological response. By delineating the cellular heterogeneity, molecular signalling networks, and phase-specific dynamics of CNS inflammation, the manuscript provides a mechanistic foundation for the development of precision immunotherapies. Clinically, these insights challenge the historical reliance on broad-spectrum anti-inflammatory agents, which have consistently failed in neurodegenerative trials due to their disruption of protective immune functions. Instead, the synthesis supports a paradigm shift towards cell-specific and temporally targeted interventions, such as selective modulation of disease-associated microglia (DAM), astrocyte phenotypic reprogramming and the strategic administration of specialised pro-resolving mediators (SPMs). Furthermore, the emphasis on biomarker-driven staging (e.g., CSF cytokine profiles, neurofilament light chain, and PET imaging of glial activation) offers a framework for patient stratification in clinical trials, enabling researchers to align therapeutic windows with the underlying inflammatory phase. For translational neuroscience and pharmaceutical development, this review underscores the necessity of integrating single-cell omics, longitudinal biomarker tracking, and computational modelling to design next-generation CNS therapeutics that harness the reparative potential of neuroinflammation while mitigating its chronic, neurotoxic trajectory.

Limitations of the Study

As a narrative synthesis of existing literature, this review is subject to several inherent limitations. First, the rapid evolution of single-cell and spatial transcriptomics has expanded our understanding of glial heterogeneity beyond traditional binary classifications (e.g., M1/M2, A1/A2), meaning some phenotypic frameworks discussed may already be undergoing refinement. Second, much of the mechanistic evidence is derived from preclinical rodent models, which exhibit notable differences in immune architecture, microglial longevity, and blood–brain barrier permeability compared with humans, potentially limiting direct clinical translatability. Third, the absence of standardised, universally validated biomarkers for staging neuroinflammatory phases across different neurological disorders complicates the direct application of temporal therapeutic strategies in clinical practice. Additionally, as a non-systematic review, there is a potential for selection bias, with emphasis placed on high-impact mechanistic studies while excluding null or negative findings. Finally, the dynamic interplay between systemic inflammation, the gut–brain axis, and peripheral immune trafficking, though increasingly recognised, could not be exhaustively covered within the scope of this manuscript. Future systematic reviews and meta-analyses focusing on standardised biomarker thresholds and cross-species translational gaps will be essential to address these constraints.

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