Review article

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Neuroinflammation: molecular mechanisms, triggers, and biomarkers for clinical stratification

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Neuroinflammation is increasingly regarded as a key factor in the progression of neurological disorders. At the same time, in clinical practice it is often interpreted in an overly simplified manner and reduced to nonspecific activation of inflammatory responses.

Objective: to integrate contemporary molecular and cellular evidence in order to conceptualize neuroinflammation as a context-dependent and stage-determined biological program, and to delineate mechanistic determinants relevant to biomarker interpretation and therapeutic stratification.

Materials and methods: A narrative analysis of contemporary experimental, translational, and clinical studies focusing on innate protective mechanisms of the central nervous system was performed. The review emphasizes PRR-mediated recognition of pathogen-associated and damage-associated molecular patterns, intracellular inflammatory signaling pathways (NF-κB, MAPK, JAK/STAT, inflammasome complexes), mechanisms of inflammatory termination and resolution, and the regulatory role of the blood–brain barrier (BBB). Particular attention was given to data on glial cell biology, neurovascular unit signaling, biomarker profiles in cerebrospinal fluid and blood, and disease-specific neuroinflammatory phenotypes.

Results: The synthesized data indicate that neuroinflammation is not a uniform pathological state but represents a dynamic, multicomponent program shaped by the balance between initiation, amplification, resolution, and chronic persistence of inflammatory responses. Two closely interrelated components can be distinguished. The first is a resident innate neuroinflammatory program, predominantly mediated by microglia, astrocytes, and endothelial cells through PRR-dependent protective signaling mechanisms. The second is an adaptive immune component characterized by infiltration of peripheral immune cells and the development of antigen-specific responses. Disruption of resolution mechanisms, insufficient clearance of damage-associated signals, and sustained PRR activation promote the development of chronic neuroinflammation and neurodegenerative changes. The functional state of the BBB emerges as a critical modifier of neuroinflammatory dynamics, directly affecting biomarker interpretation, therapeutic access and clinical response.

Conclusions: Neuroinflammation should be conceptualized as a potentially modifiable biological program rather than a fixed pathological entity. Effective diagnostic and therapeutic strategies require context- and stage-specific stratification that takes into account the dominant inflammatory component, disease phase, etiological triggers, and the functional state of the BBB. Approaches aimed at limiting inflammatory amplification, restoring resolution mechanisms, and stabilizing barrier function are likely to offer greater translational potential than nonspecific anti-inflammatory suppression.

Keywords: *neuroinflammation; pattern recognition receptors; innate protective mechanisms; microglia; blood–brain barrier; inflammasome; resolution of inflammation; biomarkers; translational neuroscience*

Introduction

Inflammation is an evolutionarily conserved, regulated protective–adaptive tissue response to injury or threat to homeostasis, aimed at limiting damage, eliminating injured structures, and initiating repair. Under conditions of effective resolution, the inflammatory process culminates in functional tissue recovery, whereas dysregulation leads to its persistence and transition into a chronic pathological state [1, 2].

Inflammation of the central nervous system (neuroinflammation) has several clinically significant features determined by the structural isolation of the central nervous system (CNS), the presence of the blood–brain barrier (BBB), and the relatively limited involvement of adaptive immune cells. In contrast to peripheral tissues, inflammatory responses within the CNS parenchyma are predominantly mediated by glial cells—microglia, astrocytes, and oligodendrocytes—

whereas neutrophil–monocyte mechanisms become dominant mainly under conditions of substantial disruption of barrier integrity [3, 4]. Microglia integrate immune, trophic, and synaptic regulatory functions, which accounts for the close relationship between inflammatory activation and neuronal dysfunction [4].

From a clinical perspective, neuroinflammation is associated with a high functional "cost": even moderate or prolonged activation of inflammatory mechanisms may be linked to impaired synaptic transmission, excitotoxicity, reduced neuroplasticity, and progression of neurodegenerative changes. These processes underlie cognitive, motor, and neuropsychiatric disturbances across a broad spectrum of acute and chronic CNS disorders.

At the molecular level, neuroinflammation engages universal inflammatory response programs, including activation of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), signaling pathways involving NF-κB, MAPK, and JAK/STAT, as well as production of key pro-inflammatory mediators, including IL-1β (interleukin-1β), TNF-α (tumour necrosis factor-α), IL-6, and HMGB1 (High Mobility Group Box 1) [5]. Of clinical relevance, these signaling cascades and regulatory circuits determine the balance between inflammatory resolution with tissue recovery and chronic persistence, the latter being associated with progressive neurodegeneration and poorer prognosis [2].

Thus, neuroinflammation should be regarded as a context-dependent manifestation of a universal inflammatory program under CNS conditions, characterized by specific cellular mechanisms, substantial influence on disease course, and potential relevance as a target for diagnostic and therapeutic interventions.

Given the clinical heterogeneity of neuroinflammation and its decisive role in determining the course and prognosis of CNS disorders, understanding the molecular and cellular mechanisms underlying inflammatory activation is of major importance. Analysis of the signaling cascades, cellular interactions, and regulatory circuits governing the initiation, maintenance, and resolution of neuroinflammation is a necessary prerequisite for the identification of diagnostic biomarkers and the development of targeted therapeutic strategies [6].

The aim of this review was to examine the key mechanisms of neuroinflammation with emphasis on their clinical and translational significance.

Mechanisms of neuroinflammation

Initiation of neuroinflammation: PAMP/DAMP → PRR

Neuroinflammation is initiated in response to a broad spectrum of injurious stimuli, including infectious agents, ischemia/reperfusion, oxidative stress, mechanical trauma, and accumulation of pathological protein aggregates during neurodegeneration [7, 8]. Under these conditions, disruption of tissue homeostasis is accompanied by the release of two major classes of inflammatory inducers: pathogen-associated molecular patterns (PAMPs) during infection and damage-associated molecular patterns (DAMPs) during sterile injury [7]. These signals are detected by PRRs.

Of clinical importance, PRR activation may occur before the appearance of overt structural abnormalities on neuroimaging, making these early molecular triggers promising targets for biomarker-based risk stratification and early therapeutic intervention [8,9].

Pattern recognition receptors in the CNS (PRR-mediated sensing)

A central event in the initiation of neuroinflammation is the activation of PRRs, which provide early sensing of both infectious agents and sterile tissue injury within the central nervous system (CNS). The principal classes of PRRs include: (1) TLRs, transmembrane receptors that recognize PAMPs and DAMPs in the extracellular space and within endosomes; (2) NLRs, cytoplasmic sensors whose activation leads to inflammasome assembly and subsequent release of pro-inflammatory cytokines; (3) RIG-I-like receptors (RLRs), intracellular sensors responsible for recognition of viral RNA; and (4) scavenger receptors (SRs), involved in the clearance of modified lipoproteins, amyloid peptides, and cellular debris [10–13].

Within brain tissue, microglia are the principal cellular carriers of PRRs. Astrocytes and oligodendrocytes also express a broad spectrum of PRRs and participate not only in the initiation of inflammatory responses but also in barrier regulation and reparative processes [3, 4]. Data obtained in recent years indicate the expression of specific PRRs on neurons, enabling them to respond to danger signals, modulate intracellular stress responses, and influence cell survival and synaptic function [8].

From a functional perspective, PRR-mediated sensing in the CNS serves as a mechanism of continuous surveillance of cerebral homeostasis. Activation of TLRs and RLRs predominantly mediates the initiation and amplification of inflammatory signaling, whereas NLR-dependent inflammasome pathways convert these signals into an effector response. In a clinical and translational context, PRR signaling is regarded as one of the earliest and potentially modifiable levels of the neuroinflammatory response, thereby creating opportunities for selective therapeutic strategies aimed at modifying disease course rather than merely suppressing inflammatory symptoms.

Chronic or dysregulated PRR activation is associated with the establishment of persistent inflammatory circuits and plays an important role in the pathogenesis of multiple sclerosis and other chronic neuroinflammatory and neurodegenerative conditions [6, 7]. In this context, PRRs and their downstream signaling cascades are considered key pathogenetic mechanisms, as well as promising therapeutic targets and biomarkers of neuroinflammatory activity [6, 7].

Molecular transduction of inflammatory signals in the nervous system

The inflammatory response in the nervous system is formed through coordinated activation of families of innate (sensory) immune receptors, including TLRs, NLRs, RLRs, and SRs. These sensors exhibit cell-specific expression patterns: the highest levels are characteristic of microglia, whereas astrocytes, oligodendrocytes, and neurons demonstrate a more limited and context-dependent profile, reflecting their involvement in homeostatic and stress-associated responses.

Toll-like receptors

TLRs are localized on the plasma membrane and within endosomes, where they mediate the primary recognition of PAMPs and DAMPs. Their activation is accompanied by recruitment of the adaptor proteins MyD88 or TRIF, which, through the TAK1 signaling

node, activate the IKK/NF-κB and MAPK/AP-1 signaling axes. As a result, transcription of pro-inflammatory mediators (IL-1β, IL-6, TNF-α), inflammatory enzymes (cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS)), chemokines, and adhesion molecules is induced. Importantly, TLR signaling provides the "priming" phase of the inflammatory response by promoting synthesis of inactive precursor forms of IL-1β and IL-18, as well as upregulation of inflammasome components. A distinct role is played by the TRIF-dependent axis (predominantly associated with TLR3 and TLR4), which leads to induction of type I interferons and secondary activation of JAK/STAT signaling. The combination of primary NF-κB/MAPK activation and secondary JAK/STAT amplification forms stable autocrine and paracrine feedback loops that determine response duration and the potential for chronic neuroinflammation [14–16].

NOD-like receptors

NLRs are cytoplasmic sensors that respond to intracellular PAMPs and DAMPs and play a key role at the post-transcriptional stage of the inflammatory response. Activation of inflammasome complexes, particularly NLRP3, leads to recruitment and activation of caspase-1, which mediates proteolytic maturation of pro-IL-1β and pro-IL-18 into their biologically active forms. Thus, NLRs integrate danger signals with the mechanisms of secretion of key cytokines and determine the intensity of the effector phase of inflammation [17, 18].

RIG-I-like receptors

RLRs are intracellular sensors of viral RNA that function in the cytosol and mediate the antiviral component of innate immunity. Following binding to viral RNA, these receptors interact with the adaptor MAVS (mitochondrial antiviral signaling protein), localized on the outer mitochondrial membrane, thereby initiating activation of the transcription factors IRF3/IRF7 and NF-κB. This leads to synthesis of type I interferons and pro-inflammatory cytokines. Functionally, RLR signaling converges with TLR pathways at the level of NF-κB and may modulate inflammasome responses through mitochondrial mechanisms, thereby linking antiviral defense with the broader inflammatory program [19].

Scavenger receptors (SRs)

SRs mediate the clearance of modified lipids, amyloid peptides, and cellular debris, thereby playing a crucial role in maintaining tissue homeostasis. In the nervous system, they are most prominently expressed in microglia, where they execute phagocytic functions, whereas in other CNS cell types they are primarily involved in regulating metabolism and the local microenvironment. Functionally, SRs act as co-receptors, enhancing the efficiency of TLR and RLR activation through ligand delivery, and they also activate the NLR inflammasome via the induction of lysosomal and mitochondrial stress [20].

Signal integration

Thus, TLRs and RLRs are responsible for the initiation and transcriptional priming of the inflammatory response; NLRs mediate the maturation and secretion of key cytokines; whereas SRs modulate the intensity and spatial organization of these processes. The coordinated interplay among these receptor systems forms a multilayered signaling network that determines the nature of neuroinflammation—ranging from an acute protective response to chronic degenerative changes [2, 4, 6, 7].

Clearance of PAMPs and DAMPs as a critical stage in the resolution of neuroinflammation

Although PRR activation and the production of proinflammatory mediators define the initiation and amplification of the neuroinflammatory response, its resolution critically depends on the efficient cellular clearance of PAMPs and DAMPs. In the CNS, this process is primarily carried out by microglia through phagocytosis, efferocytosis, and receptor-mediated clearance, including mechanisms involving SRs, complement-dependent pathways, and lysosomal degradation [21]. Astrocytes also contribute by facilitating metabolic detoxification, spatial containment of damaged areas, and maintenance of barrier integrity, whereas neurons predominantly serve as passive targets rather than active effectors of clearance [22]. With effective elimination of molecular danger patterns, PRR signaling gradually subsides, promoting a shift of glial cells toward homeostatic and reparative programs. Conversely, impaired clearance of PAMPs/DAMPs leads to their persistence within tissues, sustains chronic PRR activation, and establishes self-perpetuating inflammatory circuits that drive the transition of neuroinflammation into a chronic maladaptive state [23].

Table 1 summarizes the principal PRR platforms involved in neuroinflammation, the relationships between their dominant signaling pathways and functional consequences, and the molecular biomarkers of activation, resolution, and chronicization. The presented scheme illustrates the organization of innate neuroinflammatory signaling (from transcriptional priming to the effector cytokine response) and demonstrates how dysregulated PRR activation contributes to the establishment of persistent inflammatory circuits and neurodegenerative progression.

Termination of inflammation and mechanisms of neuroinflammatory response chronicity

The inflammatory response is neither a linear nor a self-sustaining process. Under physiological conditions, it is accompanied by the activation of termination and resolution mechanisms aimed at restoring tissue homeostasis. Crucially, the same signaling platforms that initiate inflammation (TLRs, RLRs, and NLRs) may, under specific conditions, trigger negative regulatory circuits that limit the duration and intensity of the response.

Mechanisms of inflammatory termination and resolution

Termination of inflammation involves the coordinated attenuation of PRR signaling, switching of transcriptional programs, and activation of specialized anti-inflammatory pathways. Key events include the induction of negative regulators of TLR signaling (A20, SOCS, IRAK-M), which suppress NF-κB and MAPK activation [24]; increased production of anti-inflammatory cytokines (primarily IL-10 and TGF-β), which shift the phenotype of microglia and astrocytes toward reparative programs [25, 26]; activation of specialized pro-resolving mediators (resolvins, protectins, and maresins), which reduce chemotaxis and support debris clearance [27]; inhibition of inflammasome activity and reduced secretion of IL-1β and IL-18 [28]; and efficient phagocytosis of apoptotic cells and damage-associated products (efferocytosis), which itself generates anti-inflammatory signals [29].

Within the nervous system, these processes are accompanied by the transition of microglia from a

Table 1. Integration of prr signaling with resolution, chronicity, and biomarker profiles of neuroinflammation

PRR / Platform	Key signaling pathway	Functional outcome	Activation markers	Resolution markers	Chronicity markers
TLR (TLR2/4/3/7/9)	MyD88 / TRIF → NF-κB, MAPK, IRF	Transcriptional initiation of inflammation (Signal 1)	TNF-α, IL-6, pro-IL-1β, CXCL8, IFN-β	IL-10, TGF-β, SOCS1/3	PersistentTNF-α, IL-6, STAT3- signature
RLR (RIG-I, MDA5)	MAVS → IRF3/7, NF-κB	Antiviral state + priming	IFN-α/β, ISG (MX1, OAS1)	↓IFN-I, normalization of ISGs	Chronic IFN signature, ISG persistence
NLR (NLRP3)	Inflammasome → caspase-1	Maturation of IL-1β/IL-18 (Signal 2)	IL-1β, IL-18, ASC-specks	Caspase-1 inhibition, ↓IL-1β	Recurrent activation of IL-1β/IL-18
Scavenger receptors (CD36, SR-A1)	Phagocytosis → lysosomal / mitochondrial stress	Clearance or maintenance of the DAMP loop	oxLDL, β- amyloid, HMGB1	Efferocytosis, ↓DAMPs	Cellular debris, oxLDL, sCD36
Microglia	PRR- integration	Cellular hub of neuroinflammation	sTREM2, YKL-40	Normalization of sTREM2	Chronically ↑YKL-40
Astrocytes	TLR/NF-κB, JAK/STAT	Modulation of the microenvironment	GFAP (CSF), CCL2	↓GFAP, IL-10	Sustained ↑GFAP, CCL2
Impaired clearance	Persistence of PAMPs/DAMPs → PRR reactivation	Maintenance of self-amplifying inflammatory circuits	HMGB1, mtDNA, oxLDL	Absent or reduced	IL-6, IL-1β, YKL-40, GFAP, sCD36

Note: Signal 1 refers to transcriptional priming; Signal 2 denotes inflammasome activation. ASC specks are aggregates of ASC (apoptosis-associated speck-like protein containing a CARD), indicating inflammasome assembly.

pro-inflammatory to a homeostatic or reparative state, normalization of astrocytic reactivity, and stabilization of neuron–glia interactions [30].

Features and molecular determinants of chronicity. Inflammatory chronicity develops when resolution mechanisms are insufficient or impaired. The principal processes indicating transition to the chronic phase include persistent PRR activation in response to endogenous DAMPs (mitochondrial DNA, oxidized lipids, aggregated proteins) [31]; sustained NF-κB and JAK/STAT activation, maintaining autocrine and paracrine inflammatory loops [14]; stable or recurrent activation of the NLRP3 inflammasome with chronic production of IL-1β and IL-18 [32]; impaired SR-mediated clearance of cellular and myelin debris, which sustains low-grade inflammation [30]; and phenotypic fixation of microglia and astrocytes in a reactive state accompanied by loss of homeostatic functions [33, 34].

Triggers of the neuroinflammatory process: etiological and infectious context

Despite the universality of PRR-dependent signaling mechanisms, the clinical interpretation of neuroinflammation is impossible without consideration of the etiological triggers that initiate or sustain inflammatory processes within the central nervous system. Such triggers include both infectious agents and sterile injurious factors capable of activating common PRR-mediated inflammatory programs (***Table 2***).

Of particular clinical importance are persistent or latent neurotropic infections, especially herpesviruses, which may remain within nervous tissue for prolonged periods and undergo periodic reactivation without overt manifestations of acute infection. Under such conditions, chronic or intermittent activation of RLR-dependent and TLR-dependent pathways occurs, sustaining low-grade neuroinflammation even in the absence of clinically manifest infectious disease [35].

In this context, the neuroinflammatory response may be characterized by a persistent interferon signature, inflammasome activation, and progressive BBB dysfunction, thereby shaping a phenotype of chronic neuroinflammation. Detection of viral DNA/RNA or specific antibodies in cerebrospinal fluid (CSF) and blood enables differentiation between infection-mediated neuroinflammatory processes and sterile inflammation, which is of fundamental importance for the selection of an appropriate therapeutic strategy [35].

Interpretation of PRR-mediated inflammatory signatures without etiological verification of infectious triggers may result in the misclassification of neuroinflammatory conditions and, consequently, in suboptimal therapeutic decisions [35]. Therefore, etiological verification of the pathogen or its immunological markers should be considered a contextual modifier in the interpretation of PRR activation, biomarker profiles, and treatment response.

An important, yet often underestimated, component in the initiation and maintenance of the neuroinflammatory process is inflammatory activation of the CNS vascular endothelium. Endothelial cells express PRRs and are capable of directly responding to systemic and local danger signals, including PAMPs and DAMPs. Their activation is accompanied by the induction of NF-κB-dependent and MAPK-dependent programs, expression of adhesion molecules (ICAM-1, VCAM-1), and secretion of cytokines and chemokines [36, 37].

Endothelial inflammation leads to BBB dysfunction, disruption of tight junctions, and increased permeability. Even in the absence of overt structural barrier damage, the endothelium may translate systemic inflammation into a central immune response by activating microglia and modulating neuronal function through paracrine mechanisms [36, 37].

The blood–brain barrier as a modifier of the neuroinflammatory process

The blood–brain barrier is not merely a physical boundary between the systemic circulation and the CNS, but also an active modifier of the neuroinflammatory process (***Table 3***), determining the intensity, spatial organization, and dynamics of the inflammatory response within the CNS. Its functional state changes in response to PRR-dependent signaling, as well as to the effects of cytokines, interferons, and products of tissue injury [38].

During the acute phase of inflammation or CNS injury, the BBB is frequently characterized by increased permeability, creating a therapeutic "window" while simultaneously contributing to secondary injury. In subacute and chronic conditions, the BBB may appear structurally restored while remaining functionally dysregulated, with impaired transport and persistent endothelial activation. This reduces the effectiveness of systemic therapy and increases the risk of inflammatory chronicization [39, 40].

Context-dependent manifestation of neuroinflammation across different nosologies. Although the fundamental mechanisms of neuroinflammation are universal, their manifestation differs substantially depending on the specific nosology (***Table 4***). In neurotrauma and ischemia, acute DAMP-mediated responses predominate, whereas neurodegenerative diseases are characterized by prolonged low-symptom glial activation [41]. In CNS tumors, neuroinflammation is integrated with an immunosuppressive microenvironment [42], while in chronic pain and neuropsychiatric disorders it is associated with disrupted neuron–glia communication [43, 44].

Table 2. Contextual relationship between etiological triggers and neuroinflammatory profiles

Context	What is determined?	Purpose
Suspected virus-induced inflammation	Viral DNA/RNA in the CSF	Confirmation of active or persistent infection
Latent or previous infection	IgG, CSF/serum antibody index	Identification of a potential trigger of chronicization
IFN signature without a clearly defined etiology	Antibodies + ISGs	Differentiation of sterile inflammation from infection-associated inflammation
Impaired BBB integrity	Antibodies + Q-albumin	Accurate interpretation of antibody penetration

Table 3. Therapeutic strategies in the context of the functional state of the blood–brain barrier and expected biomarkers

Therapeutic approach	Functional state of the BBB	Expected therapeutic effect	Expected biomarkers (CSF/Blood)
Corticosteroids	Acutely disrupted, "open"	Reduction of edema and suppression of cytokine release	↓IL-6, ↓TNF-α, ↓MMP-9, ↓ Q-albumin
Anti-IL-1β/anti-TNF therapy	Partially disrupted	Reduction of inflammasome and NF-κB activation	↓IL-1β, ↓IL-18, ↓CRP
JAK/STAT inhibitors	Dysfunctional, with chronic activation	Limitation of autocrine/paracrine inflammatory loops	↓STAT3-сигнатура, ↓IL-6
Antiviral therapy/IFN modulation	Acute inflammation with RLR activation	Reduction of viral load and normalization of IFN	↓IFN-α/β, ↓ISG (MX1, OAS1)
Nanoparticles, exosomes	Relatively intact	Improved drug delivery to the CNS	Targeted therapeutic markers, stable Q-albumin
Intranasal delivery	Intact	BBB bypass with localized therapeutic action	Local changes in biomarkers without systemic activation

Table 4. Nosology-specific patterns of blood–brain barrier dysfunction and mechanisms of neuroinflammation

Nosology	Typical BBB State	Dominant Mechanisms of Inflammation	Therapeutic Implications	Clinically Relevant Biomarkers (CSF/Blood)
Acute traumatic brain injury	Severely disrupted, transiently "open"	TLR/NLR activation, inflammasome activation, matrix metalloproteinases	Utilization of the therapeutic window; control of secondary injury	↑Q-albumin, ↑IL-1β, ↑TNF-α, ↑MMP-9, ↑GFAP
Ischemic stroke	Phase-dependent disruption (acute → partially restored)	TLR4, NLRP3, oxidative stress	Phase-oriented therapy; limitation of reperfusion injury	↑IL-6, ↑IL-1β, ↑S100B, ↑CRP
Neuroinfections (viral)	Disrupted	RLR → IFN-I, TLR3/7	Antiviral therapy adjusted for BBB permeability	↑IFN-α/β, ↑ISG (MX1), ↑CXCL10
Multiple sclerosis	Chronically dysfunctional	TLR/NLR signaling, adaptive immunity	Immunomodulation combined with control of barrier function	↑OCB, ↑CXCL13, ↑GFAP
Alzheimer's disease	Functionally impaired (low-grade leakage)	SR (CD36), NLRP3, DAMPs	Targeting resolution pathways and clearance mechanisms	↑Aβ, ↑p-tau, ↑YKL-40, ↑sTREM2
Parkinsonism	Partially disrupted	Microglial activation, NLRP3	Modulation of neuroinflammation	↑IL-6, ↑α-synuclein, ↑GFAP
Chronic posttraumatic encephalopathy	Dysregulated, incompletely restored	Persistent NF-κB activation, DAMPs	Combined therapy (anti-inflammatory + pro-resolution)	↑IL-6, ↑GFAP, ↑NfL
Neuro-Oncology (perifocal inflammation)	Locally disrupted	TLR/SR signaling, cytokine microenvironment	Local drug delivery and edema control	↑VEGF, ↑IL-8, ↑GFAP

Discussion

This review summarizes current concepts of neuroinflammation as a multilevel biological process arising from the interaction between sensing mechanisms, intracellular signal transduction, regulation of barrier structures, and the tissue-specific vulnerability of the CNS. Neuroinflammation is not a homogeneous pathological condition. Rather, it should be regarded as a dynamic, phase-specific program whose clinical consequences are determined by the balance among initiation, amplification, resolution, and BBB-mediated modulation [1–3].

Conceptually, it is important to distinguish at least two interconnected, yet non-identical, levels of immune activity within the CNS. The first level is the innate neuroinflammatory program, implemented predominantly by resident cells (microglia, astrocytes, and endothelial cells of the neurovascular unit) and initiated through PRR signaling in response to infectious and sterile danger signals. The second level is the adaptive immune component, characterized by the involvement of peripheral T cells and B cells, the development of clonally specific responses, and tissue-mediated injury, which may coexist with the neuroinflammatory program or predominate in certain nosologies and phases of the process [1,4]. Such stratified differentiation is required not to "divide" a single process, but to ensure accurate interpretation

of biomarkers, prognosis, and therapeutic strategy selection.

The principal conclusion is that activation of the innate neuroinflammatory program is not inherently pathological. PRR-dependent signaling provides a surveillance mechanism enabling rapid detection of infectious and sterile threats. Short-term activation of Toll-like and NOD-like receptors supports anti-infectious defense, clearance of damaged structures, and tissue adaptation. Pathological consequences arise predominantly not from activation itself, but from impaired termination and resolution, resulting in prolonged signaling, fixation of the reactive glial phenotype, and progressive tissue dysfunction [2,4]. At the same time, under conditions of a substantial contribution from the adaptive immune component (with clonal specificity and cellular infiltration), mechanisms of injury and therapeutic targets may shift from regulation of resident glia and PRR-associated pathways toward control of cellular migration, antigen-mediated responses, and effector functions of T cells and B cells [1].

The analyzed data emphasize the importance of distinguishing between the initiation phase and the persistence (chronicization) phase of neuroinflammation. At early stages, PRR-mediated activation reflects an adaptive response to acute injury, whereas prolonged activation maintained by autocrine and paracrine cytokine loops drives the transition toward a chronic, maladaptive process. This has direct translational implications: nonspecific suppression of early stages of the innate program may weaken protective mechanisms, whereas interventions aimed at controlling amplification, persistence, and/or enhancing resolution possess greater disease-modifying potential [2,4]. If the adaptive immune component predominates in a clinical context, the critical factors become the recruitment and retention phases of effector cells within the CNS, as well as the barrier mechanisms determining the intensity of infiltration. In such circumstances, the same "cytokine" signature may have different implications depending on whether it results from resident glial activation or accompanies a clonally mediated immune response [1, 3].

The BBB plays a distinct integrative role in shaping the neuroinflammatory process. It should be regarded not merely as an obstacle to drug penetration, but also as an active regulator of neuroinflammatory dynamics and therapeutic responsiveness. Inflammation-induced alterations in endothelial tight junctions, transporter expression, and neurovascular interactions transform the CNS microenvironment, influencing both immune communication and the availability of pharmacological agents. Accordingly, variability in the functional state of the BBB may explain differences in clinical responses to identical interventions depending on disease stage or individual patient characteristics [3,5–7]. Within the proposed stratification framework, the BBB has a dual role: it modulates the intensity of the innate neuroinflammatory program through endothelial activation and neurovascular signaling, while simultaneously determining the magnitude of the adaptive immune component by controlling the migration and penetration of peripheral immune cells into the CNS [3, 6].

This approach challenges the simplified use of inflammatory biomarkers. Elevated cytokine levels in blood or CSF do not invariably reflect active neuroinflammation and cannot automatically be interpreted as therapeutic targets. Interpretation should be integrative, taking into account disease phase, etiological context, and BBB status. It should also include assessment of which component predominates — the resident (innate) neuroinflammatory program or the infiltrative (adaptive immune) component. Without such differentiation, the risk of erroneous clinical decisions and overestimation of "inflammatory activity" as the sole basis for therapy substantially increases [1, 7, 8].

The situation is further complicated by the interaction between infectious and sterile triggers. Infectious insults may leave a prolonged immunological "imprint," lowering the activation threshold of the innate neuroinflammatory program during subsequent noninfectious injury. Conversely, sterile processes may mimic infectious responses through shared PRR-mediated pathways. This highlights the limitations of a purely etiological approach and substantiates the need for mechanistically grounded stratification in diagnosis and treatment [2, 3].

From a therapeutic perspective, the findings of this review support a paradigm shift from generalized anti-inflammatory suppression toward context-dependent and resolution-oriented strategies. Targeting key signaling nodes, stabilizing barrier functions, and stimulating active resolution mechanisms may provide superior outcomes compared with nonspecific cytokine blockade. At the same time, the timing of intervention is critically important: therapies effective during early stages may lose efficacy or even exert adverse effects once persistence of the neuroinflammatory program has been established or when the infiltrative adaptive immune component predominates, under which therapeutic priorities and biomarker targets may differ [1, 2, 4, 7].

Overall, neuroinflammation should be considered a modifiable biological program rather than a fixed pathological entity. Its clinical significance arises from the interaction of molecular signals, cellular responses, and barrier mechanisms that evolve over time. Recognition of this dynamic nature and of the stratification between the resident (innate) neuroinflammatory program and the infiltrative (adaptive immune) component constitutes a necessary prerequisite for translating fundamental knowledge into effective clinical strategies [1, 3].

Conclusions

Neuroinflammation is a complex, dynamic, and context-dependent biological process that extends beyond the simplified concept of local or systemic overproduction of pro-inflammatory mediators. The data summarized in this review indicate that the clinical significance of neuroinflammation is determined not by immune activation itself, but by the balance among initiation, amplification, resolution, and barrier regulation of the inflammatory response within the CNS.

A fundamental aspect is the distinction between two interconnected components of the neuroinflammatory process. The first is the innate neuroinflammatory program, implemented predominantly by resident CNS cells (microglia, astrocytes, and endothelial cells of the neurovascular unit) and initiated through PRR-dependent

sensing of infectious and sterile danger signals. Its short-term activation constitutes an essential component of immune surveillance, adaptation to injury, and tissue repair. The second is the adaptive immune component, characterized by the involvement of peripheral T cells and B cells, clonally specific responses, and tissue-mediated effects that may coexist with the innate program or predominate in certain nosologies and phases of the process.

The pathological consequences of neuroinflammation arise primarily from impaired mechanisms of termination and resolution of the innate program and/or from its sustained integration with the adaptive immune component. Persistent signaling, fixation of the reactive glial phenotype, formation of self-sustaining cytokine loops, and barrier dysfunction transform an initially protective response into a chronic pathological process underlying neurodegeneration, cognitive impairment, and reduced functional recovery.

The blood–brain barrier is a key modifier of both components of neuroinflammation. On the one hand, it regulates the intensity and spatial organization of the innate neuroinflammatory program through endothelial activation and neurovascular communication; on the other hand, it determines the magnitude and nature of the adaptive immune component by controlling the penetration and retention of peripheral immune cells within the CNS. The functional state of the BBB directly influences both biomarker interpretation and the variability of clinical responses to therapy.

The presented findings highlight the limitations of universal anti-inflammatory strategies. Effective treatment requires a context-dependent and stage-specific approach that takes into account: (1) the predominance of the innate neuroinflammatory program or the adaptive immune component, (2) the phase of the process (initiation or persistence), (3) the functional state of the BBB, and (4) the biomarker profile in blood and CSF. Under such conditions, priority should be given to strategies aimed not only at suppressing inflammation, but also at controlling amplification, stabilizing barrier functions, and stimulating active resolution mechanisms.

Overall, neuroinflammation should be regarded as a modifiable and potentially manageable biological program rather than a fixed pathological entity. A clear distinction between the resident (innate) neuroinflammatory program and the infiltrative (adaptive immune) component provides the methodological basis for accurate biomarker interpretation, personalization of therapeutic interventions, and effective translation of fundamental mechanisms into clinically meaningful solutions.

Disclosure

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Conflict of Interest

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