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# NEUROINFLAMMATION AS A CENTRAL LINK IN THE PATHOGENESIS OF NEURODEGENERATIVE DISEASES: MOLECULAR MECHANISMS, CLINICAL CORRELATES, AND THERAPEUTIC PERSPECTIVES

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***SUMMARY***

*Neuroinflammation is regarded as a central mechanism driving the progression of neurodegenerative diseases, integrating age-associated inflammation, glial dysfunction, blood–brain barrier disruption, mitochondrial stress, and systemic factors. Activation of microglia and astrocytes, involvement of the NLRP3 inflammasome, dysregulation of TREM2 signaling, disturbances in iron and lipid metabolism, as well as the influence of the microbiota and metabolic comorbidities together form a self-sustaining pathological network that exacerbates neuronal loss in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Emerging therapeutic strategies include modulation of microglia, inhibition of inflammasome-related cascades, epigenetic approaches, and nanotechnology-based delivery systems for anti-inflammatory compounds; however, their clinical efficacy remains limited. A deeper understanding of the architecture of neuroinflammation opens avenues for the development of targeted and personalized interventions.*

***KEYWORDS:*** *neuroinflammation; microglia; NLRP3 inflammasome; TREM2; neurodegeneration; blood–brain barrier.*

***CONFLICT OF INTEREST***. The authors declare no conflict of interest.

# *НЕЙРОВОСПАЛЕНИЕ КАК ЦЕНТРАЛЬНОЕ ЗВЕНО ПАТОГЕНЕЗА НЕЙРОДЕГЕНЕРАТИВНЫХ ЗАБОЛЕВАНИЙ: МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ, КЛИНИЧЕСКИЕ КОРРЕЛЯТЫ И ТЕРАПЕВТИЧЕСКИЕ ПЕРСПЕКТИВЫ*

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***РЕЗЮМЕ***

*Нейровоспаление рассматривается как центральный механизм прогрессирования нейродегенеративных заболеваний, интегрирующий возраст-ассоциированное воспаление, глиальную дисфункцию, нарушение гематоэнцефалического барьера, митохондриальный стресс и системные факторы. Активация микроглии и астроцитов, вовлечение NLRP3-инфламмасомы, дисрегуляция TREM2-сигналинга, нарушения железного и липидного обмена, а также влияние микробиоты и метаболических коморбидностей формируют устойчивую патологическую сеть, усиливающую нейрональную утрату при болезни Альцгеймера, болезни Паркинсона, боковом амиотрофическом склерозе и рассеянном склерозе. Появляющиеся терапевтические стратегии включают модуляцию микроглии, подавление инфламмасомных каскадов, эпигенетические подходы и нанотехнологические системы доставки противовоспалительных соединений, однако их клиническая эффективность остается ограниченной. Углубленное понимание структуры нейровоспаления открывает возможности для разработки таргетных и персонализированных вмешательств.*

***КЛЮЧЕВЫЕ СЛОВА:*** нейровоспаление; микроглия; NLRP3-инфламмасома; TREM2; нейродегенерация; гематоэнцефалический барьер.

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## Introduction

Neurodegenerative diseases (NDDs) represent one of the most significant groups of chronic disorders, characterized by progressive neuronal loss, impairment of synaptic transmission, and a gradual decline in cognitive and motor functions [1]. According to the Global Burden of Disease (2019) analysis, the prevalence of dementia already exceeds 57 million people, and by 2050 it is projected to increase more than two-and-a-half-fold, reaching 152.8 million patients [1]. Another large epidemiological report — GBD 2021 — indicates that disorders of the nervous system have entered the group of leading global causes of disease burden, measured in disability-adjusted life years (DALYs) [2]. Within the spectrum of NDDs, the major contribution is made

by Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and mixed forms of dementia, making neurodegeneration a key challenge for global healthcare [3].

Despite differences in clinical phenotypes, most NDDs share a set of fundamental pathological processes: accumulation of misfolded proteins, mitochondrial dysfunction, disturbed intercellular communication, and progressive chronic inflammation within the central nervous system. For a long time, the pathogenesis of these disorders was considered primarily through the lens of protein aggregates — β-amyloid, hyperphosphorylated tau, and α-synuclein. However, contemporary research convincingly demonstrates that it is sustained neuroinflammation that largely determines the rate of neurodegeneration and influences disease trajectories more substantially than the mere presence of pathological proteins [4].

The core component of this inflammatory response is glial activation. Microglia and astrocytes, responding to protein aggregates as danger-associated molecular patterns (DAMPs), trigger innate immune signaling pathways, including nuclear factor NF-κB and the NLRP3 inflammasome. These processes lead to the release of pro-inflammatory cytokines, disruption of blood–brain barrier (BBB) function, and the formation of a self-sustaining pathological cycle of inflammation and neuronal death [5, 6].

In recent years, the concept of a "neuroimmune connectome" has emerged, reflecting the tight interconnectedness of the central and peripheral immune systems. Numerous studies published in Science and Nature show that neuroinflammation is not confined to local processes within the brain but is closely linked to systemic immune, metabolic, and microbiome-related influences. This substantially broadens our understanding of NDD pathogenesis and underscores the need for an integrative, interdisciplinary approach to their study [7, 8].

The aim of this review is to provide a structured analysis of current data on the cellular and molecular mechanisms of neuroinflammation, its role in the progression of major neurodegenerative diseases, and the therapeutic potential of modulating these processes. Particular attention is paid to the interactions between glial cells, inflammatory signaling pathways, systemic risk factors, and potential therapeutic targets, allowing neuroinflammation to be considered as a central link in the pathogenesis of NDDs and a promising therapeutic direction for the future [4, 7].

**Cellular and Molecular Mechanisms of Neuroinflammation**

Microglia are the key effector cells of innate immunity in the central nervous system and form the first line of response to structural and metabolic signs of damage. Under physiological conditions, microglial cells maintain homeostasis, perform phagocytosis, monitor synaptic integrity, and participate in trophic regulation. However, under the influence of pathological proteins, mitochondrial stress, metabolic disturbances, or systemic inflammatory signals, microglia transition into activated states characterized by pronounced immune and metabolic changes [9].

Modern models distinguish several functional programs of microglial activation; among them, the conventional M1 and M2 phenotypes are not absolute but remain useful to describe a spectrum of pro-inflammatory and reparative responses. An M1-like state is associated with the production of pro-inflammatory mediators (TNF-α, IL-1β, reactive oxygen species), whereas an M2-like profile is linked to phagocytosis, restoration of the extracellular milieu, and secretion of neurotrophic factors. In chronic neurodegenerative diseases, a persistent shift toward M1-like reactivity is observed, which maintains a long-lasting inflammatory cycle and reduces the compensatory potential of microglia [10].

A central signaling node sustaining this pro-inflammatory response is the NLRP3 inflammasome. Its activation requires two sequential steps: a priming signal that upregulates the expression of inflammasome components, and a subsequent activation signal triggered by cellular stress (disrupted ion homeostasis, mitochondrial ROS, damaged proteins). As a result, caspase-1 is activated and mature IL-1β and IL-18 are released — two key mediators that exacerbate neuroinflammation and neuronal injury. Hyperactivation of the NLRP3 inflammasome has been demonstrated in many neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis [11].

Alongside microglia, astrocytes play an important role in regulating inflammatory processes. These cells respond to cytokines and damage signals by acquiring reactive phenotypes accompanied by metabolic reprogramming, increased secretion of pro-inflammatory mediators, and reduced neurotrophic support. Reactive astrocytes can contribute to synaptic dysfunction, alter neuronal inhibition, and exacerbate brain tissue damage in chronic disease [12]. Under certain conditions, they adopt toxic phenotypes associated with reduced plasticity, impaired glutamate clearance, and potentiation of microglial activation [13].

Neuroinflammation is tightly linked to disruption of the blood–brain barrier. Pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 can alter the expression of endothelial tight junction proteins, increase vascular permeability, and facilitate the infiltration of peripheral immune cells into the brain. This creates a feedback loop: peripheral inflammation exacerbates central inflammation, and central inflammation amplifies systemic immune activation, forming a stable pathological circuit [14]. In addition, microglia directly interact with BBB endothelial cells and pericytes, modulating barrier permeability and participating in the regulation of blood–brain exchange [15].

Recent studies further refine classical concepts of neuroinflammation by incorporating epigenetic and metabolic regulators. For example, m6A modifications of mRNA influence the expression of immune-response genes in microglia and astrocytes, controlling the intensity and duration of inflammatory cascades [16]. Another regulatory node is O-GlcNAc glycosylation, which is sensitive to the energetic and metabolic status of the cell. Alterations in O-GlcNAc levels affect the activity of transcription factors and signaling pathways involved in immune responses and neuronal resilience [17].

Together, these mechanisms form a multicomponent network governing neuroinflammation, involving microglia, astrocytes, BBB endothelium, cytokine signaling, and epigenetic modifications. Persistent dysregulation within this network underlies the transition from a physiological protective response to a chronic inflammatory state that drives the progression of neurodegenerative diseases.

**Neuroinflammation in Specific Neurodegenerative Diseases**

In Alzheimer's disease, neuroinflammation is considered not a secondary consequence of neurodegeneration but one of the key pathogenic components: β-amyloid and hyperphosphorylated tau trigger sustained microglial activation, formation of specific "disease-associated" microglial phenotypes around amyloid plaques, and maintenance of a chronic pro-inflammatory milieu that promotes progressive synaptic and neuronal loss [18].

Current data show that signaling through TREM2 (triggering receptor expressed on myeloid cells 2) and the NLRP3 inflammasome in microglia constitutes critical nodes through which amyloid aggregates and associated danger signals shift microglia from a phagocytic, relatively neuroprotective state into a chronically activated phenotype, leading to the release of IL-1β, TNF-α, and other mediators that aggravate neuronal damage and cognitive decline in AD [19].

In Parkinson's disease, there is a tight interplay between the accumulation of pathological α-synuclein, mitochondrial dysfunction of dopaminergic neurons in the substantia nigra, and microglial activation, which, via NF-κB and other pro-inflammatory cascades, maintains chronic inflammation and accelerates neuronal death [20].

In addition to protein aggregates, iron deposition in the basal ganglia — especially the substantia nigra — plays a major role in PD. Disrupted iron homeostasis, linked to mitochondrial dysfunction and oxidative stress, promotes the generation of highly reactive oxygen species, microglial activation, and iron-dependent forms of cell death, which correlate with more severe clinical course and motor complications [21].

In amyotrophic lateral sclerosis, pathogenesis is clearly non–cell-autonomous: reactive microglia and astrocytes form complex "disease-associated" states that at early stages may exert neuroprotective effects (trophic support and clearance of damaged structures), but with chronicity shift into neurotoxic phenotypes characterized by dysregulation of glutamate transport, enhanced oxidative stress, and activation of pro-inflammatory pathways that accelerate motor neuron death [22].

Comparative analyses of the pathogenesis of Alzheimer's disease, Parkinson's disease, and multiple sclerosis reveal that in all three disorders persistent involvement of microglia and astrocytes, release of pro-inflammatory cytokines (including IL-1β, IL-6, and TNF-α), and activation of shared signaling pathways (NF-κB, MAPK) create a unified "neuroinflammatory continuum" upon which disease-specific mechanisms are superimposed [23].

In multiple sclerosis, traditionally considered a primarily demyelinating disease, growing evidence indicates that chronic inflammation with microglial activation in the cortex, cortical demyelination, and progressive synaptic loss partially converge with mechanisms of neurodegeneration seen in Alzheimer's disease. This may explain clinical overlaps, cognitive impairment, and the phenomenon of "mixed" dementia forms in a subset of patients [24].

**Interplay Between Systemic Inflammation and Neuroinflammation**

The gut–brain axis (microbiota–gut–brain axis, MGBA) is considered a key channel linking peripheral inflammatory signals and the immune response of the central nervous system. Disruption of the intestinal microbiota (dysbiosis) alters the production of short-chain fatty acids, microbial metabolites, and endotoxins such as lipopolysaccharide (LPS), leading to activation of innate immunity, shifts in pro- and anti-inflammatory cytokine balance, and increased blood–brain barrier permeability. In turn, this promotes microglial and astrocytic activation, exacerbates neuroinflammation, and accelerates the progression of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Clinical and experimental data indicate that dysbiosis can arise long before the onset of cognitive or motor symptoms, and changes in the microbiome are associated with distinct glial responses and CNS cytokine profiles. In neurodegeneration models, transplantation of "pathogenic" microbiota enhances microglial activation, disrupts astrocyte maturation and function, and increases the accumulation of pathological proteins, whereas normalization of the microbiota partially corrects the neuroinflammatory milieu and attenuates neurodegeneration [25].

Metabolic comorbidities — obesity and type 2 diabetes — generate chronic low-grade systemic inflammation via activation of adipocytes and adipose-tissue macrophages with subsequent release of pro-inflammatory mediators (TNF-α, IL-6, MCP-1, etc.). These signals, together with insulin resistance and oxidative stress, promote glial dysfunction, impair neuronal energy metabolism, drive vascular inflammation, and remodel cerebral microvessels, thereby creating a substrate for cognitive decline and dementia. In experimental models combining Alzheimer's disease and diabetes, astrocytic and microglial alterations have been shown to precede amyloid pathology and exacerbate it, underscoring the leading role of metabolically driven neuroinflammation [26, 27].

Systemic inflammation due to chronic infections, gastrointestinal disorders, and other inflammatory conditions is also associated with more severe courses of neurodegenerative diseases. Meta-analyses and experimental studies demonstrate that peripheral inflammatory stimuli, through circulating cytokines, altered BBB permeability, and endothelial activation, enhance microglial responses, accelerate β-amyloid and pathological tau deposition, and worsen cognitive outcomes. Moreover, several infectious agents (e.g., Helicobacter pylori, herpes simplex virus) are considered modifiable risk factors that, via chronic systemic inflammation and disruption of the gut–brain axis, may intensify the neuroinflammatory component of Alzheimer's disease [28].

These findings show that systemic inflammation — whether metabolic, infectious, or driven by dysbiosis — is not merely a background condition but is actively integrated into the pathogenesis of neurodegeneration via the gut–brain axis and glial–vascular mechanisms, making neuroinflammation a point of convergence for peripheral and central pathological processes.

**Mechanisms of Chronic Inflammation and Aging**

Chronic low-grade inflammation accompanying aging (inflammaging) is considered one of the key background factors that render the brain vulnerable to neurodegeneration. With age, a persistent dysregulation of innate immunity develops, characterized by elevated levels of pro-inflammatory cytokines, altered microglial and astrocytic phenotypes, disturbed vascular homeostasis, and an increased risk of neurodegenerative diseases. In this context, any additional triggers — from protein aggregates to metabolic and vascular insults — provoke a more pronounced and poorly controlled neuroinflammatory response [4, 26, 27].

Aged microglia lose the capacity for rapid and reversible activation and instead adopt a "primed" phenotype: they maintain a heightened readiness for inflammatory responses, hyperreact to secondary stimuli, and remain in a pro-inflammatory state for longer periods. Age-related microglial changes include accumulation of damaged mitochondria, impaired autophagy, shifts in energy metabolism, and enhanced production of reactive oxygen species (ROS), all of which further reinforce pro-inflammatory programs and lower the activation threshold of the NLRP3 inflammasome. In the presence of amyloid, pathological tau, or α-synuclein, this primed status makes neuroinflammation more persistent and destructive [11, 18–20].

Disturbances in iron and lipid homeostasis become particularly important in the context of aging. In Parkinson's disease, age-associated iron accumulation in the substantia nigra and other basal ganglia structures correlates with increased oxidative stress, microglial activation, and faster progression of motor symptoms. Excess iron participates in Fenton reactions, promoting ROS generation, iron-dependent cell death, and heightened inflammatory responses in glial cells. Likewise, in metabolic comorbidities (obesity, type 2 diabetes), chronic adipose-tissue inflammation and dyslipidemia create a systemic background in which cerebral lipid disturbances (including alterations in neuronal and glial membranes) further contribute to activation of neuroinflammatory cascades [26, 27].

Mitochondrial dysfunction and oxidative stress represent another shared link between aging, systemic inflammation, and neurodegeneration. In neurons and glial cells, age-related declines in mitochondrial efficiency, impaired mitophagy, and increased ROS/RNS (reactive nitrogen species) production lead to accumulation of damaged proteins, lipids, and nucleic acids, which serve as DAMPs for microglia. This closes a vicious circle: mitochondrial stress activates microglia and inflammasomes, while pro-inflammatory cytokines and oxidative stress further deteriorate mitochondrial function, accelerating age-associated neuronal loss [4, 9, 11, 27].

Thus, aging creates a background of chronic, difficult-to-resolve inflammation in which microglial priming, glial dysfunction, iron and lipid dysmetabolism, and mitochondrial stress mutually reinforce one another. These processes are not isolated from systemic metabolic and vascular alterations, but form a unified field of chronic inflammation within which disease-specific pathogenic mechanisms of individual neurodegenerative disorders unfold [4, 9–11, 21, 26–28].

**Therapeutic Targets and Strategies**

Growing recognition of the role of neuroinflammation in NDD pathogenesis has shifted the focus from purely neuron-centered concepts toward strategies targeting glia, immune cascades, and their molecular regulators. Several classes of promising interventions are currently distinguished: microglia- and inflammasome-targeting agents, antioxidant and anti-inflammatory approaches (including nanotechnology-based formulations and phytocompounds), epigenetic therapies, and biological agents, primarily anti-amyloid monoclonal antibodies.

Microglial activity is considered one of the most straightforward points of intervention in neuroinflammation. Given the established role of the NLRP3 inflammasome in chronic microglial activation in Alzheimer's disease, Parkinson's disease, and other NDDs, small-molecule NLRP3 inhibitors are being explored as candidates to reduce IL-1β and IL-18 production and thereby mitigate neuronal damage in neurodegeneration models. Parallel efforts focus on targeting microglial receptors and "disease-associated" signaling pathways — TREM2, CD33, progranulin (PGRN), TAM receptors, and others — which regulate phagocytosis, microglial metabolism, and survival. The review by Noh et al. emphasizes that TREM2-agonist antibodies (e.g., AL002) and other microglia-targeted interventions are already undergoing clinical evaluation as potential disease-modifying therapies for AD, PD, and ALS, although they remain at early stages of development, with unresolved questions regarding long-term safety and biomarker-based patient stratification [29].

Antioxidant and anti-inflammatory strategies aim to dampen oxidative and cytokine-mediated components of neuroinflammation, with drug delivery across the BBB being a major challenge. In this regard, nanoparticles and nanocapsulated formulations of antioxidants and phytochemicals (curcumin, resveratrol, quercetin, etc.) are being actively developed, improving bioavailability, prolonging action, and potentially enhancing effects on microglia and astrocytes. A systematic review of nano-antioxidants shows that a variety of organic, lipid, and inorganic nanocarriers reduce ROS production, decrease pro-inflammatory cytokine levels, and improve cognitive and behavioral outcomes in preclinical models of Alzheimer's and Parkinson's diseases. Yet almost all data are still limited to in vitro and experimental in vivo studies, underscoring that nanotechnology-based and phyto-neuroprotective approaches currently represent an extended preclinical pipeline rather than ready-to-use clinical tools [30].

Epigenetic modulation of neuroinflammation is another promising direction, particularly in light of the role of m6A RNA modifications and O-GlcNAc glycosylation in regula-

ting immune gene expression. Alterations in the m6A profile in microglia and astrocytes affect the expression of cytokines, innate immune receptors, and signaling molecules involved in Alzheimer's disease pathogenesis, while perturbations in the O-GlcNAc cycle can reshape transcription factor activity and chromatin structure, shifting the balance between pro- and anti-inflammatory programs. Based on these findings, potential therapeutic approaches — inhibitors or activators of m6A-related enzymes (METTL3/14, FTO, etc.) and modifiers of the O-GlcNAc cycle — are being discussed as ways to "reprogram" glial responses. However, as epigenetic reviews stress, any interventions at this level carry a high risk of off-target effects, and at present this field remains largely conceptual and preclinical rather than a source of therapies ready for clinical implementation [16, 17].

Biological agents, primarily anti-amyloid monoclonal antibodies, constitute the first group of approved disease-modifying therapies for early Alzheimer's disease, demonstrating that interventions in pathological protein cascades may indirectly influence neuroinflammation. As highlighted in the review by Koga-Batko et al., aducanumab and donanemab reduce amyloid burden and in clinical trials produce a statistically significant but modest slowing of cognitive decline; their use is associated with amyloid-related imaging abnormalities (ARIA) and requires careful monitoring. Given the close relationship between amyloid pathology, microglial activation, and cytokine dysregulation, these antibodies can be considered indirect modulators of neuroinflammation; however, their effects remain limited, and they do not address the fundamental mechanisms of inflammaging, microglial senescence, and metabolic stress described above [30].

Overall, the therapeutic landscape targeting neuroinflammation currently represents a multilayered system: from direct microglia-focused interventions and nanoparticle-based delivery of antioxidants and phytochemicals to deeper epigenetic strategies and biological agents acting on the amyloid cascade [11, 16, 17, 19, 29, 30]. The key problem is that most of these approaches show convincing benefits only in preclinical models or yield relatively modest clinical effects accompanied by significant risks, which emphasizes the need for more precise patient stratification, rational combination therapies, and integration of biomarkers to monitor neuroinflammation dynamics.

## Conclusion

Neuroinflammation is a key integrative link in the pathogenesis of neurodegenerative diseases, connecting genetic predispositions, age-associated changes, immune dysregulation, metabolic disturbances, and vascular factors. Chronic activation of microglia and astrocytes, involvement of inflammasome cascades (primarily NLRP3), blood–brain barrier dysfunction, and interactions with systemic inflammation together form a self-sustaining pathological circuit that drives progressive neuronal damage and synaptic dysfunction.

Despite substantial advances in our understanding of cellular and molecular mechanisms, neuroinflammation remains a complex, multilayered, and heterogeneous process. Different neurodegenerative diseases utilize shared signaling nodes (NF-κB, NLRP3, cytokine networks) but embed them into specific pathogenic patterns — amyloid- and tau-associated inflammation in Alzheimer's disease, α-synucleinopathy and iron-mediated mechanisms in Parkinson's disease, non–cell-autonomous glial responses in ALS, and chronic meningeal and cortical inflammation in multiple sclerosis.

Current therapeutic developments — from microglia-targeted strategies and inflammasome inhibitors to nanotechnology-based platforms and epigenetic interventions — reflect the growing emphasis on precise modulation of inflammatory cascades. However, most of these approaches are still at the preclinical or early clinical stage, demonstrating promising yet limited effects. Approved agents such as anti-amyloid antibodies influence neuroinflammation only indirectly and do not eliminate the fundamental drivers of chronic inflammation.

Future progress will depend on integrating multi-omic biomarkers, developing stratified treatment approaches, modeling disease at the level of cellular networks and microglia–astrocyte interactions, and accounting for systemic factors — microbiota, metabolic disturbances, and chronic infections. Constructing comprehensive models of neuroinflammation will enable the design of more precise and personalized therapeutic strategies capable of truly modifying the course of neurodegenerative diseases.

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