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NEUROINFLAMMATION IN NEUROLOGICAL DISORDERS: MOLECULAR MECHANISMS, CLINICAL IMPLICATIONS, AND EMERGING THERAPEUTIC STRATEGIES

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ABSTRACT

Neuroinflammation is a dynamic immune response within the central nervous system that contributes to both tissue protection and neurological injury. This review examines the cellular mediators, molecular pathways, clinical consequences, diagnostic biomarkers, and emerging treatments associated with neuroinflammation across neurological disorders. Microglia, astrocytes, endothelial cells, peripheral leukocytes, cytokines, chemokines, complement proteins, reactive oxygen species, and inflammasomes interact to regulate neuronal survival, synaptic function, myelin integrity, and blood-brain barrier stability. Persistent activation of these mechanisms contributes to Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, stroke, traumatic brain and spinal cord injury, epilepsy, central nervous system infections, and neuropsychiatric comorbidities. Blood-brain barrier disruption and immune–vascular crosstalk further amplify leukocyte infiltration, oxidative damage, demyelination, and neurodegeneration. Cerebrospinal fluid, blood-based, imaging, and multi-omics biomarkers may improve early diagnosis, disease monitoring, prognostic assessment, and patient stratification. Current therapeutic approaches include corticosteroids, immunosuppressive agents, monoclonal antibodies, cytokine inhibitors, inflammasome blockers, and strategies targeting glial activation, ferroptosis, and oxidative stress. Nanotechnology-based delivery systems may enhance central nervous system penetration and reduce systemic toxicity. Integrating peripheral immune status with central molecular changes may clarify disease heterogeneity and support rational combination therapies across distinct conditions. Future progress depends on distinguishing protective from harmful inflammation, identifying stage-specific therapeutic windows, validating biomarkers, and developing precise, individualized neuroimmune interventions.

KEYWORDS: Neuroinflammation, Microglia, Blood-brain barrier, Neurodegeneration, Immunomodulatory therapy

1. INTRODUCTION

Neuroinflammation is an orchestrated immune response to infection, tissue damage, metabolic dysfunction, protein aggregation, or systemic immune activation in the central nervous system. It is now known to be a common phenomenon in a wide range of neurological disorders, not limited to ‘classic’ inflammatory disorders. Its effects are a function of the intensity, duration, anatomical site, and cell context of the response. The inflammation can either have protective functions by preventing pathogens from infecting the CNS or help the host to clear away debris and endure injury, or it can be chronic and dysregulated, leading to exaggerated neuronal dysfunction and synaptic loss, demyelination, and progressive neurodegeneration (Shi & Yong, 2025).

The central nervous system was previously thought to be rather immune-privileged; however, the available evidence suggests that there is continuous communication between neural, vascular, meningeal, and immune compartments. Microglia, the main resident immune cells of the brain and spinal cord, detect changes to the integrity of the tissue via pattern recognition receptors and quickly switch between transcriptional, metabolic, and functional states. Other cells involved in inflammatory signaling and influencing the local immune environment are astrocytes, neurons, oligodendrocytes, endothelial cells, pericytes, and infiltrating leukocytes. Such interactions occur at specific interfaces, like the blood-brain barrier, blood-cerebrospinal fluid barrier, meninges, and choroid plexus, that are responsible for immune surveillance and cellular trafficking in health and disease (Buckley & McGavern, 2022).

There is two-way communication between the nervous system and the immune system. The innate and adaptive immune system can be regulated by neural mechanisms via the autonomic, endocrine, and neurotransmitter pathways, and inflammatory mediators can modify neuronal excitability, cognition, mood, sleep patterns, and behavior. A reciprocal regulation which helps keep the body in balance, but can go awry if inflammatory signaling persists or becomes overactive (Irwin & Cole, 2011). Innate immune activation is especially important, as it serves as a mechanistic link between neurodegenerative and neuropsychiatric diseases, which have distinct clinical manifestations but share abnormalities of cytokine production, oxidative stress, glial reactivity, and synaptic function (Novellino et al., 2020).

Neuroinflammation is currently known to play a role in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, stroke, traumatic brain injury, epilepsy, and some psychiatric disorders. Microglial and astrocytic activation can be maintained by misfolded proteins, damaged mitochondria, extracellular debris, and dead neurons during neurodegenerative diseases. This causes the cytokines, chemokines, ROS and proteases to be released, which can exacerbate neuronal damage and interfere with repair processes (Adamu et al., 2024). Oxidative stress and innate immune activation can have a vicious cycle effect on each other, promoting further increases in cellular dysfunction and disease progression (Leszek et al., 2016). Although there are significant disparities in the clinical presentation of each disease and the underlying cause, it is believed that the molecular target might be shared in the pathophysiology of several progressive neurological diseases, such as MS (Dias-Carvalho et al., 2024).

Neuroinflammation is NOT always a bad thing. Immune cells can clear cell debris, limit infection, promote remyelination, activate angiogenesis, and produce trophic factors which promote tissue repair. The therapeutic objective is therefore to selectively modify the harmful inflammatory programs, while maintaining protective/reparative functions (Yong et al., 2019). The difference is one of the most important developments in the treatment of microglial receptors, cytokines, inflammasomes, complement proteins, and intracellular signaling pathways. A broadly acting effect on innate immunity might have a useful or adverse effect on homeostasis (Andreasson et al., 2016).

Chronic neuroinflammation is also a dynamic interplay between microglia, peripheral immune cells, and tissue-specific regulatory signals. Whether these interactions are protective and/or injurious might be influenced by disease stage, age, genetic susceptibility, systemic comorbidities and previous immune exposure (Müller & Di Benedetto, 2025). Association of the molecular results with the longitudinal clinical information can help explain the differences in phenotypes that arise among patients. This integration could also reveal windows of opportunity for therapeutic intervention that will cause minimal damage while not disrupting immune-mediated recovery, adaptation, or maintenance of central nervous system homeostasis. More knowledge on these mechanisms has direct clinical relevance in biomarker development, prognosis, and patient stratification, as well as therapeutic timing. The review covers the cellular and molecular mechanisms of neuroinflammation, the influence of neuroinflammation in major neurological diseases, diagnostic and therapeutic implications of neuroinflammation, and new approaches that aim to modulate neuroimmune mechanisms with greater accuracy.

Objectives of the review:

- To summarize the cellular and molecular mechanisms underlying neuroinflammation.
- To evaluate its clinical role across major neurological disorders.
- To examine emerging biomarkers and targeted therapeutic strategies.

2. Cellular Mediators of Neuroinflammation

Resident neural cells and peripheral immune populations that sense infection, tissue damage, protein deposition, and metabolic stress coordinate neuroinflammation. Microglia are the main immune sentinels of the CNS, which constantly survey the extracellular environment and quickly reverse their morphology, metabolism, and gene expression upon detecting danger signals. While activated microglia can clear cell debris, secrete trophic factors, and aid tissue repair, chronic activation can lead to neuronal dysfunction by producing cytokines, causing oxidative stress, and modulating synaptic remodeling. Astrocytes also modulate inflammatory responses through ion regulation, metabolic support of neurons, maintenance of the integrity of the blood-brain barrier, and chemokine production to regulate recruitment of immune cells. They can either regulate inflammation or exacerbate harmful inflammatory pathways in different stages of disease and in different local micro-environments (Bhusal et al., 2023).

Other cells, such as neurons, oligodendrocytes, endothelial cells, pericytes, and infiltrating leukocytes, also help to shape the neuroimmune environment. The responses of the glial cells are altered by the release of neurotransmitters and regulatory molecules by the neurons, while damage to the oligodendrocytes and myelin provides signals that activate innate immune pathways. These cellular populations interact in a reactive manner, which is important for the processes of inflammation, demyelination of tissue, survival of neurons, and subsequent repair of the tissue (Kölliker-Frers et al., 2021). Monocytes, macrophages, lymphocytes, and neutrophils are infiltrating cells that can gain access to the CNS at the time of disruption of the vascular barriers, and thus represent a link between the peripheral immune system and local neurology (Passaro et al., 2021).

Selective control of these cellular responses is needed, not generalised immune suppression. Some drugs might have anti-inflammatory effects other than their usual therapeutic purposes, and drug repurposing may help to

regulate the activation of immune cells and cytokine production in some diseases (Eslami et al., 2025). The temporal and functional heterogeneity of neuroimmune cells is crucial to identifying interventions that are able to counter neurotoxicity while retaining protective surveillance and repair functions. Figure 1 depicts the cellular mechanisms that connect neuroimmune activation and neural injury, repair, and therapeutic modulation.

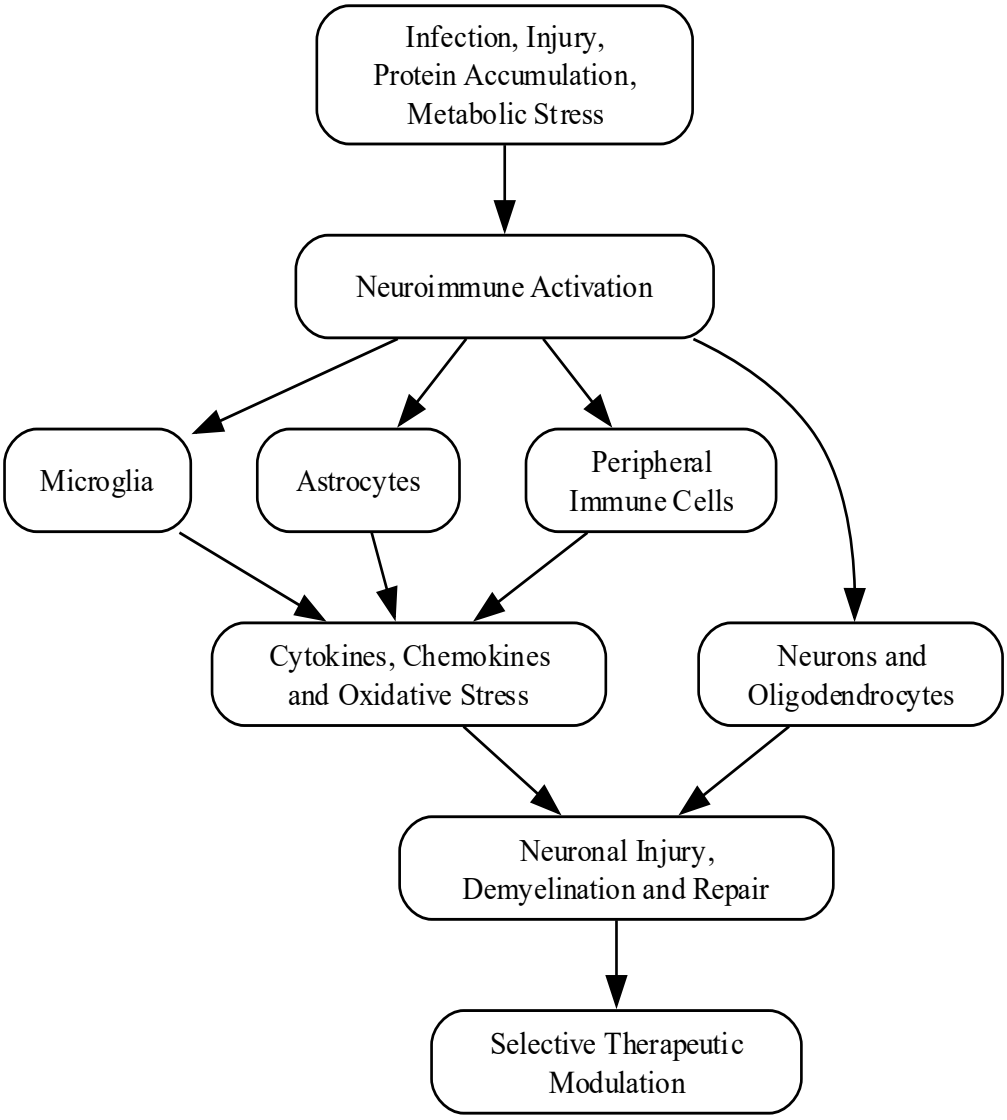

Figure 1. Cellular Pathways Linking Neuroimmune Activation to Neural Injury, Repair, and Therapeutic Modulation

3. Molecular Signaling Pathways in Neuroinflammation

A network of interconnected signaling pathways is involved in the regulation of neuroinflammation, which converts cellular stress, infection, tissue damage, and damage-associated molecular patterns into immune responses. Some pattern-recognition receptors recognize pathogenic or endogenous danger signals that trigger the activation of adaptor proteins like myeloid differentiation primary response 88. This starts downstream nuclear factor kappa B and mitogen-activated protein kinase signaling, leading to transcription of inflammatory cytokines, chemokines, adhesion molecules, and enzymes involved in oxidative stress. The continual activation of these pathways can maintain glial reactivity, affect neuron signaling, and make tissues more susceptible.

Another key modulator of neuroimmune function is the Janus kinase/signal transducer and activator of transcription pathway. Upon binding to their receptors, cytokines activate Janus kinases that, in turn, phosphorylate signal transducer and activator of transcription (STAT) proteins that enter the nucleus and alter inflammatory gene expression. The JAK/STAT3 pathway could be a therapeutic target in epilepsy and inflammatory neurological diseases, as this pathway is involved in astrocyte reactivity, microglial activation, and neuronal hyperexcitability (Abdelaziz et al., 2026).

Neuroinflammatory injury is also due to inflammasome signalling. The activation of the NOD-like receptor protein 3 (NLRP3) inflammasome enhances the activity and maturation of interleukin-1 beta and interleukin-18, which further aggravates the inflammation in the region. Many of these same signaling networks are also activated during systemic inflammatory states, and hyperactivation can result in the release of cytokines throughout the body and multicompartmental dysfunction (Tang et al., 2025). Another example of how the effects of uncontrolled

inflammatory signaling are systemic is by altering the regulation of hormones and metabolism, known as cytokine amplification (Attiq et al., 2024). The recruitment of immune cells and tissue damage are reinforced by pro-inflammatory cytokines and chemokines during inflammatory disorders (Zygner et al., 2023). The inhibition of these pathways may be useful to limit neurotoxicity while maintaining required immune defense and repair. Table 1 implies that the primary cellular and molecular pathways are involved in neuroinflammation.

Table 1. Cellular and Molecular Components of Neuroinflammation

Component	Principal function	Pathological contribution	Clinical relevance	References
Microglia	Immune surveillance, phagocytosis, debris clearance, and tissue repair	Persistent activation promotes cytokine release, oxidative stress, synaptic dysfunction, and neuronal injury	Potential target for cell-specific immunomodulation and nanotherapeutic delivery	(Bhusal et al., 2023; Silva et al., 2025)
Astrocytes	Metabolic support, ion regulation, neurotransmitter clearance, and blood-brain barrier maintenance	Reactive astrocytes amplify inflammatory signaling, leukocyte recruitment, and demyelination.	Relevant to multiple sclerosis, epilepsy, and neurodegenerative disorders	(Brambilla, 2019; Kölliker-Frers et al., 2021)
Peripheral leukocytes	Pathogen control, antigen presentation, and adaptive immune responses	Infiltration through disrupted vascular barriers intensifies tissue inflammation and autoimmunity	Important in multiple sclerosis, stroke, infection, and traumatic injury	(Passaro et al., 2021; Javidi & Magnus, 2019)
NF-κB and MAPK pathways	Regulation of inflammatory gene transcription	Sustained signaling increases cytokines, chemokines, oxidative enzymes, and adhesion molecules.	Targets for pathway-selective anti-inflammatory treatment	(Tang et al., 2025)
JAK/STAT3 pathway	Cytokine receptor signaling and regulation of immune-cell responses	Dysregulation promotes astrocyte reactivity, microglial activation, and neuronal hyperexcitability	Potential therapeutic target in epilepsy and inflammatory neurological disease	(Abdelaziz et al., 2026)
NLRP3 inflammasome	Caspase-1 activation and maturation of interleukin-1β and interleukin-18	Excessive activation sustains neurotoxicity and inflammatory tissue injury	Inflammasome inhibitors may reduce damaging immune activation	(Tang et al., 2025)

4. Cytokines, Chemokines, and Inflammatory Mediators

Neuroinflammation is initiated, amplified, and resolved by cytokines, chemokines, reactive oxygen species, complement proteins, and lipid-derived mediators. Activated microglia, astrocytes, endothelial cells, and infiltrating leukocytes release pro-inflammatory cytokines (e.g., tumour necrosis factor-alpha, interleukin-1 beta, and interleukin-6). These mediators modulate the activity of neurons, activation of glia, vascular permeability, and recruitment of immune cells. Chemokines create concentration gradients that guide monocytes, lymphocytes, and neutrophils to injured neural tissue. Continued production of cytokines and chemokines can maintain inflammatory signaling and can promote demyelination, synaptic dysfunction, and neuron loss.

Mitochondrial metabolism, phagocytosis, and enzyme-mediated inflammatory reactions are all sources of Reactive Oxygen Species. In addition to their destructive effects on other cells and molecules, ROS also play positive roles in antimicrobial defense, cellular signaling, tissue remodeling, and wound repair, suggesting that ROS may have positive physiological roles (Bryan et al., 2012). Overproduction or over-accumulation of these compounds disrupts proteins, lipids, mitochondrial components, and nucleic acids, leading to a vicious circle of oxidative stress and inflammatory activation. Mechanisms similar to this have been described in inflammatory tissue damage, where oxidant production plays a role in dysfunction and necrosis of cells (Jaeschke, 2011).

Complement activation is critical for the recognition of pathogens, clearance of debris, and immune surveillance. Excessive pruning of synapses, recruitment of macrophages, and tissue damage could be caused by chronic complement activity. Immune dysregulation in the elderly can lead to changes in the activity of complement and macrophages that can promote chronic low-grade inflammation in various tissues (Zhuang & Lyga, 2014). In the central nervous system, inflammatory mediators may disrupt endothelial junctions and compromise the integrity of the blood-brain barrier, allowing more entry of circulating immune cells and soluble factors (Shimizu &

Nakamori, 2024). Therapeutic strategies need to be able to control the activity of damaging mediators while not compromising the key functions of those mediators in defense, repair, and homeostasis. The role of neuroinflammatory mediators in synaptic dysfunction, demyelination and disruption of the blood–brain barrier is shown in Figure 2.

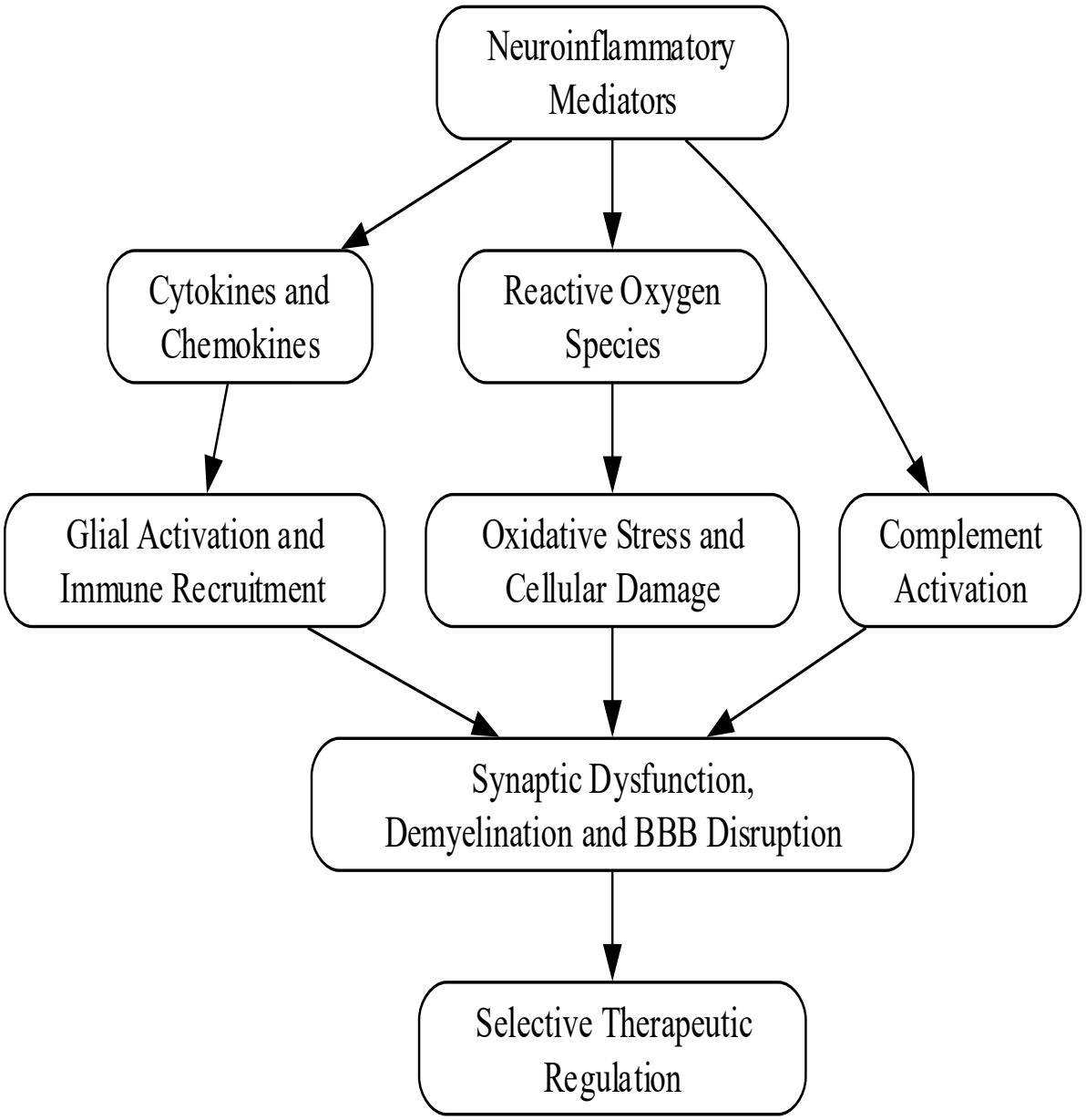

Figure 2. Neuroinflammatory Mediators Driving Synaptic Dysfunction, Demyelination, and Blood–Brain Barrier Disruption

5. Blood-Brain Barrier Dysfunction and Neurovascular Inflammation

The blood-brain barrier is the highly selective barrier between the blood and brain, composed of tight-junction proteins, pericytes, astrocytic end-feet, and surrounding extracellular matrix. It controls molecular transport, thus excluding the invasion of circulating immune cells, and maintains the ionic and metabolic milieu necessary for neuronal activity. Neuroinflammatory cytokines, oxidative stress, hypoxia, and vascular injuries may impair endothelial barrier function and allow for leakage of plasma proteins, leukocytes, and even neurotoxic substances into the CNS (Archie et al., 2021).

Brain endothelial cells are not just structural players but active players in neuroinflammation. After being exposed to inflammatory mediators, they up-regulate adhesion molecules and chemokines that facilitate leukocyte adhesion, migration, and infiltration into neural tissue. Disruption of the barrier can further exacerbate microglial and astrocytic activation, leading to a vicious cycle in which vascular dysfunction can further amplify local inflammatory signals and increase neuronal injury (Takata et al., 2021). This process plays a role in the development of neurodegenerative, demyelinating, cerebrovascular, and traumatic neurological diseases.

Now, endothelial ferroptosis is a new pathway connecting vascular damage and neuroinflammation. Iron deposition, lipid peroxidation, mitochondrial dysfunction, and decreased antioxidant defenses can lead to endothelial cell death, reduced vascular integrity, and immune–vascular crosstalk (Liu et al., 2026). It also affects

many other processes, such as nutrient supply and waste elimination, as well as cerebral homeostasis, due to the persistence of the barrier's impairment, making neurons more vulnerable. Such aberrations have been observed in various other Alzheimer and related disorders, such as Parkinson's disease and amyotrophic lateral sclerosis (ALS). (Giri et al., 2024) Preserving tight junctions, preserving oxidative injury, inhibiting endothelial activation, and inhibiting ferroptosis could be therapeutic strategies to restore barrier function and minimize subsequent neuroinflammatory damage. Table 2 shows the main inflammatory mediators and mechanisms leading to blood-brain barrier (BBB) dysfunction.

Table 2. Inflammatory Mediators and Blood-Brain Barrier Dysfunction

Mediator or mechanism	Physiological role	Effect during dysregulated neuroinflammation	Associated outcomes	References
Pro-inflammatory cytokines	Coordinate immune activation and cellular communication	Increase endothelial permeability, glial activation, neuronal dysfunction, and leukocyte recruitment	Neurodegeneration, demyelination, edema, and hyperexcitability	(Mallick et al., 2025; Zygner et al., 2023)
Chemokines	Guide immune-cell migration toward damaged tissue	Promote excessive recruitment of monocytes, lymphocytes, and neutrophils	Persistent central nervous system inflammation and tissue injury	(Zygner et al., 2023)
Reactive oxygen species	Support antimicrobial defense, signaling, and tissue remodeling	Damage proteins, lipids, mitochondria, and nucleic acids when excessively produced	Oxidative stress, necrosis, and progressive neuronal dysfunction	(Bryan et al., 2012; Jaeschke, 2011)
Complement system	Pathogen recognition, debris clearance, and immune surveillance	Chronic activation may promote synaptic pruning and macrophage-mediated injury	Cognitive decline, aging-related inflammation, and neurodegeneration	(Zhuang & Lyga, 2014)
Tight-junction disruption	Normally restricts paracellular entry into the brain	Allows plasma proteins, inflammatory mediators, and leukocytes to enter neural tissue	Amplification of local inflammation and neuronal injury	(Archie et al., 2021; Takata et al., 2021)
Endothelial ferroptosis	Not a normal homeostatic process; reflects iron-dependent lipid damage	Causes endothelial death, vascular instability, and immune–vascular crosstalk	Blood-brain barrier breakdown and secondary neuroinflammation	(Liu et al., 2026)

6. Neuroinflammation in Neurodegenerative Disorders

Neuroinflammation is a key factor in the pathogenesis and onset of neurodegenerative diseases such as Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and multiple sclerosis. These cytokines, chemokines, reactive oxygen species, and other inflammatory mediators activate microglia and astrocytes, leading to the secretion of cytokines, chemokines, reactive oxygen species, and other inflammatory mediators. These responses can support the clearance of debris and protection of tissue in the short-term, but persistent activation can lead to disturbance in the functioning of synapses and accelerate the loss of neurons and impair endogenous repair processes (Zhang et al., 2023).

Amyloid beta accumulation and tau pathology activate innate immune mechanisms, while systemic inflammation can lead to increased BBB permeability, and thus strengthen the central inflammatory process in Alzheimer's disease. In Parkinson disease, inflammation related to the aggregation of alpha-synuclein, degeneration of dopaminergic neurons, and changes in microglial functions occur. Peripheral immune activation can also have an impact on disease pathogenesis by inducing peripheral cytokines and driving immune cell influx in the CNS (Hanna et al., 2022).

Amyotrophic lateral sclerosis is associated with progressive motor neuron degeneration and ongoing microglial and astroglial activation. They can help the survival of the neurons at first, but can also take on a neurotoxic effect that can release inflammatory mediators and exacerbate damage to motor neurons (Philips & Robberecht, 2011). Astrocytes are also key players in MS as they regulate several processes such as the recruitment of leukocytes in the CNS, the integrity of the blood-brain barrier, the signaling of cytokines, demyelination, and repair of lesions (Brambilla, 2019).

Although the various diseases are different, they share the same inflammatory mechanisms, providing opportunities to treat them. Therapeutic approaches can be directed toward modulation of glial activation, blockade of detrimental cytokine signaling and pathways, repair of barrier function, and systemic inflammatory signals. Stage and cell type are still important, however, as one may need to suppress immune responses but not too much, which may otherwise impede protective clearance and repair. Figure 3 shows some common pathways of neuroinflammation in the major neurodegenerative diseases.

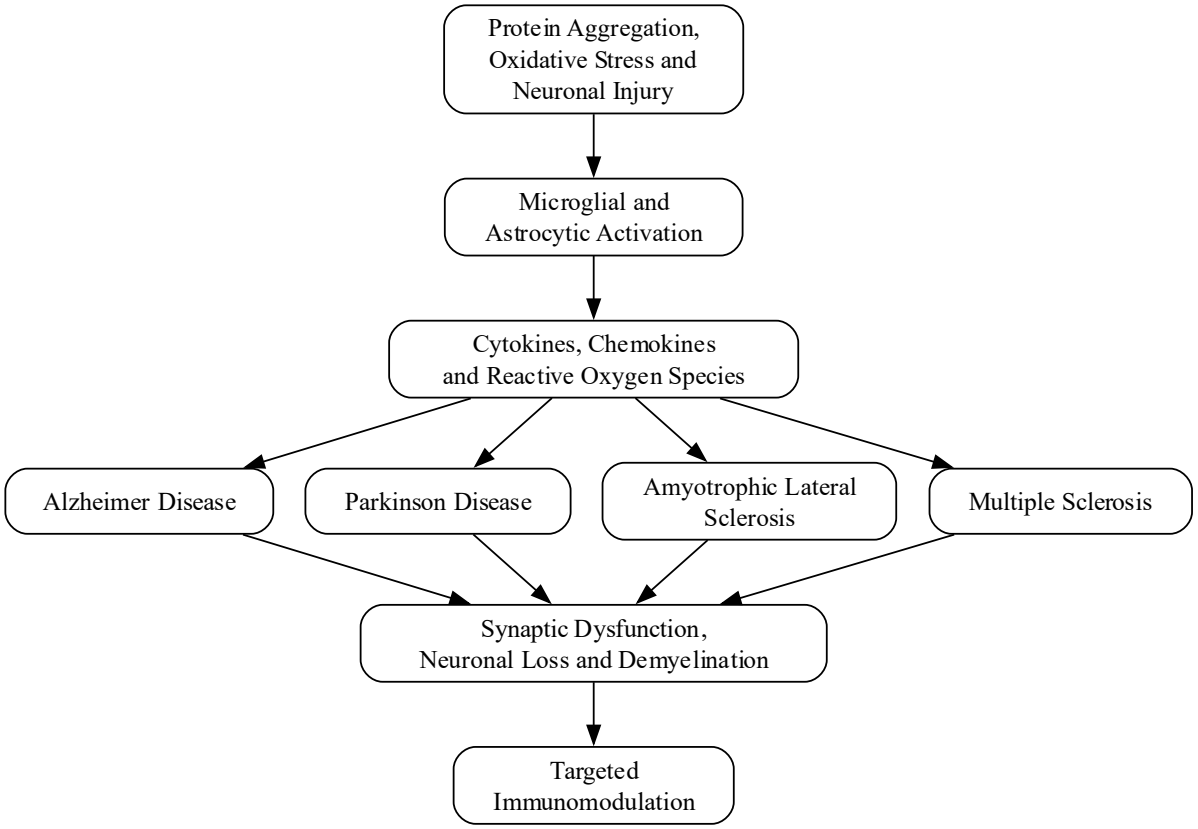

Figure 3. Shared Neuroinflammatory Pathways in Major Neurodegenerative Disorders and Their Therapeutic Targeting

7. Neuroinflammation in Autoimmune and Demyelinating Disorders

Autoimmune and demyelinating diseases are characterized by immune attacks on components of the central nervous system that lead to inflammation, myelitis, axonal dysfunction, and neurological disability. A prime example of this is multiple sclerosis, which is characterized by peripheral immune activation, blood-brain barrier breakdown, infiltration of leukocytes, and destruction of the oligodendrocytes and myelin. The demyelination disrupts saltatory conduction and causes metabolic stress to the axons, while remyelination requires recruitment of oligodendrocyte precursor cells, their maturation, and remyelination of the myelin sheaths. These reparative processes are impaired and promote the progression of neurological impairments (Bando, 2020).

In MS, the immune response occurs by T lymphocytes, B lymphocytes, macrophages, microglia, astrocytes, and soluble inflammatory mediators. These components play various roles throughout the disease process, resulting in acute inflammatory lesions, myelin destruction, and neurodegeneration. New insights in neuroimmunology have paved the way for therapeutic strategies to move beyond general immunosuppressive approaches to specific targets for immune-cell trafficking, cytokine signaling, B-cell function, and tissue repair mechanisms (Eva et al., 2023).

During the process of these interactions, platelets could also play a role in early neurovascular and axonal injury through the activation of the endothelium, adhesion of leukocytes, activation of coagulation, and the release of pro-inflammatory mediators. Their involvement in experimental autoimmune encephalomyelitis and multiple sclerosis indicates that neuroaxonal loss, which is significant in the disease, could be mediated by vascular and thromboinflammatory mechanisms (Orian, 2025).

Primary demyelinating diseases are not the only diseases that are associated with autoimmunity. Normally sequestered neural antigens can be exposed in ischemic stroke and traumatic brain injury, and can break down immune tolerance, leading to an adaptive immune response to the brain tissue. These responses can continue to cause inflammation and contribute to secondary neurological injury (Javidi & Magnus, 2019). Pathogenic autoimmunity must be suppressed while antimicrobial defense, tissue repair, and remyelination are preserved in order to be able to treat these types of diseases. Strategies based on disease-specific markers could be used to select patients who will benefit from disease-specific immunomodulation.

8. Neuroinflammation in Acute Neurological Injury

Acute neurological injury, such as ischemic stroke, haemorrhagic stroke, traumatic brain injury, and spinal cord injury, will have a rapid inflammatory response that will affect secondary tissue damage and neurological recovery. The cell damage is associated with patterns that activate the microglia, astrocytes, endothelial cells, and infiltrating leukocytes. They release cytokines, chemokines, proteases, and reactive oxygen species, which lead to BBB disruption, edema, neuronal cell death, and impaired vascular function.

The onset of acute ischemic stroke triggers excitotoxicity, oxidative stress, and innate immune activation from decreased blood supply to the brain. Hemorrhagic stroke also releases inflammation-enhancing blood components, thrombin, iron, and hemoglobin breakdown products, which can intensify the inflammation. That initial inflammatory response helps remove debris, but when inflammation persists, it can increase tissue damage and further hinder tissue function (Alsbrook et al., 2023).

In traumatic SCI, there is an initial mechanical trauma followed by secondary events like ischemia, peroxidation of lipids, demyelination, etc., and infiltration of immune cells. Anti-inflammatory, neuroprotective, cell-based, and regeneration strategies have been tested in clinical trials to minimize secondary injury and keep the existing neural pathways intact (Khaing et al., 2023). A variety of other therapeutic approaches have been aimed at corticosteroid-sensitive pathways, cytokine signaling, oxidative damage, and leukocyte recruitment, with mixed success (Singh et al., 2012).

Continuing inflammation following acute injury may change the excitability of the neurons and lead to long-term neurological sequelae. Neurotransmission and stability of neural networks are regulated by inflammatory mediators, which are also involved in the regulation of neurotransmission and stability of neural networks in epilepsy and depression (Shi et al., 2025). There is a critical timing for effective intervention, as the inflammatory response may help repair tissue, while prolonged inflammation can cause secondary degeneration. Treatment guided by the biomarkers may help to separate a protective response from a detrimental escalation of inflammatory response. The inflammatory cascade from acute neurological injury through to secondary degeneration and biomarker-guided treatment is shown in Figure 4.

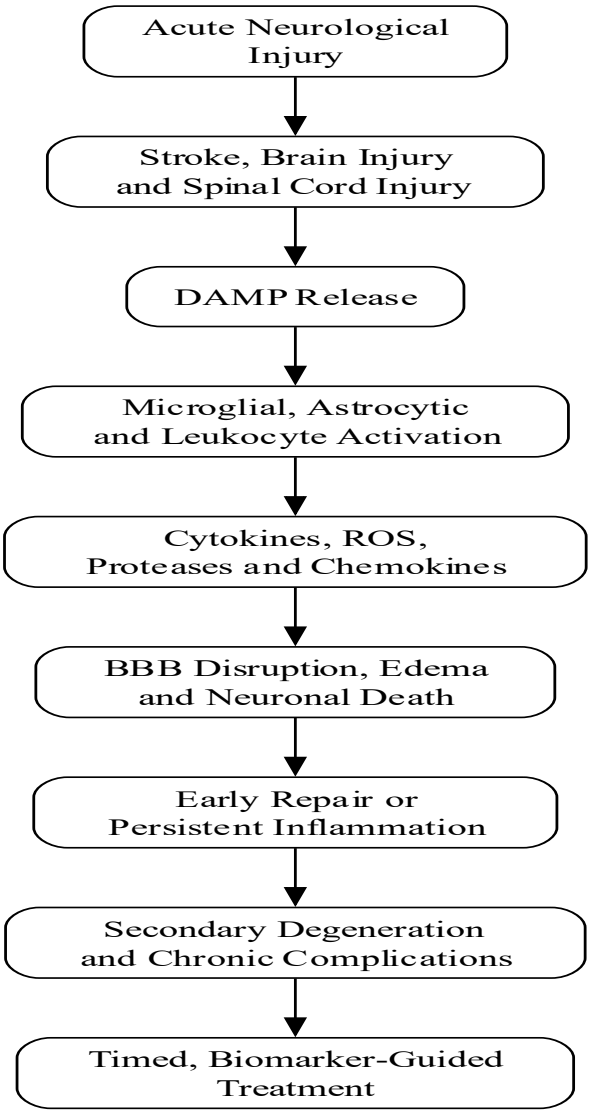

Figure 4. Neuroinflammatory Cascade From Acute Neurological Injury to Secondary Degeneration and Biomarker-Guided Treatment

9. Neuroinflammation in Epilepsy, Infection, and Neuropsychiatric Disorders

Neuroinflammation is involved in epileptogenesis, seizure recurrence, infectious brain injuries, and neurobehavioral comorbidities. Recurrent seizures trigger microglia and astrocytes, upregulate permeability of the blood-brain barrier, and trigger the release of interleukins, tumor necrosis factor alpha, prostaglandins, and reactive oxygen species. These mediators have the ability to modulate glutamatergic and gamma-aminobutyric acid signaling, to lower seizure thresholds, and to maintain hyperexcitability of the neuronal network. Inflammatory pathways are also linked to other common conditions seen in people with epilepsy, such as depression, anxiety, cognitive impairments, and behavioural changes (Mazarati et al., 2017).

This relationship may be further affected by the gut microbiota and its metabolites, gut permeability, systemic cytokine production, and vagal signaling. The gut microbiota–neuroinflammation axis may exacerbate seizures and depressivity, highlighting potential opportunities for microbiome-directed interventions (Liu et al., 2025). Infections of the central nervous system also trigger innate and adaptive immune responses. These responses prevent the spread of pathogens, but overproduction of cytokines, infiltration of leukocytes, and activation of glia can impair neural circuits and result in long-lasting cognitive or behavioral impairment (Klein et al., 2017).

The use of cerebrospinal fluid and blood markers of inflammatory and neurodegenerative processes is increasingly involved in clinical evaluation. Concurrent neuronal injury or progressive neurodegeneration can be identified by amyloid-beta, phosphorylated tau, and neurofilament proteins (Milà-Alomà et al., 2019). Biomarker panels can provide a broader separation of inflammatory activity, axonal damage, astrocytic responses, and therapeutic efficacy in neurological diseases (Gaetani et al., 2020). There are emerging blood and CSF markers that could aid disease monitoring, prognosis, and selection of treatment in MS (Chitnis et al., 2025). The combination of inflammatory biomarkers with clinical and neuroimaging data can enhance the accuracy of diagnosis and facilitate personalized therapeutic management. Table 3 proposes some of the neuroinflammatory mechanisms involved in key neurological diseases.

Table 3. Neuroinflammation Across Major Neurological Disorders

Neurological disorder	Major inflammatory triggers	Principal neuroimmune mechanisms	Clinical consequences	References
Alzheimer disease	Amyloid-β accumulation, tau pathology, mitochondrial dysfunction, and systemic inflammation	Microglial activation, astrocyte reactivity, cytokine release, complement activation, and barrier dysfunction	Synaptic loss, cognitive decline, and progressive neurodegeneration	(Zhang et al., 2023; Hanna et al., 2022)
Parkinson disease	α-Synuclein aggregation, dopaminergic neuronal injury, and oxidative stress	Microglial activation, peripheral immune signaling, mitochondrial damage, and cytokine production	Progressive dopaminergic degeneration and motor impairment	(Hanna et al., 2022; Giri et al., 2024)
Amyotrophic lateral sclerosis	Motor neuron injury, protein aggregation, and glial dysfunction	Transition of microglia and astrocytes from supportive to neurotoxic phenotypes	Progressive motor neuron loss and muscle weakness	(Philips & Robberecht, 2011)
Multiple sclerosis	Autoimmune activation, blood-brain barrier disruption, and myelin antigen recognition	T-cell and B-cell activity, macrophage infiltration, astrocyte activation, and platelet-mediated inflammation	Demyelination, axonal loss, and neurological disability	(Bando, 2020; Eva et al., 2023; Orian, 2025)
Stroke	Ischemia, hemorrhage, excitotoxicity, blood products, and oxidative stress	Microglial activation, cytokine release, leukocyte infiltration, edema, and vascular inflammation	Secondary neuronal injury and impaired neurological recovery	(Alsbrook et al., 2023)
Traumatic spinal cord injury	Mechanical tissue disruption, ischemia, demyelination, and lipid peroxidation	Cytokine signaling, immune-cell infiltration, oxidative damage, and glial scarring	Secondary degeneration, impaired conduction, and persistent disability	(Khaing et al., 2023; Singh et al., 2012)

Epilepsy	Recurrent seizures, blood-brain barrier disruption, and altered gut–brain signaling	Glial activation, cytokine release, neurotransmitter imbalance, and neuronal hyperexcitability	Seizure recurrence, depression, anxiety, and cognitive impairment	(Mazarati et al., 2017; Liu et al., 2025)
Central nervous system infection	Viral, bacterial, fungal, or parasitic invasion	Innate and adaptive immune activation, leukocyte recruitment, and cytokine production	Neural circuit disruption and persistent cognitive or behavioral impairment	(Klein et al., 2017)

10. Clinical Implications and Diagnostic Biomarkers

Good biomarkers are needed to identify the presence of neuroinflammation, the disease type, track disease progression, and assess therapeutic response. Cerebrospinal fluid is an excellent source of CNS biomarkers since it provides a direct indication of biochemical changes within the CNS. The levels of amyloid-beta, total tau, phosphorylated tau, neurofilament proteins, inflammatory cytokines, and glial markers can give information about neuronal injury, protein aggregation, and immune activation. Blood-based biomarkers, though less invasive, are more appropriate for repeated testing but may also be affected by peripheral tissues, systemic inflammation, and the integrity of the blood-brain barrier. The introduction of more sensitive assays has led to the implementation of several CSF-based biomarkers for Alzheimer's disease (AD) in plasma-based assays (Blennow, 2017).

The combination of cytokines, chemokines, complement components, oxidative stress markers, and markers of microglial and/or astrocytic activation in inflammatory biomarker panels may provide better clinical interpretation. These profiles may contribute to patient stratification and differentiate patients who have mainly inflammatory, degenerative, or mixed pathological processes. Additionally, cytokine levels can assist in administering treatments that modify immune signaling in ways that are toxic to disease-causing cells while sparing the beneficial cells to maintain protection against harmful cells (Mallick et al., 2025).

Nanotechnology can be used to improve the detection of biomarkers and monitoring of therapeutic progress with highly sensitive biosensors, targeted imaging agents, and delivery systems that can cross biological barriers. Diagnostic and immune modulation-based platforms using nanomaterials can be implemented in age-related neurological diseases (Chintapula et al., 2023). Additionally, polymeric nanoparticles can be designed to be targeted to deliver anti-inflammatory agents selectively, to alter cellular uptake, and to decrease systemic toxicity (Zhang et al., 2025). Standardized assays, validated thresholds, long-term testing, and confirmation of the fact that changes in the biomarker are correlated with changes in disease activity and clinically relevant treatment outcomes are essential for clinical translation.

11. Current and Emerging Therapeutic Strategies

Therapeutic approaches to neuroinflammation seek to downmodulate undesirable immune activation while maintaining beneficial effects, including immune responses to pathogens, removal of debris, and tissue repair. Traditional therapies consist of steroids, immunosuppressant drugs, and monoclonal anti-cytokine, anti-cell trafficking, and anti-inflammatory drugs. New therapies are addressing inhibitors of inflammasomes, microglial and astrocytic modulation, oxidative stress, and the restoration of BBB integrity. Their effectiveness can be influenced by the stage of disease, the inflammatory phenotype, or the time of treatment.

Nanomedicine is a potentially good way to enhance drug delivery to the central nervous system. Nanoparticle design can enable them to cross biological barriers, deliver therapeutic agents safely and gradually, and specifically target activated microglia over conventional systemic therapies. Microglia-targeted nanotherapeutics could decrease the production of neurotoxic cytokines, oxidative injury, and synaptic dysfunction and minimize systemic side effects (Silva et al., 2025). Analogous strategies can be employed to deliver molecules of nucleic acids, anti-inflammatory agents, and neuroprotective molecules.

Peripheral factors that affect neurological symptoms and inflammatory burden should also be taken into account for clinical management. Prosthodontic rehabilitation is not always the underlying cause or cause of resolution of temporomandibular disorders; they can include chronic pain, changes in sensory processing, and psychosocial stress (Manfredini et al., 2023). Anxiety and behavioral reactions also may alter pain perception, treatment compliance, and physiological stress, especially when undergoing dental care procedures (Alandijani et al., 2025).

A new generation of treatment models will most probably integrate targeted immunomodulation, biomarker-based patient selection, sophisticated drug delivery systems, and systemic and psychosocial factors. Avoiding excessive suppression of beneficial neuroimmune responses while improving therapeutic precision may be achieved with such integrated strategies. Table 4 proposes a list of key diagnostic biomarkers and new therapeutic approaches for neuroinflammation.

Table 4. Diagnostic Biomarkers and Emerging Therapeutic Strategies

Category	Examples	Potential application	Major limitation or challenge	References
Cerebrospinal fluid biomarkers	Amyloid-β, total tau, phosphorylated tau, neurofilament proteins, cytokines, and glial markers	Detection of neuronal injury, protein aggregation, and central immune activation	Invasive sampling and limited suitability for frequent monitoring	(Blennow, 2017; Gaetani et al., 2020)
Blood-based biomarkers	Plasma phosphorylated tau, neurofilament light chain, cytokines, chemokines, and complement proteins	Screening, longitudinal monitoring, prognostic assessment, and patient stratification	Peripheral sources and systemic inflammation may reduce disease specificity.	(Milà-Alomà et al., 2019; Chitnis et al., 2025)
Neuroimaging and multi-omics	Molecular imaging, genomics, transcriptomics, proteomics, and metabolomics	Identification of inflammatory phenotypes and integration of molecular disease signatures	High cost, methodological variability, and limited standardization	(Gaetani et al., 2020)
Cytokine and pathway inhibition	Monoclonal antibodies, JAK/STAT inhibitors, NF-κB modulators, and inflammasome inhibitors	Reduction of harmful inflammatory signaling and immune-cell activation	Broad inhibition may interfere with host defense and tissue repair	(Abdelaziz et al., 2026; Mallick et al., 2025)
Glial-targeted therapy	Microglial modulation, astrocyte regulation, and receptor-specific interventions	Suppression of neurotoxic glial phenotypes while maintaining protective functions	Cellular responses vary according to disease stage and local environment	(Bhusal et al., 2023; Silva et al., 2025)
Blood-brain barrier-directed therapy	Tight-junction stabilization, endothelial protection, antioxidant therapy, and ferroptosis inhibition	Restoration of vascular integrity and reduction of immune-cell infiltration	Limited clinical validation and difficulty achieving endothelial specificity	(Archie et al., 2021; Liu et al., 2026)
Nanotechnology-based treatment	Polymeric nanoparticles, microglia-targeted carriers, biosensors, and controlled-release systems	Improved central nervous system penetration, targeted delivery, and reduced systemic toxicity	Biocompatibility, clearance, manufacturing consistency, and regulatory barriers	(Chintapula et al., 2023; Zhang et al., 2025; Silva et al., 2025)

12. Limitations and Future Directions

The current neuroinflammation research is hampered by significant heterogeneity in terms of mechanisms of the disease, patient populations, definition of biomarkers, and experimental models. Numerous findings come from animal and/or in vitro studies, which do not necessarily mimic human neurological disease. Many of the studies are also cross-sectional, have small numbers of individuals, sampling methods vary from one study to another, and assays vary based on the platform. Neuroinflammatory parameters might be non-specific and affected by age, systemic illness, medications, and integrity of the blood-brain barrier. Immune activation has both pro- and anti-inflammatory effects, which makes interpretation of therapeutic significance difficult.

Longitudinal and multicenter studies, standardized biomarker panels, and clinically representative models should be a prerequisite in future research. A combination of genomics, transcriptomics, proteomics, metabolomics, neuroimaging, and digital monitoring could help to better stratify patients and assess disease stage. Therapeutic development should be directed towards cell-specific and pathway-selective modulation instead of general

immune suppression. To bring this realization to a safe individualized neurological care, biomarker-driven trials, targeted nanodelivery of drugs, combination therapy, and treatment timing would be key.

13. CONCLUSION

Neuroinflammation is a fundamental mechanism shared by many neurological disorders, with shared cellular, molecular, vascular and immune mechanisms. All of these, from microglia to astrocytes, from endothelial cells to peripheral leukocytes, from cytokines and chemokines to oxidative mediators, from complement proteins to inflammasome pathways, play a role in determining the survival of the neurone, function of synapses, integrity of the myelin, and tissue repair. It can have context-dependent effects: controlled inflammatory responses can lead to host defense and recovery; while sustained inflammatory activation can lead to disruption of the blood-brain barrier, neurodegeneration, demyelination, hyperexcitability and secondary injury. Such mechanisms are involved in Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, stroke, traumatic injury, infections and neuropsychiatric disorders. Improvements in the detection, monitoring, prognosis and selection of therapy through advances in CSF, blood-based, imaging, and multi-omics biomarkers are anticipated. There are new therapeutic approaches that are being developed for cytokines, glial activation, oxidative stress, endothelial dysfunction, ferroptosis, and intracellular signaling, which could provide options for more selective treatment. The potential to further enhance access to the CNS and minimize systemic toxicity with nanotechnology and targeted drug delivery systems further emphasize the benefits of these technologies. The key to future advances will be the ability to differentiate beneficial from deleterious inflammation, the discovery of therapeutic windows that are specific to the stage of the disease and the incorporation of molecular markers into personalized clinical care.

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