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NEUROINFLAMMATION AS A THERAPEUTIC TARGET IN AMYOTROPHIC LATERAL SCLEROSIS (ALS): MECHANISMS, SIGNIFICANCE, AND EMERGING INTERVENTIONS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease leading to the loss of motor neurons and progressive paralysis. Increasing evidence suggests that chronic neuroinflammation plays a key role in its development. Excessive activation of microglia, toxic reprogramming of astrocytes, and the activation of NF-κB, NLRP3, and C5a–C5aR1 signaling pathways drive neuronal damage. Literature review shows that therapeutic interventions targeting neuroinflammation demonstrate promising effects in preclinical models, but their clinical efficacy remains limited. Additionally, emerging studies suggest a role of gut microbiota in modulating inflammatory responses via the gut–brain axis. This review discusses neuroinflammatory mechanisms, their role in ALS progression, and potential therapeutic strategies, highlighting the need for further research into inflammation biomarkers and personalized therapies.

KEYWORDS

Amyotrophic Lateral Sclerosis, Neuroinflammation, Microglia, Astrocytes, Targeted Therapy, Microbiota

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Introduction

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease characterized by the progressive degeneration of neurons responsible for voluntary motor control, affecting both the motor cortex and spinal cord.[1] The disease typically manifests in late middle age and follows a relentlessly progressive course, leading to muscle weakness and atrophy. Respiratory muscle failure usually limits survival to 2–4 years after diagnosis.[2]

Currently available therapies have only a limited effect on disease progression. Numerous studies indicate that neuroinflammation is a key contributor to ALS pathogenesis. Processes such as microglial and astrocytic activation, the release of proinflammatory cytokines, and dysregulation of neuro-immune signaling play significant roles in disease development.[3] Additional factors, such as gut microbiota dysbiosis and activation of the complement system, have also been shown to exacerbate central nervous system inflammation. These findings have led to growing interest in neuroinflammation as a potential therapeutic target.

The aim of this paper is to analyze the role of neuroinflammation in ALS and to present treatment strategies targeting this mechanism.

Pathophysiology of ALS

Amyotrophic lateral sclerosis has a complex and multifactorial pathogenesis. Although the precise mechanisms leading to the degeneration of upper and lower motor neurons are not fully understood, studies suggest the involvement of multiple interacting cellular and molecular pathological processes.[4]

Neurodegenerative mechanisms

The key mechanisms contributing to motor neuron degeneration in ALS include:

- Oxidative stress, triggered by an excess of reactive oxygen species (ROS), which damages cellular DNA, proteins, and lipids;[5]
- Aggregation of pathological proteins (such as TDP-43, SOD1, and FUS), which disrupt neuronal function through the formation of insoluble cytoplasmic inclusions;[6]
- Mitochondrial dysfunction, leading to impaired energy production and increased susceptibility to apoptosis;[7]
- Glutamate excitotoxicity, a process in which excessive stimulation of glutamate receptors results in calcium influx and neuronal injury.[8]

Genetic Mutations

While most cases of ALS are sporadic, approximately 10% have a familial background. Among patients with suspected hereditary ALS, several genetic mutations have been identified. The most common is a mutation in the C9orf72 gene, which involves hexanucleotide (GGGGCC) repeat expansions that exert toxic effects at both RNA and protein levels.

Less frequent mutations include SOD1, which leads to abnormal superoxide dismutase activity and accumulation of toxic protein species, and FUS and TARDBP, which are associated with impaired RNA transport, translation, and cellular stress responses.[6]

Neuroglial Dysfunction

A growing body of evidence highlights the role of non-cell-autonomous degeneration in ALS pathogenesis, meaning that motor neuron loss occurs not only due to intrinsic neuronal defects, but also due to dysfunction of surrounding glial cells.

Activated microglia can release proinflammatory cytokines, nitric oxide, and reactive oxygen species, thereby exacerbating neuronal injury.[9] Similarly, astrocytes carrying SOD1 mutations fail to support neuronal metabolism and may actively contribute to neurotoxicity.[4]

Immune Dysregulation and the Gut Microbiota

Recent findings also emphasize the involvement of the immune system in ALS. An imbalance between proinflammatory and regulatory immune responses may lead to chronic neuroinflammation in the brain and spinal cord.[10]

Studies of the gut microbiota have revealed associations between intestinal dysbiosis and enhanced neurodegeneration in ALS. Research published in 2025 indicates that dysbiosis may promote sustained neuroinflammation by activating the immune system. ALS patients exhibit reduced microbial diversity and an increased presence of proinflammatory bacterial strains. This results in compromised gut barrier integrity and translocation of microbial toxins into the bloodstream. These toxins may cross the blood–brain barrier, triggering microglial and astrocyte activation and thus intensifying inflammatory processes within the central nervous system. The authors suggest that modulating the gut microbiome could represent a promising avenue for therapeutic intervention.[11]

The Role of Neuroinflammation in ALS

Neuroinflammation is now recognized as a significant and active component in the pathogenesis of ALS. Chronic activation of glial cells, dysregulation of proinflammatory cytokines, and immune system dysfunction play a key role in accelerating the degeneration of motor neurons.[4]

Microglia and Astrocytes

ALS is characterized by persistent microglial activation, leading to a proinflammatory M1 phenotype. This phenotype releases harmful substances such as cytokines (TNF-α, IL-1β, IL-6), nitric oxide, and reactive oxygen species. Chronic microglial activation exacerbates motor neuron damage, as demonstrated in both postmortem studies and PET imaging.[9]

Astrocytes also play a crucial role in the neuroinflammatory process. In ALS, they adopt a reactive, cytotoxic A1 phenotype. Studies have shown that astrocytes carrying SOD1 mutations lose the ability to uptake glutamate from the synaptic cleft, resulting in excitotoxicity. Moreover, they release various toxic mediators (NO, prostaglandins, cytokines), promoting oxidative stress and inducing motor neuron death. The toxic effects of these astrocytes occur independently of mutations in neurons themselves, supporting the concept of non-cell-autonomous degeneration.[12]

Molecular and Immune Pathways

Neuroinflammation in ALS involves the activation of molecular pathways that amplify inflammatory responses within the CNS.

One central player is the NF-κB pathway, a key transcriptional activator of genes encoding proinflammatory mediators. Its overactivation in microglia and astrocytes contributes to persistent inflammation and neuronal damage.[10]

The NLRP3 inflammasome is another critical component. This molecular complex responds to oxidative stress and mitochondrial dysfunction, and upon activation, increases the release of IL-1β and IL-18, further amplifying neuroinflammation and neurodegeneration.[13]

Excessive activity of the complement system, particularly the C5a–C5aR1 axis, has also been observed in ALS. Activation of this pathway promotes chemotaxis of immune cells into the CNS and contributes to neuronal injury and lysis. These processes are directly associated with motor decline.[14]

Microbiota–Neuroinflammation Axis

Several studies suggest a strong link between gut microbiota and neuroinflammatory processes in ALS. Dysbiosis leads to increased intestinal permeability, allowing lipopolysaccharides and other toxins to enter the systemic circulation. These substances may cross the blood–brain barrier, triggering microglial and astrocyte activation, and increasing proinflammatory cytokine expression. This mechanism defines the so-called gut–brain axis, which may influence both disease progression and CNS inflammation.[15]

Some microbial metabolites exhibit immunomodulatory effects and regulate immune homeostasis. Their deficiency in ALS may exacerbate inflammation and metabolic dysfunction. In SOD1 mutant animal models, dysbiosis has been linked to increased oxidative stress and glial activation. These findings support the therapeutic potential of interventions such as probiotics, anti-inflammatory diets, or fecal microbiota transplantation, which may attenuate inflammatory responses.[16]

In summary, the gut microbiota may serve both as a biomarker and a therapeutic target in ALS.

Neuroinflammation as a Biomarker and Therapeutic Target

Numerous studies support the notion that inflammation actively contributes to ALS progression. As such, inflammatory biomarkers may have both prognostic and therapeutic relevance. Elevated levels of proinflammatory cytokines (IL-6, TNF-α, IL-1β) have been observed in the serum and cerebrospinal fluid of ALS patients.[17]

The complement system also plays an important role. In ALS animal models, pharmacological blockade of the C5aR1 receptor has been shown to reduce microglial activation, suppress proinflammatory cytokine expression, and improve both motor function and survival.[14]

These findings suggest that cytokines and complement proteins may not only serve as markers of neuroinflammation, but also as targets for immunomodulatory therapies aimed at slowing motor neuron degeneration.

Table 1. Comparison of Inflammatory Pathways Involved in ALS

Inflammatory pathway	Type of activation	Impact on ALS	Therapeutic potential
NF-κB	Transcriptional activation of proinflammatory genes	Activates microglia and astrocytes; promotes chronic inflammation	NF-κB inhibitors (experimental)
NLRP3 inflammasome	Release of IL-1β and IL-18 via inflammasome activation	Exacerbates neurodegeneration via inflammation triggered by cellular stress	NLRP3 inhibitors (in preclinical studies)
C5a–C5aR1 (complement)	Chemotaxis and cytotoxicity mediated by complement system	Increases motor neuron death; shortens survival	C5aR1 antagonists (e.g., PMX205, tested in ALS models)
Gut–brain–microbiota axis	Translocation of LPS and bacterial metabolites; immune activation	Triggers microglial activation and cytokine release; worsens CNS dysfunction	Probiotics, dietary interventions, fecal microbiota transplantation

Neuroinflammation as a Therapeutic Target

The growing body of evidence highlighting the role of inflammation in ALS has led to increasing interest in neuroinflammation-targeted therapies as both promising and necessary.

Therapies Targeting Microglia and Astrocytes

Glial cells play a key role in the neuroinflammatory response in ALS. Their excessive activation leads to a cytotoxic phenotype that intensifies motor neuron degeneration, making them an attractive therapeutic target.

Current strategies include modulating microglial activity through molecules that influence activation state or phenotype. Studies report progress in developing compounds that not only suppress proinflammatory microglial activity but also enhance their neuroprotective functions.[18]

Experimental studies on astrocytes focus on restoring their capacity to clear glutamate from the synaptic cleft and reducing their contribution to neurotoxic inflammation. It has been shown that expression of the excitatory amino acid transporter 2 (EAAT2) is significantly reduced in ALS-related astrocytes, contributing to excitotoxicity and accelerated neuronal death.[19] Additionally, in response to local inflammatory cues, astrocytes can adopt different phenotypes. In ALS, there is a predominance of the cytotoxic A1 phenotype, which contributes to neuronal injury by releasing harmful factors. Strategies aimed at shifting astrocytes from the A1 to the neuroprotective A2 phenotype, as well as modulating their secretory profile, are promising directions in disease-modifying therapy research.[20]

Therapies Targeting Molecular Pathways: NF-κB, NLRP3, C5a–C5aR1

The NF-κB pathway, activated in glial cells by stress signals, promotes the transcription of proinflammatory cytokines and adhesion molecules. An emerging approach is indirect inhibition of this pathway via activation of the antioxidant Nrf2–HO-1 axis, for example through dimethyl fumarate (DMF). Clinical studies have shown that DMF reduces inflammatory cytokine levels, suggesting its potential for immunomodulatory therapy.[21]

Another critical therapeutic target is the NLRP3 inflammasome. In transgenic SOD1-G93A mouse models, administration of the selective NLRP3 inhibitor MCC950 significantly reduced microglial activation and improved motor function and survival. These findings indicate that pharmacological modulation of NLRP3 may be an effective neuroprotective strategy, particularly in early disease stages.[22]

The complement system, specifically the C5a–C5aR1 axis, contributes to neuroinflammation by recruiting immune cells and increasing glial toxicity. Animal studies in ALS have shown that blocking C5aR1 with PMX205 reduces glial activation and prolongs survival, while preserving essential immune function. These results highlight PMX205 as a strong candidate for further clinical investigation.[22]

Immunomodulation and Cellular Approaches

Beyond pharmacological inhibition of specific inflammatory pathways, broader immunomodulatory approaches are being explored, including cell-based therapies. Mesenchymal stem cells (MSCs) are capable of secreting anti-inflammatory cytokines, suppressing microglial activity, and supporting neuronal regeneration through trophic factors. Studies have shown that MSCs administered to ALS patients induce changes in gene expression in the cerebrospinal fluid, suggesting biological activity and potential immunomodulatory effects.[23]

Another approach involves intrathecal administration of allogeneic human astrocytes (AstroRx®) in ALS patients. This therapy was well tolerated, and in patients with rapidly progressing disease, a temporary slowing of motor decline was observed — supporting the potential of glial cells as immunoregulatory and neuroprotective tools.[24]

Table 2. Therapies Targeting Neuroinflammation in ALS

Therapeutic strategy	Molecular / cellular target	Research stage	Experimental outcomes
Dimethyl fumarate (DMF)	Nrf2 pathway / oxidative stress / NF-κB	Clinical phase – safety trial	Reduction of proinflammatory cytokines, activation of Nrf2
NLRP3 inhibitor (MCC950)	NLRP3 inflammasome / IL-1β / microglia	Preclinical – SOD1-G93A models	Inhibition of oxidative stress and microglial activation
C5aR1 blockade (PMX205)	Complement system – C5a/C5aR1 axis	Preclinical – ALS animal models	Decreased glial activation, extended survival
Mesenchymal stem cells (MSC)	Immunomodulation, anti-inflammatory cytokine secretion	Clinical studies (pilot trials)	Gene expression changes in CSF, immunoregulatory effects
Allogeneic astrocytes (AstroRx®)	Neuroprotective and metabolic support by astrocytes	Phase I/IIa – clinical trials	Well tolerated, possible slowing of disease progression

Limitations and Therapeutic Perspectives Related to Neuroinflammation in ALS

Although neuroinflammation is recognized as a key element in ALS pathogenesis, clinical attempts to suppress it have so far yielded limited results. Many therapies demonstrate high efficacy in preclinical settings—particularly in SOD1-G93A mouse models—yet their translation to humans often fails. Contributing factors include interspecies differences, the heterogeneous nature of ALS phenotypes, and the challenge of defining the optimal therapeutic window.[25]

Emerging approaches to ALS treatment are increasingly based on molecular profiling and personalized medicine. Techniques such as single-cell transcriptomics, proteomics, and microbiome metagenomics enable identification of patients with dominant inflammatory responses and allow for individualized therapeutic targeting.[26]

Additionally, growing interest surrounds the role of the gut microbiota in modulating neuroinflammatory processes within the CNS. Probiotic and postbiotic interventions may enhance the efficacy of pharmacological treatments by improving immune system function at both the systemic and local levels.[25]

Conclusions

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder in which chronic inflammation within the nervous system plays a central role. Activation of microglia, astrocytic dysfunction, and upregulation of proinflammatory signaling pathways all contribute to the gradual degeneration and death of motor neurons.

An increasing number of studies also point to the importance of gut microbiota composition and function in modulating immune responses and exacerbating neuroinflammation in the brain and spinal cord.

Anti-inflammatory drugs and immunomodulatory strategies have yielded promising outcomes in preclinical models, yet clinical trials have produced limited success. The main challenges include the lack of specific and sensitive inflammatory biomarkers and the significant heterogeneity of disease progression among patients.

While neuroinflammation remains a compelling therapeutic target, it is also a complex and challenging one. The greatest potential for breakthroughs in ALS treatment likely lies in personalized immunotherapeutic approaches, based on accurate inflammatory profiling of individual patients and tailored therapeutic intervention.

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