

**REVIEW**

Astrocyte- and Microglia-Derived Factors in Neuroinflammation: Impact on Neuronal and Synaptic Structure and Function

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ABSTRACT: Astrocytes and microglia are key regulators of neuronal and synaptic function through dynamic interactions with neurons and with each other. Under pathological conditions, these interactions become dysregulated, promoting reactive glial states characterized by the release of pro-inflammatory cytokines, including IL-1 β , TNF- α , and IL-6, as well as complement components such as C1q and C3, reactive oxygen species, and other inflammatory mediators that disrupt synaptic homeostasis and neuronal stability. In this review, we examine the molecular and cellular mechanisms underlying neuron-glia and astrocyte-microglia communication in physiological and neuroinflammatory conditions. We discuss how glial-derived factors influence synaptic remodeling, excitotoxicity, altered plasticity, and neuronal function, highlighting their contribution to neuroinflammation and synaptic dysfunction. Finally, we explore therapeutic strategies aimed at modulating glial reactivity and restoring synaptic homeostasis to limit neuronal damage and neurodegeneration.

KEYWORDS: Astrocytes; microglia; neuron–glia communication; neuroinflammation; synaptic remodeling; glial activation; neurodegeneration; glial-derived factors

1 Introduction

Communication between neurons and glial cells plays a fundamental role in nervous system physiology. Among glial populations, astrocytes and microglia actively modulate neuronal activity and maintain synaptic homeostasis through multiple molecular and cellular mechanisms. These cells release a wide range of signaling molecules that regulate bidirectional communication with neurons and shape synaptic function. Within this framework, the concept of the tripartite synapse proposes that perisynaptic astrocytic processes constitute an integral component of synaptic signaling and actively modulate neurotransmission.

Astrocytes and microglia perform numerous functions that are essential for maintaining central nervous system (CNS) homeostasis and proper neurotransmission. Beyond their classical roles as support cells or immune effectors, glial cells continuously sense and respond to changes in their microenvironment through tightly coordinated and reciprocal interactions. Rather than acting independently, astrocytes and microglia operate as a functional unit that dynamically regulates neuronal activity, synaptic function,

and tissue homeostasis. Disruption of this communication network has been implicated in the onset and progression of multiple neurological disorders, including neurodevelopmental and neurodegenerative diseases such as autism spectrum disorder and Alzheimer's disease (AD).

Synapses are highly dynamic structures that depend on a finely regulated balance between excitatory and inhibitory transmission, cytoskeletal stability, receptor trafficking, and trophic support. This balance is maintained through continuous bidirectional signaling between neurons and glial cells. Neurons release signals such as ATP, glutamate, and fractalkine (CX3CL1) that modulate glial surveillance and activation states [1,2]. In turn, glial cells secrete cytokines, complement components, reactive oxygen species (ROS), and other soluble mediators that influence synaptic structure and function [3]. Under physiological conditions, this crosstalk contributes to activity-dependent plasticity and homeostatic regulation. However, during chronic inflammatory states, these adaptive mechanisms may become dysregulated, promoting maladaptive synaptic remodeling.

Neuroinflammation represents an important component of CNS homeostasis and is primarily regulated by microglia and astrocytes in response to injury, infection, or altered neuronal activity. While acute inflammatory signaling can promote repair and synaptic remodeling, sustained or dysregulated neuroinflammation is increasingly recognized as a central driver of synaptic dysfunction in neurological disorders [4]. Importantly, synaptic alterations often precede overt neuronal loss, positioning the synapse as an early and vulnerable target of inflammatory imbalance.

In this review, we examine the molecular and cellular mechanisms through which glial cells communicate with neurons and with each other, and how these interactions become altered during chronic neuroinflammation. We further discuss how glial signaling pathways influence synaptic stability and neuronal function, highlighting their relevance in the pathogenesis of neurological disorders and their potential as therapeutic targets.

2 Glial Communication in Physiological Conditions

2.1 Neuron–Astrocyte Communication in Physiological Conditions

Astrocytes represent the most abundant population of glial cells in the human brain and play essential roles in maintaining neuronal homeostasis. Traditionally, their functions have been associated with metabolic support, regulation of the extracellular environment, and control of neurotransmitter availability, thereby ensuring proper neuronal signaling and synaptic fidelity [5,6].

One of the central functions of astrocytes is the regulation of glutamatergic neurotransmission through the glutamate–glutamine cycle. Synaptically released glutamate is taken up by astrocytic excitatory amino acid transporters EAAT1 and EAAT2 (GLAST and GLT-1), preventing excessive extracellular accumulation. Once internalized, glutamate is converted into glutamine by the cytosolic enzyme glutamine synthetase and subsequently released to the extracellular space, where it is taken up by neurons and reconverted into glutamate through mitochondrial enzymatic pathways [1]. This tightly regulated cycle supports sustained synaptic transmission while preserving excitatory–inhibitory balance.

Beyond neurotransmitter recycling, astrocytes modulate synaptic activity through direct structural and functional interactions with synapses. Perisynaptic astrocytic processes express high densities of EAATs, enabling precise spatiotemporal control of neurotransmitter clearance. Activity-dependent increases in extracellular potassium can induce rapid depolarizations in these processes, transiently inhibiting glutamate uptake and thereby enhancing excitatory signaling at neighboring synapses [7]. In parallel, neuronal activity regulates the structural dynamics of perisynaptic astrocytic processes. Activity-dependent remodeling of

astrocytic coverage alters the degree of synaptic ensheathment, thereby influencing glutamate clearance, synaptic isolation, and the efficacy of synaptic transmission [7,8].

Astrocytes further regulate synaptic transmission through calcium-dependent signaling. In response to neuronal neurotransmitter release, astrocytes exhibit intracellular Ca^{2+} transients tightly coupled to neuronal activity via diverse neurotransmitter and neuromodulator receptors that sense synaptic glutamate, GABA, and ATP, thereby enabling dynamic regulation of gliotransmission (e.g., glutamate, ATP, and D-serine), neurotransmitter uptake, metabolic support, and ultimately synaptic efficacy and plasticity [5,8–10]. Through these mechanisms, astrocytes and neurons form a functional synaptic unit in which glial signaling contributes to both potentiation and inhibition of synaptic transmission.

In addition to modulating synaptic transmission, astrocytes regulate synapse formation and maturation through the secretion of synaptogenic and anti-synaptogenic molecules. Astrocyte-derived thrombospondins promote the formation of structurally normal but postsynaptically silent excitatory synapses and play a key role during brain development and circuit remodeling [11]. In contrast, hevin (SPARCL1) acts as a synaptogenic organizer by bridging presynaptic neurexin and postsynaptic neuroligin, facilitating functional synapse assembly, whereas its homolog SPARC exerts anti-synaptogenic effects [12]. Through the balanced release of these factors, astrocytes contribute to the establishment, stabilization, and refinement of synaptic networks.

Astrocytes also influence neuronal function through the secretion and sensing of trophic factors. Brain-derived neurotrophic factor (BDNF), classically associated with neuronal growth and survival, can be released by astrocytes and participates in activity-dependent synaptic modulation and circuit refinement [13,14]. Astrocytes also respond to BDNF through TrkB-T1 receptors, which contribute to astrocyte maturation and functional specialization [15].

Another key physiological role of astrocytes is metabolic support. Astrocytes supply neurons with energy substrates, notably lactate, which is released through monocarboxylate transporter MCT4 and taken up by neuronal MCT2. Astrocyte-derived lactate supports synaptic plasticity, memory formation, and neuronal mitochondrial metabolism [16–18]. Astrocytic mitochondrial function is critical in this context, sustaining redox balance and ATP production required to support neuronal activity and synaptic function [19]. These metabolic responses are closely coupled to neuronal activity, as increased synaptic demand enhances astrocytic glycolytic flux and lactate release [16,20].

Recent evidence has further revealed that astrocytes are not a homogeneous population but instead display marked functional heterogeneity. Distinct astrocyte subpopulations can differentially regulate glutamatergic transmission and exert circuit-specific control over neuronal networks, expanding the traditional view of astrocytes as purely supportive cells [21]. Emerging findings suggest that astrocyte heterogeneity is partially shaped by local neuronal activity patterns, indicating that astrocyte identity and specialization are dynamically regulated by circuit-level cues [22].

Finally, astrocytes participate in synaptic remodeling during development through activity-dependent synapse elimination. They express phagocytic receptors such as MEGF10 and MERTK, members of the Tyro-Axl-MerTK (TAM) family, which mediate synaptic engulfment and pruning [23]. Genetic disruption of these pathways impairs astrocyte-dependent synapse elimination, underscoring the contribution of astrocytes to the refinement of neuronal circuits [24] (Fig. 1A).

Overall, neuronal activity represents a key determinant of astrocytic functional states under physiological conditions. Through the release of neurotransmitters, neuromodulators, and extracellular ions, neurons instruct astrocytes to adjust Ca^{2+} signaling, metabolic programs, neurotransmitter uptake, and structural interactions with synapses. This continuous neuron-to-astrocyte communication enables astrocytes to

dynamically adapt their supportive and modulatory roles to local circuit activity, reinforcing the concept of astrocytes as active partners in information processing rather than passive support cells.

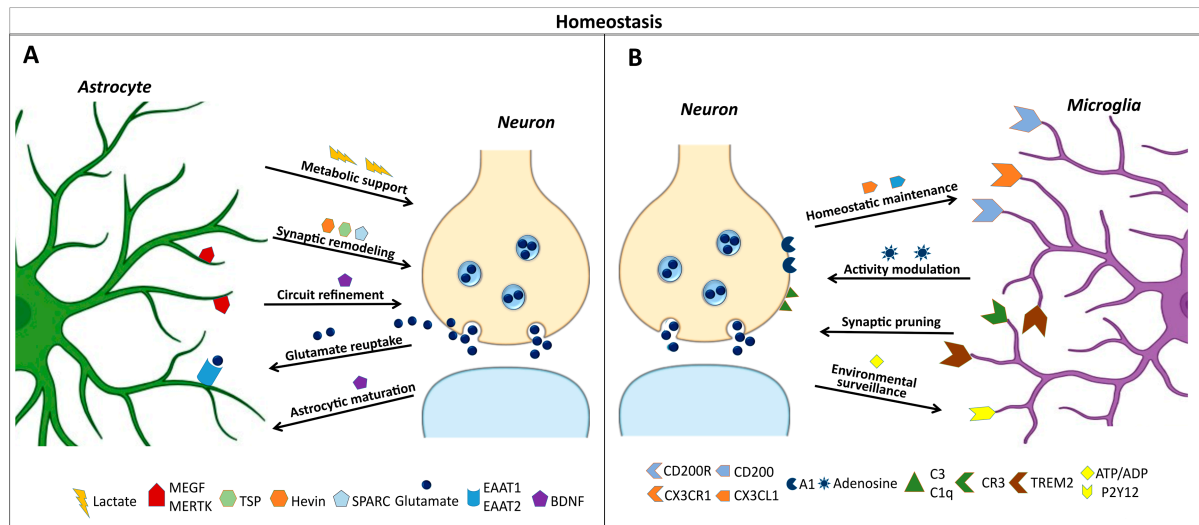


Figure 1: Glial regulation of neuronal and synaptic function under physiological conditions. (A) In the CNS, astrocytes interact with neurons to maintain neuronal integrity and synaptic function. This interaction is characterized by the release of synaptogenic and trophic factors (e.g., Hevin and BDNF), efficient glutamate uptake through EAAT1/EAAT2 transporters, metabolic support via the lactate shuttle, and regulated synaptic remodeling mediated by phagocytic receptors such as MERTK and MEGF10. **(B)** Under physiological conditions, microglia sense environmental cues to monitor neuronal activity and regulate complement-mediated synaptic pruning, thereby contributing to synaptic homeostasis and circuit refinement. Figure created using Microsoft PowerPoint with elements from BioRender.com and Smart.servier.com.

2.2 Neuron–Microglia Communication in Physiological Conditions

Microglia are the resident innate immune cells of the CNS and participate in numerous physiological processes, including maintenance of homeostasis, phagocytic clearance, and synaptic pruning, a key mechanism underlying synaptic connectivity and circuit refinement. Under basal conditions, microglia adopt a surveillance state and release trophic factors that support neuronal function and contribute to neural circuit remodeling [25].

The physiological functions of microglia are tightly regulated by neuron-derived signals that maintain homeostasis and prevent excessive inflammatory activation. Neuronal cues such as CX3CL1 and CD200 engage the microglial receptors CX3CR1 and CD200R, respectively, maintaining microglia in a homeostatic state while modulating their interactions with surrounding cells and synaptic elements [2,26]. In parallel, extracellular nucleotides released during neuronal activity, particularly ATP and ADP, are detected by the microglial purinergic receptor P2Y12, enabling directed process extension and dynamic environmental surveillance [27]. Beyond sustaining this surveillance phenotype, these neuron-derived signals also restrain excessive microglial phagocytosis, ensuring appropriate levels of synaptic remodeling without compromising circuit stability.

Consistent with their role as the macrophages of the brain, microglia phagocytose apoptotic cells, cellular debris, and aggregated proteins, while also participating in synaptic engulfment during development and circuit remodeling. During brain development, microglia play a critical role in activity-dependent synaptic pruning. Weakly active synapses are selectively tagged by complement components C1q and C3, allowing

their recognition by microglial complement system receptors and subsequent elimination [28]. Importantly, complement system deposition is closely linked to neuronal activity: reduced synaptic activity promotes C1q and C3 tagging, whereas active synapses are relatively protected from complement-mediated elimination, indicating that neurons actively instruct microglial phagocytosis during circuit refinement [29–31].

Beyond synaptic pruning, microglia regulate cell populations and circuit development through additional trophic and regulatory mechanisms. In addition to clearing dying cells, microglia can provide trophic support or, under specific physiological contexts, induce programmed cell death [32]. These processes may also be influenced by biological variables such as sex. For example, testosterone-driven endocannabinoid signaling promotes complement-dependent engulfment of viable newborn astrocytes by microglia in the developing rat amygdala [33]. Microglia also establish specialized somatic purinergic junctions with developing neurons throughout embryonic, postnatal, and adult neurogenesis. These contacts, enriched in microglial P2Y12 receptors and neuronal mitochondrial clusters, enable microglia to monitor neuronal status and support maturation processes [34].

Microglial functions are further modulated by molecular signals within the neural environment that shape synaptic organization and phagocytic activity. IL-33 has been identified as a physiological activator of microglial phagocytic programs, inducing the upregulation of pattern-recognition receptors such as macrophage receptor with collagenous structure (MARCO) and Toll-like receptor (TLR) 2 and promoting synaptic engulfment, thereby contributing to the regulation of excitatory synapse number [35]. In addition, microglial phagocytic capacity varies across the lifespan. Comparative studies have shown that aged microglia exhibit impaired phagocytic efficiency, accompanied by alterations in phagocytic receptor expression [36].

These structural and regulatory functions are particularly important during periods of increased plasticity. Experimental depletion of microglia during cortical critical periods disrupts glutamatergic synapse maturation, leading to increased spine density, immature synaptic profiles, and impaired circuit refinement, ultimately affecting experience-dependent plasticity [37].

In addition to shaping synaptic architecture, microglia contribute to the regulation of network activity by detecting neuronal activation and limiting excessive excitation. ATP released from active neurons can be metabolized by microglial enzymes into adenosine, which acts on neuronal A1 receptors to suppress neuronal responses, providing a homeostatic mechanism for activity modulation [38]. Collectively, these mechanisms underscore the essential housekeeping functions of microglia in maintaining CNS homeostasis across development and adult life [39] (Fig. 1B).

Overall, neuronal activity represents a central regulator of microglial function under physiological conditions. Through activity-dependent signals that include neurotransmitters, purines, and the selective deposition of complement system components, neurons instruct microglia to engage in synaptic surveillance, pruning, or preservation. This continuous neuron–microglia communication ensures that microglial phagocytic activity is spatially and temporally matched to circuit demands, preventing excessive synapse loss while enabling experience-dependent refinement of neural networks.

2.3 Astrocyte–Microglia Crosstalk in Physiological Conditions

2.3.1 Microglia-to-Astrocyte Signaling

Beyond their interactions with neurons, microglia also engage in extensive bidirectional communication with astrocytes, coordinating multiple aspects of CNS development and homeostasis (Fig. 2). Because microglia colonize the CNS before astrocytes, they play a critical role in astrocyte development by regulating astrocyte generation, survival, and final cell numbers. Microglia-derived interleukin-6 (IL-6) and leukemia inhibitory factor (LIF) promote astrocyte differentiation through activation of the JAK/STAT and MAPK

signaling pathways [40]. In parallel, microglia actively regulate astrocyte populations through phagocytosis of glial precursor cells. In the developing retina, astrocytes are initially overproduced and subsequently eliminated through an apoptosis-independent mechanism termed phagocyte-mediated cell death, in which microglia engulf viable astrocytes. Ablation of microglia in mice increases astrocytic density and disrupts vascular integrity, although astrocytes can partially compensate by phagocytizing each other in the absence of microglia [40,41].

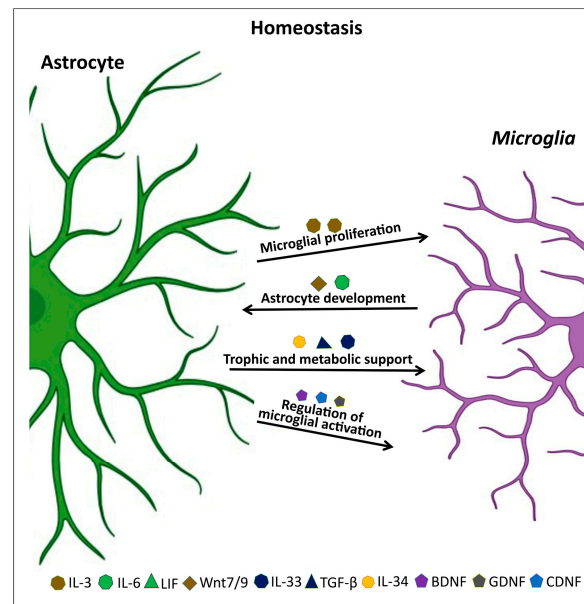


Figure 2: Astrocyte–microglia interactions under physiological conditions. Astrocytes and microglia reciprocally regulate their development and functions through the exchange of trophic factors, cytokines, and signaling molecules. Under physiological conditions, this bidirectional communication contributes to tissue homeostasis, synaptic regulation, and neuroprotection. IL: interleukin; LIF: leukemia inhibitory factor; TGF- β : transforming growth factor- β ; BDNF: brain-derived neurotrophic factor; GDNF: glial cell line-derived neurotrophic factor; CDNF: cerebral dopamine neurotrophic factor. Figure created using Microsoft PowerPoint with elements from BioRender.com and Smart.servier.com.

Microglial regulation of astrocytes during development has long-lasting functional and behavioral consequences. In the neonatal amygdala, microglia phagocytize newly generated astrocytes in a sex-dependent manner, influencing juvenile play behavior and adult sexual behavior in male rats [40]. Consistent with these findings, evidence from human development shows that microglia colonize the spinal cord as early as gestational week 9. These cells localize to ventricular and subventricular zones and closely associate with vimentin- and GFAP-positive astrocyte progenitors [42]. Similarly, during murine retinal development, microglia regulate astrocyte density and network organization, thereby shaping the astrocytic template that guides vascular growth. Disruption of microglial function increases astrocyte numbers and impairs vascular development, whereas C3/C3aR deficiency leads to persistent, unpruned astrocytic and vascular networks, indicating the involvement of multiple microglial signaling pathways [43].

Beyond developmental processes, microglia–astrocyte interactions contribute to the maintenance of CNS homeostasis through coordinated phagocytic and clearance mechanisms. Microglia and astrocytes engage in tightly regulated interactions to ensure efficient corpse removal in the CNS, a process dependent on MERTK, which is expressed by both cell types. When microglial responses are rapid, astrocytic phagocytosis

remains limited; conversely, when microglial phagocytosis is delayed or pharmacologically inhibited, astrocytes can compensate by engulfing dying cells through alternative mechanisms. Astrocytes also contribute to the clearance of microglial debris by engulfing material displaying “eat-me” signals, including components of the complement system such as C4b, thereby promoting microglial turnover and self-regulation [30,44]. Notably, in the absence of microglia, astrocytes can assume phagocytic functions, although with slower kinetics, highlighting a cooperative division of labor between these glial populations.

Microglia–astrocyte communication also plays a key role in synaptic remodeling. Recent evidence from murine models demonstrates that synaptic pruning is regulated by coordinated microglia–astrocyte interactions involving Wnt signaling pathways. Neuron–microglia communication through the CX3CL1–CX3CR1 axis induces microglial release of Wnt ligands, particularly Wnt5a and Wnt7a. These ligands activate Wnt signaling in astrocytes. This activation induces cytoskeletal reorganization and retraction of astrocytic processes, reducing astrocyte–synapse interactions and facilitating microglia-mediated synaptic pruning [45].

In addition to structural remodeling, microglia can modulate astrocytic participation in neurotransmission. Upon activation, microglia release ATP, which acts on astrocytic P2Y1 receptors. This signaling amplifies astrocytic ATP responses and promotes glutamate release. This signaling cascade activates neuronal metabotropic glutamate receptors and increases the number of excitatory synapses in the hippocampus. Experimental evidence indicates that the absence of microglia impairs ATP-dependent astrocytic transmission, whereas the presence of microglia enhances astrocytic vesicular machinery and glutamate release. Moreover, microglia regulate astrocytic network properties by modulating connexin expression and gap junction coupling, thereby influencing synaptic transmission without altering intrinsic astrocytic ion conductance. Together, these findings highlight a critical microglia–astrocyte interaction axis that shapes neuronal excitability and synaptic function in the hippocampus [46].

2.3.2 Astrocyte-to-Microglia Signaling

Astrocytes actively modulate microglial expansion, maturation, and morphological complexity. *In vitro* studies have shown that astrocyte-derived IL-3 regulates microglial proliferation [47,48], while astrocytic extracellular matrix components promote microglial maturation [48,49]. In addition, soluble astrocyte-derived factors such as macrophage colony-stimulating factor (M-CSF) induce microglial ramification, as antibodies against the M-CSF receptor inhibit this process in amoeboid microglia cocultured with astrocytes [48,49].

Astrocytes also provide essential trophic and metabolic support required for microglial survival and functional maturation. Several components of astrocyte-conditioned medium (ACM), including CSF-1/IL-34, transforming growth factor- β 2 (TGF- β 2), and cholesterol, have been identified as critical for microglial viability [43,48]. Pharmacological inhibition of CSF1R using GW2580, blockade of TGF- β 2 signaling, or cholesterol depletion with methyl- β -cyclodextrin significantly reduces microglial survival *in vitro* [47]. Notably, microglia express low levels of cholesterol biosynthesis genes, indicating a limited intrinsic capacity for cholesterol production and suggesting a reliance on astrocyte-derived or exogenous cholesterol sources. In addition to sustaining viability, astrocyte-derived factors are required for proper microglial functional competence. Microglial phagocytic capacity is markedly reduced in the absence of ACM, whereas exposure to ACM restores efficient phagocytosis and induces the upregulation of complement system-related genes, including C1qa, C1qb, C1qc, C3, Cfd, and Cfp [43,48] (Fig. 3A). These findings indicate that astrocytes not only support microglial survival but also instruct functional programs involved in synaptic remodeling and tissue homeostasis.

During neurodevelopment, astrocyte-derived IL-33 plays a central role in shaping microglial development and microglia-mediated synaptic pruning. In IL-33–deficient animals, microglial engulfment is

reduced, whereas local administration of IL-33 enhances synaptic uptake and decreases excitatory synapse numbers [44,48]. Astrocytic IL-33 signaling is also required for microglial functional competence, as it induces metabolic adaptations that support local energetic and phagocytic demands [31,44]. Furthermore, postnatal development, astrocytic IL-33 promotes microglial synapse engulfment, thereby preventing synaptic overabundance and ensuring proper maturation of thalamic and spinal cord circuits [31].

In addition to cytokine-mediated signaling, astrocytes release several neurotrophic factors that influence microglial functional states. Astrocyte-derived glial cell line-derived neurotrophic factor (GDNF), cerebral dopamine neurotrophic factor (CDNF), and BDNF have been shown to modulate microglial activation states and contribute to the regulation of microglial responsiveness under physiological conditions [50].

Overall, these observations highlight that astrocytes and microglia operate as integral partners of neuronal networks, engaging in tightly coordinated communication pathways that regulate synaptic organization, metabolic support, and circuit homeostasis (Fig. 3A). Disruption of this tightly controlled crosstalk, under conditions of injury or sustained stress, can profoundly alter glial functional states and represents a key step in the transition toward neuroinflammatory responses.

3 Transition to Neuroinflammation: Cellular Activation and Signaling Shifts

Neuroinflammation generally refers to a pathological condition that arises as a consequence of tissue injury, activation of glial cells, and infiltration of peripheral immune components. It is characterized by increased production of chemokines, cytokines, ROS, and other inflammatory mediators that can ultimately lead to synaptic dysfunction, neuronal death, and inhibition of neurogenesis [3].

At lower levels, inflammatory signaling can also occur under physiological conditions, including development, learning, memory formation, and immune-to-brain communication. However, when the intensity or duration of this response increases, it shifts toward a pathological state [51]. Despite extensive research, the precise contribution of inflammation to neurodegenerative diseases remains incompletely understood [52].

Microglia and astrocytes represent the primary cellular mediators of neuroinflammation. Under pathological conditions, their regulatory support of neuronal mechanisms becomes disrupted, leading to alterations in synaptic activity, plasticity, and circuit integrity [53]. Although glial cells drive neuroinflammation, neurons can actively modulate this process.

3.1 Glial Activation

3.1.1 Astrocyte Activation in Pathological Conditions

In pathological states, astrocytes may adopt reactive phenotypes that profoundly alter communication with neurons. Reactive astrocytes are characterized by increased expression of GFAP and morphological changes in which cellular processes become thicker and longer without major alterations in cell size compared with non-reactive astrocytes [54,55] (Fig. 3A). Reactive astrocytes can adopt A1- or A2-like phenotypes, although these classifications likely represent simplified and context-dependent reactive states rather than discrete astrocyte populations. Astrocytes A1 display neurotoxic properties and release pro-inflammatory mediators, including tumor necrosis factor α (TNF- α), IL-1 β , ROS, and IL-6. In contrast, A2 astrocytes exhibit neuroprotective features through the release of neurotrophic factors such as BDNF and GDNF [50]. Reactive astrocytes also display aberrant gliotransmitter release, metabolic dysfunction, and altered ionic regulation, changes that contribute to synaptic impairment and neurodegenerative progression. In this context, astrocytes emerge as active regulators of both neuroprotection and neurotoxicity depending on the state of the nervous tissue [5].

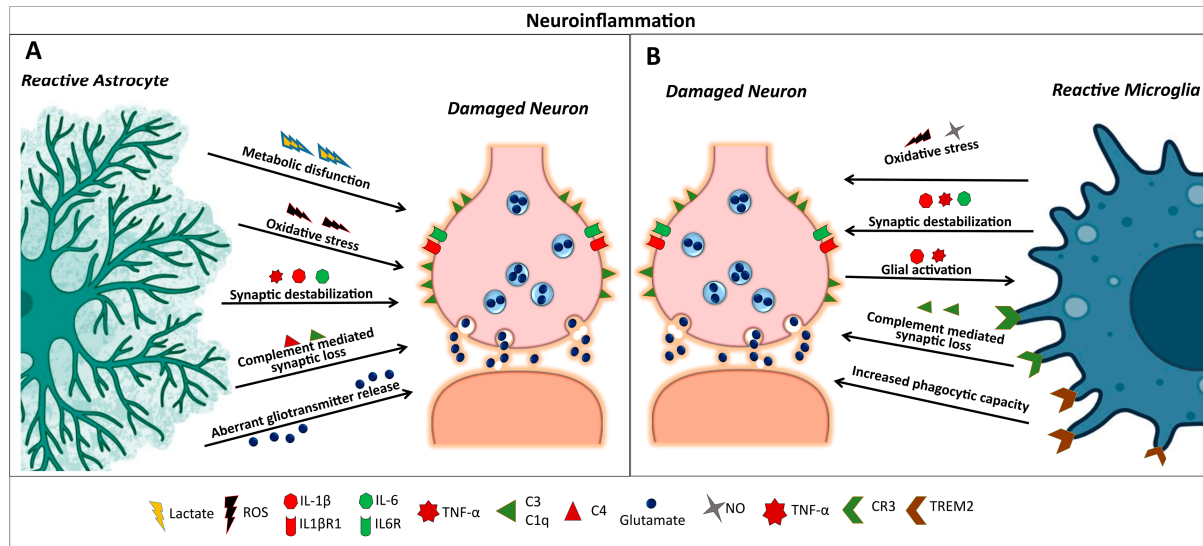


Figure 3: Glial regulation of neuronal and synaptic function under neuroinflammation. (A) During neuroinflammation, astrocytes acquire reactive phenotypes and progressively lose homeostatic functions, leading to impaired glutamate clearance, metabolic dysfunction, and the release of pro-inflammatory mediators, including IL-1 β , TNF- α , and IL-6. Together, these alterations contribute to synaptic dysfunction, neuronal damage, and synaptic loss. MEGF10: multiple EGF-like domains 10; MERTK: MER tyrosine kinase; TSP: thrombospondin; SPARC: secreted protein acidic and rich in cysteine; EAAT: excitatory amino acid transporter; BDNF: brain-derived neurotrophic factor; ROS: reactive oxygen species; IL: interleukin; TNF: tumor necrosis factor. (B) Microglia transition toward reactive phenotypes characterized by the release of pro-inflammatory cytokines (IL-1 β , TNF- α , and IL-6) and reactive oxygen/nitrogen species (ROS/NO). Reactive microglia promote excessive synaptic pruning and contribute to neuronal dysfunction, ultimately leading to synaptic loss and neurodegeneration. CR3: complement receptor 3; IL: interleukin; TREM2: triggering receptor expressed on myeloid cells 2; ROS: reactive oxygen species; NO: nitric oxide; TNF: tumor necrosis factor. Figure created using Microsoft PowerPoint with elements from BioRender.com and Smart.servier.com.

Among the molecules released by reactive astrocytes, components of the complement system play a prominent role in mediating pathological glia–neuron communication. Astrocyte-derived complement C3 mediates pathological astrocyte–neuron signaling in Parkinson’s disease (PD) through activation of the C3a receptor (C3aR), enhancing inflammatory signaling and exacerbating dopaminergic neuronal dysfunction and loss in disease models [56]. In addition, astrocytic C3 can promote microglia-mediated synaptic phagocytosis in infection-associated neurocognitive impairment. In the context of *Staphylococcus aureus* infection, astrocyte-derived C3 enhances complement-dependent synaptic tagging and facilitates excessive microglial engulfment of synapses, linking astrocytic complement system signaling to pathological synapse loss and cognitive deficits [57].

Evidence also indicates that astrocytic complement system signaling contributes to the persistence of neuroinflammation. In a laparotomy model, C3 upregulation in astrocytes was required to maintain prolonged microglial activation even after peripheral inflammation had resolved, while reduction of astrocytic C3 attenuated cognitive deficits [58]. Similarly, activation of the NOTCH signaling pathway promotes astrocyte activation in spinal cord injury. Genetic or pharmacological silencing of NOTCH reduces the expression of A1-associated markers, including C3, attenuates astrocyte-mediated neuroinflammation, and improves neuronal survival and functional recovery [59]. Complement system components such as C4 have also been implicated in exacerbating astrocyte-mediated neuroinflammation and protein aggregation

pathology in disorders, including PD [60]. In parallel, studies using induced pluripotent stem cell (iPSC)-derived astrocytes and neurons from PD patients showed that genetic or pharmacological attenuation of IL-6 receptor (IL-6R) signaling prevents neuronal death [61].

Reactive astrocytes also undergo significant metabolic reprogramming. In an experimental autoimmune encephalomyelitis (EAE) mouse model, astrocytes display increased expression of the lactate transporter MCT4, promoting glycolysis and proliferation through activation of the NF- κ B and c-Myc pathways [62]. Similarly, in human astrocyte cultures, stimulation with pro-inflammatory cytokines such as TNF- α and IL-1 β induces a metabolic shift toward glycolysis and increased lactate release, accompanied by upregulation of proteins associated with the major histocompatibility complex (MHC) class I pathway [20]. Exposure to amyloid- β further disrupts astrocytic mitochondrial dynamics and promotes a shift toward alternative energy pathways, including β -oxidation and glycolysis, highlighting extensive metabolic reprogramming under disease conditions [63].

3.1.2 Microglial Activation in Pathological Conditions

Under pathological conditions, microglia undergo a transition from a homeostatic ramified morphology to a more amoeboid and motile phenotype characterized by cytoskeletal reorganization and increased phagocytic capacity (Fig. 3B). This transformation is accompanied by reorganization of the microtubule network into a radial array through centrosome activation and suppression of Golgi-mediated microtubule polymerization. In addition, Cdk1 activity contributes to efficient cytokine trafficking and release [64]. Traditionally, microglia can polarize toward M1- or M2-like phenotypes, although increasing evidence suggests that microglial activation occurs along dynamic and heterogeneous functional spectra. M1 microglia display a pro-inflammatory profile characterized by the release of mediators such as TNF- α , IL-1 β , ROS, nitric oxide (NO), IL-6, IL-12, and IL-18. In contrast, M2 microglia exhibit anti-inflammatory and reparative properties, producing mediators including IL-4, IL-10, IL-13, TGF- β , vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), BDNF, and nerve growth factor (NGF) [50].

Pathological activation is also accompanied by metabolic remodeling. During pro-inflammatory activation, microglia shift from oxidative glucose metabolism toward glycolysis. Microglia efficiently utilize glucose and glutamine as metabolic substrates, and exposure to lipopolysaccharide (LPS) induces modest changes in glycolytic flux, reflected by limited alterations in extracellular lactate levels [65]. These metabolic adaptations amplify inflammatory signaling and contribute to a self-perpetuating cycle of microglial activation. In parallel, disruption of the CX3CL1/CX3CR1 neuron-microglia communication pathway has been linked to social behavioral deficits and altered brain development [66]. Under pathological conditions, microglia release a wide range of soluble mediators, including cytokines, chemokines, prostaglandins, NO, and trophic factors that can profoundly influence neuronal function.

In neurodegenerative diseases, these signaling pathways frequently become dysregulated. In Huntington's disease (HD), microglia exhibit elevated activation and an increased capacity to induce neuronal death. Studies using cultured neurons from wild-type and HD mice, as well as tissues from human patients, demonstrated that peripheral inflammatory signals such as microbial ligands or interferons (IFN) can stimulate microglia to secrete TNF, resulting in secondary neuronal damage [25]. Similarly, sustained activation of microglial pathways promotes pro-inflammatory states associated with synapse loss, neurotoxicity, and disease progression. Aberrant reactivation of the complement system-mediated synaptic pruning has also been implicated in progressive synapse loss in AD [67]. Post-mortem analyses from patients with multiple sclerosis (MS) further reveal that chronic neuroinflammation is associated with altered interactions between

microglia, infiltrating immune cells, and neurons, with increased microglial activation correlating with synaptic alterations and cognitive impairment [68].

3.2 Glial Inflammatory Signaling

3.2.1 Soluble Inflammatory Mediators in Glia–Neuron Communication

An important mechanism of glia–neuron communication involves the secretion of soluble factors such as cytokines, chemokines, complement system proteins, and ROS that regulate synaptic plasticity, neuronal circuit maturation, and adaptive responses to changes in tissue homeostasis. Under pathological conditions, this communication becomes dysregulated and contributes to exacerbated neuroinflammation and neurodegenerative processes [69].

Although pro-inflammatory cytokines are frequently associated with pathological inflammation, many of these molecules also play physiological roles in the CNS. For example, IFN- γ participates in immune modulation and inflammatory signaling while also regulating growth, maturation, and differentiation of glial populations. IFN- γ can be produced not only by microglia and astrocytes but also by neurons [52].

IL-1 β represents another key mediator of glia–neuron communication. Basal physiological levels of IL-1 β are present during prenatal and postnatal brain development, where the cytokine participates in neuronal migration and axonal guidance. Studies in neuronal cultures demonstrated that neurons express IL-1 receptor type 1 (IL1R1) and that IL-1 β signaling influences both neuronal migration and growth cone turning [70]. During inflammatory conditions, IL-1 β levels increase following microglial activation. Evidence from organotypic hippocampal slice cultures shows that microglia-derived IL-1 β is sufficient to disrupt synaptic homeostasis by inducing early reductions in presynaptic proteins such as synaptophysin, even when neuronal viability remains largely preserved. Experimental depletion of microglia or neutralization of IL-1 β prevents this synaptic loss, demonstrating that microglia-to-neuron cytokine signaling is a critical driver of early presynaptic injury [71]. IL-1 β also acts as a potent modulator of glial reactivity, promoting activation of both astrocytes and microglia and influencing their secretory activity, including the production of neurotrophic factors [71].

Cytokine signaling can also trigger compensatory neuroprotective responses. Cytokine stimulation has been associated with increased levels of BDNF, suggesting that activated astrocytes and microglia may shift toward a pro-survival phenotype under certain conditions. Glia-derived BDNF may therefore contribute to reduced neuronal degeneration and represent a mechanism through which inflammatory signaling is translated into trophic support [52].

IL-6 is another cytokine with significant effects on neuronal physiology. In human cortical neurons, IL-6 alters gene programs associated with extracellular matrix organization and cytoskeletal dynamics and induces persistent changes in mitochondrial respiration [72]. In models of Duchenne muscular dystrophy characterized by dystrophin deficiency, elevated IL-6 contributes to neuronal hyperexcitability in dystrophin-deficient hippocampal neurons by disrupting GABAergic regulation and intracellular Ca²⁺ homeostasis, highlighting the impact of inflammatory signaling on neuronal network stability [73].

The complement system also represents a major pathway linking neuroinflammation to synaptic dysfunction. Under inflammatory or neurodegenerative conditions, C1q is deposited at vulnerable synapses, C3 generates opsonizing fragments, and microglial complement receptor CR3 mediates synaptic engulfment [29,74]. Astrocytes can actively participate in C1q-dependent synapse elimination in disease models, while microglia can deliver C1q to synapses through extracellular vesicles, thereby amplifying complement system tagging and phagocytic clearance [29,75]. Concurrently, reactive astrocyte states and disease progression are associated with altered expression of astrocytic phagocytic receptors, while neuronal “eat-me”

signals, such as exposed phosphatidylserine and complement system tagging, increase, collectively biasing circuits toward excessive synaptic pruning and synaptopathy [74,76].

Astrocytic metabolic and mitochondrial dysfunction can further propagate neuronal damage through non-cell-autonomous mechanisms. Disruption of mitochondrial quality control in astrocytes, such as astrocyte-specific loss of the mitochondrial m-AAA protease, induces mitochondrial structural abnormalities, inflammatory activation, and impaired glutamate transporter expression. These alterations lead to excitotoxic stress and secondary neuronal dysfunction [77]. Changes in mitochondrial dynamics and localization can therefore disrupt synapse-associated astrocyte functions and link astrocytic metabolic dysregulation to synaptic vulnerability in neurodegenerative conditions [78].

TNF- α is another key mediator of neuroinflammation. It exists in both transmembrane and soluble forms and signals through TNFR1 and TNFR2 receptors. While TNFR1 triggers proinflammatory cascades, apoptosis and neurotoxicity, TNFR2 signaling promotes cell survival and anti-inflammatory responses [79]. Experimental studies demonstrate that TNF- α modulates synaptic plasticity in a concentration-dependent manner through microglia-dependent mechanisms, enhancing excitatory synaptic transmission at low levels while engaging homeostatic feedback mechanisms at higher concentrations [80]. TNF- α has also been implicated as a major mediator of brain inflammation in infection models, where pharmacological inhibition attenuates microglial activation and vascular pathology [81]. In AD mouse models, blocking TNF- α reduces β -amyloid load and alters hippocampal inflammatory proteomic profiles, suggesting a role in sustaining microglial activation and pathological signaling [82]. Despite these pathological roles, physiological levels of TNF- α contribute to synaptic scaling and homeostatic plasticity by regulating AMPA and GABA receptor dynamics [83].

ROS and free radicals represent another important class of inflammatory mediators. At physiological levels, ROS generated during mitochondrial oxidative phosphorylation participate in neuronal development and normal cellular signaling [84]. However, disruption of redox homeostasis leads to excessive ROS production and oxidative stress, which can damage neuronal structures and contribute to neurodegeneration. Microglia, acting as immune effector cells, can generate oxidative bursts in response to pathogens or damage signals through activation of NADPH oxidase and mitochondrial pathways [85–87]. Astrocytes also contribute to ROS production through mitochondrial superoxide generation and NADPH oxidase activity, particularly via NOX4 expression. Elevated ROS levels impair astrocytic glutamate uptake and increase lipid peroxidation, indicating that oxidative stress compromises key neuroprotective astrocyte functions and indirectly enhances neuronal vulnerability [88]. In human primary astrocytes, stimulation with IL-1 β induces robust ROS production that is further potentiated by IFN- γ without causing overt astrocytic cell death [89].

Together, these findings indicate that neuroinflammation not only alters the functional states of astrocytes and microglia but also reshapes the communication networks established between these glial populations. The resulting changes in cytokine signaling, complement system activation, and metabolic pathways generate a complex inflammatory environment that profoundly influences neuronal physiology and synaptic stability.

3.2.2 Astrocyte–Microglia Inflammatory Feedback Loop

Effects of Reactive Microglia on Astrocytes

Similar to physiological conditions, astrocyte–microglia interactions also play a central role in the pathogenesis and persistence of several neurological disorders. In neurodegenerative diseases such as AD, HD, PD, amyotrophic lateral sclerosis, and MS, reactive microglia have been shown to drive astrocytic pro-inflammatory activation [90] (Fig. 4). Activated microglia release mediators, including TNF- α , IL-1 α ,

and C1q [50], which are both necessary and sufficient to induce reactive astrocyte states *in vivo* and *in vitro*. Once activated, astrocytes lose their capacity to promote neuronal survival and synapse formation and can instead acquire neurotoxic properties [50,90–92].

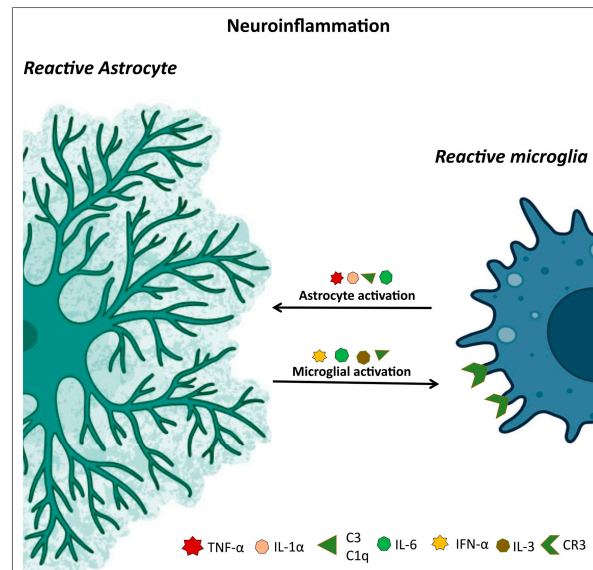


Figure 4: Astrocyte–microglia interactions under pathological conditions. In this context, both cell types establish a sustained pro-inflammatory loop driven by the release of cytokines and other mediators that reinforce their reactive states and promote chronic neuroinflammation. TNF: tumor necrosis factor; IFN: interferon; CR3: complement receptor 3. Figure created using Microsoft PowerPoint with elements from BioRender.com and Smart.servier.com.

This microglia-driven astrocytic activation has been observed in multiple disease contexts. However, inhibition of microglia-mediated astrocytic activation significantly reduces synaptic and neuronal loss [23]. These findings indicate that microglial signaling toward astrocytes represents a key driver of synaptic pathology. Similarly, in AD, reactive microglia modulate astrocyte activation induced by A β deposition. Post-mortem analyses of frontal, temporal, and cingulate cortices from AD patients showed that astrocyte activation occurs primarily in the presence of reactive microglia [91]. This activation was associated with increased tau phosphorylation, tau aggregation, and cognitive impairment.

Reactive microglia can also influence astrocyte-mediated regulation of neurotransmission. Under physiological conditions, neuronal SDF-1 activates CXCR4 receptors in astrocytes, promoting astrocytic glutamate release through signaling pathways that involve autocrine TNF- α [93]. In pathological contexts, however, excessive TNF- α released from activated microglia dysregulates this mechanism and enhances astrocytic glutamate release, promoting excitotoxicity and neuronal death [93,94].

Astrocyte–microglia communication has also been implicated in psychiatric disorders. In major depressive disorder (MDD), microglial activation is accompanied by astrocytic atrophy and apoptosis. In a murine model of depression, activated microglia release IL-6, which acts on IL-6R expressed by hippocampal astrocytes and induces astrocyte apoptosis as well as depressive-like behaviors. Knockdown of IL-6 in microglia or IL-6R in astrocytes significantly improves astrocyte survival and alleviates anxiety- and depression-like symptoms, highlighting the IL-6/IL-6R axis as a potential therapeutic target [95].

Despite these pro-inflammatory mechanisms, microglia can also promote anti-inflammatory signaling through astrocytes. Activated M2 microglia release IL-10, which acts on IL-10 receptors predominantly expressed in A2 astrocytes and induces the secretion of TGF- β . This pathway contributes to the suppression

of inflammation and supports the maintenance of the M2 anti-inflammatory phenotype of microglia while protecting synapses from the deleterious effects of A β oligomers in AD models [50,94].

Effects of Reactive Astrocytes on Microglia

Reactive astrocytes can also modulate microglial activation states through the release of cytokines and soluble mediators (Fig. 3B). Astrocyte-derived IL-6 and IFN- α have been implicated in disorders such as neuromyelitis optica spectrum disorders and cerebral interferonopathies. These cytokines induce distinct microglial responses: IL-6 promotes microglial proliferation, amoeboid morphology, and activation of phagocytic and tissue-remodeling programs through STAT3 signaling, whereas IFN- α activates STAT1-dependent pathways associated with immune surveillance, antigen processing, and MHC class I-mediated antigen presentation [96].

Astrocytes can also regulate microglial recruitment and activity in neurodegenerative conditions. In a murine AD model, astrocyte-derived IL-3 promotes microglial activation, migration, and clustering around A β aggregates, thereby facilitating A β clearance and improving cognitive performance. Disruption of IL-3/IL-3R signaling increases plaque burden and impairs memory functions, highlighting the importance of astrocyte–microglia communication in controlling amyloid pathology [97].

Other astrocyte-derived factors influence microglial survival and proliferation in pathological conditions. After ischemic stroke, astrocytes release endothelin (ET), which activates endothelin receptor B (ETBr) signaling and induces the secretion of paracrine factors such as angiopoietin-2 (Ang-2). Astrocyte-derived Ang-2 promotes microglial survival and proliferation in hypoxic environments and increases microglial cell numbers in peri-infarct regions following stroke [98].

Emerging transcriptomic studies further demonstrate that astrocyte–microglia interactions form pathological feedback loops in neurodegenerative diseases. In AD mouse models, accumulation of microglia around A β plaques induces astrocytes to adopt neurotoxic states characterized by altered expression of membrane-associated molecules, such as CD44, and secreted factors, including clusterin and ApoE. These astrocyte signals modulate microglial responses through TREM2-dependent pathways involving the adaptor protein TYROBP, thereby reinforcing microglial activation and sustaining a pathological cycle of glial reactivity and neurodegeneration, reinforcing microglial activation and sustaining a pathological loop of glial reactivity and neurodegeneration [99].

Astrocytes can also amplify microglial inflammatory responses through soluble mediators. Secreted-Frizzled-Related-Protein-1 (SFRP1), released by astrocytes after inflammatory stimulation, enhances microglial activation. This effect involves transcriptional programs associated with chronic inflammation and metabolic adaptation through hypoxia-inducible factor (HIF) and NF- κ B pathways. In experimental models of MS, SFRP1 deficiency significantly reduces disease severity and microglial activation, suggesting that astrocyte-derived SFRP1 contributes to the chronification of neuroinflammation [100].

Complement system signaling also contributes to this bidirectional glial communication. In AD, A β activates NF- κ B signaling in astrocytes, inducing the release of complement component C3. Astrocytic C3 binds to C3aR expressed on microglia and neurons, impairing A β phagocytosis and reinforcing glial activation. Blocking the C3–C3aR interaction mitigates this pathological loop, highlighting the importance of complement system signaling in sustaining neuroinflammatory responses [50,101].

Together, these findings indicate that neuroinflammation reshapes astrocyte–microglia communication into a bidirectional feedback loop in which cytokines, components of the complement system, and metabolic signals continuously reinforce glial activation. This self-sustaining signaling network amplifies

inflammatory responses and contributes to synaptic dysfunction, neuronal injury, and disease progression across multiple neurological disorders.

3.3 Neurons as Initiators and Modulators of Neuroinflammation

One of the most prominent neuronal-derived inflammatory mediators is high mobility group box 1 (HMGB1), a nuclear protein that is released into the extracellular space following neuronal stress, injury, or hyperexcitability. Once released, HMGB1 acts as a damage-associated molecular pattern (DAMP) and binds to pattern recognition receptors such as Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE) expressed in microglia and astrocytes, triggering NF- κ B-dependent transcription of pro-inflammatory cytokines [102]. In addition, neurons cell-autonomously express multiple pattern recognition receptors, including TLRs. Therefore, neurons themselves can both release HMGB1 and respond to it, establishing a feedforward signaling loop that amplifies neuroinflammation. In models of ischemic injury, neurons are the first cells to react, inducing high expression of TLR2 and TLR4 as early as one hour after the insult, which significantly precedes the activation of infiltrating or resident glia. Thus, neuronal TLRs serve as autonomous initiators of innate immune pathways within the central nervous system [103]. Neurons actively shape the neuroinflammatory environment and circuit refinement through experience-dependent immune programs. For instance, sensory experience triggers the neuronal induction of Fn14 (Fibroblast growth factor-inducible 14, a TNF superfamily receptor), which then recruits microglial-derived TWEAK (Tumor necrosis factor-related weak inducer of apoptosis) to signal the non-phagocytic disassembly of dendritic spines and synapses. Furthermore, in the adult hippocampus, IL-33 is an experience-regulated, neuron-derived cytokine whose expression increases with environmental enrichment, instructing microglia to remodel the extracellular matrix and promote synaptic plasticity [104].

4 Glial Inflammatory Signaling and Its Impact on Neuronal and Synaptic Function

4.1 Structural and Synaptic Alterations

The increased production of pro-inflammatory cytokines during neuroinflammation can profoundly affect neuronal structure and synaptic organization. Among the earliest alterations reported are changes in dendritic architecture, cytoskeletal dynamics, and receptor availability, all of which directly influence synaptic plasticity. Experimental models of inflammation have revealed rapid molecular alterations in dendritic compartments. For instance, in a LPS-induced inflammation model, levels of synaptopodin—an actin-regulating protein essential for dendritic spine stability—are significantly reduced within 24 h after LPS injection, suggesting that inflammatory signaling rapidly affects cytoskeletal elements involved in synaptic plasticity [105]. Consistent with these observations, microglial activation and elevated TNF- α levels in a mouse model of heart failure are associated with a marked reduction in dendritic spine density in frontal cortical neurons [106]. Similarly, in the APP^{swe}/PS1 Δ E9 AD mouse model, increased IL-1 β disrupts synaptic plasticity and interferes with BDNF signaling cascades, preventing the expected increase in dendritic spine density induced by environmental enrichment [107].

Inflammatory cytokines can additionally modulate dendritic spine morphology and receptor expression. A single intracerebroventricular injection of IL-6 at birth was shown to alter dendritic spine architecture in mice, modifying the relative proportions of different spine morphologies and increasing average spine length [108]. In pathological contexts, IL-6 frequently acts in concert with other inflammatory mediators such as IL-1 β and TNF- α , contributing to dendritic loss and synaptic destabilization [109]. At the transcriptional level, IL-1 β can induce synaptic downscaling through the upregulation of the transcriptional

repressor RE1-silencing transcription factor (REST), which represses genes involved in excitatory synaptic transmission and reduces excitatory receptor availability in primary cortical neurons [110].

Inflammatory environments are also associated with reductions in several proteins critical for synaptic maintenance. In LPS-induced inflammation models, elevated pro-inflammatory cytokines correlate with decreased expression of postsynaptic density protein-95 (PSD-95), BDNF, synaptophysin (SYN), and growth-associated protein 43 (GAP43), collectively increasing the vulnerability of excitatory synapses [111]. In parallel, inflammatory conditions induced by cytokine cocktails reduce the duration of GABAergic signaling in organotypic spinal cord cultures, suggesting that inflammatory signaling disrupts both excitatory and inhibitory synaptic balance [112].

Pro-inflammatory cytokines can further promote excitotoxic neuronal damage by increasing intracellular and extracellular glutamate levels through upregulation of neuronal glutaminase and impaired glutamate clearance. This effect is attenuated by NMDA receptor antagonists, implicating glutamate-mediated excitotoxicity as a major contributor to cytokine-induced neurotoxicity [113].

4.2 Trophic Imbalance and Neurotoxic Signaling

Chronic neuroinflammation disrupts the balance between neurotrophic support and pro-inflammatory toxicity, ultimately favoring neuronal vulnerability. Sustained elevation of inflammatory cytokines such as IL-1 β , IL-6, and TNF- α has been associated with reduced activity of BDNF-dependent survival and plasticity pathways, as chronic inflammatory signaling interferes with neurotrophic mechanisms that normally support neuronal maintenance [114].

Consistent with this notion, analyses of human AD brain tissue have revealed reduced expression of the BDNF receptor TrkB in the hippocampus, correlating with increased neuropathological burden. These findings suggest that impaired TrkB-mediated trophic signaling contributes to synaptic degeneration during chronic neuroinflammatory states [115]. Experimental models of global cerebral ischemia further support this link, showing that enhanced glial inflammatory responses alter the BDNF/TrkB/pCREB signaling axis in vulnerable neuronal populations [116].

In addition to BDNF signaling, other neurotrophic pathways can be modified during inflammatory responses. NGF levels are often increased under inflammatory conditions and can promote axonal sprouting and dendritic arborization. Although such remodeling may initially represent a compensatory mechanism, it can also contribute to maladaptive circuit reorganization [117].

4.3 Alterations in Synaptic Plasticity

At the functional level, inflammatory signaling profoundly alters the mechanisms underlying synaptic plasticity. Cytokines such as IL-1 β and TNF- α modulate receptor trafficking, glutamatergic transmission, and intracellular Ca²⁺ dynamics, thereby disrupting the balance between LTP and LTD. In parallel, inflammatory mediators alter synaptic scaling mechanisms and excitation/inhibition balance through changes in AMPA and GABA receptor expression and membrane localization [110,112]. These alterations impair synaptic efficacy and contribute to network hyperexcitability and cognitive dysfunction.

Inflammatory signaling interferes with homeostatic mechanisms that regulate synaptic strength. One such mechanism is synaptic scaling, a form of homeostatic plasticity that maintains stable postsynaptic responses during changes in network activity [118,119]. Under physiological conditions, TNF- α released by glial cells participates in the regulation of this process [120]. However, during neuroinflammatory states, excessive TNF- α release from activated glia promotes increased AMPA receptor membrane insertion and alters glutamate dynamics in the synaptic cleft, thereby contributing to excitotoxicity, cytoskeletal

destabilization, and spine loss [83,119]. In addition, TNF- α can impair GABAergic neurotransmission, leading to a reduction in inhibitory synaptic strength. This effect is mediated, at least in part, by decreased surface expression and increased internalization of GABA A receptors, ultimately contributing to an imbalance between excitation and inhibition under inflammatory conditions [121].

Inflammatory mediators also disrupt long-term forms of synaptic plasticity essential for learning and memory. IL-1 β suppresses long-term potentiation (LTP) in hippocampal neurons by interfering with signaling pathways required for activity-dependent protein synthesis in dendrites, while simultaneously promoting long-term depression (LTD), ultimately weakening synaptic connectivity and contributing to cognitive deficits [122,123].

4.4 Oxidative Stress, Calcium Dysregulation, and Neuronal Hyperexcitability

Oxidative stress represents another major mechanism through which neuroinflammation alters neuronal physiology. ROS generated during inflammatory responses modify key molecular determinants of neuronal excitability through oxidation and nitrosylation of ion channel subunits, altering the gating properties and conductance of voltage-gated sodium, potassium, and calcium channels that are essential for action potential initiation, propagation, and neurotransmitter release [124].

Activated microglia represent a major source of ROS in inflammatory environments through NADPH oxidase activity. Increased microglial ROS production has been shown to promote neuronal injury in co-culture systems, highlighting the contribution of oxidative stress to inflammation-driven neurotoxicity [125].

Neuroinflammatory conditions also disrupt intracellular Ca²⁺ homeostasis, thereby affecting synaptic integration and plasticity mechanisms such as LTP and LTD [126]. Elevated Ca²⁺ levels can promote cytoskeletal destabilization and the expression of “eat-me” signals, facilitating complement system-dependent synaptic pruning [127]. Consistently, electrophysiological studies have demonstrated that altered Ca²⁺ dynamics are associated with changes in neuronal excitability and membrane hyperpolarization, ultimately impairing synaptic integration and functional plasticity [128].

Beyond these molecular alterations, exposure to pro-inflammatory cytokines induces membrane depolarization, lowers action potential threshold, and increases neuronal excitability [129,130]. In parallel, inflammatory mediators enhance Na⁺ currents [130] and alter intracellular Ca²⁺ dynamics, thereby affecting neuronal firing and synaptic transmission. At the network level, these ion channel alterations result in increased calcium transient amplitudes and enhanced neuronal synchrony, consistent with a state of hyperexcitability and circuit dysfunction. This effect is further amplified by cytokine-induced reductions in GABAergic inhibitory currents, shifting the excitation/inhibition balance toward excitation [131]. Importantly, local presynaptic calcium accumulation has been shown to trigger phagocyte-mediated synapse removal, establishing a direct mechanistic link between electrophysiological dysfunction and synapse loss [127].

4.5 Circuit Dysfunction and Behavioral Consequences

Beyond molecular and cellular alterations, accumulating evidence indicates that neuroinflammation critically impacts neural circuit function and behavioral outcomes. Pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6 not only modulate synaptic plasticity and neurotransmission but also disrupt large-scale brain network activity. Inflammatory signaling impairs dopaminergic transmission within mesolimbic pathways by reducing dopamine synthesis and altering neurotransmitter dynamics, ultimately affecting reward-processing circuits [132]. In humans, elevated peripheral inflammatory markers such as C-reactive protein are associated with reduced connectivity between the ventral striatum and prefrontal regions, a key

circuit underlying motivation and reward valuation. Importantly, these circuit-level disruptions correlate with motivational deficits observed in neuropsychiatric conditions [132].

In parallel, chronic inflammatory states compromise hippocampal-dependent memory processes through impaired synaptic remodeling, aberrant synaptic pruning, and disrupted trophic support [133]. Pro-inflammatory cytokines such as IL-1 β and TNF- α alter hippocampal plasticity and weaken the cellular basis of memory formation, leading to deficits in learning and memory performance [133,134]. At the clinical level, chronic neuroinflammation is strongly associated with cognitive decline and memory impairment in neurodegenerative disorders, further supporting a causal link between inflammatory signaling and disrupted neural circuit function [135].

Altogether, the structural, molecular, and functional alterations described above illustrate how inflammatory signaling originating from glial cells progressively disrupts neuronal homeostasis and neural circuit integrity (Fig. 3). Understanding how these glia-driven mechanisms contribute to synaptic dysfunction and neuronal vulnerability may provide important insights for the development of therapeutic strategies aimed at restoring neural circuit function in neuroinflammatory and neurodegenerative disorders.

Collectively, the evidence discussed throughout this review supports an integrated model in which neuroinflammatory signaling emerges from dynamic interactions between neurons, astrocytes, and microglia across multiple levels of organization. Neuronal stress signals together with glial-derived inflammatory mediators, including cytokines, complement components, and ROS, alter neurotransmission, synaptic plasticity, dendritic stability, and excitation/inhibition balance, promoting aberrant synaptic remodeling and circuit dysfunction. Sustained disruption of neuron–glial communication ultimately contributes to cognitive impairment, behavioral alterations, and neurodegeneration across multiple neurological disorders.

5 Therapeutic Implications and Emerging Strategies

Dysregulated activation of astrocytes and microglia contributes to neurodegeneration, synaptic dysfunction, and disease progression. Consequently, modulation of glial reactivity, metabolism, and intercellular communication has emerged as a promising therapeutic strategy aimed not only at slowing disease progression but also at alleviating neurological symptoms.

5.1 Modulation of Astrocyte and Microglia Reactive Profiles

Multiple strategies focus on controlling microglial inflammatory responses. Modulation of IFN- γ signaling through miRNA-155 and inhibition of inflammatory mediators such as TNF- α , IL-1 β , TLR2, and TLR4 are being actively investigated to reduce microglia-driven neuroinflammation and improve cognitive outcomes [136]. Pharmacological agents, including non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and antibiotics such as minocycline, have also been shown to attenuate microglial activation and improve memory deficits in murine models of AD [136–138].

Astrocyte phenotypes can also be therapeutically reprogrammed. Targeting the C3a–C3aR or Notch signaling pathways has been proposed to shift astrocytes from neurotoxic to neuroprotective states. For example, in a murine ischemic stroke model, post-acute intranasal administration of C3a modulated astrocytic responses, increased synaptogenic factor expression, enhanced cortical connectivity, and improved motor performance [139]. Similarly, inhibition of Notch signaling reduced A1 astrocyte differentiation and decreased neuronal apoptosis in spinal cord injury models [59].

Some interventions aim to modulate both astrocytes and microglia simultaneously. Hypoxic post-conditioning, which involves exposure to mild hypoxia after ischemic events, activates endogenous neuroprotective mechanisms and suppresses both astrocytic A1 and microglial M1 inflammatory profiles [140].

Another promising approach involves modulation of serotonergic signaling. Serotonin receptors expressed in astrocytes and microglia regulate their inflammatory responses, and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and fluvoxamine have been shown to suppress astrocytic A1 polarization while promoting a shift of microglia from a pro-inflammatory reactive state toward an neuromodulatory phenotype through serotonin receptor 5-HT_{2B} signaling [141,142]. In addition, fluoxetine has been reported to enhance microglial phagocytosis and autophagy, although high doses may induce oxidative stress, highlighting the context-dependent effects of serotonergic modulation [143].

Together, these studies indicate that glial reactivity is dynamic and context-dependent. Future therapies may aim to selectively reprogram astrocytes and microglia toward neuroprotective phenotypes rather than broadly suppressing glial activity.

5.2 Targeting Glial Metabolism

Because inflammatory activation is closely linked to metabolic reprogramming, targeting cellular metabolism has emerged as another therapeutic strategy. One molecule that has received particular attention is Pyruvate Kinase M2 (PKM2), a glycolytic enzyme that promotes pro-inflammatory metabolic shifts toward aerobic glycolysis. PKM2 interacts with signaling pathways including HIF-1 α , STAT3, NF- κ B, and the NLRP3 inflammasome, thereby contributing to inflammatory responses in microglia [144,145]. Therapeutic approaches, therefore, aim to inhibit PKM2 expression, prevent its nuclear translocation, or promote its tetrameric form to limit its pro-inflammatory functions. However, because PKM2 can exert neuroprotective effects in neurons and endothelial cells [145,146], strategies targeting this enzyme should focus on cell-specific modulation rather than global inhibition.

5.3 Targeting Glial Communication Pathways

Another promising strategy involves restoring physiological communication between astrocytes, microglia, and neurons.

Modulation of astrocyte–microglia signaling pathways, such as IL-3/IL-3R α and IL-6/IL-6R, has shown encouraging results. In a murine model of MDD, inhibition of microglial IL-6 release or astrocytic IL-6R expression improved astrocyte survival and alleviated behavioral symptoms [96]. In AD models, astrocyte-derived IL-3 enhanced microglial recruitment to amyloid plaques, promoting amyloid clearance and improving memory performance [97].

Targeting astrocyte–neuron interactions has also demonstrated therapeutic potential. In PD models, excessive astrocytic IL-6 signaling contributes to dopaminergic neurite degeneration, whereas pharmacological blockade of IL-6R with the monoclonal antibody tocilizumab rescues neuronal survival [61]. Similarly, administration of recombinant FGF21 in ischemic stroke models suppresses astrocyte-mediated inflammation, enhances neurotrophic factor production, and preserves synaptic protein expression [147].

Neuron–microglia signaling pathways are another major therapeutic target. Regulatory axes such as CX3CL1–CX3CR1 and CD200–CD200R1 limit microglial inflammatory responses and maintain CNS homeostasis. Experimental enhancement of CX3CL1 signaling exerts neuroprotective effects in models of stroke, hemorrhage, and neurodegeneration [148,149], while activation of the CD200R1 pathway promotes a shift toward anti-inflammatory microglial phenotypes and improves synaptic integrity [150].

Finally, modulation of microglial phagocytic capacity has gained increasing attention. Complement system factors such as C1q and C3 regulate synaptic pruning, but excessive complement system activation contributes to synapse loss in neurodegenerative disorders. In experimental models of AD, inhibition of the C3/C3aR

pathway reduces synaptic loss and improves cognitive performance [50,101,136,151]. Similarly, increasing TREM2 signaling enhances microglial phagocytosis and improves behavioral outcomes in AD models [136,152].

Together, these approaches highlight that restoring physiological communication between neurons and glial cells represents a promising direction for the development of disease-modifying therapies.

6 Conclusions and Future Perspectives

CNS physiology does not rely exclusively on neuronal networks but instead depends on an integrated cellular system composed of neurons and glial cells. Within this framework, neuron–glia and glia–glia communication represent fundamental regulators of synaptic homeostasis.

Astrocytes and microglia, key components of the tripartite synapse, actively participate in synaptic development, maturation, and plasticity. Astrocytes regulate neurotransmitter recycling, release synaptogenic factors, and provide metabolic support through mechanisms such as the lactate shuttle [1,11,12,18]. Microglia contribute to synaptic refinement and circuit remodeling through complement system-mediated pruning and regulation of neuronal excitability [28,37,38].

A key concept emerging from recent studies is that astrocytes and microglia do not operate independently but instead function as a coordinated network. Through reciprocal signaling, these glial populations coordinate synaptic remodeling, metabolic support, and phagocytic activity. Microglia regulate astrocyte development and population dynamics through phagocytosis and soluble mediators such as IL-6 and LIF [40,41], while astrocytes shape microglial maturation and functional programs through factors including IL-3, IL-33, and M-CSF [42,44,48].

Altogether, the evidence discussed in this review highlights that the functional integrity of the CNS depends on the dynamic communication established between neurons, astrocytes, and microglia. Importantly, neurons not only respond to inflammatory cues but can also actively initiate and shape neuroinflammatory signaling through the release of damage-associated molecules and activity-dependent immune mediators. Rather than acting independently, these cells form an integrated signaling network that continuously adapts to neuronal activity and environmental cues. Under physiological conditions, this interaction maintains synaptic homeostasis, supports circuit refinement, and ensures proper neuronal function. However, when this tightly regulated communication becomes disrupted, glial cells can transition toward reactive phenotypes that amplify neuroinflammation and compromise neuronal function. In neurodegenerative diseases, sustained astrocyte and microglial activation generates self-reinforcing inflammatory loops characterized by metabolic reprogramming, complement system activation, and persistent cytokine signaling [50,91,100]. These processes contribute to synaptic dysfunction, neuronal vulnerability, and progressive circuit degeneration.

Future research should therefore focus on elucidating the molecular mechanisms that regulate glial heterogeneity and intercellular communication. Understanding how glial cells integrate neuronal and environmental cues may ultimately enable the development of therapeutic strategies aimed at restoring physiological glial functions while preventing pathological activation. In this context, experimental approaches combining single-cell transcriptomics, spatial proteomics, human iPSC-derived neuron–glia co-culture systems, and *in vivo* imaging techniques will be particularly valuable to characterize context-dependent glial states and define how astrocyte–microglia communication evolves during disease progression. These strategies may also facilitate the identification of cell-specific therapeutic targets and the development of interventions aimed at restoring physiological neuron–glia communication while limiting chronic neuroinflammation. Ultimately, therapeutic interventions aimed at reestablishing balanced neuron–glia–glia signaling may represent a promising avenue to preserve synaptic function and limit neurodegeneration in inflammatory and neurodegenerative disorders.

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Abbreviations

The following abbreviations are used in this manuscript:

ACM	Astrocyte-conditioned medium
AD	Alzheimer's disease
Ang-2	Angiopoietin-2
BDNF	Brain-derived neurotrophic factor
Ca ²⁺	Calcium ion
CX3CL1	Fractalkine
CNS	Central nervous system
DAMP	Damage-Associated Molecular Pattern
EAE	Experimental autoimmune encephalomyelitis
ET	Endothelin
ETBr	Endothelin receptor B
Fn14	Fibroblast Growth Factor-inducible 14
HD	Huntington's disease
HIF	Hypoxia-inducible factors
HMGB1	High Mobility Group Box 1
HPC	Hypoxic post-conditioning
IFN	Interferon
IGF-1	Insulin-like growth factor 1
IL	Interleukin
IL1R1	IL-1 receptor type 1
IL-6R	IL-6 receptor
iPSC	Induced pluripotent stem cell
LIF	Leukemia inhibitory factor
LPS	Lipopolysaccharide
LTD	Long-term depression
LTP	Long-term potentiation
M-CSF	Macrophage colony-stimulating factor
MDD	Major depressive disorder
MERTK	MER tyrosine kinase
MHC	Major histocompatibility complex
MS	Multiple sclerosis
Na ²⁺	Sodium ion

NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NGF	Nerve growth factor
NO	Nitric oxide
NSAIDs	non-steroidal anti-inflammatory drugs
PD	Parkinson's disease
PKM2	Pyruvate Kinase M2
RAGE	Receptor for Advanced Glycation End products
REST	RE1-silencing transcription factor
ROS	Reactive oxygen species
SFRP1	Secreted-Frizzled-Related-Protein-1
SSRIs	Selective serotonin reuptake inhibitors
TGF- β	transforming growth factor- β
TLR	Toll-like receptors
TNF- α	tumor necrosis factor α
TREM2	Triggering receptor expressed on myeloid cells 2
TWEAK	Tumor necrosis factor-related Weak inducer of apoptosis
VEGF	Vascular endothelial growth factor

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