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Glial gene–protein networks in neuroinflammation and disease transitions

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Abstract

Neuroinflammatory responses emerge from interacting molecular configurations rather than from uniform activation programs. This review examines how extracellular cues, receptor and sensor systems, intracellular signaling pathways, gene and protein effectors, and reciprocal microglia–astrocyte communication combine to shape glial function across neurological disease. Particular attention is given to nuclear factor kappa B, Janus kinase/signal transducer and activator of transcription 3 (STAT3), transforming growth factor beta, interferon-associated signaling, purinergic receptors, inflammasome pathways, ion and water transport systems, complement, and extracellular matrix regulation. Mechanistic comparisons show that pathway identity alone does not determine biological output: receptor context, interacting molecular partners, glial cell type, signal duration, disease phase, and local tissue environment alter whether related regulatory modules support surveillance, clearance, repair-associated remodeling, persistent inflammation, or tumor-associated niche organization. These principles are compared across Alzheimer's disease, Parkinson's disease, stroke, and glioblastoma, revealing substantial differences in initiating signals, temporal organization, cellular interactions, and evidentiary strength. Transcriptomic, proteomic, cerebrospinal fluid, blood, and spatial profiling further demonstrate that measurable glial states require interpretation by biological source and validation level. Experimental interventions targeting NLR family pyrin domain-containing protein 3, astrocytic water-channel systems, microglial populations, STAT3-associated signaling, and glioblastoma microenvironmental interactions illustrate that therapeutic effects depend not only on the molecular target but also on the glial and disease configuration in which it operates. A configuration-based interpretation of glial gene–protein networks therefore provides a mechanistic basis for comparing disease states, evaluating biomarkers, and matching molecular interventions to biologically defined therapeutic windows.

Keywords: Neuroinflammation; Microglia; Astrocytes; Gene–protein networks; Microglia–astrocyte crosstalk; Neurodegeneration; Stroke; Glioblastoma

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1. Introduction

Neuroinflammation is not produced by a single glial activation program. Microglia and astrocytes alter receptor expression, intracellular signaling, transcriptional programs, secreted mediators, transport systems, metabolism, and extracellular interactions as tissue conditions change.[1-5] Contemporary single-cell, spatial, and mechanistic studies have consequently revealed substantial molecular heterogeneity within both glial

populations, including states associated with surveillance, injury responses, inflammatory persistence, tissue remodeling, and disease-specific microenvironments.[6-9] These findings have made broad labels such as "activated microglia" or "reactive astrocytes" increasingly insufficient for explaining how glial responses influence neurological disease.

A remaining problem is that molecular heterogeneity is often described without fully resolving why the same regulatory pathway can have different functional consequences across diseases or stages. Studies of glial heterogeneity and microglia–astrocyte communication have established substantial molecular and functional diversity within and between these glial populations.[2,3,5-10] Disease-focused studies in neurodegeneration, ischemic injury, and glioblastoma further show that related glial programs operate within markedly different pathological environments.[11-15] Pathway identity alone, however, does not explain whether a response supports surveillance, clearance, repair, persistent inflammation, or tumor-associated remodeling. Nuclear factor kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3), transforming growth factor beta (TGF-β), interferon-associated signaling, purinergic receptors, inflammasome pathways, cytokines, and extracellular matrix programs recur across multiple neurological conditions, yet their biological significance changes with the molecular system in which they are engaged.

Neurodegenerative disease, stroke, and glioblastoma provide particularly informative contrasts. Neurodegenerative disorders expose glial cells to prolonged protein-associated, synaptic, metabolic, and neuronal stress.[3-5,15] Ischemic injury instead produces abrupt metabolic failure, tissue damage, vascular disruption, and temporally evolving inflammatory and repair responses.[9,13] Glioblastoma continuously exposes resident and recruited cells to tumor-derived cytokines, metabolites, extracellular vesicles, immune-regulatory signals, and spatially organized extracellular niches.[11,12,14] Similar glial molecular systems therefore operate under fundamentally different initiating conditions, temporal structures, and tissue constraints.

The relevant mechanistic unit is consequently not an isolated pathway but a regulatory configuration: extracellular input → receptor or sensor → intracellular signaling node → gene and protein effectors → cellular and tissue output. The functional consequence of a pathway depends on the receptor through which it is engaged, interacting signaling partners, signal strength and duration, the responding glial cell type, reciprocal microglia–astrocyte communication, disease stage, and local tissue environment. This configuration-based view distinguishes the presence of a molecular pathway from the network context that gives that pathway biological meaning.

Using this framework, the review first defines major glial molecular modules and then examines how microglia and astrocytes deploy them differently. The review analyzes reciprocal glial signaling as a distinct regulatory layer, then compares network reconfiguration across homeostatic regulation, repair-associated responses, persistent inflammation, and tumor-associated remodeling. Alzheimer's disease, Parkinson's disease, stroke, and glioblastoma are then compared to identify which molecular components are shared and which configurations are disease-specific. Transcriptomic and proteomic evidence is used to evaluate how these configurations can be resolved experimentally and translated into biomarkers, while intervention studies are examined to determine how therapeutic effects depend on the molecular target, glial population, disease phase, and tissue environment.

2. Molecular basis of glial regulation in neuroinflammation

Glial responses can be understood as molecular configurations linking extracellular inputs, receptors or sensors, intracellular signaling nodes, downstream gene and protein effectors, and tissue-level outputs.[8,10] These components should not be interpreted independently. Activation of the same intracellular pathway may produce different biological consequences depending on the upstream receptor through which it is engaged, the strength and duration of signaling, concurrent molecular inputs, the responding glial cell type, and the local disease environment.[9,15] The mechanistic unit of interest is therefore not an isolated pathway name, but the configuration in which that pathway operates.

Glial regulation can accordingly be considered across four connected levels: extracellular and disease-associated inputs; receptor and intracellular signaling modules; gene and protein effectors; and functional tissue consequences.[8] Differences in these linked levels help explain why related glial pathways can support distinct outcomes across neurodegeneration, ischemic injury, and glioblastoma.[9,12,15]

2.1. Upstream activating cues

The first level of glial regulation involves extracellular signals that indicate a loss of tissue homeostasis. Among the most immediate of these are damage-associated molecular patterns released from stressed, injured, or dying cells. These molecules signal disruption of cellular

integrity and have been implicated in the initiation of glial sensing, innate immune signaling, and early inflammatory responses after tissue injury.[16,17] Their relevance is especially evident in acute injury and degenerative settings, where cell damage and altered extracellular composition provide a direct molecular context for glial activation.[9,16]

Cytokines and chemokines form a second major class of activating cues. Unlike damage-associated signals, which often reflect local tissue disruption, cytokines and chemokines act more explicitly as intercellular communication molecules. They influence how glial cells interpret inflammatory conditions, interact with neighboring neural and vascular cells, and either amplify or constrain local responses.[18,19] Their effects depend on concentration, timing, receptor expression, and the broader molecular state of the tissue, making them particularly important in determining whether neuroinflammatory signaling remains transient or becomes sustained.[10,15,18]

Oxidative and metabolic stress provide another important source of glial activation. Altered redox balance, mitochondrial dysfunction, impaired energy metabolism, and changes in extracellular metabolic conditions have all been linked to inflammatory signaling and functional reprogramming in glial cells.[20-22] These cues are particularly relevant in conditions marked by chronic cellular stress or energetic failure, including neurodegenerative disease and ischemic injury, where metabolic disturbance may both reflect and reinforce inflammatory pathology.[21,23]

Certain activating signals are especially characteristic of particular disease contexts. In neurodegenerative disorders, misfolded or aggregated proteins can serve as persistent sources of cellular stress and receptor-mediated glial stimulation, thereby contributing to prolonged inflammatory signaling.[7,15,24] In stroke, ischemia-related signals—including hypoxia, nutrient deprivation, cell death, and reperfusion-associated stress—create a rapidly changing molecular environment that influences both the timing and intensity of glial responses.[9,25,26] In glioblastoma, tumor-derived factors, extracellular vesicles, altered metabolites, and matrix-associated signals may redirect glial behavior toward immune-modulatory and tumor-supportive states that differ from more classical injury-associated responses.[27-29]

The functional significance of these upstream cues depends in part on the receptor systems through which they are detected. Damage-associated ligands may engage pattern-recognition and purinergic receptors; cytokines act through receptor complexes linked to NF-κB or Janus kinase (JAK)/STAT signaling; and tumor-derived or matrix-associated signals can activate growth-factor, immune-regulatory, or adhesion-linked pathways. Consequently, similar extracellular disturbances can produce different downstream programs when receptor availability, receptor coupling, or concurrent signaling inputs differ across glial cell types and disease states.[8,16,18,27-29]

Upstream cues therefore acquire biological meaning through the receptor and signaling systems available to the responding glial cell. Differences in ligand identity, receptor expression, signal strength, duration, and coincident inputs influence which intracellular modules are recruited and which downstream gene and protein programs become dominant.[8,10,21]

2.2. Intracellular signaling pathways

Extracellular signals are converted into glial responses through receptor-coupled and intracellular signaling modules that control transcription, ion flux, metabolism, cytoskeletal behavior, and protein effector production. The same downstream pathway can be engaged through different upstream receptors and can produce different outputs depending on signal duration, pathway crosstalk, cell type, and disease environment. Mechanistic interpretation therefore requires tracing the sequence from receptor engagement to intracellular signaling and downstream effector production rather than assigning a fixed biological function to a pathway name alone.[8,30]

Nuclear factor kappa B functions as a convergence point for several inflammatory receptor systems. Engagement of cytokine receptors, pattern-recognition receptors, or other stress-responsive pathways can promote the phosphorylation and degradation of inhibitor of kappa B, allowing NF-κB complexes to translocate to the nucleus and regulate transcription of inflammatory genes, including cytokines, chemokines, and additional immune-response mediators.[31,32] In microglia, this signaling architecture has been linked to amplification of innate immune programs and sustained inflammatory output, while astrocytic NF-κB activation can alter inflammatory mediator production and tissue-support functions.[30,31,33,34] Its biological effect therefore depends not only on NF-κB activation itself, but also on the initiating receptor, duration of nuclear signaling, and concurrent transcriptional environment. Persistent engagement is especially relevant when inflammatory cues remain unresolved.

Signal transducer and activator of transcription 3 is activated principally downstream of cytokine and growth-factor receptors that signal through JAKs. Receptor engagement promotes JAK-dependent STAT3 phosphorylation, dimerization, and nuclear translocation, where STAT3 regulates transcriptional programs involved in reactive remodeling, cytoskeletal reorganization, and injury-associated adaptation.[34-36] In astrocytes, this

pathway has been linked to scar-associated responses and structural remodeling after injury, including signaling connected to interleukin (IL)-10/STAT3 and JAK2/STAT3 axes.[34,37] Microglial STAT3 signaling appears more variable and may contribute to inflammatory or adaptive responses depending on the upstream cytokine environment and disease model.[29,38] Thus, STAT3 is better interpreted as a receptor-coupled transcriptional module whose output depends on the ligand–receptor context rather than as a fixed marker of glial reactivity.

Transforming growth factor beta signaling illustrates how a common regulatory pathway can support different glial programs across disease states. Binding of TGF-β ligands to TGF-β receptor complexes activates intracellular SMAD signaling and can interact with additional non-SMAD pathways, altering transcriptional programs involved in immune regulation, extracellular remodeling, and cellular-state maintenance.[39,40] In microglia, TGF-β signaling has been linked to regulation of homeostatic and disease-associated states, including in Alzheimer-related contexts, whereas in glioblastoma the same signaling family participates in tumor-associated immune and microenvironmental regulation.[40,41] The functional consequence therefore depends on the receptor context, interacting pathways, and tissue environment rather than on TGF-β activity alone.

Interferon-associated signaling links immune stress to sustained transcriptional reprogramming. Type I interferons bind interferon receptors and activate JAK–STAT signaling, promoting the formation of interferon-responsive transcriptional complexes and inducing interferon-stimulated genes. Upstream innate sensing pathways can further reinforce this response; for example, cyclic GMP–AMP synthase–stimulator of interferon genes (STING) signaling has been linked to age-associated inflammation and neurodegenerative pathology.[42,43] In microglia, persistent interferon-responsive programs are associated with disease-related immune states, whereas astrocytic interferon signaling can be modified by regulatory mechanisms such as suppressor of cytokine signaling 1-associated feedback.[42-45] These pathways are therefore most informative when the upstream sensor, interferon receptor signaling, and downstream transcriptional program are considered together rather than treating an interferon signature as a single uniform glial state.

Purinergic signaling demonstrates particularly clearly why receptor identity matters. Extracellular adenosine triphosphate (ATP) and related nucleotides can engage several purinergic receptors with distinct signaling properties, so "purinergic activation" should not be treated as a single functional category.[46-48] P2Y12 is a G_i-coupled G-protein-coupled receptor expressed by microglia. It is associated with surveillance, process extension, chemotaxis, and rapid migration toward sites of tissue disturbance. Experimental loss of P2Y12 alters microglial dynamics, injury responses, and microglia–neuron interactions, supporting a role for this receptor in spatial sensing and directed microglial behavior.[49,50]

P2X7, in contrast, is an ATP-gated cation channel that becomes particularly relevant under conditions of high or sustained extracellular ATP. P2X7 activation promotes ionic flux and can facilitate inflammatory signaling, including coupling to inflammasome-associated mechanisms and release of inflammatory mediators.[51-53] Human microglial studies further indicate that P2X7 contributes differently from other ion-channel systems to ATP-driven neuroinflammatory responses.[52] The contrast between P2Y12 and P2X7 therefore illustrates a central principle of glial network regulation: the same extracellular ligand can produce surveillance- and migration-associated responses through one receptor configuration and inflammatory amplification through another.

Inflammasome signaling provides a second example of a multistep regulatory module. In microglia, danger-associated inputs can promote priming of inflammasome components through inflammatory transcriptional pathways, while subsequent cellular stress, ionic disturbance, or purinergic signaling can favor assembly and activation of inflammasome complexes such as NLR family pyrin domain-containing protein 3 (NLRP3). Activated NLRP3 promotes caspase-1-dependent processing of IL-1β and IL-18, thereby converting upstream danger sensing into release of mature inflammatory mediators.[17,54,55] P2X7-dependent ionic signaling can intersect with this process, linking extracellular ATP accumulation to inflammasome-associated inflammatory amplification.[51-53] Experimental inhibition of NLRP3 has shown disease-modifying effects in selected neurodegenerative models, although the importance and cellular specificity of this pathway vary across disease contexts.[17,56]

These pathways are therefore better understood as interacting regulatory modules than as fixed markers of particular glial functions. NF-κB, JAK/STAT, TGF-β, interferon, purinergic, and inflammasome signaling can intersect at multiple levels, including transcriptional regulation, cytokine production, ion signaling, and feedback between microglia and astrocytes. Evidence is strongest where receptor perturbation, pathway inhibition, or genetic manipulation links a defined molecular event to a downstream functional change; associations based only on expression or pathway enrichment establish molecular

participation but not necessarily causal control. Apparent differences among studies may also reflect cell type, disease stage, signal duration, experimental model, and the specific molecular readout examined. The biological output of these pathways should therefore be interpreted from the complete receptor–signaling–effector configuration rather than from pathway activation alone.

2.3. Protein-level mediators and effectors

Receptor-coupled signaling becomes biologically consequential through changes in gene expression, protein abundance, secretion, channel and transporter activity, and extracellular matrix composition. These downstream effectors translate intracellular pathway activity into intercellular communication and tissue-level change.[8,57]

Cytokines are among the principal mediators of glial inflammatory signaling. Produced by microglia, astrocytes, and other cells within diseased tissue, they regulate local inflammatory tone, influence neighboring neural and vascular cells, and help determine whether responses remain transient or become sustained.[8,19] Their effects vary with timing, concentration, and receptor context, and have been linked to both early injury responses and longer-term inflammatory persistence across neurodegenerative, ischemic, and tumor-associated conditions.[26,58]

Chemokines function more specifically in spatial coordination and cellular recruitment. In glial biology, they have been associated with positioning reactive cells, reinforcing local inflammatory microenvironments, and coordinating communication among glial, immune, and vascular compartments.[26,58] Their importance is especially evident in conditions involving dynamic tissue reorganization, including stroke and glioblastoma, but they are also relevant to chronic inflammatory signaling in neurodegenerative disease.

Ion channels also contribute to glial effector function. In astrocytes, they are closely tied to potassium and water homeostasis, while in both astrocytes and microglia they influence membrane responsiveness, calcium-dependent signaling, and interactions with surrounding cells.[59,60] Under pathological conditions, altered channel expression or activity has been associated with disrupted homeostatic support, inflammatory signaling, and changes in the local extracellular environment.[61,62]

Extracellular matrix-associated proteins extend glial molecular activity into structural regulation of the tissue environment. Through effects on matrix composition, adhesion, and signaling availability, these proteins influence tissue architecture, cellular movement, and persistence of inflammatory or tumor-associated microenvironments.[63,64] Their relevance is particularly apparent in injury-associated remodeling and glioblastoma, where extracellular change is closely linked to disease progression.

Downstream signaling also alters the expression, localization, or activity of membrane proteins that shape subsequent cellular responsiveness. Such changes can modify transporter function, ion and water handling, adhesion, and the sensitivity of glial cells to cytokines, chemokines, growth factors, or extracellular stress signals.[8,65] In this way, the effector layer includes not only secreted mediators but also changes in membrane and extracellular proteins that reshape the signaling environment and influence later rounds of glial communication.

Cytokines, chemokines, ion and water transport systems, extracellular matrix-associated proteins, and other regulated membrane or secreted effectors therefore constitute the principal downstream layer through which intracellular signaling is converted into tissue-level consequences.

2.4. Functional outcomes of molecular activation

Functional outcomes emerge from combinations of receptor activity, intracellular signaling, and downstream effectors rather than from individual molecules acting in isolation. The same regulatory component may therefore contribute to different tissue consequences depending on the molecular configuration in which it is engaged.[9,66]

One major outcome is inflammatory amplification. Through production of cytokines, chemokines, and other signaling molecules, glial cells can reinforce local inflammatory circuits, influence neighboring cells, and prolong communication within neural and vascular compartments.[26,67] In some settings, this may support early containment of injury, whereas persistent amplification has been linked to chronic inflammatory exposure and tissue dysfunction.

Phagocytosis and debris clearance represent another important consequence of glial activation. Microglia are central to these functions, although astrocytes may also contribute in selected contexts. Through coordinated sensing and engulfment pathways, glial cells remove damaged cells, protein aggregates, myelin debris, and other extracellular material that would otherwise sustain tissue stress.[68,69] These processes may support recovery, but when dysregulated, they may also be associated with excessive synaptic loss or persistent inflammatory signaling.

Synaptic modulation provides an important link between molecular inflammatory signaling and circuit-level dysfunction. Through secreted mediators, receptor signaling, and control of the local extracellular environment, glial cells influence synaptic maintenance, pruning,

and transmission-related stability.[70,71] In pathological conditions, altered glial molecular states have been linked to disrupted synaptic regulation and loss of network homeostasis, particularly in chronic neurodegenerative and inflammatory settings.[38,72]

Glial molecular activation also affects metabolic support and metabolic disruption. Astrocytes are central to metabolic support of neural tissue, but both astrocytes and microglia undergo metabolic changes under inflammatory conditions.[73,74] These shifts may contribute to adaptation in some settings, but they have also been associated with oxidative stress, energetic imbalance, and reinforcement of inflammatory persistence in neurodegeneration, ischemia, and tumor-associated disease.

Another key outcome is extracellular remodeling. By regulating matrix-associated proteins and other structural mediators, glial cells influence tissue architecture, cellular migration, and the local signaling environment.[75,76] After injury, such remodeling may contribute to stabilization and repair-associated reorganization, whereas in chronic disease or glioblastoma it may support persistence of maladaptive or tumor-supportive tissue states.[64,77]

In tumor settings, glial activation may also become associated with immune suppression. Rather than simply amplifying classical inflammatory signaling, tumor-associated glial cells may adopt molecular programs that limit effective anti-tumor responses and help maintain permissive microenvironments.[29,78,79] This is particularly relevant in glioblastoma, where glial signaling may contribute to extracellular remodeling, altered immune communication, and sustained tumor support.

These molecular relationships—from extracellular input and receptor engagement to intracellular signaling, effector regulation, and tissue-level output—are summarized in Figure 1.[63,80,81] The principal molecular modules linking upstream glial signals to intracellular mechanisms and downstream functional outputs are compared in Table 1.

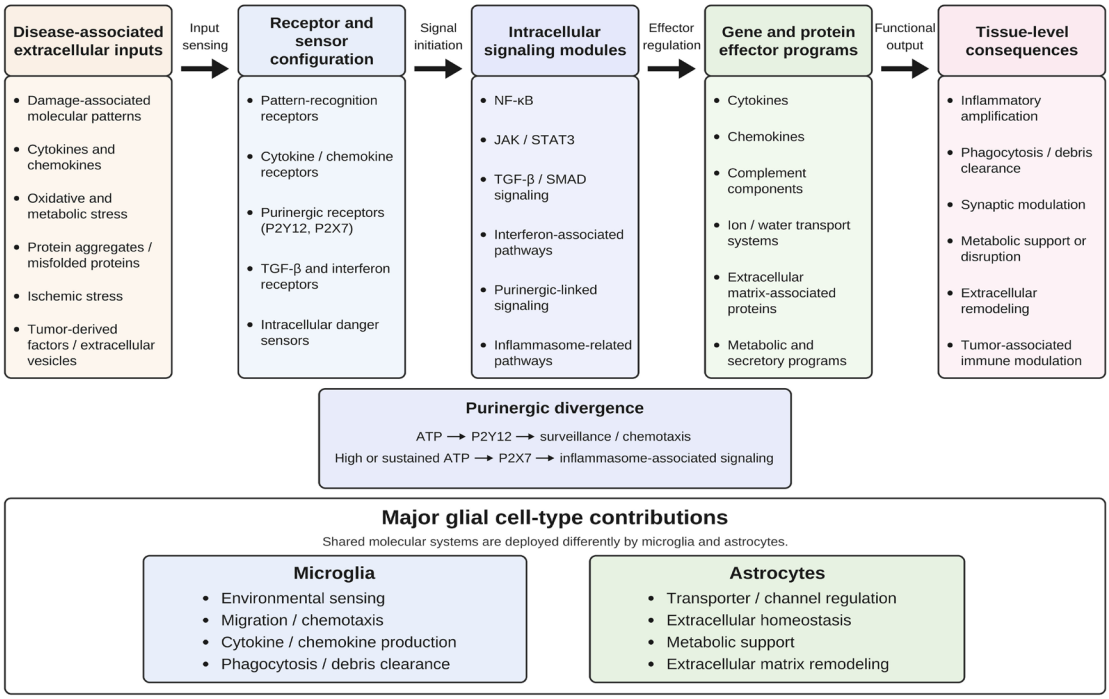


Figure 1. Molecular architecture of glial neuroinflammatory regulation. Disease-associated extracellular inputs are interpreted through receptor and sensor configurations, intracellular signaling modules, and downstream gene and protein effector programs that produce distinct tissue-level consequences. Purinergic signaling illustrates receptor-dependent divergence, with P2Y12 associated with surveillance and chemotaxis and P2X7 linked to inflammasome-associated signaling under high or sustained extracellular ATP. The lower panel highlights predominant functional contributions of microglia and astrocytes within this shared regulatory architecture.
Abbreviations: ATP: Adenosine triphosphate; JAK: Janus kinase; NF-κB: Nuclear factor kappa B; STAT3: Signal transducer and activator of transcription 3; TGF-β: Transforming growth factor beta.

Table 1. Molecular regulatory modules linking upstream signals to glial outputs in neuroinflammation

Molecular node	Upstream trigger/ receptor context	Major intracellular mechanism	Predominant glial context	Major downstream output	Disease/stage context	Evidence basis	References
P2Y12	Extracellular purines released during physiological surveillance or focal tissue disturbance	G_i-coupled purinergic signaling linked to process extension, motility, and directed chemotaxis	Predominantly microglia	Surveillance, injury localization, microglial process dynamics, microglia–neuron interaction	Homeostasis and early injury responses	Loss-of-function studies demonstrate altered microglial dynamics and injury responses	50
P2X7	High or sustained extracellular ATP during cellular stress or tissue injury	ATP-gated cation flux coupled to inflammatory signaling and inflammasome-associated mechanisms	Predominantly microglia; astrocytic involvement in selected contexts	Inflammatory mediator release, amplification of ATP-dependent neuroinflammatory signaling	Sustained injury, chronic inflammatory stress, neurodegenerative settings	Human microglial mechanistic evidence combined with glial receptor synthesis	51,52
NF-κB	Cytokine receptors, pattern-recognition receptors, cellular stress and injury-associated signaling	IKK/IκB-dependent NF-κB activation and nuclear transcription of inflammatory genes	Microglia and astrocytes	Cytokine/chemokine expression, inflammatory amplification, modification of tissue-support and repair programs	Acute injury and persistent inflammatory states; disease-specific effects vary by cell type	Cell-specific experimental manipulation in microglia and astrocytes	30,33
JAK/STAT3	Cytokines and growth-factor receptor signaling, including IL-10-associated regulation	JAK-dependent STAT3 phosphorylation, dimerization and transcriptional regulation; interaction with cytoskeletal programs	Especially astrocytes; context-dependent microglial involvement	Astrogliosis, cytoskeletal remodeling, AQP4 regulation, scar-associated and injury-adaptive responses	Spinal cord injury and other injury/ remodeling states	Experimental pathway manipulation links STAT3 signaling to astrocytic remodeling and neurological outcome	35,36
TGF-β/SMAD	TGF-β ligands acting through TGF-β receptor complexes	SMAD-dependent transcription with additional non-SMAD pathway interactions	Microglia and astrocytes	Maintenance or alteration of glial state, immune regulation, extracellular remodeling and microenvironmental control	Alzheimer's disease and glioblastoma; context-dependent homeostatic versus disease-associated effects	Disease-focused mechanistic synthesis; effects vary strongly with cellular and tissue context	39,40
cGAS–STING/ type I interferon	Cytosolic DNA sensing, cellular stress and interferon-receptor signaling	cGAS–STING activation and downstream type I interferon/JAK–STAT transcriptional programs; SOCS1-associated feedback	Strongly represented in microglia; astrocytic regulation in selected inflammatory contexts	Interferon-stimulated gene expression and persistent immune-state reprogramming	Aging, neurodegeneration and chronic CNS inflammation	Genetic/ pharmacological evidence for cGAS–STING plus experimental interferon/SOCS1 modulation	42,43,45

(*Cont'd...*)

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Table 1. (*Continued*)

Molecular node	Upstream trigger/ receptor context	Major intracellular mechanism	Predominant glial context	Major downstream output	Disease/stage context	Evidence basis	References
NLRP3 inflammasome	Danger-associated signals, cellular stress, ionic disturbance and P2X7-associated ATP signaling	Inflammasome assembly → caspase-1 activation → processing of IL-1β and IL-18	Mainly microglia	Mature inflammatory mediator release and amplification of innate immune signaling	Neurodegeneration, ischemic injury and persistent inflammatory stress	Mechanistic synthesis plus post-symptomatic pharmacological inhibition in amyloid/ tau neurodegeneration	17,56
AQP4/TRPV4 water–ion regulatory module	Osmotic disturbance, ischemia-like stress, extracellular ionic changes and astrocytic injury signaling	Coordinated water permeability and volume-regulatory channel activity; interaction with broader transporter systems	Astrocytes	Astrocyte swelling, volume recovery, edema-related extracellular regulation	Ischemic stress and acute CNS injury	Genetic deletion and knockdown studies demonstrate context-dependent effects on astrocyte swelling and injury response	59,62
Astrocyte-derived complement C3	Inflammatory astrocytic signaling and extracellular complement activation	Complement-dependent tagging/signaling coupled to microglial recognition and phagocytic machinery	Astrocyte-to-microglia interaction	Microglial synapse recognition and phagocytosis	Neuroinflammatory and neurodegenerative-like synaptic injury contexts	Experimental astrocyte–microglia interaction evidence	82

Abbreviations: AQP4: Aquaporin 4; ATP: Adenosine triphosphate; cGAS: Cyclic GMP–AMP synthase; CNS: Central nervous system; IKK: IκB kinase; IL-1β: Interleukin-1 beta; IL-10: Interleukin-10; IL-18: Interleukin-18; IκB: Inhibitor of nuclear factor kappa B; JAK: Janus kinase; NF-κB: Nuclear factor kappa B; NLRP3: NLR family pyrin domain containing 3; SOCS1: Suppressor of cytokine signaling 1; STAT3: Signal transducer and activator of transcription 3; STING: Stimulator of interferon genes; TGF-β: Transforming growth factor beta; TRPV4: Transient receptor potential cation channel subfamily V member 4.

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3. Microglial molecular responses across disease stages

Microglia deploy the regulatory modules described above through functions centered on environmental sensing, directed migration, phagocytic clearance, inflammatory signaling, and neural tissue remodeling. Their distinctive biology reflects the coupling of receptor-mediated surveillance to rapid cytoskeletal responses, engulfment pathways, transcriptional reprogramming, and communication with neurons, astrocytes, vascular cells, and infiltrating immune populations.[83-86] Changes in these coupled systems influence whether microglial activity remains surveillance-oriented, supports clearance and repair, becomes persistently inflammatory, or is redirected within tumor-associated environments.

3.1. Homeostatic microglial functions

Homeostatic microglia maintain continuous surveillance through receptor systems that detect neuronal activity, extracellular nucleotides, synaptic change, and subtle disturbances in tissue integrity.[87-90] P2Y12-linked purinergic sensing is one example of how extracellular signals are coupled to process extension and directed movement without requiring a full inflammatory program. This surveillance state also supports selective interaction with synaptic structures and controlled removal of cellular material, establishing a receptor-responsive baseline from which later injury-associated programs emerge.

3.2. Early injury and stress responses

Acute tissue disturbance shifts microglial signaling from surveillance toward localization, inflammatory communication, and initiation of clearance programs. Damage-associated ligands, extracellular ATP, altered metabolites, and signals from injured neurons or vascular cells engage receptor systems that modify motility, transcription, and cytoskeletal behavior.[87,91] The resulting response couples rapid movement toward disturbed tissue with production of cytokines and chemokines and recruitment of engulfment pathways.[91,92] In acute injury settings such as stroke, these processes are further shaped by interaction with damaged neurons and the local vasculature, integrating microglial sensing and clearance within a broader multicellular injury response.[92]

3.3. Microglial remodeling functions

Microglial remodeling is distinguished by receptor-dependent recognition and engulfment of apoptotic cells, myelin debris, extracellular aggregates, and other damaged material.[68,83,89] Phagocytic clearance reduces persistent sources of danger signaling, but the same machinery can become maladaptive when recognition or engulfment extends to stressed but potentially recoverable synaptic elements. The functional significance of microglial remodeling therefore depends on what is recognized, what is removed, and whether clearance resolves or perpetuates local stress.

Microglial remodeling also includes synapse-related effects. Under pathological conditions, microglial molecular programs may influence pruning, elimination of stressed synaptic structures, and reorganization of local circuit environments.[89,90] These responses may support adaptation after injury, but prolonged or dysregulated remodeling has also been linked to synaptic loss and functional decline. At this stage, microglia participate not only in clearance but also in shaping the structural and signaling conditions that influence subsequent repair or dysfunction.[83-85]

3.4. Persistent inflammatory microglial states

Persistent microglial inflammatory states are maintained by continued molecular input rather than simple continuation of an earlier response. Repeated exposure to protein aggregates, unresolved debris, vascular disturbance, metabolic stress, and cytokine signaling can sustain immune-gene expression, inflammatory mediator production, NF-κB- and interferon-associated programs, and altered metabolic activity.[31,72,84,93,94] These reinforcing inputs can maintain microglial responsiveness even when the initiating injury has changed or partially resolved.

In neurodegenerative disease, persistent stimulation by misfolded proteins, synaptic stress, and chronic tissue dysfunction can maintain these programs over prolonged periods, whereas after acute injury persistent vascular, structural, or metabolic abnormalities may provide a different source of continued activation.[72,84,93,95] The important distinction is therefore the molecular source of reinforcement rather than duration alone.

3.5. Tumor-associated microglial changes

In glioblastoma, tumor-derived cytokines, metabolites, extracellular vesicles, and matrix-associated cues reconfigure microglial signaling toward immune modulation, extracellular remodeling, and support of tumor-associated niches.[28,77] Rather than representing a simple extension of inflammatory activation, this state involves altered receptor engagement and sustained interaction with tumor-derived signals that modify cytokine output, immune-cell communication, and matrix regulation.

Tumor-associated microglia have been linked to restricted anti-tumor surveillance, altered cytokine

signaling, and extracellular conditions that favor tumor persistence and invasion.[85,96,97] The same broad regulatory systems used during injury sensing and remodeling are therefore redirected by a distinct upstream environment toward different tissue-level consequences.

Microglial regulation is therefore distinguished by coupling receptor-mediated sensing to motility, phagocytosis, inflammatory transcription, and tissue remodeling, with the balance among these functions changing according to the signals encountered.

4. Astrocytic molecular responses across disease stages

Astrocytes deploy glial regulatory networks primarily by controlling extracellular composition, neurotransmitter handling, ion and water balance, metabolic exchange, vascular signaling, and structural organization. These functions depend on coordinated transporter, channel, receptor, metabolic, and extracellular matrix systems that can be altered by inflammatory and disease-associated signaling.[19,98,99] Astrocytic involvement in neuroinflammation therefore emerges not only through cytokine production, but through changes in the molecular systems that determine the physical and metabolic environment in which neurons, glia, and vascular cells operate.

4.1. Homeostatic astrocytic roles

Homeostatic astrocytic function depends on coordinated transporter and channel systems that regulate neurotransmitter and ionic conditions. Glutamate uptake and recycling limit extracellular excitatory signaling, while potassium-handling mechanisms, exchangers, and water transport proteins stabilize ionic and osmotic conditions required for neuronal activity.[100-102] These systems are dynamic components of astrocyte–neuron signaling rather than passive background functions.

Astrocytes also coordinate metabolic exchange with neurons and vascular cells, coupling local energy demand to substrate availability and vascular supply.[101] Together, transporter, channel, and metabolic systems establish the extracellular and energetic baseline, and disruption of this baseline becomes a major component of astrocytic pathology in injury and disease.

4.2. Astrocytic responses to injury and inflammation

When tissue homeostasis is disturbed, astrocytes alter their molecular programs in ways that affect inflammatory signaling, neuronal support, and local extracellular regulation. A prominent feature of this stage is the induction of cytokine and chemokine signaling, which enables astrocytes to participate actively in local inflammatory communication rather than simply responding to mediators released by other cells.[19,103] These signaling changes influence neighboring astrocytes, microglia, neurons, vascular cells, and infiltrating immune populations, and may help determine whether local responses remain limited or become sustained.

Injury-associated cytokine and receptor signaling also alters astrocytic transporter, channel, and metabolic functions, linking inflammatory communication to changes in extracellular regulation.[9,26,104] Microglial and neuronal inputs can therefore reshape not only astrocytic mediator production but also the homeostatic systems that regulate neurotransmitter, ionic, and metabolic conditions.

Another key molecular feature of this stage is altered expression of transporters and ion channels. Changes in glutamate transport systems, potassium-handling mechanisms, water channels, and receptor-linked signaling pathways can reshape extracellular neurotransmitter balance, ionic stability, and local excitability conditions.[105-107] These alterations can modify extracellular glutamate, potassium and water balance, thereby changing neuronal excitability and local extracellular stability.[108,109]

4.3. Barrier and vascular interactions

Astrocytes have a distinct and critical role within the neurovascular unit. Through signaling interactions with endothelial cells, perivascular structures, and extracellular matrix components, they contribute to the regulation of blood–brain barrier properties, vascular communication, and local homeostatic balance.[110,111] These roles make astrocytic biology especially important in diseases where vascular dysfunction and inflammatory signaling intersect.

Under pathological conditions, astrocytic molecular changes can influence barrier integrity through altered signaling to endothelial cells and modification of perivascular microenvironments.[112,113] Such changes may affect permeability, exchange between central and peripheral compartments, and the degree to which inflammatory signals are contained or propagated. This is particularly relevant in ischemic injury and inflammatory disease, where barrier disruption is closely linked to tissue damage and prolonged neuroinflammatory response.

Astrocytes are also involved in vascular signaling related to perfusion, metabolic demand, and tissue oxygenation. In ischemic conditions, these roles become especially significant because vascular compromise, hypoxia, and altered nutrient delivery strongly affect astrocytic signaling and transporter function.[109,114] In parallel, changes in water-handling systems may contribute to edema and further destabilize local tissue conditions. Barrier- and vascular-

related astrocytic responses therefore represent a specific molecular dimension of neuroinflammation, rather than a secondary feature of general glial activation.

4.4. Reactive remodeling and tissue reorganization

Reactive astrocytic remodeling involves coordinated changes in morphology, cytoskeletal organization, adhesion signaling, and extracellular matrix-associated gene and protein expression.[115-117] These changes alter how astrocytes organize tissue around injury sites and influence communication with neighboring neural, glial, and vascular cells. Scar-associated responses are one manifestation of this remodeling, in which astrocytes contribute to formation of structural boundaries through changes in adhesion-related pathways and matrix-associated proteins.[115,117,118]

Extracellular matrix remodeling also changes the signaling properties of the local tissue environment. By modifying matrix composition and the retention, presentation, or diffusion of extracellular mediators, astrocytes can influence cellular movement, receptor exposure, and intercellular communication.[115,119,120] Astrocytic remodeling therefore changes not only tissue structure but also the spatial distribution and persistence of extracellular signals, linking matrix composition directly to later cellular behavior.

4.5. Tumor-associated astrocytic responses

In glioblastoma, tumor-derived cytokines, growth-related signals, altered metabolites, extracellular vesicles, and matrix-associated cues reconfigure astrocytic signaling, transporter activity, and metabolic interactions within the tumor microenvironment.[121,122] These inputs can shift astrocytes away from homeostatic regulation toward programs that alter immune communication, extracellular composition, and local metabolic support.

Astrocytes within glioblastoma-associated environments have been linked to cytokine and receptor signaling patterns that may influence recruitment, restriction, or redirection of local immune responses.[123,124] Through interactions with tumor cells, microglia, and other stromal elements, astrocytes can contribute to signaling conditions associated with reduced anti-tumor surveillance and persistent immune dysregulation.

Astrocytic contributions also extend to extracellular and metabolic niche organization. By modifying matrix composition, metabolite availability, and intercellular signaling exchange, astrocytes may help establish conditions that support glioblastoma cell survival, invasion, and local adaptation.[121,122,125] The tumor-associated astrocytic state is therefore characterized by coordinated changes in immune signaling, transporter and metabolic function, and extracellular matrix regulation within a chronically evolving tumor niche.

Astrocytic regulation is distinguished by integrating inflammatory signaling with transporter, channel, metabolic, vascular, and extracellular matrix systems. Disease-associated changes in these modules alter the biochemical and structural environment surrounding neural tissue, giving astrocytes a regulatory role that complements but is mechanistically distinct from the sensing, migration, and phagocytic functions emphasized in microglia.

5. Microglia–astrocyte crosstalk in neuroinflammatory progression

Microglia and astrocytes are coupled through reciprocal signaling rather than functioning as independent inflammatory compartments. Microglia-derived cytokines, chemokines, purines, complement-associated signals, and extracellular changes can modify astrocytic transcription, transporter activity, and mediator release, while astrocyte-derived signals alter microglial receptor responsiveness, cytokine production, phagocytic behavior, and persistence of activation.[7,82,126]

The biological effect of this reciprocity depends on the direction and duration of feedback. Negative, self-limiting interactions can limit mediator accumulation and support restoration of tissue stability, whereas feed-forward signaling can sustain cytokine exposure, extracellular disturbance, and chronic activation. Tumor-derived signals can further redirect these interactions toward immune suppression and niche maintenance.

5.1. Cytokine-mediated reciprocity

Microglia-derived cytokines can alter astrocytic gene expression, transporter activity, and secretion of secondary mediators.[7,98] These changes can modify glutamate handling, extracellular ion regulation, and astrocytic inflammatory output, thereby extending microglial signaling into the extracellular and metabolic functions controlled by astrocytes.

Astrocyte-derived cytokines and chemokines can in turn alter microglial sensitivity to local damage cues, inflammatory mediator production, and engagement with synaptic or extracellular material.[19,126] Depending on the mediators involved and the surrounding tissue state, this feedback may restrain microglial activation or reinforce inflammatory signaling and prolong mediator production.

The functional consequence of cytokine reciprocity therefore depends on the identity, concentration, timing,

and persistence of exchanged signals rather than on the direction of communication alone. Self-limiting feedback can restrict inflammatory exposure, whereas sustained bidirectional signaling can reinforce activation across both glial populations.[7,19,126]

5.2. Purinergic and receptor-mediated communication

Extracellular purines provide a rapid shared signal through which tissue disturbance can coordinate microglial and astrocytic responses.[46,127] In microglia, receptor identity is critical: P2Y12-associated signaling favors process extension and directed migration, whereas stronger or sustained ATP exposure can engage P2X7-associated ionic and inflammatory mechanisms. Astrocytes respond through distinct purinergic receptor repertoires that influence intracellular calcium signaling and mediator release.

The consequences of ATP accumulation therefore depend on which receptor systems each cell type engages. Transient purinergic signaling may coordinate localization and early tissue responses, whereas sustained extracellular ATP can reinforce inflammatory communication and alter the balance between microglial sensing and astrocytic extracellular regulation.

5.3. Complement-related and extracellular signaling

Complement-associated signaling links glial inflammatory communication to recognition and removal of synaptic material. Complement components within the extracellular environment can modify the molecular tagging of synaptic structures and their subsequent interaction with microglial recognition and engulfment systems, while astrocytes can influence the extracellular signaling conditions in which these processes occur.[82,90] The resulting effect on synaptic preservation or elimination therefore depends on the interaction between extracellular complement-associated signals and microglial clearance mechanisms rather than on either glial population alone.

Extracellular matrix remodeling provides a second layer of interaction. Matrix-associated proteins released or regulated by microglia and astrocytes can alter adhesion, molecular diffusion, and the retention or presentation of cytokines, chemokines, and growth-related signals within the extracellular space.[63,75,128] These changes modify not only tissue structure but also the concentration and duration of signals encountered by neighboring glial cells.

The extracellular matrix can therefore influence the persistence of glial feedback by controlling how readily signaling molecules accumulate, disperse, or remain locally available for receptor engagement. Changes in matrix composition may consequently shorten or prolong reciprocal microglia–astrocyte signaling and alter the spatial extent of inflammatory communication.[63,75,128]

5.4. Functional consequences of glial crosstalk

The consequences of reciprocal glial signaling depend on how feedback is organized. Self-limiting exchange can restrict mediator spread, promote debris clearance, and help restore extracellular stability.[127] When cytokine exchange, purinergic signaling, and extracellular retention of inflammatory mediators become self-reinforcing, the same interaction network can prolong synaptic, metabolic, and vascular disturbance.[7,127] In glioblastoma, tumor-derived signals redirect this reciprocity toward immune modulation, matrix remodeling, and metabolic support of tumor-associated niches.[77,129]

What distinguishes these outcomes is not simultaneous activation of microglia and astrocytes, but the direction, persistence, and molecular composition of the feedback loop. Crosstalk can therefore amplify, restrain, or redirect cell-specific programs, linking local signaling to tissue recovery, inflammatory persistence, or tumor-associated remodeling (Figure 2).

6. Network reconfiguration across glial disease states

Transitions among homeostatic regulation, repair-associated responses, persistent inflammation, and tumor-associated remodeling involve changes not simply in pathway activity, but in the configuration and persistence of interacting glial regulatory systems.[72,99] The molecular distinction between these states therefore lies in which extracellular inputs predominate, which receptors and signaling pathways are engaged concurrently, how long those signals persist, which effector programs are sustained, and how reciprocal microglia–astrocyte interactions modify the local tissue environment.[72,124]

Homeostatic states are characterized by coordinated surveillance, extracellular regulation, metabolic support, and restrained inflammatory signaling. Following injury, these systems can be transiently reconfigured toward sensing, phagocytosis, inflammatory containment, and structural remodeling.[34,72] Persistent inflammatory states emerge when activating inputs, receptor signaling, cytokine exchange, metabolic stress, or extracellular feedback remain sustained sufficiently to reinforce rather than resolve glial activation.[72,124] In glioblastoma, related molecular systems are reorganized within a tumor-derived signaling environment that favors immune modulation, extracellular matrix remodeling, metabolic adaptation, and maintenance of tumor-supportive niches.[124,130] These states

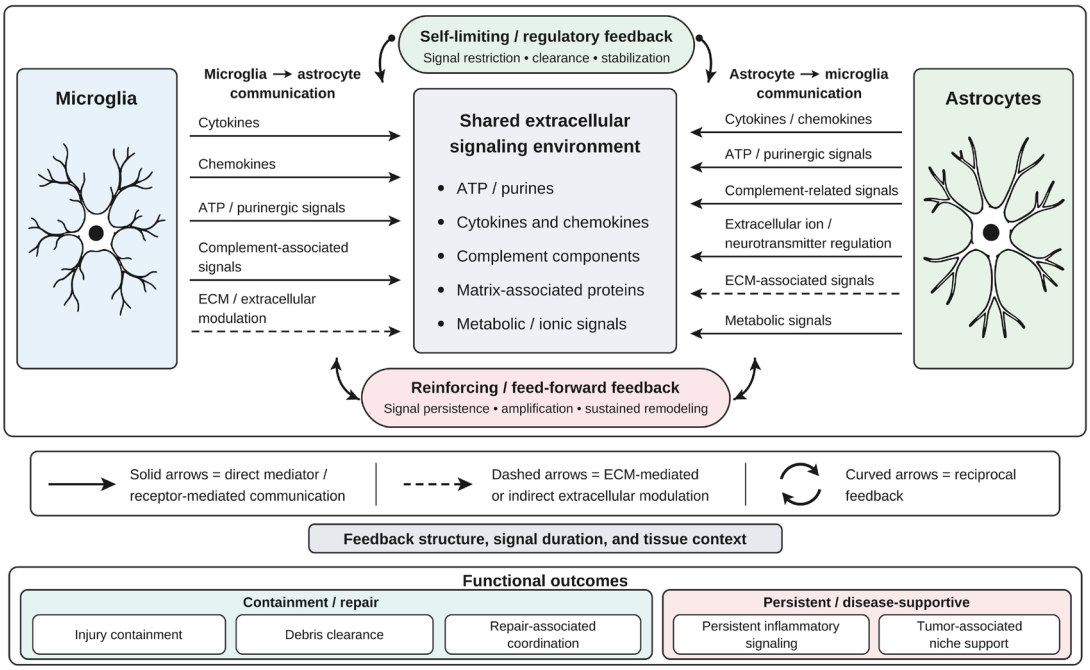


Figure 2. Reciprocal microglia–astrocyte signaling in neuroinflammation. Microglia and astrocytes exchange cytokines, chemokines, purinergic signals, complement-related mediators, metabolic signals, and extracellular matrix-associated influences within a shared signaling environment. Self-limiting feedback can restrict, clear, and stabilize signals, whereas reinforcing feedback can sustain inflammatory signaling and tissue remodeling. Functional outcomes depend on feedback structure, signal duration, and tissue context; solid arrows indicate direct mediator- or receptor-mediated communication, dashed arrows indicate ECM-mediated or indirect extracellular modulation, and curved arrows indicate reciprocal feedback.
Abbreviations: ATP: Adenosine triphosphate; ECM: Extracellular matrix.

therefore reflect differences in molecular organization and persistence rather than the simple presence or absence of individual pathways.

6.1. Homeostatic regulation

In the healthy central nervous system, glial cells maintain stable tissue conditions through molecular programs that regulate extracellular composition, synaptic signaling, metabolic exchange, vascular interaction, and surveillance of local stress signals. Microglia contribute through continuous sensing of cellular and synaptic integrity, while astrocytes regulate neurotransmitter clearance, potassium and water balance, metabolic support, and the biochemical composition of the extracellular environment.[72,131,132] These are active regulatory functions that preserve local stability under physiological conditions.

6.2. Repair-associated responses

When tissue homeostasis is disrupted, glial programs may shift toward responses that help limit injury and support recovery. Repair-associated responses differ from early activation by placing greater emphasis on clearance, extracellular reorganization, and local stabilization rather than initial sensing and inflammatory induction alone. At this stage, microglia engage phagocytic pathways more fully, while astrocytes more clearly alter extracellular regulation, metabolic support, and structural organization in ways that can protect surrounding tissue.[133-135]

Debris clearance is central to this phase. Removal of apoptotic cells, myelin fragments, extracellular aggregates, and damaged cellular material reduces continued exposure to danger signals and may lower the level of local inflammatory stimulation. In parallel, astrocytic regulation of extracellular ions, neurotransmitter levels, and water balance may help restore microenvironmental conditions needed for tissue recovery.[68,134]

Repair-associated responses may also include controlled extracellular remodeling. Changes in matrix-associated proteins, adhesion-related signaling, and glial communication can help reorganize injured tissue and preserve surrounding neural elements.[26,34,136,137] This is especially relevant after ischemic injury, where the balance

between timely clearance, extracellular stabilization, and restoration of tissue support may strongly influence outcome.[26,133]

6.3. Persistent inflammatory states

In some disease settings, glial activation does not resolve after the repair-associated phase, but is maintained by continued exposure to protein aggregates, unresolved debris, vascular dysfunction, metabolic stress, and reciprocal inflammatory signaling between microglia and astrocytes.[7,72,138] Persistent inflammatory states are marked by sustained cytokine and chemokine production, repeated receptor activation, ongoing inflammatory pathway engagement, and extracellular conditions that continue to stimulate both glial populations.[72,139] These features support a model in which chronic dysfunction can be sustained by active molecular reinforcement rather than reflecting only a delayed return to baseline.

Feed-forward signaling loops are a major component of this stage. Reciprocal cytokine exchange, purinergic signaling, and extracellular retention of inflammatory mediators may keep glial activation elevated and prolong disruption of synaptic, metabolic, and vascular stability.[72,139] Such mechanisms are particularly relevant in neurodegenerative disease and after injury when structural damage or metabolic disturbance persists.

Once molecular reinforcement persists, inflammatory mediator exposure, synaptic instability, extracellular dysregulation, and progressive tissue dysfunction can become coupled features of the same glial state.[7,24,72] This coupling distinguishes persistent inflammation from a transient response that is simply slow to resolve.

6.4. Tumor-associated remodeling

In glioblastoma, glial molecular programs are reshaped by a tumor environment enriched in cytokines, altered metabolites, extracellular vesicles, and matrix-associated cues. Under these conditions, microglial and astrocytic responses are redirected away from homeostatic support or repair-related functions and toward activities that help sustain the tumor niche. This includes changes in immune communication, extracellular structure, and local metabolic conditions that differ from those seen in classical injury or degeneration.[140,141]

One major feature of this stage is local immune suppression. Glial cells within glioblastoma-associated tissue have been linked to signaling states that weaken effective anti-tumor surveillance, alter cytokine balance, and reduce conditions favorable for productive immune clearance.[28,79,124] Rather than simply amplifying inflammation, glial signaling in this context may help maintain an immune environment permissive to continued tumor survival.

Extracellular remodeling is also central. Microglia and astrocytes influence matrix composition, adhesion-related signaling, and distribution of growth- and inflammation-related molecules within the tumor microenvironment.[97,142] These changes may support tumor cell movement, local invasion, and persistence of signaling gradients that favor niche stability. In parallel, metabolic adaptation becomes important because glial cells may alter local metabolite availability, signaling exchange, and support functions in ways that help glioblastoma cells persist under stressful microenvironmental conditions.[97,143]

Tumor-associated remodeling is therefore distinguished by sustained coupling of immune-regulatory, extracellular matrix, and metabolic programs to tumor niche maintenance.[124,140,142] The relationships among homeostatic, repair-associated, persistent inflammatory, and tumor-associated glial configurations, along with their disease-specific trajectories, are summarized in Figure 3.

7. Disease-specific perspectives

Related glial regulatory systems recur across neurodegenerative diseases, ischemic injury, and glioblastoma, but the molecular configurations in which they operate differ substantially. Neurodegenerative disorders are shaped by disease-specific proteinopathies, chronic neuronal stress, regional vulnerability, and progressive circuit dysfunction; stroke is dominated by abrupt metabolic and vascular disruption followed by temporally ordered inflammatory and reparative responses; and glioblastoma exposes glial cells to sustained tumor-derived signals that reshape immune communication, extracellular matrix organization, and metabolic support.[12,72,144] These differences alter which receptors are engaged, which intracellular pathways are sustained, how microglia and astrocytes interact, and whether shared molecular modules support clearance, persistence, tissue repair, or pathological niche maintenance.

7.1. Disease-specific glial configurations in neurodegeneration

Neurodegenerative diseases share prolonged glial exposure to neuronal stress and progressive tissue dysfunction, but the upstream signals and dominant regulatory interactions are not equivalent across disorders. Protein species, anatomical vulnerability, neuronal populations, and disease tempo differ substantially, producing distinct glial configurations despite overlap in inflammatory, metabolic,

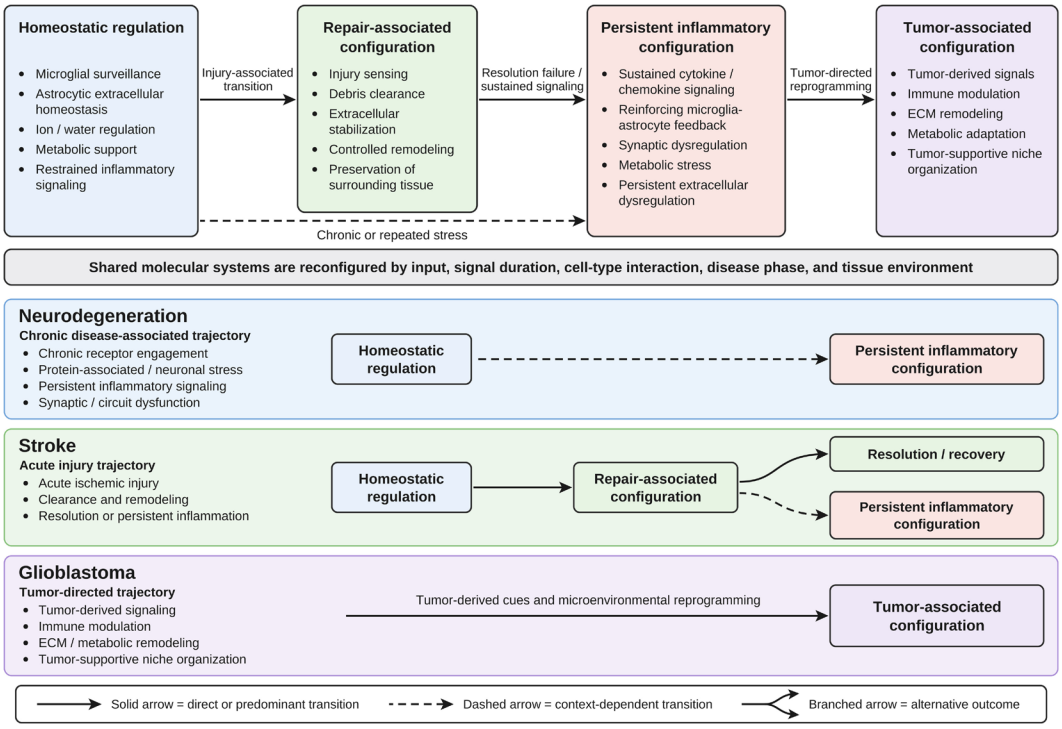


Figure 3. Network reconfiguration across glial disease states. Glial regulatory systems can adopt homeostatic, repair-associated, persistent inflammatory, or tumor-associated configurations depending on the initiating input, signal duration, cell-type interactions, disease phase, and tissue environment. Neurodegeneration, stroke, and glioblastoma follow distinct trajectories through or toward these configurations rather than a fixed universal sequence. Solid arrows indicate direct or predominant transitions, dashed arrows indicate context-dependent transitions, and branched arrows indicate alternative outcomes.
Abbreviation: ECM: Extracellular matrix.

and extracellular pathways.[15,38,66] Alzheimer's disease and Parkinson's disease illustrate this distinction particularly clearly.

7.1.1. Alzheimer's disease

In Alzheimer's disease, glial regulation develops within a tissue environment dominated by amyloid-β deposition, tau-associated pathology, synaptic dysfunction, and progressive neuronal stress. Microglia accumulate around amyloid plaques and adopt disease-associated transcriptional and proteomic states that differ from homeostatic surveillance programs, while astrocytes show region- and stage-dependent changes in inflammatory signaling, extracellular regulation, and interactions with plaque-associated microglia.[4,99,145]

Several receptor and signaling systems are especially relevant in this setting. Microglial responses to amyloid-associated stress involve disease-associated receptor programs, TGF-β-related regulation, interferon-responsive signaling, and inflammatory transcriptional pathways, while astrocytic responses include changes in cytokine signaling and NF-κB-associated programs.[24,40,41] Spatial studies further indicate that microglia and astrocytes form coordinated molecular niches around amyloid plaques rather than responding independently, demonstrating that local glial crosstalk is shaped directly by the distribution of disease pathology.

The biological consequences of these interactions are not uniformly detrimental. Microglial recognition and phagocytic programs may contribute to containment or clearance of extracellular material, whereas persistent inflammatory signaling, altered complement-associated interactions, and prolonged astrocytic dysfunction can become associated with synaptic disturbance and loss of extracellular homeostasis. Alzheimer's disease therefore illustrates a chronic network configuration in which protein

aggregation, local glial crosstalk, receptor remodeling, and progressive circuit dysfunction evolve together rather than as a single inflammatory process.

Evidence across Alzheimer's disease also differs in what it can establish mechanistically. Human single-cell, spatial, and multimodal studies provide strong evidence that microglial and astrocytic states vary with anatomical location and pathological burden, but these datasets are primarily observational and do not by themselves establish whether a given glial state promotes, restrains, or follows local pathology.[4,99,145] Mechanistic studies of specific receptors and signaling pathways provide stronger evidence for causal relationships, but their effects may depend on experimental model, disease stage, and the molecular pathology being reproduced.[24,40,41] Convergence between human molecular mapping and pathway-directed experiments is therefore more informative than either evidence type alone.

7.1.2. Parkinson's disease

Parkinson's disease presents a different glial environment, shaped by α-synuclein accumulation, dopaminergic neuronal stress, mitochondrial dysfunction, and regional vulnerability within the nigrostriatal system.[1] These features provide a distinct set of upstream signals from those dominant in Alzheimer's disease, even though both disorders engage inflammatory transcriptional programs, metabolic stress pathways, and microglia–astrocyte communication.

Experimental models of α-synuclein-associated pathology indicate that microglia participate in inflammatory signaling, extracellular remodeling, and interactions with degenerating neural tissue. In an α-synuclein overexpression model, microglial depletion altered both neurodegeneration and extracellular matrix remodeling, supporting the view that microglial contributions extend beyond cytokine production to structural regulation of the disease environment.[128] Astrocytic responses are less completely defined in this literature but may include altered metabolic support, inflammatory signaling, and extracellular regulation in regions exposed to persistent neuronal stress.

The Parkinson's disease configuration therefore differs from the Alzheimer's disease configuration not simply in the initiating protein species, but in the anatomical substrate, neuronal population under stress, and relative contribution of metabolic and extracellular remodeling pathways. The mechanistic evidence discussed here is also weighted more heavily toward experimental α-synuclein models than on direct molecular characterization of human glial states. Similar inflammatory modules may therefore occur in both disorders while differing in causal importance, regional distribution, and evidentiary strength.

7.1.3. Shared and divergent features across neurodegenerative disorders

Alzheimer's disease and Parkinson's disease share several broad glial regulatory modules, including inflammatory transcriptional signaling, cytokine and chemokine exchange, metabolic stress responses, extracellular remodeling, and prolonged microglia–astrocyte communication. Their molecular meaning differs, however, because these modules are engaged by different proteinopathies, operate within different anatomical and cellular environments, and evolve alongside distinct patterns of neuronal vulnerability.

In Alzheimer's disease, plaque- and tau-associated tissue niches provide substantial spatial and molecular evidence for coordinated glial responses linked to synaptic and extracellular pathology. In Parkinson's disease, α-synuclein-associated models support a role for microglia in inflammatory and extracellular remodeling, but the relative contribution of comparable astrocytic and microglial configurations in human disease is less completely resolved.[1] The strongest cross-disease conclusion is therefore not that the same glial pathways play equivalent roles, but that recurrent molecular modules are embedded within different pathological substrates and supported by evidence of unequal mechanistic depth. Treating "neurodegeneration" as a single inflammatory state would obscure both these biological differences and these differences in evidentiary strength.

7.2. Stroke and ischemic injury

Stroke produces an abrupt molecular transition driven by loss of oxygen and nutrient delivery, metabolic failure, cellular injury, ionic disturbance, vascular disruption, and release of damage-associated signals.[144,146-148] Unlike chronic neurodegeneration, these initiating events are temporally concentrated, allowing the sequence from early danger sensing to clearance, remodeling, and either resolution or persistent dysfunction to be distinguished more clearly.

During the acute phase, extracellular ATP, damage-associated molecules, hypoxia-related stress, and vascular breakdown engage microglial sensing pathways and alter astrocytic ion, water, and barrier regulation.[92,146,148] Microglial migration, inflammatory mediator production, and early phagocytic activity occur alongside astrocytic changes in extracellular homeostasis and neurovascular

signaling. The functional effect of these responses depends strongly on timing and intensity rather than on the presence of inflammatory signaling alone.

As injury evolves, the molecular balance shifts toward debris clearance and tissue reorganization. Microglial phagocytosis reduces cellular debris and ongoing danger signaling, while astrocytic regulation of neurotransmitters, ions, water, and extracellular structure contributes to stabilization of the peri-injury environment.[9,92,149,150] Matrix remodeling and intercellular signaling become increasingly important as injured tissue transitions from acute containment toward structural and functional reorganization.

Later outcomes depend on whether vascular, metabolic, and inflammatory disturbances contract or remain active. Resolution is associated with declining danger signaling and restoration of extracellular regulation, whereas persistent vascular dysfunction, tissue stress, and reciprocal glial signaling can maintain inflammatory activity beyond the acute phase.[151,152]

Interpretation of these phase-dependent effects requires particular attention to experimental timing. A pathway associated with injury amplification during the hyperacute period may participate in clearance or remodeling later, so studies performed at different post-ischemic intervals can reach apparently different conclusions without necessarily contradicting one another.[146,151,152] Likewise, interventions that reduce an early inflammatory readout do not automatically establish improved long-term tissue recovery. In stroke, temporal resolution is therefore part of the mechanism itself: molecular effects should be interpreted together with the phase at which they are measured and the functional endpoint used.

7.3. Glioblastoma

Glioblastoma exposes microglia and astrocytes to sustained tumor-derived cytokines, growth-related factors, extracellular vesicles, altered metabolites, and matrix-associated signals.[12,27] These inputs reconfigure receptor signaling, inflammatory communication, metabolic exchange, and extracellular matrix regulation, producing glial states that differ fundamentally from acute injury responses.

Tumor-associated microglia and astrocytes participate in immune modulation through altered cytokine and receptor signaling, changes in immune-cell recruitment, and interactions that can reduce effective anti-tumor surveillance.[28,29,121,153] In this setting, glial signaling is reorganized within a tumor-controlled microenvironment rather than simply intensified as generalized inflammation.

Extracellular matrix and metabolic remodeling add further layers to tumor–glia interaction. Glial regulation of adhesion, matrix composition, signaling molecule distribution, and metabolite availability can create spatial conditions that support glioblastoma cell movement, invasion, and adaptation.[12,122,153,154] These processes link inflammatory signaling to structural and metabolic niche maintenance rather than to repair.

Continuous tumor-derived input therefore couples glial immune, extracellular, and metabolic programs to maintenance of spatially organized tumor niches.

Evidence for these interactions also spans different levels of inference. Spatial and tissue-mapping studies establish that glial, immune, metabolic, and extracellular programs are organized within distinct glioblastoma niches, whereas perturbation-based studies are required to determine whether individual glial signals are necessary for tumor maintenance or invasion.[153-155] Interpretation is further complicated by the overlap between resident microglia and infiltrating macrophage populations within glioblastoma, which can share molecular programs while differing in origin and potentially in function.[153] Thus, association with a tumor-supportive niche should not be interpreted automatically as proof that a specific glial pathway independently drives tumor progression.

Comparison across Alzheimer's disease, Parkinson's disease, stroke, and glioblastoma shows that shared glial pathways are reused within fundamentally different pathological configurations. Alzheimer's disease emphasizes plaque- and tau-associated glial niches and progressive synaptic dysfunction; Parkinson's disease combines α-synuclein-associated stress with selective neuronal vulnerability and metabolic disturbance; stroke is defined by rapid temporal transitions from acute injury signaling to clearance and remodeling; and glioblastoma continuously redirects glial programs through tumor-derived immune, metabolic, and extracellular cues. The principal distinction among these conditions is therefore not whether inflammatory, purinergic, cytokine, metabolic, or extracellular pathways are present, but how they are configured, sustained, and coupled to disease-specific tissue states. These shared and disease-specific molecular configurations are compared in Table 2.

Table 2. Disease-specific glial molecular configurations across Alzheimer's disease, Parkinson's disease, stroke, and glioblastoma

Disease/context	Dominant initiating signals	Major glial molecular configuration	Distinctive microglia–astrocyte interactions	Temporal/spatial feature	Major tissue consequence	Evidence basis/major limitation	References
Alzheimer's disease	Amyloid-β deposition, tau-associated pathology, synaptic stress, progressive neuronal dysfunction	Disease-associated microglial states; astrocytic inflammatory and extracellular-regulatory programs; TGF-β-, interferon-, cytokine-, and NF-κB-associated signaling	Coordinated microglial and astrocytic responses around plaque-associated tissue niches; phagocytic, inflammatory, complement-related, and extracellular-regulatory interactions	Chronic and spatially heterogeneous; glial states vary with anatomical region and pathological burden	Synaptic disturbance, altered extracellular homeostasis, persistent inflammatory signaling, progressive circuit dysfunction	Strong human single-cell, multi-region, and astrocyte transcriptomic evidence; mechanistic direction remains partly model-dependent	4,24,99,145
Parkinson's disease	α-Synuclein accumulation, dopaminergic neuronal stress, mitochondrial/metabolic dysfunction, nigrostriatal vulnerability	Persistent microglial inflammatory signaling coupled to extracellular matrix remodeling and neuronal–glial stress responses; astrocytic contributions are less completely resolved	Microglial responses to degenerating dopaminergic tissue and α-synuclein-associated stress; probable astrocytic metabolic and extracellular support/remodeling interactions	Chronic and regionally selective, centered on vulnerable nigrostriatal circuitry	Dopaminergic neurodegeneration, inflammatory persistence, extracellular matrix remodeling, motor dysfunction	Causal evidence is weighted toward experimental α-synuclein models; direct human glial mechanistic evidence is less developed	1,128
Stroke/ischemic injury	Abrupt hypoxia, nutrient deprivation, ionic disturbance, ATP release, DAMPs, vascular disruption, metabolic failure	Early microglial sensing and cytokine production followed by phagocytic clearance; astrocytic ion/water, metabolic, barrier, and extracellular-remodeling responses	Dynamic microglia–astrocyte–vascular communication; early inflammatory signaling can transition toward debris clearance and tissue reorganization	Strongly time-dependent: hyperacute sensing → acute inflammation → clearance/remodeling → resolution or persistent dysfunction	Injury containment, debris removal, edema/extracellular disturbance, repair-associated reorganization or chronic post-ischemic inflammation	Extensive experimental and mechanistic literature; conclusions depend strongly on sampling time and endpoint	144,146,149,151
Glioblastoma	Tumor-derived cytokines, extracellular vesicles, metabolites, ATP, hypoxia, growth-related and matrix-associated cues	Tumor-directed immune signaling, myeloid reprogramming, astrocytic niche support, extracellular matrix remodeling, metabolic adaptation	Reciprocal signaling among tumor cells, microglia/macrophages, and astrocytes; EV/PD-L1 signaling, ATP-dependent interactions, immune suppression, and niche remodeling	Spatially organized and continuously reinforced by distinct tumor niches	Reduced anti-tumor surveillance, invasion, immune suppression, metabolic support, and maintenance of tumor-associated niches	Strong human spatial and tissue-mapping evidence plus experimental interaction studies; resident microglia and infiltrating macrophages can be difficult to distinguish functionally	12,28,153-155

Abbreviations: ATP: Adenosine triphosphate; DAMPs: Damage-associated molecular patterns; EV: Extracellular vesicle; NF-κB: Nuclear factor kappa B; PD-L1: Programmed death-ligand 1; TGF-β: Transforming growth factor beta.

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8. Transcriptomic, proteomic, and biomarker implications

Transcriptomic and proteomic profiling resolves glial heterogeneity at a level that broad labels such as "activated" or "reactive" cannot capture. Across homeostatic, repair-associated, persistent inflammatory, and tumor-associated settings, these approaches distinguish signaling programs that are transient, sustained, regionally restricted, or redirected by the local microenvironment.[1,155,156]

These datasets also resolve measurable combinations of inflammatory mediators, receptor systems, transport-related changes, metabolic pathways, and extracellular matrix programs across neurodegeneration, stroke, and glioblastoma.[1,155] Their interpretation remains constrained by timing, tissue context, cellular composition, and analytical method; an omics signature alone does not define a fixed biological state.

8.1. Molecular heterogeneity revealed by modern profiling

One of the clearest contributions of modern profiling is the demonstration that glial populations are molecularly heterogeneous in ways that complicate simple labels such as "activated microglia" or "reactive astrocytes".[1,156] Transcriptomic studies have shown that glial cells within the same broad population may differ in inflammatory mediator expression, receptor signaling, metabolic programs, transporter regulation, extracellular matrix-associated pathways, and stress-responsive gene expression. This heterogeneity indicates that broad glial categories can conceal molecular states that differ by disease setting, anatomical location, and stage.

Proteomic profiling adds an important layer because many biologically relevant differences in glial behavior are expressed at the level of protein abundance, localization, secretion, and modification.[156] This is particularly important for pathways emphasized throughout this review, including cytokine output, receptor-mediated communication, purinergic signaling, transporter activity, and extracellular matrix remodeling, all of which depend on protein-level regulation as well as transcript abundance. Proteomic data therefore help distinguish transcriptional potential from molecular output, but neither transcript abundance nor protein abundance alone establishes pathway activity or functional consequence. Protein localization, post-translational modification, secretion, receptor availability, and interaction with other signaling components can all alter biological output without corresponding directly to transcript levels.[156]

State-associated variation is especially important. Modern profiling suggests that glial populations may contain subgroups enriched for surveillance-related programs, phagocytic and debris-processing functions, cytokine-rich inflammatory signaling, altered metabolic regulation, extracellular remodeling, or tumor-associated immune-modulatory activity.[1,155] This variation helps explain why glial responses differ not only between diseases, but within the same disease as tissue conditions shift from early disturbance to prolonged dysfunction or tumor-associated adaptation.

Regional and temporal differences further reinforce this point. Glial signatures may vary between lesion core and peri-lesional regions, between gray and white matter, between vascularly compromised and more preserved tissue, or between tumor-associated and non-tumor tissue. They may also differ substantially between early injury phases, later persistent inflammatory states, and disease conditions marked by chronic receptor engagement or extracellular remodeling.[1,155,156] Regional and temporal heterogeneity is therefore a biological property of glial states rather than merely a source of analytical variability.

8.2. Disease-stage molecular signatures

A major implication of these profiling approaches is that different disease stages may be associated with distinguishable molecular patterns in glial populations. In repair-associated settings, these patterns may include increased expression of molecules involved in phagocytic clearance, lysosomal processing, extracellular stabilization, transporter-mediated restoration of local homeostasis, and signaling systems associated with tissue reorganization.[13,157] These profiles differ from early danger-sensing responses because they are more closely tied to removing damaged material, restoring extracellular balance, and locally containing injury.

In persistent inflammatory states, molecular signatures may instead show sustained cytokine and chemokine expression, continued engagement of inflammatory receptor pathways, altered transporter and channel regulation, metabolic stress programs, and extracellular conditions associated with prolonged activation of both microglia and astrocytes.[13,157] These features are particularly relevant to chronic neurodegeneration and to post-injury tissue that fails to return to homeostasis, where inflammatory signaling remains biologically active well beyond the initial insult.

In glioblastoma, glial molecular signatures may show a different combination of features. These can include altered immune-regulatory signaling, extracellular matrix-related programs, receptor systems linked to tumor–glia communication, and metabolic changes associated with adaptation to the tumor niche.[155] These patterns are important because they suggest that tumor-associated glial

states are not simply prolonged inflammatory versions of injury responses, but disease-specific molecular configurations shaped by continuous interaction with the tumor microenvironment.

No single marker is likely to capture repair, persistent inflammation, or tumor-associated remodeling. More informative signatures will combine transcripts and proteins related to clearance, inflammatory reinforcement, extracellular organization, metabolic adaptation, and local signaling exchange, with interpretation anchored to disease stage and tissue context.[13,155,157]

8.3. Biomarker candidates across sample types and validation levels

Glial biomarker interpretation depends not only on the molecular candidate but also on the biological compartment in which it is measured. Tissue-based molecular signatures provide the most direct spatial association with glial cell states, whereas cerebrospinal fluid (CSF) proteins offer a less direct reflection of central nervous system activity but can be measured in living individuals. Blood-based biomarkers are more accessible but generally have lower anatomical and cellular specificity. These differences make biomarker performance dependent on sample source, disease stage, and the biological process represented rather than on marker identity alone.

Tissue and spatial profiling provide the greatest resolution for linking candidate molecular signatures to specific glial populations and pathological niches. In Alzheimer's disease, single-cell and spatial studies distinguish plaque-associated microglial and astrocytic programs from glial populations in less affected regions, while spatial profiling in glioblastoma resolves immune, metabolic, and extracellular matrix-associated programs across anatomically distinct tumor niches.[1,14,99,145,155] These signatures are biologically informative because cellular identity and local pathology can be examined directly, but their use as routine clinical biomarkers is limited by tissue accessibility, sampling bias, and the inability of most tissue studies to support longitudinal monitoring.

Cerebrospinal fluid provides stronger evidence for measurable glial biomarker candidates in living patients. In Alzheimer's disease, glial fibrillary acidic protein (GFAP) and soluble triggering receptor expressed on myeloid cells 2 (sTREM2) represent astrocyte- and microglia-associated candidates, respectively. In a study of 478 individuals, CSF GFAP was associated with presynaptic and postsynaptic dysfunction, whereas associations between CSF sTREM2 and synaptic markers varied according to amyloid status and clinical stage; these relationships were examined across independent Translational Biomarkers in Aging and Dementia and Alzheimer's Disease Neuroimaging Initiative cohorts.[158] Larger proteomic studies further support multicomponent approaches. Multi-cohort CSF proteomics identified more than 2,000 Alzheimer-associated proteins and produced a validated 10-protein model with high discrimination of biomarker and clinical status across the Alzheimer continuum.[159] A separate analysis of 834 individuals identified 109 dysregulated microglia-related CSF proteins and an 18-protein panel that differed between preclinical and dementia-stage Alzheimer's disease.[160] These findings provide substantially stronger validation than an isolated expression association, but the panels remain disease- and cohort-dependent rather than universal indicators of glial activation.

Blood-based measurements offer a different balance between accessibility and biological specificity. Plasma GFAP is the most developed astrocyte-associated candidate in Alzheimer's disease and has shown elevation across the disease continuum, while blood YKL-40 has also been associated with Alzheimer-related clinical stage. A systematic review and meta-analysis of 36 studies involving 3,366 individuals across the Alzheimer continuum and 4,115 cognitively unimpaired participants found significantly higher blood GFAP and YKL-40 levels in Alzheimer's disease, with both increasing at more advanced clinical stages [161]. However, these proteins are not specific to Alzheimer's disease or to a single glial state, and their concentrations can reflect broader neurological or inflammatory processes. Their principal advantage is accessibility for repeated measurement, whereas disease specificity, assay standardization, and interpretation alongside established pathology markers remain important limitations.

These candidates illustrate why biomarker interpretation should incorporate both biological source and validation level. Tissue signatures provide high cellular and spatial resolution but limited accessibility; CSF GFAP, sTREM2, and multiprotein panels provide direct central nervous system-associated measurements with increasing cohort-level validation; and blood GFAP or YKL-40 offer substantially greater accessibility but lower disease and cellular specificity. Composite signatures may improve discrimination by combining information from several molecular processes, but increased statistical performance does not by itself establish that a panel represents a discrete glial state. The strongest biomarker evidence therefore combines reproducibility across independent cohorts with defined sample type, disease stage, molecular interpretation, and an explicit account of competing biological sources.

Representative glial-associated biomarker candidates and molecular signatures across tissue, CSF, and blood are compared in Table 3.

Table 3. Glial-associated biomarker candidates and molecular signatures across tissue, cerebrospinal fluid, and blood

Candidate/ signature	Glial association	Disease/ context	Sample type	Biological interpretation	Validation evidence	Specificity/major limitation	References
Alzheimer's disease tissue/ spatial glial signatures	Microglial and astrocytic transcriptional states	Alzheimer's disease	Postmortem brain tissue; single-cell/ single-nucleus and multi-region profiling	Resolves region- and pathology-associated microglial and astrocytic states and their relationship to disease burden	Large human multi-region and astrocyte-focused transcriptomic datasets	High cellular/spatial resolution but invasive tissue source; mainly observational and unsuitable for routine longitudinal monitoring	99,145
Glioblastoma spatial glial signatures	Myeloid, astrocytic, immune, metabolic, and extracellular niche programs	Glioblastoma	Resected human tumor tissue; spatial/multimodal profiling	Identifies anatomically organized tumor–glia niches and spatially distinct immune/ metabolic programs	Human spatial atlases and tissue-mapping studies	Strong spatial resolution but limited clinical accessibility; association with a niche does not establish causal pathway function	14,155
CSF GFAP	Astrocyte-associated	Aging and Alzheimer's disease	CSF	Reflects astrocytic reactivity; associated with presynaptic and postsynaptic dysfunction	Evaluated across 478 individuals in TRIAD and ADNI cohorts	Not specific to Alzheimer's disease or to one astrocytic state; interpretation depends on disease stage and coexisting pathology	158
CSF sTREM2	Microglia-associated	Aging and Alzheimer's disease	CSF	Reflects microglial TREM2-associated activity; relationships with synaptic markers vary with amyloid status and clinical stage	Evaluated in the same multi-cohort study of 478 individuals	Stage- and amyloid-dependent; does not represent a single uniform microglial state	158
10-protein CSF proteomic model	Multicellular / glial-containing proteomic signature	Alzheimer's disease continuum	CSF	Composite protein signature associated with AD biomarker and clinical status and progression toward symptomatic disease	Multi-cohort CSF proteomics; >2,000 AD-associated proteins identified; 10-protein model validated across cohorts	Composite signal is not glia-specific and requires external clinical validation before routine use	159
18-protein microglia-associated CSF panel	Microglia-associated	Preclinical and dementia-stage Alzheimer's disease	CSF	Captures changes in microglia-related proteins across clinical disease stages	834 individuals; 109 dysregulated microglia-related proteins identified; 18-protein classifier derived across stages	Protein profiles do not map uniquely onto discrete transcriptomic microglial states; stage and cohort dependence remain	160
Blood GFAP	Astrocyte-associated	Alzheimer's disease continuum	Plasma/blood	Accessible marker associated with astrocytic reactivity and increasing clinical disease stage	Systematic review/meta-analysis of 36 studies, including 3,366 participants across the AD continuum and 4,115 cognitively unimpaired individuals	Greater accessibility but lower CNS, disease, and cell-state specificity than tissue or CSF measurements	161
Blood YKL-40 (CHI3L1)	Astrocyte-associated inflammatory marker	Alzheimer's disease continuum	Plasma/blood	Associated with astrocytic/ inflammatory activity and clinical disease stage	Same systematic review/ meta-analysis; significantly elevated across the AD continuum	Not specific to Alzheimer's disease or astrocytes alone; may reflect broader inflammatory processes	161

Abbreviations: AD: Alzheimer's disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; CHI3L1: Chitinase-3-like protein 1; CNS: Central nervous system; CSF: Cerebrospinal fluid; GFAP: Glial fibrillary acidic protein; TRIAD: Translational Biomarkers in Aging and Dementia; sTREM2: Soluble triggering receptor expressed on myeloid cells 2.

8.4. Limits and challenges

Despite their value, transcriptomic and proteomic approaches have important limitations. One major challenge is inferring cell state from molecular data alone. Glial signatures often reflect mixtures of signaling pathways, transitional conditions, and local environmental inputs rather than discrete, stable categories.[1,162] This is particularly relevant in neuroinflammation, where responses may shift gradually and overlap across repair, persistence, and remodeling.

Overlap across disease contexts is another challenge. Cytokine-rich signaling, metabolic stress, receptor-mediated activation, and extracellular remodeling appear in neurodegeneration, stroke, and glioblastoma, but with different temporal organization and pathological meaning. Distinguishing shared inflammatory logic from disease-specific molecular patterns therefore requires careful attention to region, stage, and microenvironment.[1,155]

Technical and biological variability also complicate interpretation. Differences in tissue source, sampling strategy, bulk versus single-cell methods, computational analysis, patient heterogeneity, and disease timing can all alter the signatures observed.[1,162] Even well-supported glial patterns may therefore vary across studies, making replication and standardization essential.

Cross-study comparison is further limited by differences in biological system. Findings derived from mouse injury models, xenografted human cells, cultured glia, resected tumor tissue, postmortem brain, CSF, and peripheral samples interrogate different levels of the same biology and should not be treated as interchangeable. Experimental systems permit stronger causal perturbation but simplify the cellular and temporal complexity of human disease, whereas human tissue provides direct disease relevance but is often observational and constrained by sampling stage. Agreement across these complementary approaches provides stronger evidence than replication within a single model type alone.

Clinical translation requires validation that preserves biological context. Molecular profiles can generate candidate biomarkers or therapeutic targets, but a signature should not be mapped directly onto a clinical category until its reproducibility, cellular source, disease stage, and relationship to functional biology have been established.[1,155,162]

9. Translational considerations

Therapeutic manipulation of glial gene–protein networks depends on matching a defined molecular intervention to the glial population and disease configuration in which that target is functionally active. Current evidence includes interventions at inflammasome, transporter, transcriptional, cellular, and tumor-microenvironmental nodes, allowing therapeutic principles to be evaluated against measurable molecular and disease outcomes rather than inferred from pathway association alone.

9.1. Evidence from specific molecular interventions

NLR family pyrin domain containing 3 inhibition provides one of the clearest examples of pathway-directed glial intervention in neurodegenerative disease. In an experimental model incorporating amyloid- and tau-associated pathology, post-symptomatic inhibition of NLRP3 improved cognitive performance and reduced measures of neurodegeneration.[56] This intervention links a defined inflammasome pathway to a functional outcome after pathology is established, providing stronger causal evidence than expression of inflammasome-associated genes alone. Its interpretation remains model-specific, however, because NLRP3 activity can arise from different cellular and molecular inputs across neurological diseases and should not be treated as a universal marker or target of glial pathology.

Aquaporin 4 (AQP4) manipulation tests a distinct therapeutic axis centered on astrocytic water handling. Experimental AQP4 knockdown in astrocytes exposed to oxygen-glucose deprivation was associated with neuroprotective effects, demonstrating that modulation of a water-transport system can alter injury-related cellular responses rather than merely serving as a marker of astrocytic reactivity.[62] Related experimental work involving AQP4 and transient receptor potential cation channel subfamily V member 4 further indicates that channel composition influences astrocyte swelling and volume recovery under ischemia-mimicking conditions.[59] These findings support transporter and channel systems as mechanistically tractable targets in ischemic stress, but they also illustrate why intervention cannot be reduced to simple enhancement or suppression of AQP4: localization, injury phase, osmotic conditions, and interacting channel systems influence the resulting phenotype.

Microglial depletion tests a broader cellular intervention rather than a single molecular node. In an α-synuclein overexpression model of Parkinson's disease, microglial depletion reduced neurodegeneration and altered extracellular matrix remodeling.[128] The result supports a causal contribution of microglia to both neuronal injury and structural remodeling within that model, extending the therapeutic question beyond inflammatory mediator production alone. At the same time, depletion removes surveillance, clearance, signaling, and remodeling

functions simultaneously and therefore does not identify which microglial program should be targeted selectively in human disease. The study is consequently more informative as evidence of causal microglial involvement than as a direct therapeutic blueprint.

The spinal cord injury evidence also shows why STAT3 cannot be assigned a single therapeutic direction. In spinal cord injury, regulatory T-cell-associated IL-10/STAT3/protein kinase C/vimentin signaling attenuated astrogliosis and was associated with improved neurological recovery.[35] This finding supports the capacity of STAT3-linked signaling to participate in repair-associated astrocytic remodeling under defined injury conditions, rather than establishing STAT3 inhibition as a generally desirable strategy. Therapeutic interpretation must therefore distinguish whether a pathway maintains pathological signaling or participates in a compensatory or restorative program at the time of intervention.

9.2. Disease-stage timing

Therapeutic timing changes the meaning of pathway modulation because the function of a glial program can change during disease progression. The post-symptomatic NLRP3 study is informative in this respect because pathway inhibition was applied after amyloid- and tau-related pathology was established rather than only before disease development.[56] It therefore provides evidence that at least within that experimental setting, sustained inflammasome activity remained therapeutically modifiable after symptom-related pathology had emerged.

Timing is particularly complex after ischemic injury. Early microglial sensing and phagocytosis participate in the localization of injury and debris clearance, while astrocytic transporter, channel, vascular, and extracellular responses contribute to the stabilization of damaged tissue.[9,92] Later persistence of inflammatory and metabolic disturbance may create a different therapeutic target. An intervention that suppresses an early sensing or clearance mechanism could therefore have a different effect than inhibiting the same pathway after inflammatory reinforcement has become established.

Outside acute injury, therapeutic windows are less discretely defined because compensatory and pathological programs may coexist in chronic neurodegeneration, while continuous tumor signaling can repeatedly re-establish targetable states in glioblastoma.

9.3. Microenvironment-directed strategies

Glioblastoma provides a setting in which treatment can modify pathological cell–cell communication as well as tumor cells themselves. Glioblastoma-derived extracellular vesicles have been shown to alter programmed death-ligand 1 expression in accessory macrophages after radiotherapy, demonstrating that treatment can reshape tumor–myeloid signaling within the microenvironment.[28]

The radiotherapy–extracellular vesicle result shows that treatment can alter the signaling niche as well as the tumor-cell compartment. Interventions directed at extracellular matrix organization, macrophage or microglial immune signaling, or tumor-induced checkpoint pathways may alter the niche in which glial and immune cells operate.[29,63,78,79] Their effects are likely to depend on the cellular composition and anatomical niche of the tumor, because resident microglia, infiltrating macrophages, astrocytes, and tumor cells can participate in overlapping but non-equivalent signaling programs.

Microenvironment-directed strategies therefore seek to interrupt specific tumor–glia or tumor–myeloid interactions that sustain immune suppression, matrix organization, or metabolic support rather than broadly suppressing glial activity.

9.4. Matching intervention to molecular state

Molecular profiling may become therapeutically useful when it identifies the pathway or glial configuration that an intervention is designed to modify. A marker of astrocytic injury, a microglial immune signature, or a multicomponent inflammatory panel is not itself a therapeutic indication; its value depends on whether it identifies a biological state in which the proposed target is active and causally relevant. The biomarker evidence discussed above therefore supports treatment selection only when molecular classification can be linked to a defined intervention mechanism.

Target selection should incorporate the molecular node, the glial population in which it is operating, the disease phase, and the surrounding tissue environment. NLRP3 inhibition, for example, is most informative when inflammasome-associated signaling contributes to the active pathological configuration; altering AQP4-related biology is meaningful only within the astrocytic and osmotic context in which that transport system functions; and tumor microenvironment intervention requires evidence that the targeted signaling interaction is sustaining a particular glioblastoma niche. Molecular stratification is therefore useful not because it labels glial activation, but because it can potentially connect a measurable state to a mechanistically matched intervention.

9.5. Current limitations

The principal translational limitation is the gap between mechanistic intervention in experimental systems and

selective treatment in human disease. NLRP3 inhibition, AQP4 manipulation, and microglial depletion can establish causal relationships within defined models, but each intervention acts within a specific pathological configuration and may affect multiple functions simultaneously. Evidence that an intervention changes a model phenotype therefore does not establish that the same target, modulation direction, dose, or timing will be beneficial in human disease.

Cellular specificity is a second limitation. Molecular targets such as STAT3, purinergic receptors, inflammasome components, transport systems, and cytokine pathways are not restricted to one stable glial state, and some are expressed across multiple neural or immune compartments. Therapeutic effects may therefore reflect changes in several interacting cell populations rather than selective correction of the intended glial program. This problem is particularly important in glioblastoma, where resident microglia and infiltrating macrophages can share molecular features while differing in origin and functional contribution.

Therapeutic specificity will therefore likely require matching a molecular target to the glial population, disease phase, and tissue configuration in which it is functionally important, while preserving necessary surveillance, clearance, metabolic, vascular, and tissue-support functions. Progress toward this goal will depend on convergence between causal perturbation studies, human molecular profiling, biomarker-defined states, and interventions tested within explicit biological windows. The progression from molecular profiling and biomarker interpretation to context-matched intervention, along with the principal constraints on translation, is summarized in Figure 4. Representative experimental interventions modifying glial molecular programs and their context-dependent outcomes are compared in Table 4.

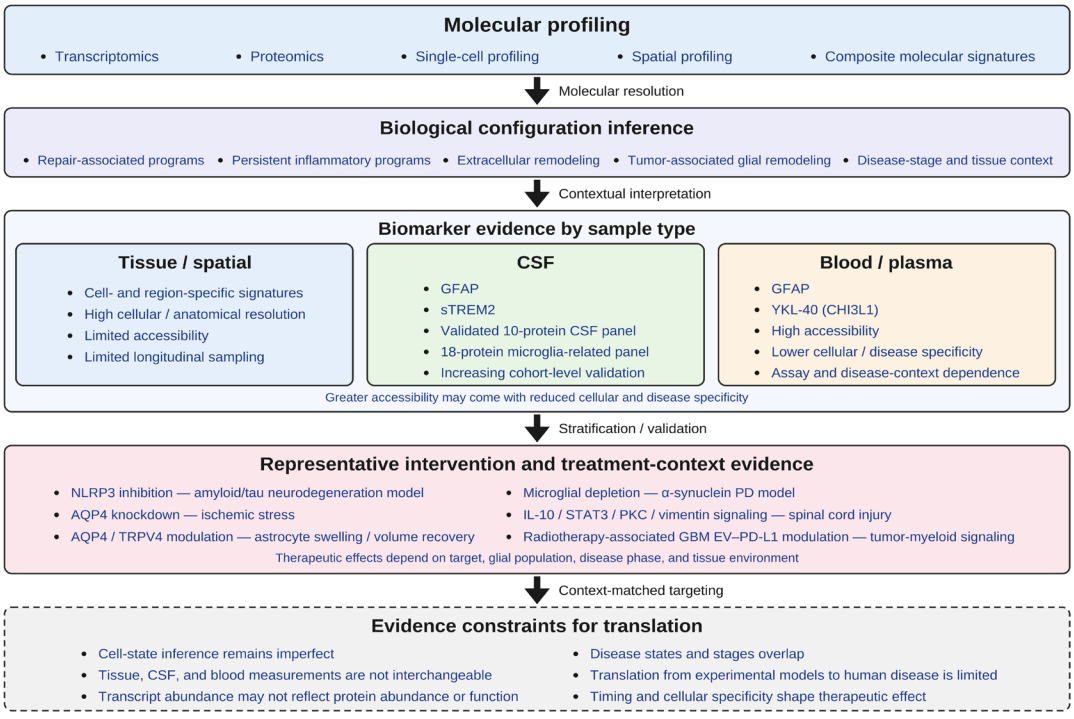


Figure 4. From molecular profiling to biomarker interpretation and targeted intervention. Transcriptomic, proteomic, single-cell, and spatial approaches provide molecular resolution for interpreting glial configurations across disease states. Biomarker evidence differs by sample type: tissue and spatial profiling provide high cellular resolution; CSF supports candidates such as GFAP and sTREM2 and validated multielement signatures; and blood or plasma offers greater accessibility but lower cellular and disease specificity. Representative intervention and treatment-context evidence illustrates how therapeutic effects depend on the molecular target, glial population, disease phase, and tissue environment, while translation remains constrained by cell-state inference, sample comparability, molecular-to-functional discordance, model-to-human differences, and treatment timing.
Abbreviations: AQP4: Aquaporin-4; CSF: Cerebrospinal fluid; EV: Extracellular vesicle; GBM: Glioblastoma; GFAP: Glial fibrillary acidic protein; IL-10: Interleukin-10; NLRP3: NLR family pyrin domain containing 3; PD: Parkinson's disease; PD-L1: Programmed death-ligand 1; PKC: Protein kinase C; sTREM2: Soluble triggering receptor expressed on myeloid cells 2; STAT3: Signal transducer and activator of transcription 3; TRPV4: Transient receptor potential cation channel subfamily V member 4.

Table 4. Experimental interventions modifying glial molecular programs across neurological disease contexts

Target/ molecular program	Specific intervention	Predominant cellular context	Disease/ experimental context	Mechanism examined	Observed outcome	Major limitation/context dependence	References
NLRP3 inflammasome	Post-symptomatic pharmacological NLRP3 inhibition	Predominantly microglia-centered inflammasome signaling	Experimental amyloid- and tau-associated neurodegeneration	Suppression of NLRP3-dependent inflammasome activity after pathology was established	Improved cognitive performance and reduced measures of amyloid/tau-associated neurodegeneration	Preclinical model; does not establish equivalent benefit across human AD or other diseases in which NLRP3 is engaged by different upstream signals	56
AQP4	Astrocytic AQP4 knockdown	Astrocytes	Oxygen-glucose deprivation model of ischemic stress	Reduction of AQP4-mediated water transport during injury-related osmotic stress	Neuroprotective effects and attenuation of injury-associated astrocytic responses	*In vitro*/experimental ischemia model; effects of AQP4 depend on localization, osmotic conditions, and injury phase	62
AQP4/TRPV4	Genetic deletion of AQP4, TRPV4, or both	Astrocytes	Ischemia-mimicking hypoosmotic, hyperkalemic, and oxygen-glucose deprivation conditions	Modification of astrocytic water permeability and volume-regulatory channel interactions	AQP4 deletion reduced swelling, whereas combined AQP4/TRPV4 deletion altered volume recovery	Genetic model addressing channel function rather than a directly translatable therapeutic regimen; outcome depends on the specific osmotic/injury condition	59
Microglial survival / CSF1R-dependent microglial population	PLX5622-mediated microglial depletion	Microglia	α-Synuclein-overexpression mouse model of Parkinson's disease	CSF1R-dependent depletion of microglia and disruption of microglial inflammatory/ remodeling contributions	Reduced neurodegeneration, preserved dopaminergic neurons, improved motor phenotype, and altered extracellular matrix remodeling	Broad depletion removes surveillance, clearance, signaling, and remodeling functions simultaneously; does not identify which microglial program should be selectively targeted in human PD	128
IL-10/STAT3/ PKC/vimentin axis	Regulatory T-cell/ IL-10-associated modulation of astrocytic STAT3/ PKC/vimentin signaling	Astrocytes within a T-cell–astrocyte regulatory interaction	Experimental spinal cord injury	IL-10-dependent STAT3/ PKC signaling regulates astrocytic vimentin expression and reactive remodeling	Reduced astrogliosis and CSPG deposition, enhanced axonal remodeling, and improved neurological recovery	Demonstrates a repair-associated STAT3 configuration rather than supporting universal STAT3 inhibition; specific to injury context and signaling direction	35
Glioblastoma EV–PD-L1 immune axis	Radiotherapy-associated modulation of glioblastoma-derived extracellular-vesicle signaling to macrophages	Tumor-associated macrophages / myeloid cells within the GBM microenvironment	Experimental glioblastoma under radiotherapy	Uptake of tumor-derived extracellular vesicles modifies macrophage PD-L1 and immune-suppressive signaling	Radiotherapy altered tumor–myeloid communication; GBM EV exposure increased macrophage PD-L1-associated immune-suppressive features	Mechanistic treatment-context evidence, not a validated glial-directed therapy; resident microglia and infiltrating macrophages are not functionally interchangeable	28

Abbreviations: AD: Alzheimer's disease; AQP4: Aquaporin 4; CSPG: Chondroitin sulfate proteoglycan; CSF1R: Colony-stimulating factor 1 receptor; EV: Extracellular vesicle; GBM: Glioblastoma; IL-10: Interleukin-10; NLRP3: NLR family pyrin domain containing 3; PD: Parkinson's disease; PD-L1: Programmed death-ligand 1; PKC: Protein kinase C; STAT3: Signal transducer and activator of transcription 3; TRPV4: Transient receptor potential cation channel subfamily v member 4.

10. Conclusion

Glial function cannot be inferred from molecular-node identity alone. NF-κB, STAT3, TGF-β, interferon-associated signaling, purinergic receptors, inflammasome pathways, and related regulatory systems acquire different functional significance according to the receptors and upstream inputs that engage them, their interacting molecular partners, signal duration, and the responding glial compartment. Microglia preferentially couple environmental sensing to migration, phagocytosis, and immune signaling, whereas astrocytes integrate inflammatory regulation with transporter, metabolic, vascular, and extracellular matrix systems. Reciprocal signaling between these populations can restrain, amplify, or redirect both programs.

Disease-specific organization further modifies these molecular outputs. Alzheimer's disease and Parkinson's disease impose chronic but distinct neurodegenerative substrates; stroke produces a rapidly evolving sequence of metabolic failure, inflammatory signaling, clearance, and remodeling; and glioblastoma reorganizes glial programs within an immune-regulatory, metabolic, and extracellular niche. The recurrence of a pathway across these conditions therefore does not imply equivalent function, causal importance, or therapeutic relevance.

Molecular measurement is subject to the same principle. Tissue and spatial profiling provide greater cellular and anatomical resolution, whereas CSF and blood biomarkers offer greater accessibility with lower cellular and disease specificity. Composite signatures may improve discrimination, but their biological interpretation depends on source, disease stage, and validation across independent cohorts. Intervention studies similarly show that NLRP3 inhibition, astrocytic water-channel manipulation, microglial depletion, STAT3-associated modulation, and targeting of glioblastoma microenvironmental interactions have meaning only within the cellular and disease configurations in which they were tested.

Therapeutic precision therefore depends on identifying the molecular target, the glial population in which it operates, the upstream signals engaging it, the network partners modifying its output, and the disease phase in which that configuration is functionally important. Molecular heterogeneity is thus not merely a descriptive feature of neuroinflammation; it is a mechanistic property that influences disease comparison, biomarker interpretation, and intervention design.

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