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Astrocytes: Initiators of and Responders to Inflammation

Allison Soung and Robyn S. Klein

Abstract

We are in the midst of a glial renaissance; astrocytes, essential for brain homeostasis and neuroprotection, have experienced resurgence in focused analyses. New roles in synaptic plasticity, innate immunity and control of recruited immune cells have placed astrocytes at the center of central nervous system functions. Astrocytes have been shown to receive and convey information to all neural cell types in a coordinated effort to respond to injury and infection, initiating reparative mechanisms. Astrocytes detect injury and infection signals from neurons, microglia, oligodendrocytes and endothelial cells, responding by secreting cytokines, chemokines and growth factors, which may activate immune defenses. While regional heterogeneity in astrocyte form and function has been appreciated since the early 1990s, technologic advances have allowed scientists to show only that astrocytes may be as individualized as neurons. Adult astrocytes may undergo a morphological and functional transformation referred to as astrogliosis. Newly generated astrocytes exhibit heterogenous phenotypes; thus, some remove toxic molecules, restore blood-brain barrier function, and promote extracellular matrix components to support axonal growth and repair, while others inhibit neuronal repair and regeneration. This chapter will introduce some of the cellular and molecular components involved in astrocyte responses induced by inflammatory mediators or pathogens during neuroinflammation or neuroinfectious diseases.

Keywords: astrocyte, cytokines, chemokines, pathogens, viruses, bacteria, astrogliosis

1. Introduction

Astrocytes are a principle participant in central nervous system (CNS) responses to neurological disorders or diseases [1–3]. During development and homeostasis, astrocytes coordinate immune responses by regulating microglia activation and blood-brain barrier (BBB) formation [4, 5]. Through dedicated molecular cascades, astrocytes also provide growth factors to neurons, support synapse formation, and help regulate extracellular balance of ions and neurotransmitters, making these glial cells essential for brain homeostasis [6, 7]. In response to CNS injury and disease, astrocytes undergo a process termed astrogliosis, a multifactorial and complex remodeling of astrocytes [7–10]. Despite the use of a single term to describe astrocyte reaction to insult, astrogliosis results in a spectrum of heterogenous changes in a context specific manner that vary with etiology and severity of

Figure 1. *Astrogliosis is typically characterized by hypertrophy of astrocyte processes. Expression of GFAP+ astrocytes (green) and DAPI (blue) in a mock-infected mouse CA3 hippocampus (A) and in a West Nile virus-infected CA3 hippocampus 7 days post infection (B). Viral infection triggers reactive astrogliosis in the hippocampus, in which the processes of activated astrocytes show hypertrophy.*

CNS injury [9–13]. Classically, this process is characterized by upregulation of glial fibrillary acid protein (GFAP) and vimentin, key astrocyte intermediate filaments, and hypertrophy of astrocyte processes [14] (**Figure 1**). Changes in astrocyte biochemistry and physiology that may result in the secretion of anti-inflammatory and pro-inflammatory factors also contribute to this process [10, 15–17].

2. Astrogliosis

Functionally, astrogliosis results in the expression of molecules that provide neurotrophic support to injured neurons, isolate damaged area and CNS inflammation from healthy CNS tissue, rebuild and maintain a compromised BBB, and contribute circuitry remodeling around the lesioned region [7, 9–12, 18]. Consistent with this, studies using animal models of traumatic brain injury, spinal cord injury, and autoimmunity, all reveal that the loss of reactive astrocytes during acute processes leads to the exacerbation of clinical symptoms, recruit of immune molecules, changes in BBB integrity, and neuronal death [7, 10, 19]. The overall goals of these functional reactions are therefore beneficial for the CNS. However, past research has also highlighted detrimental and inhibitory effects of astrogliosis, including augmentation of inflammation, as well as inhibition of neuronal repair and axonal growth [20, 21]. The dual outcomes of astrogliosis highlight the time- and context-specific way this process may be regulated. Future studies of this process may ultimately determine mechanisms to manipulate astrogliosis as a therapeutic target to improve CNS injury outcomes [10, 22].

Astrogliosis is induced and regulated by a variety of extracellular molecules, such as neurotransmitters, steroid hormones, cytokines and neurodegeneration-associated molecules (**Table 1**). Intracellular signaling pathways, such as cyclic AMP (cAMP), signal transducer and activator of transcription 3 (STAT3), nuclear factor kappa B (NFκB), Rho-kinase, and calcium have all been observed to induce the expression of GFAP or vimentin [11, 45–47]. Extracellular signaling pathways, including responses to epidermal growth factor (EGF), fibroblast growth factor

Signaling pathway	Injury	Chemokines/cytokines released	Immune/functional outcome	References
ER α signaling	EAE		Reduction of leukocyte molecules	[23]
Gp103/IL-6 signaling	EAE	Downregulation of IL-17 and IFN γ	Reduction of T cell infiltration, inhibition of astrocyte apoptosis, improvement of disease course	[24, 25]
	Infection	Downregulation of IFN γ	Inhibition of astrocyte apoptosis, decrease of pathogen burden	[25]
IL-1 β signaling	Traumatic injury, infection		Increase of GFAP expression	[26, 27]
IL-17 signaling	EAE	Upregulation of CXCL2	Increase of leukocyte infiltration, worsen disease course	[28]
IFN γ signaling	EAE	Downregulation of CCL5, IL-1 β and TNF	Improved course of disease	[24]
	Traumatic injury		Increase of GFAP expression	[29]
TNFR1 signaling	EAE		Increases of T cell infiltration, worsen disease course	[30]
NF κ B signaling	EAE	Upregulation of CCL2, CCL5, CXCL10, IL-1 β , IFN γ , and TNF; downregulation of IL-6	Reduction of leukocyte molecules, increase in axon pathology, worsen disease course	[31]
	Ischemia, traumatic injury	Upregulation of CCL2, CCL5, CXCL10, IL-6, TGF- β and TNF	Increase of leukocytes molecules, reduction of GFAP expression, increase of neuronal damage	[31–33]
Notch signaling	Ischemia		Reduction of leukocyte molecules, increase of GFAP expression, increase of astrocyte proliferation	[34, 35]
SHH signaling	EAE		Maintenance of BBB	[36]
Soc3 signaling	Traumatic injury		Increase of leukocyte molecules, increase of GFAP expression	[37]
STAT3 signaling	Traumatic injury		Reduction of leukocyte molecules, inhibition of GFAP expression	[37, 38]
	Traumatic injury		Increase of GFAP and vimentin expression	[39, 40]

Signaling pathway	Injury	Chemokines/cytokines released	Immune/functional outcome	References
TGF- β signaling	Traumatic injury		Increase of leukocyte molecules, increase of GFAP expression, increase of ECM components	[41–43]
	Infection	Inhibition of NF κ B signaling; downregulation of CCL5	Reduction of T cell infiltration, decrease of neuronal death	[44]

A variety of intracellular signaling molecules have been shown to induce reactive astrogliosis or to modulate aspects of the reactive astrogliosis process. In response to a range of CNS injuries, all cell types within the CNS, such as neurons, microglia, other astrocytes, endothelium, and pericytes, can release signaling molecules that are able to trigger astrogliosis.

BBB = blood-brain barrier, CCL = chemokine (C-C motif), CXCL = chemokine (C-X-C motif) ligand, ER = estrogen receptor, Gp = glycoprotein, IL = interleukin, IFN = interferon, NF κ B = nuclear factor kappa B, EAE = experimental autoimmune encephalomyelitis, ECM = extracellular matrix, SHH = sonic hedgehog, Soc3 = suppressor of cytokine signaling 3, STAT3 = signaling transducer and activator of transcription 3, TGF = transforming growth factor β , TNF = tumor necrosis factor.

Table 1.
Triggers of reactive astrogliosis.

(FGF), sonic hedgehog (SHH), and albumin, can also regulate astrocyte proliferation [9, 48–50]. Specific pro- and anti-inflammatory effects of reactive astrocytes may be regulated separately. Thus, the genetic ablation of STAT3 within astrocytes, or its associated membrane receptor gp130, leads to increased inflammation during autoimmune disease, traumatic injury and infection [24, 37–39, 51], while genetic deletion of NF κ B or the suppressor of cytokine signaling 3 (Soc3) signaling pathway in astrocytes decreases the recruitment of immune cells [31, 32, 37]. Furthermore, recruited immune cells release numerous cytokines that may further stimulate astrocyte activation (**Table 1**). In addition, recent studies indicate that microglia critically induce astrogliosis via expression of pro-inflammatory cytokines, including interleukin (IL)-1 β , tumor necrosis factor (TNF), and interferon (IFN)- γ [26, 52, 53].

In response to injury, reactive astrocytes were previously believed to migrate to the lesion site. Recent live imaging studies, however, indicate that astrocytes do not migrate towards the lesion site [54]. Instead, astrocytes remain in their tiled-domains and become hypertrophic [54, 55]. Neither proliferation nor migration of astrocytes contribute to the total increase of GFAP positive cells observed at lesion sites. This has led to a new focus on identifying other sources for adult astrocytes. Currently, there is evidence that radial glia, neuronal progenitor cells (NPCs) within the subventricular (SVZ) and subgranular (SGZ) zones, locally proliferating glia, in addition to NG2+ cells may all contribute to newly generated pools of reactive astrocytes after injury [56].

3. Astrocytes as the gatekeeper to the CNS

During homeostasis, astrocyte end-feet enwrap the brain microvascular endothelial cells, helping maintain the integrity of the BBB. Their physical interaction with the BBB allows astrocytes to influence the entry of peripheral immune cells into the CNS during injury or disease as well as modulating their activity once entering the CNS parenchyma. In health, astrocytes, along with multiple other cell types, support the BBB as well as express localizing cues that restrict leukocytes

access into the CNS parenchyma [17, 57–59]. However, CNS damage caused by stroke, traumatic injury, infection, autoimmune disease, and neurodegenerative disorders leads to the disruption of the BBB, which may increase the CNS entry of immune cells [24, 25, 38, 39, 60–66].

During injury or infection, astrocytes detect molecular changes in their extracellular environment and in neighboring cells. In stroke, astrocytes become reactive when oxygen and glucose deprivation occurs [67, 68]. In most neurological disorders, the release of neurotransmitters and adenosine triphosphate (ATP) from damaged neurons is detected by astrocytes via P2X and P2Y purinergic receptors [69, 70]. During viral infections, toll-like receptors (TLRs), such as TLR3, 7, and 9, and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), are expressed on neurons, astrocytes, and microglia. These receptors are examples of pattern recognition receptors (PPRs) that are differentially activated by pathogen-associated molecular patterns (PAMPs) derived from invading bacteria, fungi, or viruses [71]. Activation of TLRs and RLRs by PAMPs or damage-associated molecular patterns (DAMPs) have been shown to contribute to neuronal damage, induce microglia and astrocyte activation and production of cytokines, including type I IFNs [72–74]. Type I IFNs, along with numerous other innate cytokines, such as IL-6, IL-1 β , IFN- γ , and TNF, have been shown to regulate BBB integrity through a variety of different mechanisms that include the regulation of Rho GTPases, activation of matrix metalloproteinase 9 (MMP9), and suppression of other pro-inflammatory cytokines, including IL-1 β , IL-6, and TNF [75, 76]. In support of this, the genetic astrocyte-specific deletion of the type I IFN receptor, IFN α β R (IFNAR), results in enhanced BBB permeability in a murine viral infection model [77].

The entry of leukocytes into the CNS parenchyma involves their passage across the BBB, whose permeability is regulated by astrocytes and pericytes, as well as multiple other cell types [57–59]. Once leukocytes traverse the BBB, they localize within perivascular spaces and where they interact with numerous cell types, including astrocytes [78]. Astrocytes, thus, take part in both the recruitment and restriction of leukocytes in the CNS [58, 59, 151]. Their functions, however, occur in a context-specific manner via specific signaling events. It is remarkable how astrocytes are able to respond to a diverse number of signaling mechanisms in the orchestration BBB disruption, the recruitment of leukocytes, and the amplification of their pro-inflammatory effects [17, 57, 79, 80], while also being capable of contributing to BBB repair, restricting leukocyte trafficking, and exerting anti-inflammatory effects that promote the resolution of inflammation [6, 9–11].

4. Reactive astrocytes as a physical barrier

At the site of injury, newly proliferated astrocytes form scars, in which bundles of reactive astrocytes polarize with extracellular matrix (ECM) components and physically surround the lesioned site [38]. The earliest studies focused on the formation of the astrocyte scar and its importance in repairing the BBB after traumatic brain injury [61, 62]. Astrocyte scars form a physical, functional barrier that restricts the entry of leukocytes after traumatic brain injuries, ischemia, neurodegeneration and autoimmune inflammation [37, 38]. This is achieved through the upregulation of ECM proteins, such as fibronectin and laminin, as well as chondroitin sulfate proteoglycans (CSPGs) [41, 42, 81–84]. Structural proteins, such as GFAP and vimentin, have also been shown to be important for the formation of the astrocyte scar [14]. Mice with global genetic

deletion of these molecules display increased inflammation and pathology as well as worsened functional outcomes in various CNS injury models, such as ischemia, traumatic injury, autoimmune inflammation, infection, and neurodegeneration [11, 63, 64, 85–88].

The astrocyte scar is also important for localizing immune cells and limiting the invasion of infectious pathogens, to the lesion site. For example, the genetic deletion of GFAP+ cells leads to increases in immune cell infiltrations in murine models of traumatic injury and autoimmunity [60, 61]. Genetic loss of GFAP expression also increases pathogen burden in various infections, including *Staphylococcus aureus* and *Toxoplasma gondii* [89]. Multiple studies have shown that the restriction of leukocyte entry and migration after infection, autoimmune inflammation, and traumatic brain injury is mediated by astrocyte anti-inflammatory functions via the JAK2-STAT3 signaling pathway in GFAP+ cells [25, 38, 39]. The genetic deletion of astrocyte derived STAT3 signaling prevents scar formation and limits immune cell infiltration in a spinal cord injury model [39]. These observations suggest that the astrocyte scar serves as a functional barrier to restrict cytotoxic inflammatory molecules and cells.

Studies genetically deleting essential components of the ECM, such as MMP9, or inhibiting signaling pathways, including Rho/ROCK, to block CSPG activity have shown astrogliosis to exacerbate inflammation after traumatic injury or autoimmune inflammation as well as preventing axonal growth and behavioral recovery [81, 90–92]. The astrocyte scar has also been shown to exhibit a diverse array of molecules known to prevent axonal growth, such as CSPGs, semaphoring 3A, keratan sulfate proteoglycans (KSPGs) and ephrins/Eph receptors [19, 93, 94]. The complexity of astrocytes in producing, recruiting and restricting inflammatory cells and other molecules have made these cells a difficult target for potential therapeutic manipulation.

5. Astrocytes as a regulator of the innate immune response

After CNS injury or infection, reactive astrocytes release molecules that attract, recruit and facilitate the migration of immune cells to the lesion site (**Figure 2**). Astrocytes express leukocyte adhesion molecules, including vascular cell adhesion and intercellular adhesion molecules, in models of ischemia, autoimmunity, and infection [30, 33, 95]. Specifically, in an ischemia model, astrocytes release NF- κ B, which increases both vascular cell adhesion and intercellular adhesion molecules [33, 96]. These adhesion molecules promote intercellular interactions that contribute to the trafficking of immune cells to the lesion site.

Like microglia, the resident macrophages of the CNS, astrocytes play a role in innate immune responses by producing cytokines and chemokines, such as type I and II IFNs and TNF, that promote the expression of hundreds of interferon-stimulated genes (ISGs), such as those that participate in inflammatory cell infiltration [97, 98]. Microglia also upregulate the expression of numerous receptors and produce various chemokines after CNS injury, such as chemokine (C-X3-C motif) receptor 1 (CX3CR1) and chemokine (C-C motif) receptor 2 (CCR2) [99]. Similarly, reactive astrocytes also express many of these receptors and chemokines, suggesting that astrocytes and microglia communicate via chemokines. In fact, astrocyte release of chemokines has been shown to be important for attracting peripheral and CNS myeloid cells to the lesion site. In models of traumatic injury and parasitic infection, astrocytes are a source of chemokine (C-C motif) ligand 2 (CCL2) [100, 101]. Astrocytes have also been shown to produce chemokine

Figure 2.

Reactive astrocytes regulate immune responses. Activation of astrocytes, either directly by purinergic receptors or PRRs or indirectly, promote expression of inflammatory cytokines and chemokines as well as growth factors. The astrocyte response to molecular changes in their microenvironment shapes the recruitment and activation of peripheral immune cells, modulation of the BBB, and cell-cell interaction (not shown). ATP = adenosine triphosphate, BAFF = B-cell activating factor, BBB = blood-brain barrier, CCL = chemokine (C-C motif), CXCL = chemokine (C-X-C motif) ligand, DAMPs = damage-associated molecular pattern, IL = interleukin, IFN = interferon, PAMP = pathogen-associated molecular pattern, PRR = pattern recognition receptor, TNF = tumor necrosis factor.

(C-X3-C motif) ligand 1 (CXCL1) and CXCL1, detected by monocytes and microglia, in response to viral infection and spinal cord injury, respectively [102–104].

After entry into the brain, or activation within the brain, innate immune cells demonstrate a spectrum of phenotypes, ranging from pro- and anti-inflammatory states, and can express a variety of cytokines and chemokines, including IL-1 β , IFN- γ , and TNF, that contribute to neuroinflammation [105]. Reactive astrocytes have a demonstrated role in modulating immune responses by releasing cytokines that stimulate microglia and macrophages to adopt either pro- or anti-inflammatory responses. For example, after injury or infection, astrocytes have been shown to release cytokines, such as IFN- γ , TNF, and IL-12, that shift microglia and macrophages to a more pro-inflammatory phenotype [106, 107]. Under similar conditions, however, astrocytes have also been observed to produced cytokines, including IL-10 and transforming growth factor beta (TGF- β), which can shift monocytes towards a less inflammatory states [108–110]. These findings support the notion that astrocyte responses may be context dependent.

6. Astrocytes as a regulator of the adaptive immune response

During the adaptive immune response, astrocytes are a major source of T and B cells chemoattractants. Reactive astrocytes express CCL5 as well as CXCL10 in infection models, both chemoattractants of T cells [111–113]. In viral infection models, CXCL10 has been shown to be an important ligand for CXCR3 on CD8 $^{+}$ T cells [114]. The recruitment of such CXCR3 $^{+}$ T cells results in improved viral control and survival after infection [115]. In brain samples from patients with multiple

sclerosis, astrocytes have been shown to express CXCL12, a T cell chemoattractant, and B-cell activating factor (BAFF), a B cell chemoattractant [116, 117]. Like their influence on microglia and macrophages, cytokines released by reactive astrocytes can shift T cells to adopt either a more beneficial or detrimental phenotype. For example, reactive astrocytes during autoimmunity release pro-inflammatory cytokines, including TNF, IFN- γ , and IL-17, which may induce T cells to adopt a more pro-inflammatory state. However, astrocytes have also been shown to release IL-10 that shifts T cells towards the anti-inflammatory spectrum [23, 24, 32, 118, 119]. Similarly, in a murine spinal cord injury model reactive astrocytes have been shown to release anti-inflammatory TGF- β [31]. Further studies examining the influences of reactive astrocytes on T cells are needed to better understand the long-term effects of astrogliosis on adaptive immune cells during CNS recovery after injury.

7. Reactive astrocytes as a pro-inflammatory regulator

Reactive astrocytes can release a variety of molecular signals that contribute to the inflammatory state of the CNS after injury or disease by directly activating immune defenses with the release of cytokines, chemokines, and other growth factors (**Table 2**). Recent advancements in astrocyte transcriptome analysis have begun to reveal the context specific production of pro-inflammatory molecules by astrocytes as well as molecular triggers that induce their production. Analysis of the astrocyte transcriptome after *in vivo* exposure to lipopolysaccharide (LPS) or infection significantly promoted the production of a pro-inflammatory, neurotoxic molecular profile [26, 52]. However, the astrocyte transcriptome shifts towards an anti-inflammatory, neuroprotective profile in an *in vivo* ischemia model [52]. Future studies should utilize single-cell sequencing techniques to transcriptionally define individual astrocyte responses during health and disease.

Despite the number of astrocyte transcriptome data available, few studies have attempted to elucidate mechanisms and signaling cascades that mediate astrocyte pro-inflammatory production. Recent studies have indicated NF κ B and SOCS3 as transcriptional regulators of pro-inflammatory astrocytes after a traumatic brain injury and during autoimmune inflammation [31, 32, 37]. In a model of autoimmunity, genetic deletion of astrocyte derived NF κ B results in increased expression of ECM components and pro-inflammatory cytokines [129]. Astrocytes have also been shown to release CCL2 and CXCL10 to recruit perivascular leukocytes during autoimmune inflammation [124–126]. While the role of CCL2 and CXCL10 is diverse, evidence suggests that these molecules produced by astrocytes promote leukocyte migration in the CNS parenchyma [124]. In an autoimmune inflammation model, IL-17 inflammatory induction has been shown to be mediated by astrocyte Act1 signaling. Genetically deleting Act1/IL-17 signaling from astrocytes in an EAE model prevents the induction of pro-inflammatory cytokines [28]. Reactive astrocytes can also shift towards a more pro-inflammatory state by overexpressing pro-inflammatory cytokines. In spinal cord injury and autoimmune models, the overexpression of IL-6 in astrocytes leads to increased immune cell infiltration. The proinflammatory cytokine, IL-1 β , produced by astrocytes, has also been shown to initiate a signaling cascade that releases vasoactive endothelial growth factor (VEGF), leading to increased BBB permeability and leukocyte leakage [127, 128]. In general, there is also evidence that astrocytes contribute to triggering inflammatory responses due to increases in neuronal activity in epilepsy, neuropathic pain, and stress [130].

Type	Astrocyte molecule	Immune outcome	References
<i>Anti-inflammatory function</i>			
Cytokines	IL-6 and IL-10	Activation of numerous anti-inflammatory signaling pathways	[95, 120]
Growth factors	TGF- β	Activation of numerous anti-inflammatory signaling pathways	[121, 122]
	SHH	Maintenance of BBB, increase of astrocyte proliferation	[36, 123]
Intracellular signaling molecules	STAT3	Suppression of multiple pro-inflammatory signaling pathways	[37–39]
Receptors	ER α and Gp130	Suppression of multiple pro-inflammatory signaling pathways	[23, 25]
<i>Pro-inflammatory function</i>			
Chemokines	CCL2 and CCL5	Increase recruitment of leukocytes	[95, 120, 122, 124, 125]
	CXCL1, CXCL10, and CXCL12	Increase recruitment of leukocytes	[95, 120, 122, 126]
Cytokines	IL-6, IL-17, IL-1 β , and TNF	Activation of numerous pro-inflammatory signaling pathways	[95, 120–122]
Growth factors	VEGF	Increase of BBB permeability, increase of leukocyte infiltration	[127, 128]
Intracellular signaling molecules	NF κ B and Soc3	Activation of numerous pro-inflammatory signaling pathways	[31, 32, 37]
	Act1	Activation of IL-17-mediated pro-inflammatory signaling pathways	[28]
<i>As immune-competent cells, astrocytes can detect injury signals and respond with the release of cytokine, chemokines, and growth factors as well initiating intracellular signaling pathways. Data suggests that the downstream effects of astrocyte activation is context- and time-dependent, and that both factors as well as other microenvironment stimuli can shift reactive astrocytes to either a more beneficial or detrimental phenotype.</i>			
<i>Act = actin, CCL = chemokine (C-C motif), CXCL = chemokine (C-X-C motif) ligand, Gp = glycoprotein, IL = interleukin, IFN = interferon, NFκB = nuclear factor kappa B, EAE = experimental autoimmune encephalomyelitis, SHH = sonic hedgehog, Soc3 = suppressor of cytokine signaling 3, STAT3 = signaling transducer and activator of transcription 3, TGF = transforming growth factor β, TNF = tumor necrosis factor, VEGF = vascular endothelial growth factor.</i>			

Table 2.
Pro- and anti-immune responses of astrocyte molecules.

8. Reactive astrocytes as an anti-inflammatory regulator

Despite the growing body of work that suggests pro-inflammatory roles for astrocytes, there is an equal amount of evidence suggesting these cells limit inflammation. Recent loss-of-function experiments have also revealed essential anti-inflammatory roles of astrocytes after a variety of CNS injury and disease states (**Table 2**). These studies have also revealed specific molecular mechanisms that mediate these anti-inflammatory roles. The astrocyte TGF- β response seems to selectively affect astrocyte cytokine and chemokine production after ischemia in murine models. The genetic deletion of TGF- β signaling in astrocytes leads to diffused inflammation and enhances myeloid cell activation [43, 44]. After toxoplasmic encephalitis, the genetic loss of astrocyte TGF- β signaling can lead to the increase of infiltrating T cells. Notably, in both examples, astrocyte TGF- β signaling controls infiltration immune cell number but not necessarily

the immune response profile. Astrocyte signaling involving gp130, a receptor for IL-6, or estrogen receptor 1 α has also been shown to be anti-inflammatory. In autoimmune and infection models, the genetic deletion of gp130 from astrocytes results in increased inflammatory cytokine production [24, 25]. Similar outcomes, such as increased myeloid infiltration and mortality, are observed in autoimmune models when estrogen receptor 1 α is conditional deleted from astrocytes [23]. During autoimmunity, mice deficient in functional IFN γ signaling in astrocytes result in exacerbated disease and mortality due to enhanced leukocyte infiltration and an upregulation of inflammatory gene expression, including CCL1, CCL5, CXCL10, and TNF [119]. These mice also had a reduction in anti-inflammatory cytokines, such as IL-10 and IL-27, when compared to mice with functional IFN γ in astrocytes [119].

9. Reactive astrocytes as a neuroprotector of the CNS

In addition to astrocyte regulation of the immune response, these glial cells can respond to CNS injury by altering neuronal function or survival. Neuronal insults result in the release of numerous signals, including increased glutamate production, ATP release and vascular damage. During numerous CNS disease states, including stroke, traumatic injury, epilepsy, neurodegeneration, and viral infection, injured and dying neurons release glutamate, which is harmful to neurons [131–134]. Astrocytes have been shown to take up excessive extracellular glutamate and dampen the neurotransmitter's excitotoxicity on neurons, resulting in decreased neuronal death [135]. *In vitro* studies have also shown that glutamate signaling in astrocytes decrease their production of CCL5, a T cell chemoattractant, reducing overall neuroinflammation [136].

10. Reactive astrocytes as a neurotoxin of the CNS

Inflammation itself can unfortunately impair astrocyte uptake of glutamate, which leads to increased neuronal toxicity and a positive feedback of neuroinflammation [137]; for example, in an *in vitro* study TNF, released by microglia, signals to astrocyte to release glutamate, increasing excitotoxicity [138]. Neuronal injury and death also lead to the release of potassium and ATP. Both potassium and ATP can activate the inflammasome complex, which is an innate immune mechanism that when activated, resulting in the production of proinflammatory cytokines and increased inflammatory responses. The activation of the inflammasome complex, in this case, is through pannexin 1 channels, expressed by astrocytes [139, 140]. Pannexin 1 channels are opened by potassium and ATP, and once opened, activate the inflammasome complex, leading to the increased production of pro-inflammatory mediators, such as IL-1 β , reactive oxygen and nitrogen species, and CCL2, a myeloid cell chemoattractant [139, 141–143]. ATP also can induce the release of glutamate from astrocytes, which can contribute to overall excitotoxicity [144]. During health, astrocytes release stored glycogen which is converted to lactate and transported to metabolically support neurons [145]. Neurons can resist excitotoxicity when astrocytes increase their glycogen uptake and lactate delivery [146]. Pro-inflammatory cytokines, including IL-1 β as well as IFN- γ , TNF, and IL-6, negatively impacts this process by reducing glycogen storage and lactate transport in astrocytes that is necessary as an energy source of neurons [147, 148].

11. Conclusions

Despite the recent advances in defining the role of astrocytes in regulating neuroinflammation, our understanding of these complex glial cells is only beginning. A few studies have demonstrated astrocyte polarization after various CNS injuries [26, 52, 95]. In this model, “A1” reactive astrocytes are pro-inflammatory, neurotoxic while “A2” reactive astrocytes are anti-inflammatory, neuroprotective. Future research, however, is needed to determine whether, like the inflammatory microglia and macrophages, reactive astrocytes shift phenotypes along a spectrum of responses. The amount of new technology available to researchers will also make it possible to further dissect the complexity of astrocytes. Single-cell transcriptional profiling techniques, specifically, can be used as a tool to identify astrocyte subtypes as well as intracellular signaling networks. This method has already been utilized to reveal distinct astrocyte types with regionally restricted distribution in the healthy mouse brain [149]. A key goal, however, for researchers in the future will be to elucidate signaling networks that are relevant to CNS injury and disease and how immune pathways influence astrocyte reactivity.

While current research focuses primarily on astrocyte interactions with other CNS cell types, such as neurons, microglia, pathogens and infiltrating immune cells, future studies will need to examine how other biologic variables, including age and sex, influence astrocyte effects within the central and peripheral immune systems. Additionally, there is already some evidence that astrocyte immune regulation is influenced by the gut microbiome [150], but the implications and effects of this process on health and disease are unknown.

In summary, astrocytes exhibit diverse and sometimes conflicting roles in the setting of neuroinflammatory diseases. These multipurpose glia cells not only sense and influence damaged neurons but appear to summate multiple signals to develop specific responses that modulate neuroinflammation. It is our hope that understanding how astrocytes receive and response to information as they perform these differential roles will lead to therapies that specifically target astrocytes during CNS injury and disease.

Abbreviations

ATP	adenosine triphosphate
BAFF	B-cell activating factor
BBB	blood-brain barrier
cAMP	cyclic AMP
CCL	chemokine (C-C motif) ligand
CCR	chemokine (C-C motif) receptor
CNS	central nervous system
CSPG	chondroitin sulfate proteoglycan
CXCL	chemokine (C-X-C motif) ligand
CXCR	chemokine (C-X-C motif) receptor
DAMP	damage-associated molecular pattern
ECM	extracellular matrix
EGF	epidermal growth factor
FGF	fibroblast growth factor
GFAP	glial fibrillary acid protein
IFN	interferon
IL	interleukin

ISG	interferon-stimulated gene
KSPG	keratan sulfate proteoglycan
MMP9	matric metalloproteinase 9
NFκB	nuclear factor kappa B
NPC	neural progenitor cell
PAMP	pathogen-associated molecular pattern
PPR	pattern recognition receptor
RIG-I	retinoic acid-inducible gene I
RLRs	RIG-I-like receptor
SGZ	subgranular zone
SHH	sonic hedge hog
SOC3	suppressor of cytokine signaling 3
STAT3	signal transducer and activator of transcription 3
SVZ	subventricular zone
TGF-β	transforming growth factor beta
TLR	toll-like receptor
TNF	tumor necrosis factor
VEGF	vasoactive endothelial growth factor

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