Neurotherapeutics (2016) 13:685–701
DOI 10.1007/s13311-016-0477-8

REVIEW

Astrocytes: Integrative Regulators of Neuroinflammation in Stroke and Other Neurological Diseases

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Published online: 27 September 2016

Abstract Astrocytes regulate neuroinflammatory responses after stroke and in other neurological diseases. Although not all astrocytic responses reduce inflammation, their predominant function is to protect the brain by driving the system back to homeostasis after injury. They receive multidimensional signals within the central nervous system and between the brain and the systemic circulation. Processing this information allows astrocytes to regulate synapse formation and maintenance, cerebral blood flow, and blood–brain barrier integrity. Similarly, in response to stroke and other central nervous system disorders, astrocytes detect and integrate signals of neuronal damage and inflammation to regulate the neuroinflammatory response. Two direct regulatory mechanisms in the astrocyte arsenal are the ability to form both physical and molecular barriers that seal the injury site and localize the neuroinflammatory response. Astrocytes also indirectly regulate the inflammatory response by affecting neuronal health during the acute injury and axonal regrowth. This ability to regulate the location and degree of neuroinflammation after injury, combined with the long time course of neuroinflammation, makes astrocytic signaling pathways promising targets for therapies.

Keywords Astrocyte · Neuroinflammation · Glial scar · Stroke · Brain injury

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Astrocytic Functions in the Healthy Central Nervous System

Astrocytes play 2 major roles in the resting central nervous system (CNS): they integrate signals and maintain homeostasis between its nervous, immune, and vascular components. Several excellent reviews exist on the biology of astrocytes [1–4]. Briefly, their morphology and location within the brain is ideal for their integrative role. Astrocytic processes contact each synapse and astrocytic endfeet make up the internal layer of the blood–brain barrier (BBB), which allows them to react to local changes in neuronal activity, as well as respond to systemic perturbations in the rest of the body. They provide trophic and functional support to neurons by transporting glucose, neurotrophic factors, and neurotransmitters such as glutamate. In addition, astrocytes keep the immune system quiescent at baseline by regulating the permeability of the BBB and microglial activation states.

There is significant astrocyte heterogeneity in morphology and function. Although astrocyte heterogeneity studies have been slowed down by lack of pan-astrocyte surface markers [5], we are beginning to understand how and why astrocytes vary, and to develop new tools to study them. Studies using human glial fibrillary acidic protein (GFAP)–enhanced green fluorescent protein mice show that brain region determines astrocyte morphology, density, and proliferation level [6], as well as gene expression [7]. Even within the same brain regions (olfactory bulb, spinal cord), astrocytes in different layers can manifest different morphological characteristics [8, 9] and develop in response to different factors [10]. Cortical astrocytes are divided into 2 main morphological subtypes: protoplasmic astrocytes, which are located in the gray matter, and fibrous astrocytes, which are found in the white matter [3]. Resting protoplasmic cortical astrocytes have a globoid morphology and occupy distinct, nonoverlapping

domains, which coordinate the formation and functions of synapses [3, 11].

Astrocytes play major roles in neuronal function. They coordinate formation and function of synapses during development [11–13] and provide baseline trophic support to neurons by accumulating intracellular energy reserves in the form of glycogen granules that they can convert to lactate to supply to neurons [14]. Glutamate transporter expression by astrocytes functions to remove the neurotransmitter glutamate from the synaptic cleft, and is not uniform, varying according to developmental stage (more early than late) and brain region (most in radial glia) [15]. Importantly, the same trophic functions astrocytes have in an uninjured brain can be employed to reduce neuronal injury in disease, including stroke.

Higher-order functional diversity is also conferred by differences in astrocytic connections. Astrocytes occupy distinct, nonoverlapping domains in resting CNS [11] and can be coupled to each other via gap junctions (reviewed in [16]). They can be more strongly coupled within brain regions that function together. For example, within the whisker barrel cortex astrocytes are more coupled within barrels that control the same whisker than between barrels that control different whiskers [17]. Astrocytes are also coupled to oligodendrocytes [18] and support them via lactate transfer [19].

Finally, astrocytes are able to coordinate immune responses in the healthy brain at key points during its development by regulating microglial activation [13] and BBB induction [20]. The same immunoregulatory and neuroprotective mechanisms that allow astrocytes to maintain homeostasis in the healthy brain are utilized in astrocytic responses to injury, including stroke.

Stroke and Astrocytes

Stroke kills 12 % of all people worldwide, making it the second most common cause of mortality (http://www.who.int/mediacentre/factsheets/fs310/en/). Neuroinflammation peaks during the first week after stroke, known as the subacute period [21]. There is a growing body of evidence that astrocytes are important *in situ* regulators of the neuroinflammatory response to stroke. Astrocytes become reactive in the subacute time frame of 2 days to 1 week after stroke and form a scar around stroke core by 2 weeks [22].

The majority of our knowledge of reactive astrocyte functions in neuroinflammatory responses stems from research using disease models other than stroke. For example, spinal cord injury (SCI), traumatic brain injury (TBI), and brain infection models have all been used to understand what role astrocytes play in influencing the location, duration, and physical extent of neuroinflammation in the brain. In the following sections of this review we give examples of all of these models, as well as stroke. Although many of these astrocytic roles may be the same across neuroinflammatory states, some are known to be different, and the current state of knowledge is only beginning to uncover the complexity of astrocytic responses. Therefore, we highlight studies of astrocyte functions in stroke and emphasize differences in astrocytic roles in distinct neuroinflammatory states when information is available.

Reactive Astrocytes in Central Nervous System Disease

During central nervous system (CNS) injury astrocytes sense molecular changes in their extracellular environment and in cells to which they are coupled, and alter their morphological and functional characteristics to adopt a "reactive" phenotype. The history of how the term "reactive" developed is nicely summarized elsewhere [23]; the first mention of astrocyte changes in disease was in 1895 and strong GFAP expression became the hallmark of reactive astrocytes in the 1970s. In addition to upregulation of GFAP, reactive astrocytes alter their morphology and gene expression.

As would be expected by their locations throughout the brain and their functions in the normal brain, astrocytes become reactive when they sense injury. In stroke, this includes oxygen and glucose deprivation, and in most neurological injuries and diseases the release of neurotransmitters, as well as adenosine triphosphate (ATP) from damaged neurons [24–26]. During infection astrocytes can be invaded by intracellular pathogens or activated by lipopolysaccharide and other ligands of innate immunity that bind to Toll-like receptors (reviewed in [27, 28]). Furthermore, immune cells that invade the site of injury or infection release a variety of cytokines that further stimulate astrocyte activation (Tables 1 and 2).

Differences in the strength of these signals leads to a spectrum of astrocyte "reactivity". In general, the most activated and morphologically distinct astrocytes are observed adjacent to the injured region, with less activated astrocytes farther away in the remaining healthier tissue [34, 37, 47]. Reactive astrocytes proliferate, become hypertrophied, upregulate the expression of intermediate filament proteins, cytokines and chemokines, and cluster into polarized bundles around the injured region. The polarized astrocytes combine with extracellular matrix (ECM) components to form a scar, which walls off the injured region from neighboring healthier tissue.

Astrocyte activation typically occurs during the time period that coincides with peak inflammatory response. In CNS injuries such as stroke, TBI, and SCI, the initial tissue destruction that is caused by ischemia or physical trauma is followed by a subacute period that lasts up to a week, during which the tissue can be further damaged by inflammation [69, 78]. This subacute period coincides with astrocyte activation and their expression of cytokines; however, changes in astrocyte morphology and astroglial scars can persist chronically [79]. By

Table 1 Astrocytic signaling in neuroinflammation: the physical barrier

Signaling pathway	Injury	Physical barrier components	Changes in the immune response	Changes in outcomes	Reference(s)
CD36 signaling	Ischemia	Increases GFAP expression		Reduces cell death, reduces infarct size	[22]
Notch signaling	Ischemia	Increases GFAP expression and induces astrocyte proliferation	Inhibits CD45+ cell infiltration		[29]
GFAP and vimentin expression	Ischemia			Stimulate the formation of gap junctions, glutamate transport, PAI-1 expression	[30]
NF-kB signaling	Ischemia	Reduces leukocyte adhesion molecules, reduces GFAP expression	Increases CD11b + leukocyte infiltration, increases iNOS expression	Increases neuronal damage	[31]
	SCI	Reduces GFAP expression and astrocyte morphological changes, reduces the expression of the ECM components neurocan and phosphacan		Increases neuronal damage	[32]
	EAE	Increases leukocyte adhesion molecules	Inhibits CD45+ leukocyte, CD3+ T lymphocyte and B220+ B lymphocyte infiltration	Increases demyelination and axonal pathology, worsens outcomes	[33]
STAT3 signaling	SCI	Induces astrocyte polarization and morphological changes	Inhibits CD45+ leukocyte infiltration	Reduces cell death	[34]
	SCI	Inhibits GFAP expression	Inhibits CD11b + leukocyte infiltration	Improves motor outcomes	[35]
	SCI	Increases GFAP and vimentin expression, induces astrocyte morphological changes	Inhibits CD45+ leukocyte infiltration	Improves motor outcomes	[36]
	SCI	Increases GFAP and vimentin expression, induces astrocyte morphological changes		Promotes regeneration of axons when exogenous growth factors are added	[36, 37]
Socs3 signaling	SCI	Increases GFAP expression	Increases CD11b + leukocyte infiltration	Worsens motor outcomes	[35]
SOX9 signaling	SCI	Increases GFAP expression, increases the expression of ECM components neurocan, brevican, and aggrecan		Prevents axonal outgrowth, worsens motor outcomes	[38]
MMP2 production	SCI	Increases GFAP and CSPG expression		Increases axonal outgrowth, improves motor outcomes	[39]
GFAP+ cell proliferation	SCI		Inhibits CD45+ cell infiltration	Reduces cell death, closes BBB, improves motor outcomes	[40]
TGF-β signaling	TBI	Increases GFAP expression, increases the expression of ECM component neurocan		Prevents axonal outgrowth	[41]

Table 1 (continued)

Signaling pathway	Injury	Physical barrier components	Changes in the immune response	Changes in outcomes	Reference(s)
	TBI	Increases the expression of ECM component tenascin C			[42]
	TBI	Increases GFAP expression and astrocyte proliferation, increases the expression of ECM components fibronectin and laminin	Increases neutrophil and macrophage infiltration		[43]
GFAP+ cell proliferation	TBI		Inhibits CD45+ monocyte, macrophage, neutrophil, and lymphocyte infiltration	Reduces cell death, prevents axonal outgrowth, closes BBB	[44, 45]
IL-1β signaling	TBI	Increases GFAP expression		Closes BBB	[46]
CDC42 signaling	TBI	Induces astrocyte proliferation, polarization, and morphological changes			[47]
IFN-γ signaling	TBI	Increases GFAP expression			[48]
JNK/c-jun signaling	EAE	Increases GFAP expression and astrocyte proliferation			[49]
GFAP+ cell proliferation	EAE		Inhibits Iba1+ microglia and macrophage, Ag4/7+ neutrophil, and CD3+ T lymphocyte infiltration	Increases demyelination and axonal pathology, worsens outcomes	[50]
TNFR1 signaling	EAE	Increases leukocyte adhesion molecules	Increases CD4+ T lymphocyte infiltration	Increases demyelination, worsens outcomes	[51]
Gp130/IL-6 signaling	EAE	Inhibits astrocyte apoptosis	Inhibits CD4+ and CD8+ T lymphocytes, increases FoxP3+ regulatory T lymphocyte (Treg) differentiation	Reduces demyelination, improves outcomes	[52]
	Parasitic infection	Increases GFAP+ astrocyte numbers, inhibits astrocyte apoptosis		Reduces pathogen burden, improves recovery	[53]
GFAP expression	Parasitic infection			Reduces pathogen burden	[54]
	Bacterial infection		Inhibits MHC II+ myeloid cell infiltration	Reduces pathogen burden, improves recovery	[54]

For each signaling pathway, the normal pathophysiological role of the pathway is stated. GFAP = glial fibrillary acidic protein; PAI-1 = plasminogen activator inhibitor-1; NF-kB = nuclear factor kappa B; iNOS = inducible nitric oxide synthase; SCI = spinal cord injury; ECM = extracellular matrix; EAE = experimental autoimmune encephalomyelitis; Socs3 = suppressor of cytokine signaling 3; STAT3 = signal transducer and activator of transcription 3; SOX9 = SRY-Box 9; MMP2 = matrix metalloproteinase 2; CSPG = chondroitin sulfate proteoglycan; BBB = blood–brain barrier; TGF = transforming growth factor β; TBI = traumatic brain injury; IL = interleukin; CDC42 = cell division cycle 42; IFN = interferon; JNK = c-Jun N-terminal kinase; TNFR1 = tumor necrosis factor receptor 1; Gp130 = glycoprotein 130; FoxP3 = forkhead box P3; MHC = major histocompatibility complex

Table 2 Astrocytic signaling in neuroinflammation: the molecular barrier during neuroinflammation

Signaling pathway	Injury	Chemokines and cytokines released by astrocytes	Changes in the immune response	Changes in outcomes	Reference(s)
No pathway manipulated	Ischemia	CCL2, CXCL1, CXCL2, CXCL10, IL-6			[55]
No pathway manipulated	SCI	CCL2, CXCL1, CXCL2			[56]
NF-kB signaling	Ischemia	Upregulates CCL2, CXCL10, TNF-α	Increases CD11b + leukocyte infiltration, increases iNOS expression	Increases neuronal damage	[31]
	SCI	Upregulates CCL5, CXCL10, IL-6, TGF-β		Increases neuronal damage, worsens motor outcomes	[32]
	EAE	Upregulates CCL2, CCL5, CXCL9, CXCL10, IFN-γ, IL-1β, TNF-α; downregulates IL-6, IL-12	Inhibits CD45+ cell, CD3+ T lymphocyte, and B220+ B lymphocyte infiltration	Increases demyelination and axonal pathology, worsens outcomes	[33]
No pathway manipulated	TBI	CCL2, CCL5			[57]
	TBI	CCL2			[58]
IL-6 expression	TBI		Increases expression of genes involved in leukocyte recruitment and complement cascade	Reduces proapoptotic gene expression	[59]
	EAE	Upregulates CCL5, CCL12, IL-6, IL-17, TNF-α, TGF-β	Increases CD11b + leukocyte, Ly6G+ neutrophil, CD11c + dendritic cell, CD4+ and CD8+ T lymphocyte, B220+ B lymphocyte infiltration	Atypical course of disease	[60]
	Viral infection			Reduces pathogen burden	[61]
CIITA/MHC II signaling	EAE	Upregulates IFN-γ, IL-2		Worsens outcomes	[62]
IFN-γ signaling	EAE	Downregulates CCL5, IL-1β, TNF-α		Improves outcomes	[63]
ER1-α signaling	EAE		Reduces CD11b + CD45hi macrophage and CD3+ CD45hi T lymphocyte infiltration	Reduces demyelination, improves outcomes	[64]
Act/IL-17 signaling	EAE	Upregulates CXCL2, CXCL20	Increases F4/80+ macrophage, Ly6G+ neutrophil, and CD4+ and CD8+ T lymphocyte infiltration	Worsens outcomes	[65]
FasL expression	EAE	Downregulates GM-CSF, IFN-γ, IL-17 IL-23, TNF-α	Reduces CD4+ T lymphocyte infiltration, increases FoxP3+ Treg differentiation	Reduces demyelination, improves outcomes	[66]
IL-12 expression	EAE			Accelerates disease onset	[67]
TGF-β expression	EAE		Increases MHC II+ myeloid cell infiltration	Worsens outcomes	[68]
TGF-β signaling	Ischemia	Upregulates itself and thrombospondin-1	Reduces myeloid cell infiltration and activation	Improves functional outcomes	[69]
	Parasitic infection	Limits astrocytic NF-kB signaling and CCL5 release	Limits T lymphocyte infiltration and myeloid cell activation	Limits neuronal death	[70]
No pathway manipulated	Parasitic infection	CCL2, CXCL10			[71]
No pathway manipulated	Bacterial infection	CCL2			[72]
	Bacterial infection	CXCL1, CXCL10			[55]

Table 2 (continued)

Signaling pathway	Injury	Chemokines and cytokines released by astrocytes	Changes in the immune response	Changes in outcomes	Reference(s)
Gp130/IL-6 signaling	EAE	Upregulates TGF-β2; downregulates IFN-γ, IL-17, IL-23	Inhibits CD4+ and CD8+ T lymphocytes, increases FoxP3+ Tregs	Reduces demyelination, improves outcomes	[52]
	Parasitic infection	Upregulates IL-27; downregulates IFN-γ		Reduces pathogen burden, improves recovery	[53]
GFAP expression	Parasitic infection			Reduces pathogen burden	[54]
	Bacterial infection	Downregulates IFN-γ, IL-27	Inhibits MHC II+ myeloid cell infiltration	Reduces pathogen burden, improves recovery	[54]
No pathway manipulated	Viral infection	CX3CL1			[73]
	Viral infection	CXCL10			[74]
	Viral infection	CXCL1			[75]
	Viral infection	IL-1β, IL-6, TNFα			[76]
TLR3/PI3K signaling	Viral infection	CXCL10, IFN-β, TNF-α			[77]

For each signaling pathway, the normal pathophysiological role of the pathway is stated. CCL2 = chemokine (C-C motif) ligand 2; CXCL1 = chemokine (C-X-C motif) ligand 1; CXCL2 = chemokine (C-X-C motif) ligand 2; CXCL10 = chemokine (C-X-C motif) ligand 10; IL = interleukin; SCI = spinal cord injury; NF-kB = nuclear factor kappa B; TNF = tumor necrosis factor; iNOS = inducible nitric oxide synthase; TGF = transforming growth factor; EAE = experimental autoimmune encephalomyelitis; CCL5 = chemokine (C-C motif) ligand 5; CXCL9 = chemokine (C-X-C motif) ligand 9; IFN = interferon; TBI = traumatic brain injury; Ly6G = lymphocyte antigen 6 complex locus G6D; CCL12 = chemokine (C-C motif) ligand 12; CIITA = class II major histocompatibility complex transactivator; MHC = major histocompatibility complex; CX3CL1 = chemokine (C-X3-C motif) ligand 1; ER = estrogen receptor; FasL = Fas ligand; CXCL20 = chemokine (C-X-C motif) ligand 20; GM-CSF = granulocyte-macrophage colony stimulating factor; FoxP3 = forkhead box P3; Treg = T regulatory lymphocyte; Gp130 = glycoprotein 130; GFAP = glial fibrillary acidic protein; TLR3 = Toll-like receptor 3; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase

comparison, the acute phase of bacterial, viral, and parasitic infections is defined as the initial pathogen invasion of the CNS, which can take hours to weeks, depending on the pathogen and the route of infection [28, 54, 70, 80]. Astrocytes are strongly activated during this acute phase of infection as well as at the first peak of immune infiltration in models of autoimmune encephalomyelitis [50].

Regardless of the cause of CNS injury, the response of reactive astrocytes can be summarized by 2 general mechanisms that share the purpose of limiting inflammation. Conceptually, these 2 mechanisms produce a double barrier. The first, "physical", barrier is the astrocytic scar, which is formed by polarized bundles of reactive astrocytes together with ECM components and physically surrounds the injured region [34]. Although there is some evidence that ECM components can directly activate immune cells after injury [81], the primary role of the ECM remains structural; therefore, for the purpose of this review it will be classified as part of the physical barrier. The second, "molecular", barrier is composed of the signaling molecules that are produced and secreted by astrocytes to regulate the infiltration and activation of immune cells. These molecules, which include chemokines and cytokines, are not fixed to a specific physical location but instead diffuse away from reactive astrocytes, creating signaling gradients throughout the injured tissue. Finally, reactive astrocytes may indirectly modulate inflammation by altering neuronal responses to ongoing metabolic and toxic injuries.

Reactive Astrocytes Form a Physical Barrier

The physical barrier formed by astrocytes has primarily been studied not only in the context of traumatic brain and spinal cord injuries but also occurs after stroke [22, 34]. It primarily serves to wall off and limit inflammation to the injured region (Table 1). It is formed by proliferating astrocytes that upregulate intermediate filament proteins, including GFAP and vimentin [82]. In addition, astrocytes adjacent to the injury site change their morphology to become hypertrophied, elongated, and polarized. During polarization, elongated astrocytes aggregate into bundles that are clustered first orthogonal, and then parallel to the injury site. These astrocyte bundles surround the injured tissue and invading immune cells [34, 47]. Although the astrocytes farther away from the injury site also become hypertrophied, they do not form bundles, and retain their original nonoverlapping domains instead [83, 84].

Reactive astrocytes further strengthen the physical barrier to inflammation by augmenting intercellular connections and by producing ECM components. After injury, reactive astrocytes upregulate connexin family proteins, which form gap junctions and thus augment intercellular connections [85]. In addition, reactive astrocytes upregulate the expression of ECM proteins fibronectin, laminin, and tenascin [41–43]. as well as chondroitin sulfate proteoglycans (CSPGs), including neurocan, CSPG4 (also known as nerve/glial antigen-2) and CSPG6 [39, 41, 43, 86–88]. These ECM components combine with polarized astrocytes to form a tight barrier that physically impedes immune cells from escaping the injury site. During infection, a similar physical barrier is formed by $GFAP^+$ hypertrophied astrocytes and ECM components. This barrier surrounds the infectious foci that contain pathogens, damaged neurons, and invading immune cells [76, 89–91].

The reactive astrocyte barrier is crucial for localizing immune cells and, when present, infectious pathogens in the injured region. For example, ablating proliferating $GFAP^+$ cells exacerbates immune cell infiltration in rodent models of TBI and experimental autoimmune encephalomyelitis [44, 50]. Similarly, knocking out GFAP increases the pathogen burden during a bacterial infection with *Staphylococcus aureus* or a parasitic infection with *Toxoplasma gondii* [54]. In contrast, knockout of GFAP by itself does not affect stroke size [30]. Since GFAP is a structural protein, these results likely represent the functions of the physical, rather than molecular, barrier formed by astrocytes.

Although the physical barrier formed by astrocytes is essential to limit tissue damage during peak inflammation, its role in the late postinjury period has not been as clear. There is some evidence that it can become disadvantageous later after injury by preventing axonal outgrowth and behavioral recovery. In particular, CSPGs that are produced in the scar have been shown to impede axonal outgrowth [92–94]. Similarly, although astrocyte proliferation and upregulation of ECM components limit cell loss early after TBI, they are also associated with less axonal outgrowth and worse motor outcomes later in the recovery period [39]. However, recent groundbreaking work in SCI has demonstrated that exogenous growth factor application can improve axonal outgrowth more effectively in the presence of a normal scar than in animals with impaired astroglial scar formation [37].

Reactive Astrocytes Secrete a Molecular Barrier

In addition to forming a scar around the injury site, reactive astrocytes can regulate the immune response by secreting chemokines and cytokines that diffuse throughout the injury site and surrounding regions. This molecular barrier to inflammation mediates immune cell infiltration and function in injuries that evoke both innate and adaptive immune responses. Intracellular signaling pathways of chemokines and cytokines in astrocytes, as in other immune cells, interact in networks that contain both pro- and anti-inflammatory components (Tables 2 and 3).

Table 3 Astrocytic responses to central nervous system (CNS) damage signals that alter neuronal function

CNS damage signal	Condition	Astrocytic homeostatic response	Astrocytic immune response	Consequences	References
Metabolic need	Excitotoxic damage	Upregulates astrocyte lactate and glutamate transporters		Improves neuronal resistance to excitotoxicity	[95]
	Stimulation with proinflammatory cytokines (IL-1β, TNF-α)	Reduces glycogen storage and lactate transport			[96]
Glutamate	Models of multiple sclerosis	Increases glutamate transporter expression and glutamate uptake		Reduces excitotoxicity and associated damage	[97]
	Stimulation with proinflammatory cytokines, reactive oxygen and nitrogen species	Increases glutamate transporter expression		Reduces excitotoxicity and associated damage	[98]
	Stimulation with proinflammatory cytokines	Releases glutamate in a calcium-dependent manner		Increases excitotoxicity and associated damage	[99]
	IL-1β signaling in viral encephalomyelitis	Reduces glutamate transporter expression	Increases immune response	Increases neuronal damage	[100]
	Stimulation of astrocytic glutamate receptors		Reduces astrocytic CCL5 secretion		[101]
	TNF-α signaling	Increases glutamate release		Increases excitotoxicity and associated damage	[102]
Potassium and/or associated neuronal hyperexcitability	Ischemia	Causes potassium uptake		Reduces neuronal depolarization and associated damage	[103]
	Epilepsy (mouse model)		Increases astrocytic IL-1β expression, increase immune response		[104]
	Epilepsy (human samples)		Increases astrocytic NF-kB signaling		[105]
	Potassium signaling via pannexin channels	Increases ATP release	Increases astrocytic inflammasome signaling	Increases apoptosis	[106]
ATP release	Increased ATP in human astrocytes		Increases astrocytic inflammasome signaling, IL-1β production		[107]
	Increased ATP in mouse spinal cord astrocytes		Increases astrocytic IL-6 and TNF-α production		[108]
	ATP receptor activation in cultured mouse astrocytes		Increases astrocytic CCL2 production		[109]
	Increased ATP in mouse astrocyte culture	Increases glutamate transporter expression and glutamate uptake		Increases excitatory postsynaptic current frequency	[110]

IL-1β = interleukin; TNF = tumor necrosis factor; MS = multiple sclerosis; CCL5 = chemokine (C-C motif) ligand 5; NF-kB = nuclear factor kappa B; ATP = adenosine triphosphate

The innate immune response is immediate, stereotyped, and forms the first line of defense against injury. In stroke, it typically peaks between 12 h and 3 days after the injury occurs [111]. The innate response has both humoral and cellular components. The humoral component of the innate immune response includes the complement system and blood coagulation cascades, while its cellular component consists of basophils, eosinophils, mast cells, natural killer cells, and myeloid cells. Activated myeloid cells perform phagocytosis, which is essential to clear pathogens and dead cell debris from the injury site (reviewed in [112]). Acute injury or infection in the CNS attracts and activates both peripheral myeloid cells, such as macrophages and neutrophils, and CNS-resident myeloid cells - microglia.

By contrast, the adaptive immune response develops over a longer time scale, typically peaking between 1 and 3 weeks, depending on the injury or pathogen [69, 113]. Adaptive immunity is activated and stimulated by components of the innate immune response, and has been well reviewed elsewhere [114–118]. The adaptive immune response is initiated by antigen presentation using major histocompatibility complex (MHC) II molecules, which are expressed on proinflammatory myeloid cells. The effector cells of the adaptive immune response are T and B lymphocytes, which invade the inflamed CNS from the periphery and destroy pathogens both by direct cytotoxicity and by antibody-mediated responses. Reactive astrocytes can regulate the adaptive immune response by releasing cytokines and chemokines, some of which are also used to mediate the innate immune response [119].

Astrocytes are commonly considered part of the cellular component of the innate immune response. Indeed, astrocytes act as key but not sole controlling members of the networked immune response to injury. While they instruct microglia, peripheral macrophages, and other immune cells they, in turn, also receive reciprocal signals from those cells. However, unlike other immune cells, astrocytes are CNS-derived and fine-tuned to sense changes in neuronal function. Their ability to sense both neuronal firing and immune responses, and their anatomical tiling within the brain makes astrocytes well-suited to determine the site, size, and character of the immune response.

Astrocytic Regulation of the Innate Immune Response

One of the functions of reactive astrocytes after CNS injury is to release molecules that attract immune cells specifically to the injured region and facilitate their infiltration from vasculature into the CNS tissue. In models of ischemia, bacterial infection and EAE, astrocytes express leukocyte adhesion molecules, such as intercellular adhesion molecules and vascular cell adhesion molecules [31, 51, 55]. Astrocytic nuclear factor kappa b (NF-kB) signaling has also been demonstrated to increase both intercellular adhesion molecule and vascular cell adhesion molecule expression in tissue [31]. These leukocyte adhesion molecules may stimulate the extravasation of immune cells into the site of injury.

In addition, reactive astrocytes release chemokines, which bind to specific receptors on both peripheral and CNS myeloid cells to attract them to the site of injury. For example, astrocytes are an important source of the peripheral macrophage chemoattractant C-C motif chemokine ligand 2 (CCL2; also known as macrophage chemoattractant protein 1) in TBI and parasitic infection [58, 71]. Astrocytes also produce the microglial chemoattractant chemokine CXC3L1 (C-X3-C motif ligand 1) in response to viral and prion infections, and the neutrophil chemoattractant chemokine CXCL1 (C-X-C motif ligand 1) after spinal cord injury [56, 73, 120].

After entry into the brain (unless already present, as is the case with microglia that are at the injury border) innate immune cells exhibit a complex array of phenotypes, which can be pro- or anti-inflammatory, and many cells may express cytokines and chemokines consistent with both. This is reviewed in depth elsewhere in this issue by Kim and Cho [121], and recently by Cuartero et al. [122]. More simplistic functional phenotypes can be useful to represent what is happening at set timepoints in an injury or infectious response. Proinflammatory macrophages and activated microglia express high levels of MHC II, present antigens to T lymphocytes and further activate both adaptive and innate immune responses by releasing proinflammatory cytokines, such as interleukin (IL)-1β, interferon (IFN)-γ and tumor necrosis factor (TNF)-α [123]. Proinflammatory macrophages can also be neurotoxic, for example, by expressing inducible nitric oxide synthase, which induces the formation of reactive oxygen and nitrogen species and causes free radical damage to surviving tissue [124]. This is also exemplified by data on phagocytosis after stroke, where microglial phagocytosis after neonatal stroke is beneficial [125] but phagocytosis after stroke can also cause bystander injury to neurons [126].

By contrast, anti-inflammatory macrophages are defined by lower MHC II expression, reduced antigen presentation and lower inducible nitric oxide synthase production. Their major function is to dampen inflammatory responses by expressing the anti-inflammatory cytokines IL-4, IL-10, and tumor growth factor (TGF)-β [127] (reviewed in [128]). Anti-inflammatory macrophage responses may function to limit damage that could otherwise be caused by excessive inflammation. For example, IL-4, IL-10, and TGF-β are all neuroprotective in stroke models [129–131].

While it is clear that astrocyte functions after stroke are overall beneficial [30], it is likely that careful coordination of both pro- and anti-inflammatory innate immune responses is required to maximize recovery after stroke. Reactive astrocytes play an essential role in regulating immune responses by releasing cytokines that can stimulate macrophages to adopt either pro- or anti-inflammatory phenotypes. The specific immunoregulatory mechanisms that are likely employed by astrocytes after stroke can be extrapolated from research in other

models of neuroinflammation. For example, after injury or infection, astrocytes can release cytokines that induce more proinflammatory microglia and macrophages (IFN-γ, IL-12, and TNF-α) [76, 77, 132]. However, under similar conditions, astrocytes also have been shown to produce the anti-inflammatory cytokines IL-10 and TGF-β, which could then induce monocytic lineage cells to alter towards less inflammatory phenotypes [32, 55, 76].

Activated microglia can release chemokines such as CCL2 and CXCL1, as well as the proinflammatory cytokines IL-12 and TNF-α, and the anti-inflammatory cytokines IL-10 and TGF-β [133, 134]. Thus, reactive astrocytes could potentially affect the molecular barrier not only by directly producing chemokines and cytokines, but also indirectly, by stimulating the chemokine and cytokine secretion from activated microglia and invading macrophages.

Astrocytic Regulation of the Adaptive Immune Response

In an analogous role to their functions in the innate immune response, reactive astrocytes are a major source of T and B lymphocyte chemoattractants during the adaptive immune response. They express the T lymphocyte chemoattractants CCL5, and CXCL10 in infection models [57, 74, 75]. In addition, human astrocytes express the B lymphocyte chemoattractant B-cell activating factor, as well as the T lymphocyte chemoattractant CXCL12, in brain samples from patients with multiple sclerosis [135, 136].

However, controlling T lymphocyte migration is not sufficient to regulate the adaptive immune response, because once T lymphocytes invade the injured tissue, they can differentiate into distinct functional subtypes, which have both beneficial and toxic functions. For example, $CD4^+$/IFN-γ^+ T helper (Th) 1 lymphocytes are primarily neurotoxic, while $CD4^+$/$FoxP3^+$ T regulatory lymphocytes are neuroprotective (reviewed in [137]).

In models of injury, EAE and infection, reactive astrocytes release cytokines that can induce T lymphocytes to adopt either pro- or anti-inflammatory phenotypes. Astrocytes that are stimulated by EAE or infectious pathogens *in vivo* primarily release proinflammatory cytokines, such as IFN-γ, TNF-α, and IL-17, but also anti-inflammatory IL-10 [32, 52, 62, 63, 66]. Meanwhile, in a SCI model reactive astrocytes release anti-inflammatory TGF-β [33].

Astrocyte Immunoregulatory Functions are Shaped by the Intracellular Signaling Pathways that are Activated After Injury

In a similar manner to the astrocyte physical barrier, the molecular barrier to inflammation is controlled by which intracellular signaling pathways are activated in astrocytes (Table 2). Transcriptome analyses of reactive astrocytes after stroke and in a model of bacterial infection revealed that there is a partially overlapping set of activated intracellular signaling pathways and astrocytic components of the molecular, as well as the physical barrier that are upregulated in each condition [55]. Studies on how astrocyte transcriptomes are shaped by proinflammatory stimuli such as lipopolysaccharide and IFN-γ *in vitro* and an anti-inflammatory stimulus, TGF-β, *in vitro* and *in vivo* have further demonstrated how intracellular signaling shapes the pattern of gene expression [138, 139].

The cues that determine whether astrocytes will shape innate and adaptive immune cells to adopt a proinflammatory or an anti-inflammatory phenotype are not completely understood. However, emerging evidence supports a model where astrocytes become pro- or anti-inflammatory based on which of their intracellular signaling pathways get activated.

NF-kB and IL-17 pathways appear to be proinflammatory in reactive astrocytes. Thus, inhibiting astrocytic NF-kB is strongly anti-inflammatory in SCI, ischemia, and EAE [31–33]. Similarly, astrocytic knockout of Act1/IL-17 signaling prevents the IL-17-mediated induction of proinflammatory cytokines in EAE [65].

However, astrocyte signaling that involves either gp130 or estrogen receptor 1α is anti-inflammatory. Astrocytic deficiency of gp130 signaling, which is a receptor for the cytokine IL-6, exacerbates inflammatory cytokine production in EAE and in parasitic infection [52, 53]. Conditional deletion of estrogen receptor 1α in astrocytes leads to similar outcomes in EAE: it increases both myeloid and lymphoid cell infiltration and reduces survival [64].

Reactive astrocytes can be induced to adopt a proinflammatory phenotype not only by inhibiting an anti-inflammatory signaling pathway, but also by overexpressing proinflammatory cytokines. Thus, increasing astrocytic production of proinflammatory cytokines, including TNF-α, IL-12, IL-17, or the T lymphocyte chemoattractant CXCL10, exacerbates T lymphocyte and myeloid cell infiltration into the CNS at baseline and in EAE [67, 140–144]. Similarly, overexpressing astrocytic IL-6 increases immune cell infiltration in SCI and EAE and reduces pathogen burden during viral infection [59–61]. However, overexpressing the typically anti-inflammatory cytokine TGF-β in astrocytes during EAE also attracts more mononuclear leukocytes [68], possibly owing to its involvement in Th17-mediated autoimmunity [145].

It is difficult to know how much overexpressing cytokines in astrocytes tells us about normal astrocyte function. These studies typically involve a GFAP promoter, which upregulates gene transcription during injury and so to some degree may reflect the physiological increase of each cytokine in reactive astrocytes, but transgenic mouse models may also produce supra-physiologic amounts of any given gene and/or may not replicate physiological time courses. In any case, valuable information may be learned about therapeutic strategies even when the transgenic overexpression of a cytokine is not physiologic.

A second potential confounding factor in studying how astrocytic cytokines regulate the immune response is that many cytokines can directly target invading pathogens or surviving neurons independently from their effects on immune cells. For example, IL-1β is thought to damage neurons in epilepsy directly [146], while TGF-β is neuroprotective in stroke [131, 147] and its signaling is required in neurons to promote survival [148]. Similarly, IFN-γ and IL-6 have been shown to reduce the parasite burden, as well as activate immune cells during *Toxoplasma* infection [149, 150]. In this case, since immune cell activation commonly leads to reducing the parasite burden, it can become difficult to determine which effects of astrocytic cytokines control the immune response, and which alter it by affecting the parasite burden directly.

Reactive Astrocytes can Indirectly Regulate Neuroinflammation by Affecting Neuronal Function and Survival

Astrocytes are physiologically connected to neurons at baseline and retain these connections during injury. Thus, in addition to their immunoregulatory functions, astrocytes can also respond to CNS damage signals by altering neuronal survival and function (Table 3). During injury CNS neurons release a variety of relatively standardized signals; those induced by stroke include excess glutamate, ATP release by injured neurons, and vascular damage.

Dying neurons in stroke, TBI, and during epileptiform activity release glutamate, which is toxic to neurons. However, even at baseline astrocytes are able to counteract glutamate overload by expressing high-affinity glutamate transporters that remove glutamate and protect neurons [151]. In large stroke or other high-stress injuries glutamate uptake by astrocytes is further stimulated by increased extracellular glutamate levels and glucocorticoids [98, 152].

Glutamate signaling in astrocytes also instructs them to reduce neuroinflammation by decreasing CCL5, a major T lymphocyte chemoattractant, *in vitro* [101]. However, inflammation can also impair astrocytic uptake of glutamate, further exacerbating neuronal damage [100], which would, in turn, increase neuroinflammation. For example, when the inflammatory cytokine TNF-α is released by microglia in slice cultures, it signals to astrocytes to release glutamate and amplify excitotoxicity [102].

In summary, astrocyte functions can be viewed as a delicate balance: first, in response to neuronal damage, astrocytes reduce both glutamate excitotoxicity and inflammation, but once the inflammation crosses a certain threshold, it is able to override astrocyte anti-inflammatory functions. This balance is well summarized in a review [98], and appears to be determined by both the type of injury and the cytokines present in the astrocyte environment. It could be speculated that injuries that involve acute changes in glutamate release, such as stroke, TBI, and epilepsy [153], primarily stimulate astrocyte anti-inflammatory functions in response to glutamate. Meanwhile, infections and autoimmune disorders, especially those associated with the release of TNF-α [154, 155], tend to have a less acute course and appear to override the "typical" astrocyte response of limiting injury and instead increase inflammation and excitotoxic injury.

In addition to glutamate, neuronal death also induces the release of potassium and ATP from dying cells. Both compounds are able to activate the inflammasome, which is an innate immune mechanism to activate inflammation, via pannexin 1 channels. Pannexin 1 is expressed by astrocytes in mice [156] and humans [107] and connects astrocytic cytoplasm to the extracellular space. In the brain pannexin 1 channels are linked with ATP receptors and can also be opened by potassium [106]. Once activated, astrocytic pannexin 1 channels are able to stimulate the inflammasome, which, in turn, increases the expression of proinflammatory mediators, such as IL-1β and reactive oxygen and nitrogen species [157], TNF-α [108], and the myeloid cell chemoattractant CCL2 (macrophage chemoattractant protein 1) [109]. Finally, ATP also binds to astrocytes and induces them to release glutamate, which contributes to excitoxicity [110].

Astrocytes also affect neuronal health directly by providing metabolic support to neurons by releasing stored glycogen, which is converted to lactate and transported to neurons for energy [158]. Increased glucose uptake and lactate delivery improves neuronal resistance to excitotoxicity [95]. Glucose utilization can also be harmful by increasing the production of reactive oxygen and nitrogen species [96], so is tightly regulated. Both glutamate and the proinflammatory cytokines IFN-γ, IL-1β, IL-6, and TNF-α are sufficient to increase glucose utilization in astrocyte cultures, while the anti-inflammatory cytokines IL-4 and IL-10 to reduce glucose utilization [96, 159].

Interactions Between Signaling Pathways in Astrocytes: Integrating the Signal and Future Research Directions

Astrocytes receive and emit many signals, and can exert both harmful and helpful effects on the neuroinflammatory response and neural outcomes after injury. As both neurally derived cells with neural functions and also innate immune cells with immune functions, astrocytes truly sit at the nexus of the nervous system and the immune system. One illustration of this is astrocytic production of thrombospondin-1, which has functions in both the CNS and immune systems. At baseline, thrombospondin-1 reduces angiogenesis [160]

and promotes excitatory synaptogenesis [12]. It is also a strong chemoattractant for monocytes [161], and after stroke, it improves recovery [162].

We are also beginning to understand key intracellular pathways that modify astrocytes. Perhaps unsurprisingly, key immunoregulatory pathways in astrocytes, including NF-kB, STAT3 (signal transducer and activator of transcription 3), and TGF-β signaling mediators, also serve immunoregulatory functions in other cell types. These intracellular pathways influence multiple astrocyte output functions in response to CNS injury (Tables 1 and 2). Astrocytic NF-kB inhibition in EAE reduces the expression of both ECM components and proinflammatory cytokines [32]. Similarly, astrocytic STAT3 signaling inhibition both impedes scar formation and increases immune cell infiltration after SCI [34, 35]. In contrast, astrocytic TGF-β signaling inhibition selectively affects astrocytic cytokine and chemokine production without altering the physical barrier, and seems to act to localize but not specify the immune response [69, 70]. In stroke, astrocytic TGF-β signaling acts to restrict the number of activated microglia and macrophages, while in toxoplasmic encephalitis it restricts the number of T lymphocytes. Notably, in both stroke and toxoplasmic encephalitis, astrocytic TGF-β signaling is required to control the number of invading immune cells and their physical localization but in neither case does it alter the character of the immune response.

Despite all of the recently accumulated knowledge on astrocytic function, our understanding is poised on the cusp of a truly comprehensive knowledge of the complexity of astrocyte functions in neurological disease, and particularly in stroke. Pro- and anti-inflammatory macrophages have been characterized, respectively, as "M1" and "M2", similar to Th1 and Th2 lymphocytes [133]. However, with macrophages the designation has not been as useful as in lymphocyte biology owing to rapid shifts in cell phenotypes along multidimensional axes under different inflammatory conditions. Similar astrocyte polarization in injury states may also occur [163]. In this paradigm "A1" reactive astrocytes are detrimental and "A2" reactive astrocytes are beneficial. Future studies will determine if this is a useful paradigm; in other words, whether there are a limited number of pathways that determine whether an astrocyte is primarily pro- or anti-inflammatory. Or, conversely, it may be that the small number of intracellular pathways that we now know to influence astrocyte output are actually just the tip of the iceberg. Instead, astrocytes may be such complex integrators of their multitudinous inputs that true understanding will require definition of a much higher number of intracellular pathways, and the ways in which they interact, to truly predict the astrocytic output in different disease contexts.

Newer techniques are now available and beginning to yield more information on astrocyte complexity, making it possible to define the signaling pathway networks in reactive astrocytes. These include sorting of individual astrocytes from adult mouse brain [55] and generating astrocyte-specific translatomes directly from spinal cord tissue [37]. Proteomics analysis, similar to studies on multiple sclerosis markers [164], may also aid in identifying astrocyte subtypes, potential novel markers, and intracellular networks. In combination with techniques such as laser-capture microdissection that can identify transcriptomes in cells based on their location relative to the stroke [165], or injury [37], a key objective for astrocyte biologists will be to discover if there exists a set of the main polarizing pathways that are functionally relevant in disease, and to dissect which immune and CNS injury signals induce reactive astrocyte polarization. If all pathways are similarly important, these new techniques should help us understand the rules that astrocytes utilize to integrate the multidimensional input they receive, and allow us to predict their output.

Aside from understanding the multitude of CNS inputs that astrocytes receive from neurons, glia, pathogens, and responding immune cells, we will need to understand how physical and temporal distance from a neurological lesion influences astrocytic responses. In addition, factors that influence systemic inflammatory state (e.g., age, sex, obesity, hypercholesterolemia, and diabetes) are also likely to influence astrocytic immune functions. For example, gut microbiota can influence astrocytic regulation of immune responses [166]. Astrocytes in patients with multiple sclerosis and EAE mice express aryl hydrocarbon receptors that directly respond to microbial metabolites of tryptophan to reduce inflammation and disease severity in mouse models [166]. Finally, there are important differences between mouse and human astrocytes that will be important to understand in order to translate findings in mouse models to humans with neurological diseases [167].

Conclusion

The last couple of decades have greatly enhanced our understanding of astrocytes as participants in and regulators of the neuroinflammatory response in neurological diseases, including stroke.

One major reason that astrocytes are a particularly desirable therapeutic target for stroke is because they can sense and directly affect damaged neurons and also simultaneously regulate inflammation. Also, astrocyte activation is physically restricted to the stroke border and present during the days to weeks after stroke, providing a therapeutically useful time window. Understanding how astrocyte functions are regulated by their intracellular pathways beyond the few described

above will suggest specific therapeutic mechanisms and broaden our understanding of astrocytes as mediators of responses to CNS injury. Eventually, this knowledge could potentially be applied to targeting astrocytes to limit inflammation in other neurological diseases and even to understanding the role of glial cells in immune regulation in organ systems outside the CNS.

Acknowledgments This work was supported by the National Institutes of Health, National Institute of Neurological Disorders and Stroke, R01 NS067132.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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