

New advances on glial activation in health and disease

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Author contributions: Lee KM was primary author on this manuscript; MacLean AG supervised and edited the manuscript.

Conflict-of-interest: The authors declare no conflicts of interest.

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Received: October 28, 2014

Peer-review started: November 6, 2014

First decision: December 12, 2014

Revised: January 23, 2015

Accepted: February 9, 2015

Article in press: February 11, 2015

Published online: May 12, 2015

and neurodegenerative disease are now aimed at targeting astrocyte responses to such insults including astrocyte activation, astrogliosis and other morphological changes, and innate and adaptive immune responses.

Key words: Astrocyte; Microglia; Neuroinflammation; Aging; Alzheimer's; Neurodegeneration

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Core tip: Over the past decade, research has begun to elucidate the role of astrocyte activation and changes in astrocyte morphology in the progression of neural pathologies, which has led to glial-specific interventions for drug development. This review addresses astrocyte response to central nervous system (CNS) injury and disease in relation to astrocyte activation, immune response, and changes in morphology. Further discussion addresses potential therapeutics targeting astrocytes, which consider these heterogeneous responses to CNS insults.

Lee KM, MacLean AG. New advances on glial activation in health and disease. *World J Virol* 2015; 4(2): 42-55 Available from: URL: <http://www.wjgnet.com/2220-3249/full/v4/i2/42.htm> DOI: <http://dx.doi.org/10.5501/wjv.v4.i2.42>

Abstract

In addition to being the support cells of the central nervous system (CNS), astrocytes are now recognized as active players in the regulation of synaptic function, neural repair, and CNS immunity. Astrocytes are among the most structurally complex cells in the brain, and activation of these cells has been shown in a wide spectrum of CNS injuries and diseases. Over the past decade, research has begun to elucidate the role of astrocyte activation and changes in astrocyte morphology in the progression of neural pathologies, which has led to glial-specific interventions for drug development. Future therapies for CNS infection, injury,

INTRODUCTION

In addition to being the support cells of the central nervous system (CNS), glial cells, specifically astrocytes, are now recognized as active players in the regulation of synaptic function, neural repair, and CNS immunity^[1,2]. Astrocytes are among the most structurally complex cells in the brain, and activation of these cells has been shown in a wide spectrum of CNS injuries and diseases. Over the past decade, research has begun to elucidate the role of astrocyte activation and changes in astrocyte morphology in the progression of neural pathologies,

which has led to glial-specific interventions for drug development. Future therapies should look at targeting astrocyte responses to CNS insults including astrocyte activation, astrogliosis and other morphological changes, and innate and adaptive immune responses.

Astrocytes are the most numerous cells in the mammalian brain, yet much remains to be learned about their functional and morphological characteristics. Astrocytes have well-characterized roles in regulating cerebral blood flow, water transport, and extracellular concentrations of ions, metabolites, and neurotransmitters^[3]. Their processes comprise an important component of the blood-brain barrier (BBB), directly contacting endothelial cells with vascular endfeet and contributing to the structural and functional integrity of the BBB. Importantly, astrocytes contribute to the CNS's response to injury and infection^[4,5]. Recent studies have demonstrated the importance of astrocytes in innate and adaptive immune responses in the CNS and the roles that astrocyte morphology plays in these functions.

Astrocyte heterogeneity: Differences between protoplasmic and fibrous astrocytes

Although several types of astrocytes have been identified, pathological studies tend to classify them as protoplasmic or fibrous based on their morphology and localization in the CNS^[6,7]. Protoplasmic astrocytes are found in gray matter and are generally spongiform in nature. The processes of protoplasmic astrocytes spread radially from the cell body and have extensive fine branching that is distributed uniformly around the cell. The dense and complex ramifications of these fine processes extend from the primary processes reaching out to synaptic connections and contributing to metabolic, homeostatic, and BBB functions^[8].

Fibrous astrocytes, on the other hand, are present in white matter and have fewer, but longer, processes that extend along axon bundles providing structural support for axonal tracts^[9]. Studies indicate that both fibrous and protoplasmic astrocytes make contacts with blood vessels^[10]; however, fibrous astrocytes also send processes that contact axons at the nodes of Ranvier^[11] while protoplasmic astrocytic foot processes ensheath neuronal synapses^[12]. Additionally, protoplasmic astrocytes occupy their own domains in relatively independent structural units^[13], defining the micro-architecture of the parenchyma by "tiling" the gray matter. These domains are most clearly defined in areas of high synaptic density, such as the hippocampus, which suggests that domain organization may be important for modulation of synaptic transmission^[14]. Disruption of protoplasmic astrocytic domains is observed during glial scar formation in CNS trauma and infection as well as in the epileptic brain^[15,16]. Fibrous astrocytes, on the other hand, show extensive intersection of their processes, and therefore, do not appear to have the same organization as protoplasmic astrocytes^[17].

Astrocyte functions in the CNS

Gray and white matter astrocytes provide extensive metabolic support to the CNS as well as regulate water homeostasis and energy metabolism^[18]. Through gap junction communication, astrocytes can relay information from neurons to blood vessels in order to coordinate oxygen and glucose delivery with the energy demands of the tissue^[19]. Astrocytes also control extracellular ion concentrations; for instance, clearing extracellular potassium through inward rectifying channels^[20] and gap junction coupling^[21]. Furthermore, glutathione release by astrocytes provides antioxidant support^[22] protecting other neural cell types against the toxicity of various compounds by supplying glutathione precursors to neighboring cells^[23].

Astrocytes greatly outnumber neurons in the brain and play many roles essential for modulating synaptic formation and normal neurotransmission^[24]. Astrocytes have the potential to release their own chemical signals, or "gliotransmitters," such as glutamate, ATP, gamma-aminobutyric acid (GABA), and D-serine through Ca²⁺ mediated exocytosis, diffusion through pore channels, or the cysteine-glutamate antiporter system^[25]. Furthermore, studies have shown that astrocyte-neuron lactate shuttles couple synaptic plasticity and glucose metabolism in order to facilitate learning and memory^[26]. By forming connections to neuronal synapses as well as to each other through gap junctions, astrocytes can modulate neuronal activity and metabolic function.

The tripartite synapse, which includes astrocytic processes at the synaptic cleft, has thus replaced the traditional concept of a synapse as a contact between two neurons^[27]. Recently, Bernardinelli and colleagues demonstrated a bidirectional interaction between synapses and astrocytes^[28]. Synaptic activity, specifically long-term potentiation (LTP), was shown to regulate plasticity of astrocytic processes. In turn, coverage and motility of astrocytic endfeet in hippocampal synapses have been shown to predict synapse stability^[29]. For example, LTP increases the surface area of the astrocyte process enwrapping a synapse and the number of synapses receiving astrocyte coverage^[30]. Dynamic changes in astrocyte morphology were also found in electron microscopy studies of the visual cortex of rats raised in a complex environment^[31,32]. Astrocytes display a structural response to glutamate by increasing the number of astrocytic processes and surface filopodia contacting neuronal synapses^[12]. These actin-based cytoskeletal arrangements are closely linked to transformations in neighboring neuronal and vascular elements and appear as motile as dendritic processes in neurons^[33].

Research increasingly shows that astrocytes also serve important roles as an integral player in the brain's defense system^[6]. In the adaptive immune system, astrocytes have phagocytic and antigen presentation capabilities^[34,35], and summarized in Table 1. Astrocytes are able to express major histocompatibility complex (MHC) class

Table 1 Immunological molecules expressed in astrocytes and associated conditions

Immunological molecules	Effects	Conditions
Class II MHC	Autoimmune reactions	MS
ICAM-1, VCAM-1	Increased expression of pro-inflammatory cytokines	MS, AD
B7 (B7-1, B7-2)	T cell activation and differentiation	EAE
CD40	Promotes production of cytokines, chemokines, and neurotoxins	MS
CD1 (CD1b)	Antigen presentation to specialized T-cells	MS

MHC: Major immunohistocompatibility complex; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; CD: Cluster of differentiation; MS: Multiple sclerosis; AD: Alzheimer's disease; EAE: Experimental autoimmune encephalitis.

I and II antigens and co-stimulatory molecules when stimulated by IFN- γ *in vitro*, which are important in T-cell activation and antigen presentation^[4]. The expression of MHC class II antigens in astrocytes *in vivo*, however, is controversial. Examination of post-mortem samples from multiple sclerosis (MS) patients showed evidence of MHC class II expression in astrocytes located in active MS lesions. Additionally, in MS lesions, reactive astrocytes express CD1 molecules (particularly CD1b), which then present lipid antigens to specialized T-cell subsets^[36], suggesting that astrocytes can participate in the presentation of non-peptide antigens to T cells. When stimulated, astrocytes also produce a wide array of cytokines and chemokines, which serve as immunological mediators in innate immune function^[1]. Glial cells may also perpetuate the progression and severity of brain pathologies associated with chronic inflammation, such as diabetes^[37] and Alzheimer's disease (AD)^[38]. Since astrocytes may serve as potential therapeutic targets, it is important to understand their functional and immunological roles in the CNS.

ASTROCYTE ACTIVATION: OVERVIEW

Astrocytes respond to CNS trauma and infection through a heterogeneous process that occurs on a continuum of molecular and cellular events. Generally, astrocytes react to CNS disturbances with increases in intermediate filament expression, progressive cellular hypertrophy and proliferation^[39,40]. Reactive astrocytes also respond with a diverse combination of intracellular and extracellular events including activation of ERK^[41] and c-Fos^[42] signaling pathways, increased production of cytokines and chemokines, and the recruitment of monocytes/microglia to the injured area^[4]. Recent research suggests that reactive astrocytes are key players in a number of neurological diseases, such as Alexander's disease, amyotrophic lateral sclerosis (ALS), and AD, underscoring the need for a better understanding of reactive astrocytes^[43-45].

Accumulating evidence indicates that reactive astrogliosis is not a simple all or none response. Instead, astrocyte activation is variable in regards to changes in cell morphology, proliferation, and molecular expression, all of which can be modified in a context-specific manner to different CNS insults^[8,16,39,46-48]. Additionally, these molecular and cellular changes are graded in a

manner that coincides with the level of injury to the CNS^[49]. Recent studies monitoring the progression of reactive gliosis show that a wide range of morphological changes occur in astrocytes and that their response varied depending on astrocyte subtype, type of injury and the location relative to the lesion site^[15,50,51]. For instance, gray and white matter astrocytes show different responses in reactive gliosis, with more dramatic morphological changes often observed in the gray matter^[15]. The signals that drive the reactive phenotype also differ with respect to the type and extent of injury sustained^[10,39]. For example, studies indicate that CNS injuries, such as ischemia and stab wounds, produce reactive astrocytes with neural stem cell potential, while astrocytes in neurodegenerative models lack such capabilities^[52,53].

Reactive astrocytes: Beneficial or harmful?

Astrocyte activation has often been classified into two categories: the first of which is beneficial and occurs soon after the CNS insult, and the second, which occurs later, inhibits neuronal regeneration, and contributes to sustained inflammation in the CNS^[54,55]. Perhaps the most well studied astroglial reaction is the formation of the glial scar from proliferative reactive astrocytes. Following an insult resulting in neuronal damage, astrocytes surround and isolate dying neurons. This is thought to prevent contact between dying and healthy neurons, preventing the progression of tissue damage, but may ultimately impede any functional recovery^[56]. Studies examining selectively ablated dividing astrocytes after spinal cord injury found that depletion of reactive astrocytes results in greatly expanded invasion of inflammatory cells beyond the lesion center resulting in a larger lesion volume and more extensive motor deficits^[57]. This suggests that the glial scar prevents inflammatory processes from spreading to healthy tissue. The glial scar reaction also produces a wide range of molecules, including tenascin-C, chondroitin sulfate proteoglycan, and matrix metalloproteinases (MMP), which inhibit axonal regeneration^[58,59].

Alternatively, further evidence shows that cytokine-activated astrocytes produce energy substrates and trophic factors for neurons and oligodendrocytes, aid in antioxidant support, promote revascularization, and restore CNS homeostasis^[60]. For instance, TGF-beta signaling in astrocytes limits immune cell migration and decreases pro-inflammatory cytokine/chemokine

production, limiting neuronal injury in *Toxoplasma gondii* infection^[61]. Astrocytes also defend against oxidative stress, containing high concentrations of antioxidants^[23], and neuroprotection by reactive astrocytes is, thus, thought to occur through upregulation of glutathione following oxidative stress^[62,63].

Intermediate filaments, such as glial fibrillary acidic protein (GFAP) and vimentin, are upregulated in reactive astrocytes. While this increase aids in CNS protection and axonal regeneration, it has proved to be a double-edge sword. Intermediate filaments are thought to assist with synaptic elimination after lesion, guidance of axonal regrowth, formation of neuromuscular contacts, and timing of recovery^[64]. Conditional ablation of proliferating astrocytes leads to increased inflammation and increased neuronal death in spinal cord injury models and in experimental autoimmune encephalitis^[10]. However, studies in *GFAP^{-/-}Vim^{-/-}* aged mice demonstrated increased cell survival/proliferation in the hippocampus compared to control mice^[65]. Astrocytes of null mice exhibit fewer morphologic changes and less glial scarring after CNS insult than mice devoid of intermediate filament deficiencies^[66], indicating that chronically reactive astrocytes may restrict neurogenesis with increasing age. Furthermore, the absence of intermediate filament proteins has also been shown to decrease reactive gliosis, and subsequently, photoreceptor degeneration that results from retinal injury^[67].

Astrogliosis can be classified as anisomorphic, where astrocytes surround a lesion forming a glial scar, or isomorphic, whereby astrocytes remain distal to the site of injury and promote neurite outgrowth and facilitate synaptogenesis^[68]. Activation of astrocytes and other glial cells influence the rate and intensity of regeneration of peripheral nerves in the peripheral nervous system after injury^[64]. Experimentally, prevention of reactive gliosis improved the integration of neural progenitor cells grafted into the rodent hippocampus^[69], indicating that the survival and generation of new neurons may benefit from astroglial modifications. Overall, activation of astrocytes may be both beneficial and harmful in the setting of CNS trauma and/or disease. More research is needed to clarify therapeutic potential in astroglial responses.

Functional consequences of astrocyte activation

In the healthy CNS, astrocytes play an important role in maintaining homeostatic balance, directing the development of synapses, uptake and clearance of neurotransmitters, and modulation of cerebral blood flow^[2,19]. However, the degree to which reactive astrocytes maintain these functions, or gain new ones, remains to be elucidated. Recent studies in a transgenic mouse model of AD observed aberrant GABA production in reactive astrocytes surrounding amyloid plaques in the hippocampus^[45]. GABA, an inhibitory gliotransmitter, binds to neuronal GABAergic receptors inhibiting neuronal

synaptic release and impairing synaptic plasticity and memory function. Furthermore, studies in genetic null animal models can examine both benefits and detriments associated with gain or loss of reactive astrocytes^[70]. As mentioned above, loss intermediate filament expression attenuated reactive astrocytosis resulting, in some cases, progression of neuronal death and inflammation, and in others, increased neuronal survival. Further research will clarify the timing and situational consequence of activated astrocytes.

As such, therapeutics targeting astrocyte activation, like a recently developed TrkA agonist, has shown promise by reducing reactive gliosis and subsequent neural sequelae of neuroinflammation^[71]. Additionally, *in vitro* studies have shown that reactive astrogliosis can be suppressed by up-regulation of mitofusin 2 (Mfn2), a key protein in mitochondrial networks^[72]. Increasing Mfn2 expression in cells attenuated injury-induced astrocytic hyperplasia, activation-relevant protein synthesis, and cellular proliferation. Based on the impact of reactive astrogliosis in neurodegenerative pathologies, novel drugs targeting gliosis may be suitable for therapeutic applications in a wide number of neurological conditions.

CHANGES IN ASTROCYTE MORPHOLOGY

It is well established that astrocytes carry the potential to change their morphology in reaction to CNS injury^[73] as well as in interactions with CNS vasculature^[74] and neurons^[12]. In the same way that neuronal dendrites are adaptable and respond to changes in CNS activity by altering their structure, astrocytic processes dynamically alter their morphology and interact with synapses in response to their environment^[75]. Morphological changes in astrocytes have been documented in chronic stress^[76], traumatic brain injury^[77], neurodegenerative disease^[78], CNS viral and bacterial infections^[79,80], and behavioral and mood disorders^[81,82]. Experimentally, changes in astrocyte morphology have been reported after ethanol administration^[83], dietary-induced obesity^[84], and physical exercise^[85]. These structural changes can be detected not only at the level of their cell body and proximal processes, but more importantly, through their fine, lamellate distal processes that surround synapses and ensheath axonal nodes^[86]. Effective regulation of the perisynaptic space is attributed, in part, to astrocyte morphology^[87], and perturbations in fine morphology of these glial cells can ultimately contribute to synaptic dysfunction and disrupted neurotransmission^[88].

Astrocyte hypertrophy

Astrocyte hypertrophy is postulated to serve many functions in neuronal protection and recovery and repair. After traumatic injury, stroke, infection, or other severe CNS insult, areas of focal tissue damage become

filled with inflammatory, fibrotic, and other cells that derive from the perivascular cells, endothelia, bone marrow, and meninges. These tissue lesions become surrounded by reactive astrocytes forming glial scars that serve to separate necrotic from healthy tissue^[10,89]. Astrocytes and other glial cells surround infected or necrotic tissue providing a physical barrier between the CNS insult and healthy tissue. Longer and more complex processes would allow the astrocytes to envelop synaptic terminals and influence synaptic transmission through gliotransmitter release and neurotransmitter clearance^[90,91]. In experimental entorhinal lesions in the rat, hypertrophic astrocytes line the denervated outer molecular layer of the dentate gyrus, potentially providing trophic support for the sprouting process^[92]. Furthermore, astrocytes with more complex morphologies could come about as a compensatory mechanism for neuronal and synaptic degeneration^[93,94]. Studies have shown a significant increase in GFAP-positive hypertrophic astrocytes in the hippocampus in AD patients^[95].

The hypertrophic response in astrocytes may depend on the type and extent of CNS injury. It is hypothesized that glial scars are formed in two ways: one, through newly proliferated, elongated astrocytes that extensively overlap to form scar borders and secondly, through hypertrophic stellate reactive astrocytes that are derived from local populations of mature astrocytes^[51]. In contrast to microglia, which proliferate at a high frequency, reactive astrocytes proliferate very little in chronic disease^[53,78]. In a chronic disease model, low degrees of astrocyte proliferation were observed in the presence of pronounced astrocyte hypertrophy^[53]. Hypertrophy, but not proliferation, of GFAP-positive astrocytes also occurs alongside increased expression of proteins expressed in neural stem cells^[96,97]. Clarifying the roles that subsets of astrocytes have in injury response will have important implications for future therapeutics.

Astrocyte atrophy

While astrocyte hypertrophy/astrogliosis serves to contain brain damage and assist in neuronal survival^[39], the converse can be said about astroglial degeneration and atrophy. Atrophy of astrocyte processes has been detected in normal aging^[98] and chronic stress^[76] as well as in the early stages of various neurodegenerative diseases including AD^[99] and ALS^[44]. Atrophic astrocytes result in reduced support for neuronal networks, which may ultimately decrease neuronal connectivity and plasticity. We have recently shown that, in the setting of simian immunodeficiency virus (SIV) infection and SIV-induced encephalitis, gray and white matter astrocytes retract their processes resulting in an overall decreased arbor irrespective of encephalitic status^[79]. It is hypothesized that reduced numbers of astrocytes is directly linked to disruptions in cognitive behavior and that astrocyte loss may be a primary driver of

pathology^[100,101]. Furthermore, Tynan *et al.*^[76] observed decreases in astrocyte morphology without concomitant reductions in astrocyte number in rodents exposed to chronic stress. We observed similar effects in macaques that exhibited self-injurious behavior, a classic behavior following social stress^[81]. This suggests that atrophy and decreased GFAP expression, rather than reductions in astrocyte number, are related to neuropathological changes in stress and mood disorders^[76].

Conversely, global CNS insults, such as ischemia/hypoxia, induce changes in astrocyte morphology that are distinctly different from focal insults. Studies examining hypoxia/ischemia in the neonatal pig model showed significant decreases in astrocytic processes (length and number) with hypertrophy of the cell body post-insult^[102]. These changes were observed in both white and gray matter astrocytes and were evident as soon as eight hours after the insult and were concurrent with dysfunction in glutamate clearance^[102].

Furthermore, increasing or decreasing the numbers and sizes of astrocytes impacts the volume and alters the composition of the space between astrocytes^[103]. As a consequence of this, there would be neuronal dysfunction through excitotoxicity^[104], homeostatic imbalances^[105,106], damage to synapses^[107,108]. For instance, post-mortem examinations of human brains following TBI show enlarged perivascular spaces, which potentially reflect astrocyte retraction^[109]. The uncoupling of astrocytes and microvascular endothelium can interfere with homeostasis and metabolic support – ultimately resulting in an imbalanced energy supply to the brain^[110].

Factors controlling astrocyte morphology

There are two distinct mechanisms whereby astrocytes can be activated in the absence of infectious agents. In the first, gap junction proteins are down regulated^[111] restricting the overall syncytia of astrocytes. This would also alter the morphology of the astrocytes including the number of synapses they can form with neurons and the BBB. Alternatively, changes in astrocyte morphology can occur as a consequence of immune regulation and inflammation^[112].

Several genes are implicated in morphological alterations in astrocytes. GFAP, an intermediate filament protein highly expressed in white matter astrocytes and a subset of gray matter astrocytes, is thought to modulate astrocyte motility and shape, providing structural stability to processes^[113]. Studies in GFAP-null mice have shown that GFAP as well as vimentin, an intermediate filament necessary to stabilize GFAP, are required for proper glial scar formation in the injured CNS^[66]. Additionally, fibroblast growth factor (FGF) signaling has been shown to be responsible for alterations in astrocyte morphology during glial activation^[114]. The blockade of FGF signaling at the site of reactive gliosis reduced astrocyte branch formation and minimized hypertrophic responses during reactive gliosis. Selective deletion of transcription factor, signal

Table 2 Immune function of astrocytes

Pattern recognition receptors (expressed in astrocytes)	Effects	Conditions
TLRs (TLR2, TLR3, TLR4, TLR5, TLR9)	Upregulation cytokine/chemokine expression, induction of costimulatory molecules	Viral and bacterial infection, DAMPs
NOD receptors (NOD1, NOD2)	Upregulation of pro-inflammatory cytokines through NF- κ B	Bacterial CNS infections
Scavenger receptors (SR-BI, SR-MARCO, RAGE, SRCL)	Mediates adhesion/uptake of A-beta in the CNS	AD
Mannose receptors (expressed)	Receptor-mediated endocytosis, CD4 independent HIV-1 entry	HIV
Complement factors (C1q, C4, C2, C3, C3d, C5, C5b-9, C6, C8)	CNS inflammation, cell activation and astrogliosis	TBI, synaptic plasticity, Pick's disease, MS
Complement receptors (CR1, CR2, C3aR, C5aR)	CNS inflammation, cell activation and astrogliosis	TBI, synaptic plasticity

TLR: Toll-like receptor; NOD: Nucleotide-oligomerization domain; SR: Scavenger receptor; RAGE: Receptor for advanced glycation end products; DAMP: Damage-associated molecular pattern; TBI: Traumatic brain injury; CNS: Central nervous system; SR-BI: Scavenger receptor class B type I; SR-MARCO: Scavenger receptor - macrophage receptor with collagenous structure; SRCL: Scavenger receptor C-type lectin; CR1: Complement receptor type 1; CR2: Complement receptor type 2; C3aR: Complement component 3a receptor; C5aR: Complement component 5a receptor; NF- κ B: Nuclear factor kappa-light-chain enhancer of activated B cells; AD: Alzheimer's disease; HIV: Human immunodeficiency virus; MS: Multiple sclerosis.

transducer and activator of transcription 3, from astrocytes disrupted glial scar borders, which allowed the spread of inflammatory cells from the site of injury and increased neuronal loss^[51]. Furthermore, studies have shown that aquaporin-4 (AQP4) is important for sustaining astrocyte morphology, indicating a functional role of AQP4 in astrocyte plasticity. Knockdown of AQP4 in primary cultures resulted in a drastic reduction in membrane water permeability, impaired cell growth, and altered cell morphology^[115] as well as the down-regulation of three genes (glucose transporter 1, hexokinase, and metallothionein-1) involved in brain edema.

Furthermore, changes in astrocyte morphology may not necessarily be permanent and can change with amelioration of CNS insult^[116] and/or the administration of therapeutic medication (Lee *et al.*, under review). Recovery in changes in astrocyte morphology, such as decreases in process hypertrophy and an increase in primary processes, has been observed two weeks after optic nerve injury^[117]. We showed that changes in astrocyte morphology associated with self-injury in rhesus macaques were reversed with opioid antagonist treatment. Furthermore, valproate has been shown to reduce the overlap between adjacent astrocytic domains seen in epilepsy^[16]. Valproate was also used to treat a transgenic mouse model of AD. The investigators found that APP/PS1 mice had markedly improved symptoms as well as decreased astrogliosis and microgliosis after valproate treatment^[118].

ASTROCYTE ACTIVATION AND INFECTIOUS DISEASE

Immune function of astrocytes

The CNS is considered an immune-privileged system with the presence of the BBB, low levels of MHC molecules, and the absence of lymphatic irrigation^[119]. Increasing evidence shows that astrocytes participate in local innate immune responses triggered by a variety of insults.

Astrocytes are an important source of cytokines and have the capacity to respond to a wide variety of cytokines themselves^[60]. In the resting state, glial cells express a wide variety of receptors for inflammatory cytokines, chemokines, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs)^[120,121]. Once activated, glial cells have the capacity to induce numerous other receptors and inflammatory mediators following stimulation from other CNS cells, infiltrating leukocytes, and/or invading pathogens^[1]. Additionally, both microglia and astrocytes display an array of receptors involved in innate immunity and damage detection, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domains, double-stranded RNA-dependent protein kinases, scavenger receptors, and mannose receptors^[122,123], and summarized in Table 2.

These pattern-recognition receptors detect infectious particles and damage-associated molecules associated with CNS trauma and neurodegeneration^[124]. TLRs, type I transmembrane receptors most commonly found in innate immune cells, are highly expressed in microglia and have also been observed in astrocytes^[125]. Under resting physiological conditions, astrocytes express TLR3^[126] as well as low levels of TLR2, TLR4, TLR5, and TLR9^[127,128]. Binding of PAMPs to TLRs on astrocytes alters cytokine secretion, cytoskeletal protein expression, and adhesion^[126].

Viral infection of astrocytes

Astrocytes can be targeted, as well as directly infected, by several pathogens and possess the ability to recognize structures belonging to various types of pathogens. For example, astrocytes display functional CXCR4 and CCR5 co-receptors, which render them permissive to HIV-1 infection^[129,130]. Direct infection of astrocytes has also been demonstrated in SIV^[131], group B streptococcal bacteria^[132], Borna virus^[133], and herpes simplex virus^[134]. Furthermore, TLRs may also increase or decrease susceptibility to viral infection in astrocytes, depending on the viral agent studied. For example, in rodent models,

Table 3 Mediators of astroglial function

Mediators	Examples	Effects on astroglial function
Cytokines	IL-6, IFN β , TNF- α , TGF- β , GM-CSF, BAFF, IL-1 β , MCP-1, RANTES	Increase BBB permeability, astrocyte activation, endothelial cell activation, microglial and monocyte activation, differentiation and proliferation, immunosuppression, release of neuroprotective mediators
Chemokines	CCL2, CCL5, CCL20, CXCL10, CXCL1, CXCL1, CXCL2, CX3CL1	Recruitment of monocytes and macrophages, dendritic T cells, T and B lymphocytes, and neutrophils/regulation of myelination and microglial activity, astrocyte proliferation and survival, migration of microglia and neural progenitors
Trophic Factors	EGF, FGF, NGF, BDNF, VEGF, IGF1	Astrocyte activation and morphological modification, neuronal/astrocytic survival, differentiation, function, and regeneration, oligodendrocyte survival, remyelination, neurogenesis
Endothelins	Et1, Et3	Inhibit gap junction coupling, disrupts direct intercellular communication in astrocytes, intracellular and extracellular ion homeostasis, metabolic trafficking, cellular swelling

IL: Interleukin; IFN: Interferon; TNF: Tumor necrosis factor; TGF: Transforming growth factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; BAFF: B-cell activating factor; MCP: Monocyte chemoattractant protein; CCL: Chemokine ligand; CXCL: CXC motif ligand; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; NGF: Nerve growth factor; BDNF: Bone derived neurotrophic factor; VEGF: Vascular endothelial growth factor; IGF: Insulin-like growth factor; Et: Endothelin.

TLR3 in astrocytes protect against herpes simplex virus type-2 infection^[134], but has been reported to mediate entry of West Nile Virus into the CNS, causing encephalitis^[135].

Furthermore, recent evidence indicates that TLRs are also capable of sensing endogenous ligands produced during stress or injury called DAMPs, linking TLRs with the host response to CNS damage^[136]. Astrocytes can express receptors for DAMPs^[137]. Endogenous DAMP molecules released from damaged neurons can bind to TLR2 on nearby glia, and in turn, activate glial cells during CNS trauma and infection^[138]. As such, astrocyte and microglial activation was decreased in TLR2-null mice^[138]. Interestingly, studies in an intracerebral hemorrhage stroke model utilizing TLR2-null mice found no differences in microglial activation, indicating that inflammation and neurotoxicity were mediated by TLR2 on astrocytes^[124]. Since TLRs have been implicated in both infectious and noninfectious diseases of the CNS^[122], understanding their potential to influence the course of neuroinflammation is important in developing new therapeutic interventions aimed at minimizing tissue damage during neuroinflammatory disorders.

Following infection and/or activation, astrocytes secrete cytokines and chemokines, such as CXC motif ligand 10 (CXCL10), Chemokine ligand 2 (CCL2), interleukin-6 (IL-6), and BAFF, which influence both innate and adaptive immune responses^[4]. These responses are important in eliciting local CNS immune responses through inflammatory mediators and recruiting additional immune effector cells from the peripheral circulation. Increased CCL2 secretion in astrocytes initiates the recruitment of immune cells and activation of glial cells in the CNS during chronic neuroinflammatory disease and autoimmune inflammation^[139]. Experimentally, astrocytes activated by heat-killed bacteria or lipoproteins react by secreting chemokines, proliferate, or enter apoptosis^[140]. For instance, astrocyte infection by *Brucella* has been shown to induce MMPs, which are known to induce tissue remodeling^[80,141]. In cultured

astrocytes, viral mimic poly(I:C) induces the expression of several cytokines (TNF- α , IL-6, IFN β , granulocyte-macrophage colony-stimulating factor and transforming growth factor) and chemokines (CCL2, CCL5, CCL20, CXCL8 and CXCL10)^[142]. Astrocytes can also express receptors for and respond to a wide variety of other growth factors and cytokines, including, but by no means limited to, TNF- α , EGF, FGF, endothelins and interleukins (for review, see^[143]). Such factors can induce the expression of molecules associated with reactive astrogliosis, such as GFAP, and have also been implicated in astrocyte proliferation^[144]. The downstream effects are summarized in Table 3.

Astrocyte contributions to sustained inflammation

Evidence has demonstrated that astrocytes contribute to sustained inflammation in the CNS after trauma or infection^[145,146] and growing research implicates sustained glial inflammation in neurodegenerative disorders^[147]. Chronically activated microglia and astrocytes can release reactive oxygen intermediates, nitric oxide, inflammatory cytokines, which are toxic to neurons. In AD, amyloid β -peptide (A β) peptides activate astrocytes, which increase production of inflammatory mediators^[148]. Furthermore, astrocytes are able to remove and degrade A β , and chronically activated astrocytes may eventually lose their neuroprotective functions^[149]. Furthermore, in a rodent model of multiple sclerosis, investigators found that the enzyme, *LacCer*, which promotes astrocyte activation and controls the transcription of genes related to neuroinflammation and neurodegeneration, is upregulated in astrocytes^[150].

One mechanism by which astrocytes may contribute to sustained inflammation in the CNS is through upregulation of inflammatory pathways modulated by TLR expression. A single injection of LPS in aged rats, which mimics systemic infection in the elderly, resulted in sustained astrocyte activation and prolonged increases in cytokine expression^[151]. Increases in astrocytic TLR2 have been implicated in sustained inflammation

by increasing the likelihood of the cells to respond to subsequent inflammatory insults^[152]. HIV infection increases TLR2 expression in astrocytes, which can increase susceptibility to additional insults, either from a secondary/opportunistic infection or from a second round of virus entering the brain^[79,153]. Additionally, enhanced TLR expression would upregulate the secretion of proinflammatory cytokines by astrocytes^[154,155], triggering a self-sustaining inflammatory loop and long-term glial activation.

Astrocytes can release both pro- and anti-inflammatory factors, contributing crucially to inflammatory processes in the CNS. In addition, the astrocytes that are part of the BBB are among the first cells to encounter blood-derived leukocytes entering the brain during certain types of neuroinflammatory insult^[156]. Increased leukocyte migration also occurs in neurological conditions such as stroke or multiple sclerosis. As such, astrocytes are strategically located to influence direct interactions with leukocytes or interaction with endothelial cells of the BBB^[157]. Under inflammatory conditions, the integrity and function of the BBB is modified and enables greater leukocyte passage into the CNS^[158]. Recent studies examining human T-lymphocytic virus type-1 infection in the CNS show that astrocytes contribute to positive feedback loop that promotes chronic inflammation. Infected T cells produce INF- γ , which causes astrocytes to secrete CXCL10 and recruit more infected T cells, creating an immunological positive feedback loop^[159]. Another study by Owens and colleagues demonstrate that astrocyte ablation results in enhanced inflammatory monocyte cell migration into the CNS^[160,161]. Furthermore, astrocytes mediate microglial activation through RANTES-dependent mechanism in Borna disease virus infection^[162], indicating that activated astrocytes produce soluble factors that activate microglia.

Therapies targeting astrocyte contributions to chronic inflammation

Chronic activation of the innate immune system can indirectly contribute to neuropathology and neuronal death. Sustained neuroinflammation is implicated in HIV-associated neurocognitive disorder^[163], neurodegenerative disease^[150], and chronic pain^[164], and compromises CNS function causing progressive neurodegeneration and BBB compromise^[165]. In the clinical setting, pharmacological antagonists and immunosuppressive agents can be used to prevent chronic CNS inflammation responses. Such therapies can be appropriated from existing medications or can be the result of new developments in glial-activated neuroinflammation research^[166]. The development of novel therapeutic interventions targeted at glial activation pathways and glia-mediated inflammation appears to be promising and may lead to more effective prevention and treatment of neuroinflammation and resulting pathologies. For example, riluzole, the only FDA-approved treatment for

amyotrophic lateral sclerosis (ALS), enhances astrocytic glutamate uptake through increased GLT-1 activity reducing the activation of neurons by glutamate^[167]. Riluzole also stimulates astrocytic synthesis of NGF, BDNF and GDNF in culture^[168] as well as increase levels of BDNF and TGF-1 β in patients with Huntington's disease^[169]. Further research into novel methods for targeting inflammation by reducing the activity of glutamatergic system activation are thus necessary^[112].

Generally, astrocytic function in neuroprotection is greatly compromised during chronic neuroinflammation. New perspectives for therapeutic approaches include the replacement of dysfunctional astrocytes or pharmacological treatments that specifically target detrimental signaling pathways while preserving their neuroprotective functions. Signaling pathways, such as JNK and p38 MAPK, were found to be relevant to reactive gliosis in response to a variety of cytokines and pathogenetic stimuli; and as such, several MAPK inhibitors have been characterized *in vitro* and in animal models as potential therapeutic interventions targeting reactive astrocytes^[170,171].

Chronically proinflammatory astrocyte and microglia phenotypes, showing a reduction in genes involved in neuronal support and neuronal signaling, may contribute to neuronal dysfunction and cognitive decline in AD^[172]. Astrocytes contribute to the clearance of amyloid β -peptide^[173]. In sporadic AD, impaired removal of A β contributes to elevated extracellular levels that drive amyloid plaque pathogenesis. Enhancing lysosomal function in astrocytes with transcription factor EB, a master regulator of lysosome biogenesis, could promote A β uptake and catabolism and attenuate plaque pathogenesis^[174]. Furthermore, reactive astrocytes have recently been shown to produce and release the inhibitory gliotransmitter, GABA, which impaired synaptic plasticity in a rodent model of AD^[45]. Increased GABA synthesis and/or release may become a therapeutic target for treating memory impairment in neurodegenerative disease.

DIRECTIONS AND THERAPEUTICS

Research into the morphological changes in astrocytes will provide insight into the pathophysiology of the disease. In the future, disease models will consider "gliopathies" as a part of disease etiology. Further research on acute changes in astrocyte morphology would help elucidate the dynamics of astrocyte morphology. For example, analysis through the xCELLigence system provides data output in real time and is thought to measure cell adhesion^[175]. Studies using the xCELLigence system have shown that astrocytes exposed to cytokine treatment show loss of cellular adhesion^[176] and cell death^[177]. These changes occurred 24-48 h prior to astrocyte cell loss, demonstrating the ability of xCELLigence to detect changes in astrocyte composition long before cell death.

Furthermore, targets of intervention would seek to limit the inflammatory process where inflammatory environment is cytotoxic to the surrounding cells, or where glial cell damage would impact the ability of the CNS to repair itself. Reactive astrocytes have already emerged as an attractive target for improved recovery after stroke^[178]. Regardless of the type of ischemic injury, reactive astrocytes express hyperpolarization-activated cyclic nucleotide-gate channels, which have potential as a therapeutic target in post-stroke therapy^[179]. Post-traumatic axonal regeneration can be enhanced by inhibition of chondroitin sulfate proteoglycans produced by reactive astrocytes^[180].

Potential therapeutics targeting astrocytes should consider the heterogeneous responses to CNS insults including astrocyte activation, astrogliosis and other morphological changes, in addition to innate and adaptive immune responses. A key role in establishing a therapeutic intervention for astrocytes in CNS insults would be to clarify of the role of glial activation and the formation of the glial scar. A hallmark of CNS injury of any origin is the formation of scar tissue composed of activated or reactive astrocytes and microglia surrounding a distinctly inflammatory response. The cost-benefit analysis of the formation of this scar is debated as it restricts axonal growth within the lesion. However, several studies indicate that this process may have potential neuroprotective functions. Reactive astrocytes can also serve as potential sources of new neurons in the brain, replenishing the neurons damaged by neurodegenerative disease. Guo and colleagues have demonstrated the reprogramming of reactive astrocytes generated by brain injury or in a mouse AD model into functional glutamatergic neurons *in vivo*^[181]. Astrocytes represent an important therapeutic target in a number of neurological conditions, specifically where astrocyte activation exacerbates brain injury or where astrocyte loss may reduce BBB integrity or neuronal support. While CNS research in the past decade has dramatically shifted its focus to include astrocytes and other glial cells, more research to further clarify the roles of these cells in CNS injury and damage is needed to produce effective therapeutic interventions.

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P- Reviewer: Pimentel-Coelho PM, Riva N **S- Editor:** Ji FF

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