Opposing Roles for Reactive Astrocytes following Traumatic Brain Injury

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Key Words

Glia • Neurotrauma • Astrocyte • Gliosis • Neuroprotection • Inflammation • Brain edema • Controlled cortical impact, synaptic

Abstract

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States. Current medical therapies exhibit limited efficacy in reducing neurological injury and the prognosis for patients remains poor. While most research is focused on the direct protection of neuronal cells, non-neuronal cells, such as astrocytes, may exert an active role in the pathogenesis of TBI. Astrocytes, the predominant cell type in the human brain, are traditionally associated with providing only structural support within the CNS. However, recent work suggests astrocytes may regulate brain homeostasis and limit brain injury. In contrast, reactive astrocytes may also contribute to increased neuroinflammation, the development of cerebral edema, and elevated intracranial pressure, suggesting possible roles in exacerbating secondary brain injury following neurotrauma. The multiple, opposing roles for astrocytes following neurotrauma may have important implications for the design of directed therapeutics to limit neurological injury. As such, a primary focus of this review is to summarize the emerging evidence suggesting reactive astrocytes influence the response of the brain to TBI.

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Traumatic brain injury (TBI) is a leading cause of death and disability in the United States [1], placing a large economic burden on society (~USD 1.8 million/patient) due to a significant loss of productive years and the necessity for long term care. Although preventative measures (e.g. use of helmets, seat belts) have reduced the incidence of TBI, 1.5 million Americans suffer from a head injury annually and up to 2% of the population may live with neurological symptoms resulting from a brain trauma [2]. TBI, which affects twice as many patients as stroke injury, primarily results from motor vehicle accidents, falls, sports-related accidents, and military injuries. Despite exhaustive medical therapy, the prognosis for TBI patients remains poor, due in part to the development of cerebral edema, elevated intracranial pressure, neuronal and vascular injury, and long-term cognitive dysfunction. Thus, an improved mechanistic understanding of the pathogenesis of TBI is needed to develop more proactive strategies for intervention. The identification of novel neuroprotective compounds remains a primary interest; however, other cell types, such as astrocytes, may provide additional therapeutic targets to limit neurological injury. The idea that astrocytes actively contribute to the sequelae following a brain trauma is a relatively unexplored area of research; however, astrocytes may exhibit functions that appear diametrically opposed following neurotrauma. A primary focus of this review is to summarize the emerging evidence suggesting reactive astrocytes may exert both protective and detrimental roles following TBI.

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Role of Astrocytes in Brain Physiology and Disease

The Neurovascular Unit (NVU) is organized into discrete units comprised of neurons, astrocytes, and blood vessels. Astrocytes, the predominant cell type within the NVU, are ten-fold more prevalent in the human brain as compared to neurons [3]. A distinguishing feature of the adult human brain is the complexity and diversity of cortical astrocytes, which are nearly three times larger and contain tenfold more primary processes than rodent astrocytes [4]. Although beyond the scope of this review, the reader is directed toward an excellent, comprehensive discussion of the possible complex roles that astrocytes may serve in the human brain [4]. Although additional studies are required, these interesting findings indicate astrocytes may exert an important influence on human brain function. The dogmatic view of astrocytes as ‘brain glue’, providing structural scaffolding for surrounding neurons and blood vessels, was recently challenged by the notion that astrocytes may actively influence brain physiology [5]. Astrocytes are anatomically in juxtaposition to both neurons and blood vessels and contribute to the formation of the blood-brain barrier (BBB) [6–8], regulate cerebral blood flow in response to neuronal activity [9, 10], provide metabolic substrates for neurons [11, 12], and regulate oxidative balance in the brain [13]. Astrocytes constitutively express multiple ion transporters and neurotransmitter receptors, indicating an important role in the regulation of brain pH and neuronal excitability, and release soluble factors to promote neuronal signaling, survival and synaptic plasticity [14–18]. Furthermore, stimulation of astrocytic metabotropic glutamate receptors causes vasodilation whereas α_1 - or β -adrenergic activation induces vasoconstriction, suggesting astrocytes can also mediate neuronal activity-dependent changes in blood flow [19]. Together, these findings support an active role for astrocytes in the regulation of brain physiology beyond structural support.

Astrocytes: Friend or Foe following TBI?

Although astrocytes clearly promote brain function in the uninjured brain, it remains unclear whether these beneficial roles are preserved, augmented, or lost by astrocytes after a head trauma. Following experimental TBI [20–22] or neurotrauma in humans [23], astrocytes undergo a phenotypic change deemed ‘reactive astrogliosis’, a process characterized by cellular hypertrophy and hyperplasia, cytoplasmic enlargement, elongated cytoplasmic processes, and increased expression of the glial-specific intermediate filament, glial fibrillary acidic

protein (GFAP) [24, 25]. S100 β , a marker of reactive astrogliosis, is elevated in the serum [26, 27] and CSF [28] of TBI patients and serum concentrations of GFAP correlate with clinical outcome following TBI [29]. Taken together, these data imply the magnitude of the astrocytic response may dictate the severity of brain injury in patients. While brain injury correlates with reactive astrogliosis, conflicting data also implicates astrocytes in brain protection/repair following TBI. The evidence documenting the diametrically opposing actions of astrocytes following injury is reviewed in the following sections.

Protective Role of Reactive Astrocytes following TBI

Reactive Astrocytes Restrict Tissue Damage following TBI

Delineating the precise contributions of reactive astrogliosis following brain trauma was previously hindered by the technical difficulties associated with studying the function of astrocytes in vivo. The generation of transgenic mice in which the herpes simplex virus thymidine kinase (HSV-TK) gene was specifically targeted to astrocytes using the glial fibrillary acidic protein (GFAP) promoter, provides a unique experimental model to study the reported conflicting effects of reactive astrocytes following TBI. As GFAP expression is dramatically upregulated following brain injury, subsequent ganciclovir administration (which is converted to a toxic compound by thymidine kinase) ablates reactive astrocytes without affecting nonreactive astrocytes that are spatially removed from the site of injury [30]. Elimination of reactive astrocytes reduced glial scar formation, exacerbated the magnitude and duration of inflammatory activation, and prolonged leukocyte infiltration, as compared to nontransgenic control mice, following forebrain stab injury or spinal cord injury [31, 32]. Conditional astrocyte ablation also exacerbated neural tissue damage and increased the inflammatory response following moderate TBI [33, 34]. These data support the hypothesis that reactive astrocytes form a protective scar to contain the brain injury to a defined region, thereby sparing adjacent non-injured tissue from secondary injury [35]. Reactive astrocytes may also generate an adaptive inflammatory response to aid in the removal of damaged and dead tissue from the site of injury, creating an improved niche for a subsequent reparative response [30, 36, 37].

Reactive Astrocytes Repair the BBB following Injury

The immunologically privileged status of the brain is maintained by BBB, which prevents the entry of large, blood-derived macromolecules. Brain injury increases the permeability of the BBB, promoting vasogenic edema and elevated intracranial pressure. Ablation of reactive astrocytes reversed the endogenous ability of the BBB to repair, denuded astrocytic endfeet from blood vessels, and increased vasogenic edema following forebrain stab wound injury or spinal cord injury [31, 32]. In an eloquent study, restoration of BBB integrity was induced by grafting astrocytes from nontransgenic mice into animals following removal of reactive astrocytes [31], demonstrating an important role for astrocytes in BBB repair following a brain injury. These findings are consistent with increased microvascular damage, disruption of the BBB, and an exaggerated inflammatory response following primary astrocyte loss in rodents [38–40].

Reactive Astrocytes Allow Regenerative Process following TBI

Cognitive dysfunction and long-term disability are a frequent result of diffuse axonal loss and neuronal damage. Reactive synaptogenesis, an endogenous repair mechanism, may provide limited neural regeneration following traumatic axonal injury [41, 42]. Thus, an improved understanding of this process may identify novel therapeutic targets to augment the reparative capacity of the brain. Prior to synaptic repair/regeneration, damaged extracellular matrix proteins must be degraded and cellular debris removed to establish a favorable environment for axonal regeneration. Reactive astrocytes release matrix metalloproteinases (MMP), a class of enzymes that exhibit diverse roles in the brain, including brain remodeling, synaptic function, degradation of the neurovascular matrix, BBB disruption, cerebral edema, and hemorrhagic transformation [43–52]. Of particular interest, MMP-3 modifies damaged extracellular matrix proteins and contributes to the clearance of necrotic debris, suggesting a possible reparative role. MMP-3 is expressed in reactive astrocytes in regions undergoing reactive synaptogenesis following TBI [53], aiding in the establishment of an environment that is conducive for neuritic outgrowth, synaptogenesis, and synapse maturation. In contrast, extended expression of MMP-3 may negatively affect brain recovery, demonstrating the importance of tight spatial and temporal regulation in mediating the biological actions of this enzyme [53]. Together, these data raise the possibility that astrocyte-derived MMP-3 may promote brain recovery and restoration of function-

ally active synapses following brain injury, a finding which could be therapeutically exploited in the future.

Reactive astrocytes may establish an improved niche to permit neuronal reconnectivity and functional brain repair following TBI. Tissue culture studies also support a role for astrocyte-derived soluble factors, including cholesterol [54–56], tumor necrosis factor- α (TNF- α) [57, 58], thrombospondin [59], and TGF- β [14, 60] in directly promoting neuroplasticity and increased synaptic strength. Although significant work remains to delineate the precise functions of these factors following TBI, the temporal expression pattern may determine functional outcome. For example, TNF- α exacerbates neurovascular injury and BBB disruption following TBI [61]; however, continual exposure to glial-derived TNF- α preserved synaptic strength at excitatory synapses, in part, by modulating AMPA receptor trafficking [57, 58]. Thus, TNF- α may exhibit a biphasic effect with the early expression of TNF- α promoting the degenerative process and the delayed expression contributing to synaptic repair. Similarly, TGF- β is produced by reactive astrocytes [62, 63] and is increased in the CSF of TBI patients [64]. Although TGF- β may enhance synaptogenesis [60], it also induces the expression of GFAP, laminin, and fibronectin, which limit axonal regeneration via the generation of the glial scar [63, 65, 66]. Delineating the precise role for each factor following TBI is technically challenging, but the advent of conditional and cell-type specific transgenic mice should provide new insights into the role(s) for these and other factors following brain injury. An improved understanding of the temporal expression and functional roles for each of these factors may result in the development of novel therapeutics, which exploit the beneficial aspects and minimize the detrimental effects of reactive astrocytes.

Potential Damaging Roles for Astrocytes following TBI

Nearly one-third of hospitalized TBI patients die from injuries that are secondary to the initial trauma, including increased neuroinflammation, disruption of the BBB, neuronal excitotoxicity, brain edema, and intracranial hypertension [67]. In addition to displaying protective and reparative functions, reactive astrocytes may also exert detrimental roles to exacerbate secondary brain injury. The following sections provide an overview of the evidence supporting a damaging role for reactive astrocytes following a head injury.

Glutamate Excitotoxicity

Glutamate excitotoxicity is an important cause of neuronal damage following head injury [68, 69]. Concentrations of glutamate within the brain and CSF correlate with the severity of injury following TBI [70–74], supporting a possible benefit of limiting glutamatergic signaling. Consistent with this assertion, administration of antagonists to the NMDA receptor (a glutamate receptor subtype) reduced brain injury in animal models of TBI [31, 75, 76]. Unfortunately, clinical trials with NMDA receptor antagonists were associated with intolerable side effects, poor drug efficacy, limited therapeutic windows, and interference with normal synaptic transmission. Thus, targeting the NMDA receptor likely represents a suboptimal therapeutic target, demonstrating the need to identify novel strategies to limit excitotoxicity [77–80]. The astrocytic glutamate transporters, GLT-1 and GLAST, regulate extracellular glutamate and limit neuronal excitotoxicity by clearing excess glutamate [81–85]. However, both GLT-1 and GLAST are downregulated following TBI in rodents [86] and humans [87], suggesting dysfunctional regulation of astrocytic glutamate transporters may exacerbate neuronal excitotoxicity following head trauma. It is therefore tempting to speculate that modulation of glial glutamate transporters may represent a novel approach to limit secondary excitotoxicity after head injury. Together, these findings imply that preservation of astrocytic function and viability may reduce secondary neuronal injury following TBI, at least in part, by maintaining glutamate homeostasis.

Inflammation

The activation of the complex inflammatory cascade is an important, yet incompletely understood, component of the brain response to an injury. Although it remains controversial whether inflammation is beneficial or detrimental following TBI [88, 89], the acute release of pro-inflammatory cytokines clearly influences multiple cell types in the CNS. This section provides a brief overview of several pro-inflammatory mediators which localize in reactive astrocytes and which may influence outcome following TBI. For more comprehensive coverage of inflammation and head injury, the reader is directed toward several excellent reviews [88, 89].

Tumor necrosis factor- α (TNF- α) is a 17-kDa peptide that activates TNF receptors (TNFR) on glia and neurons [90, 91]. TNF- α is elevated in the CSF of neurotrauma patients within the first 24 h of injury [28] and the acute release of TNF- α from neurons and/or glia is a primary mediator of inflammatory activation and gliosis follow-

ing experimental TBI [92–101]. Mice deficient in TNF- α exhibit improved motor performance, enhanced spatial memory acquisition, and decreased brain injury following TBI, suggesting a possible detrimental role for TNF- α following head trauma [61, 93]; however, another report suggested these mice recovered motor function more slowly than wild-type controls following TBI [102]. Additionally, exogenous TNF- α induced resistance to acidosis and calcium ionophore toxicity in astrocytes [103], indicating a protective function following brain injury [104, 105]. Consistent with a possible beneficial role for endogenous TNF- α , TNFR-deficient mice exhibited an exacerbation of lesion volume and BBB disruption following experimental TBI [106]. These effects were associated with the delayed activation of the NF κ B transcription factor and reduced expression of the antioxidant enzyme, manganese superoxide dismutase (MnSOD), following injury in TNFR-deficient mice [106]. These results suggest endogenous TNF- α may upregulate antioxidant pathways to preserve tissue function. Although the mechanisms underlying these differential effects remain unknown, the divergent effects of TNF- α likely represent a balance between opposing signaling pathways to regulate survival and death [96, 107, 108]. Along these lines, TNF- α induces an acute inflammatory response via activation of NF κ B and AP-1 transcription factors [109–111]; however rapid, transient activation of the JNK signaling pathway, which enhances AP-1 and NF κ B-mediated transcription, induces survival signaling whereas prolonged activation is associated with proapoptotic signaling [108, 112, 113]. Consequently, an improved understanding of the temporal pattern of TNFR activation may provide important new insights into the dual role of TNF- α .

Fas (CD95) is a transmembrane glycoprotein within the TNF- α receptor superfamily that binds Fas ligand (FasL) to regulate microglial apoptosis and pro-inflammatory activation in astrocytes [114]. Fas, which is implicated in excitotoxic neuronal cell death *in vivo* [115], is acutely increased following experimental TBI and remains elevated for more than three days following injury [116, 117]. Fas inhibition attenuates cellular damage following TBI, stroke, and spinal cord injury [61, 118–121], suggesting a detrimental role following brain injury. In contrast, Fas may also promote regeneration within the nervous system [122], including neuritic outgrowth and branching [123, 124], functional recovery following sciatic nerve and spinal cord injury [119, 124], and protection against neurodegeneration in experimental models of Parkinson's disease [125].

Arachidonic acid, which promotes glial swelling and brain edema (see next section for discussion) [126], is converted to prostaglandins by cyclo-oxygenase (COX) enzymes [127–129]. The inducible COX isoform, COX-2, is expressed in both neurons and glia following experimental TBI [130]. COX-2-dependent prostaglandin formation is implicated in brain injury following TBI, including increased white matter injury, vasoconstriction, BBB disruption, brain edema, elevated intracranial pressure, and cognitive and motor dysfunction [129–133]. In support of a damaging role for COX-2, nimesulide, a potent non-steroidal anti-inflammatory drug (NSAID), reversed TBI-induced motor and cognitive dysfunction in rats [133, 134]. In contrast, the FDA-approved COX-2 inhibitor, celecoxib, worsened motor performance following TBI [135] and rofecoxib failed to limit brain injury [132]. Thus, despite a large body of evidence suggesting an injurious role for COX-2, the ability of COX-2 inhibitors to limit neurological injury following TBI remains controversial. Coupled with an increased risk of vascular dysfunction associated with current COX-2 inhibitors, these data do not support therapeutic targeting of COX-2 to improve outcome following brain injury.

IL-1 β is rapidly induced following a brain injury and induces the reactive astrocytotic phenotype [136, 137]. Elevated concentrations of IL-1 β in the CSF of neurotrauma patients are associated with an unfavorable clinical outcome [28, 138, 139] and IL-1 β gene and protein expression directly correlate with injury severity following experimental TBI in rodents [140]. IL-1 β is induced in both neurons and glial cells and the administration of neutralizing antibodies against IL-1 β attenuated hippocampal neurotoxicity following TBI, suggesting an important role for IL-1 β in neuronal injury following brain trauma [125]. In further support of an injurious role, IL-1 β increases the production of other pro-inflammatory mediators, including COX-2, prostaglandins, nitric oxide, matrix metalloproteinases, TNF- α and may regulate further production of IL-1 β , providing a positive feedback loop of inflammatory activation [141–143]. In contrast, IL-1 β may also exhibit protective and/or regenerative effects in the brain by increasing the expression of trophic factors, including fibroblast growth factor [144], transforming growth factor- β 1 [145], ciliary neurotrophic factor [146], nerve growth factor [147], and insulin-like growth factor [148]. As with other astrocyte-derived factors, these data support a dual role for IL-1 β following brain injury and emphasize the likely importance of spatial and temporal regulation in mediating biological activity.

Brain Edema

Brain edema, defined as the abnormal accumulation of fluid within the brain parenchyma, is a serious neurological complication that contributes to elevated intracranial pressure, brain herniation, and a poor prognosis following head trauma [149–152]. Clinically, the degree of swelling on the first computed tomography (CT) scan directly correlates with patient outcome, demonstrating the need to reduce acute brain edema following head injury [153]. The mechanisms underlying the development of brain edema following TBI remain poorly defined; however, both vasogenic and cellular edema may contribute to brain swelling [154]. Vasogenic edema, which originates when fluid from blood vessels enters the brain secondary to traumatic opening of the BBB, was long believed to be the primary form of fluid accumulation [155–157]. In contrast, recent studies suggest cellular edema, which is caused by fluid accumulation within cells following an injury, may be more prevalent following TBI [158, 159]. Disruption of ionic homeostasis following brain injury is a primary cause of cellular edema by increasing sodium entry into the brain, causing tissue swelling [160–162]. Astrocytic swelling, an important component of cellular edema [163], occurs within the first hours following cortical contusion in humans [164] and is associated with the accumulation of extracellular potassium ions and a reduction in extracellular sodium, calcium, and chloride ions [165, 166]. Astrocytic swelling also inhibits glutamate uptake while inducing the release of excitatory amino acids (e.g. glutamate), contributing to the activation of ligand-gated ion channels and ionic movement against the electrochemical gradient [167]. Although significant work remains, the therapeutic targeting of Na⁺/H⁺ transporters, Na⁺/Ca²⁺ exchangers, or Na⁺/K⁺/2Cl⁻ cotransporters may promote a mechanism to restore ionic homeostasis. This possibility is supported by the ability of fluorenyl drugs to alleviate astrocytic swelling and cellular edema following brain injury [168, 169].

Aquaporins, a family of water transporters consisting of 11 members, provide another possible therapeutic target to limit brain water accumulation following head injury. Aquaporin-4 (AQP4), which is expressed primarily in the perivascular endfeet of astrocytes [170], mediates fast water transport in cultured astrocytes [171], suggesting a possible role in the rapid formation of edema following brain injury. While an understanding of the relationship between AQP4 and brain edema remains incomplete [172], AQP4 appears to increase cellular edema, yet aids in the resolution of vasogenic edema [173]. In support of a role for AQP4 in water retention, transgenic mice that

are deficient in AQP4 exhibited improved survival, decreased brain edema, and a reduction in the swelling of pericapillary astrocytic foot processes following ischemic stroke or acute water intoxication model of brain edema [174–177]. With respect to TBI, AQP4 is elevated within or around the injury site and was associated with increased brain edema and disruption of the BBB [135, 178–180], supporting a role for AQP4 in the development of brain edema following TBI. It is also interesting that genetic deletion of AQP4 also attenuated scar formation, an effect which may be attributed to the role of AQP4 in astrocyte migration to the injury site. Although still poorly understood, AQP4 may affect astrocytic morphology during migration and glial scar formation by facilitating water movement [181, 182]. Together, these studies suggest AQP4 may exert diverse roles on astrocytic function following brain injury, implicating AQP4 as a future therapeutic target following brain injury.

Wound Healing

The pioneering work of Ramon y Cajal nearly one century ago remarked that injured axons within the CNS were unable to regenerate following a brain injury. Although protective functions for the glial scar are proposed (see above sections) reactive astrocytes also may limit functional recovery following brain trauma. Within the first days following brain injury, reactive astrocytes restrict tissue injury by migrating from the uninjured tissue to the area of injury. Subsequently, reactive astrocytes express the structural filament proteins, GFAP and vimentin, and interdigitate their processes to create dense plexus – a process called anisomorphic gliosis [183–185]. The newly formed glial scar, which consists of deposited extracellular matrix molecules, likely restricts neural repair and axonal regeneration following TBI [183, 186]. This notion is supported by the observation that axonal regeneration is increased in transgenic mice lacking the genes for GFAP or vimentin, which are preferentially expressed by reactive astrocytes [187]. Chemical removal of glial cells from the medial forebrain bundle following transection of the nigrostriatal tract also resulted in the dramatic and rapid growth of new axons through the gli-

al-free zone [188]. However, astrocytes reappeared within one week and formed an anisomorphic glial scar, which correlated with the absence of new regenerating fibers. Similarly, genetic ablation of reactive astrocytes increased axonal growth following a stab wound injury through the cortex and hippocampus [31]; further indicating the glial scar may limit axonal regeneration following a brain injury. Although these data suggest that removal of reactive astrocytes may be a beneficial therapeutic strategy to promote brain repair, astrocytic ablation was also associated with a failure of the BBB to reseal following injury [31]. These interesting data suggest astrocytes contribute to multiple processes and emphasize the importance of understanding the temporal regulation of reactive astrocytic factors in the pathogenesis of TBI.

Future Roles for Astrocytes as Therapeutic Targets following TBI

TBI remains a major health issue, debilitating or killing a large number of young adults. Unfortunately, most clinical trials have proven unsuccessful and the current treatment strategies remain limited. Although the precise contributions of reactive astrocytes to the pathogenesis of TBI remain controversial and largely unexplored, recent data suggest the possibility of targeting astrocytes to limit neurovascular injury and promote functional brain repair. For example, an improved understanding of the temporal and spatial regulation of inflammatory mediators may improve the therapeutic targeting of these pathways to exploit the beneficial aspects (e.g. clearance of tissue debris, improved niche for neural repair) and minimize the associated pathology associated with inflammation (edema, neuronal damage). The advent of cell-specific, single gene knockout mice may clarify the opposing functions currently associated with reactive astrocytes following TBI. These exciting possibilities should provide a fruitful area of future research to further elucidate the mechanisms underlying the brain response to head trauma and could yield novel treatment strategies, which potentiate the protective aspects of reactive astrocytes while minimizing the deleterious effects.

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