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"Targeting astrocytes in CNS injury and disease: A translational research approach"

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Abstract

Astrocytes are a major constituent of the central nervous system. These glia play a major role in regulating blood-brain barrier function, the formation and maintenance of synapses, glutamate uptake, and trophic support for surrounding neurons and glia. Therefore, maintaining the proper functioning of these cells is crucial to survival. Astrocyte defects are associated with a wide variety of neuropathological insults, ranging from neurodegenerative diseases to gliomas. Additionally, injury to the CNS causes drastic changes to astrocytes, often leading to a phenomenon known as reactive astrogliosis. This process is important for protecting the surrounding healthy tissue from the spread of injury, while it also inhibits axonal regeneration and plasticity. Here, we discuss the important roles of astrocytes after injury and in disease, as well as potential therapeutic approaches to restore proper astrocyte functioning.

1. INTRODUCTION

Astrocytes constitute 50% of all the cells in the central nervous system. They are responsible for a wide variety of functions, from regulating synaptic activity to preventing the spread of injury. Because they are present in such large numbers and perform such a diverse array of functions, astrocytes have received a great deal of attention. In particular, much focus has been given to understanding the role of astrocytes after injury, where they are thought to have both beneficial and detrimental effects. Understanding the complexity of their interactions and functions during development, in a healthy adult, and after trauma could have important therapeutic implications. Manipulating the astrocyte response to enhance their beneficial interactions and minimize their negative properties after injury could promote regeneration and functional recovery.

2. ASTROCYTE DEVELOPMENT

During development, astrocytes arise from radial glia, which reside in the neuroepithelium and express both vimentin and nestin. They are capable of generating both neurons (Malatesta et al., 2000) and astrocytes (Morest and Silver, 2003). Radial glia begin to differentiate into astrocytes after neurogenesis is complete and begin to express brain lipid binding protein (BLBP; Barry and McDermott, 2005), a common marker for astrocyte progenitors, as well as the glutamate transporters GLAST (Shibata et al., 1997) and GLT-1 (Furuta et al., 1997). As radial glia differentiate, they also begin to express A2B5 (Hirano and Goldman, 1988) and low levels of GFAP. During this time, they maintain their contact with the pial surface, but retract their basal attachment to the ventricular zone. As they translocate to their destination in the gray or white matter, they upregulate expression of GFAP as they lose their bipolar morphology and form additional processes (Malatesta et al., 2000; Voigt, 1989; Yang et al., 1993a, 1993b). In the spinal cord, after the initial wave of neurogenesis is complete (~E9–11), progenitors in the ventricular zone begin to differentiate into astrocytes (E12.5). The patterning in development establishes astrocyte heterogeneity, which may have important implications in adulthood and after injury (Chaboub and Deneen, 2012).

Unlike neurons and oligodendrocytes, which become post-mitotic and take on a distinct morphology upon terminal differentiation, astrocytes are able to locally proliferate in the postnatal cortex and spinal cord, and can dramatically alter their shape. Postnatally, astrocytes in the forebrain also continue to arise from subventricular stem cells (Lundgaard et al., 2014). In the intact spinal cord there is limited proliferation of astrocytes and ependymal cells postnatally, but in response to injury, inflammatory cytokines cause adult astrocytes as well as ependymal cell progenitors to proliferate and generate reactive astrocytes (Barnabé-Heider et al., 2010; Magnus et al., 2008).

Astrocytes have evolved in both number and complexity (Freeman and Rowitch, 2013). The nervous system in invertebrates is comprised of only 15% glia, in contrast to mammals which are comprised of almost 90% glia. Therefore, astrocytes in mammals differ from those in lower species. For instance, glial cell development in *Drosophila* is controlled by the transcription factor glial cell missing (gcm). When gcm is mutated in *Drosophila*, progenitors are shifted from a glial to neuronal fate and ectopic expression of gcm forces all CNS cells to become glia (Hosoya et al., 1995). However, manipulating the homologue of this transcription factor in mouse models has no effect on glial cell development (Kim et al., 1998), suggesting that mammalian astrocytes develop differently from those in more primitive species. There are also important differences between species with regards to their response to injury. Injury to the CNS induces adult mammalian astrocytes to form walls around the lesion and produce a large amount of chondroitin sulfate proteoglycans (CSPGs). Conversely, glial cells in lower vertebrates do not produce large amounts of reactive matrix and, in addition, they migrate into the lesion environment and form bridges to promote axon regeneration, a behavior that better reflects that of immature mammalian astrocytes (Goldshmit et al., 2012; Zukor et al., 2011). Finally, there is currently little evidence of heterogeneity of astrocytes in lower organisms such as *Drosophila* or C. elegans (Freeman

and Rowitch, 2013), whereas astrocytes in vertebrates have regional diversification that leads to a high degree of functional and morphological heterogeneity.

3. ASTROCYTE HETEROGENEITY

Astrocytes have long been characterized as two distinct classes, based primarily on morphology, as first described by Ramon y Cajal (Ramon y Cajal, 1909). However, these two classes of astrocytes also differ in their developmental origin, their location, and their antigenic phenotype (Miller and Raff, 1984). Protoplasmic astrocytes are found in the gray matter, have long processes, and are very bushy. These cells do not express easily detectable levels of GFAP, as assessed by immunohistochemistry, in an uninjured setting. They are commonly identified using the marker S100β (Chaboub and Deneen, 2012). They envelop neuronal cell bodies and synapses. Protoplasmic astrocytes are also largely arranged in non-overlapping domains (Bushong et al., 2002). Conversely, fibrous astrocytes have short branched processes, populate the white matter, and express GFAP. The majority of fibrous astrocytes also express A2B5 (Miller and Raff, 1984). Because they are located in the white matter, they are able to interact with nodes of Ranvier (Ffrench-Constant et al., 1986; Raine, 1984).

Different brain regions possess astrocytes with different functions and morphologies. Recent studies have demonstrated that the genetic and molecular expression profiles of astrocytes isolated from different brain regions vary significantly. Using RNA microarray analyses on astrocytes isolated from postnatal day 1 optic nerve, cerebellum, brainstem, and neocortex, Yeh and colleagues reported that astrocytes from these different brain regions could be individually identified on the basis of their distinct molecular patterns (Yeh et al., 2009). The inherent diversity of astrocytes based on their local environment may have important implications for their functions and response to insult or disease. For instance, region-specific pathology in AD may result, in part, from regional differences in reactive gliosis (Höke et al., 1994). Astrocytes cultured from different CNS regions, including the cerebral cortex, hippocampus, cerebellum, and spinal cord showed different responsiveness to substrate bound beta-amyloid peptide *in vitro*. Only hippocampal and cortical astrocytes matured *in vitro* had reactive morphological changes, increased CSPG deposition, and alterations in proteoglycan metabolism when cultured on substrate-bound beta-amyloid peptide, suggesting regional differences in astrocyte populations can trigger different responses to amyloid insult.

There are many studies suggesting that functional differences also exist between immature and mature astrocytes in mammals. One major difference between immature and mature astrocytes is their ability to support or inhibit axon growth. During development, neuronal growth cones, especially near crossing points at the midline, are closely associated with astrocytes, suggesting that immature astrocytes provide a highly favorable substrate for axon outgrowth (Grafe and Schoenfeld, 1982; Silver et al., 1982, 1993). These astrocytes retain their primitive radial architecture and express high levels of GFAP. In certain circumscribed regions (eg. the roof plate of the spinal cord and tectum) CSPGs secreted by radial astrocytes provide guidance boundaries for developing axons as they migrate toward their targets (Powell and Geller, 1999; Powell et al., 1997a, 1997b; Snow et al., 1990; Wu et al., 1998).

Mature astrocytes do not appear to have the same ability to promote robust neurite outgrowth as their embryonic counterparts, but they do have growth promoting capacities (Davies et al., 2011; Filous et al., 2010). In adult mammals, injury to the CNS causes mature astrocytes to become reactive and assume a phenotype similar to boundary astrocytes during development, leading to the formation of a glial scar that surrounds the damaged tissue (Cregg et al., 2014; discussed below). However, such injuries in immature mammals or lower species result in a more reparative type of reactive astrogliosis. After CNS injury in immature mammals, reactive astrocytes support regeneration through or around the lesion (Barrett et al., 1984). Whereas mature astrocytes in the glial scar have a well-established role in inhibiting regeneration, transplantation of fetal rat spinal cord astrocytes is able to improve the regenerative capacities of adult rat neurons after spinal cord injury (SCI) (Reier et al., 1986). Similarly, hippocampal neurons cultured on explanted scar tissue isolated from either immature or mature animals displayed more extensive neurite outgrowth when cultured on scar tissue from younger animals (Rudge and Silver, 1990). Retinal ganglion cells isolated from either rats or fish had the ability to grow on embryonic astrocytes, but this growth was diminished on monolayers of astrocytes from adult animals (Bähr et al., 1995), again suggesting inherent differences between immature and mature glia. These differences may have crucial implications in the context of injury. One study reported that transplanted immature cortical astrocytes have the ability to suppress scar formation in the adult rat brain. Additionally, immature astrocytes were able to migrate into surrounding CNS tissue and become associated with host blood vessels. Transplanting mature cortical astrocytes did not affect scar formation, nor were they able to migrate from their site of implantation. Furthermore, transplanted mature astrocytes were more susceptible to phagocytosis by the host immune system (Smith and Miller, 1991). Another study also reported the ability of transplanted immature, but not mature, astrocytes to migrate into the site of injury, where they form permissive bridges that enable axon regeneration (Filous et al., 2010). Similar effects were observed when transplanting immature astrocytes derived from fetal glial-restricted progenitors (Davies et al., 2006; Haas and Fischer, 2013). It is also important to note that, unlike mature astrocytes, immature astrocytes do not produce massive amounts of chondroitin sulfate proteoglycans (CSPGs), a major inhibitory component of the glial scar, in response to injury (Dow et al., 1994). Together, these data strongly suggest inherent differences that arise in astrocytes as they mature.

4. NORMAL FUNCTIONS OF ASTROCYTES

Astrocytes were once thought to be passive support cells for neurons. It is now clear that these cells play an active role in regulating key functions of the nervous system. Astrocytes are important for maintaining homeostasis, formation of the blood brain barrier (BBB), regulating synaptic formation and function, and neuronal trophic support.

4.1 Role in the BBB

Astrocytes are known to play an active role in the function and maintenance of the BBB (for review see Alvarez et al., 2013). The BBB serves to regulate and limit the exchange between the nervous system and the vasculature. Endothelial cells of the vasculature in the brain form tight junctions, which limit the passive diffusion between the blood and CNS. Astrocytic

endfeet contact the endothelial cells of the brain vasculature and are responsible for their formation of tight junctions (Janzer and Raff, 1987). The presence of astrocytes or astrocyte-conditioned media was sufficient to induce tight junctions and BBB behavior in cultured endothelial cells (Alvarez et al., 2011; Neuhaus et al., 1991). Because astrocyte processes both enwrap synapses and contact the endothelial cells of the BBB, they are able to modulate blood flow based on neural activity. Glutamate-mediated calcium signaling within astrocytes increases blood flow in the cortex (Zonta et al., 2003).

CNS injury often leads to disruption of the BBB, which ultimately affects the behavior of astrocytes. After CNS injury, Bardehle *et al.* found that only astrocytes adjacent to the vasculature proliferate (Bardehle et al., 2013), consistent with the idea that these cells act as injury sensors due to their polarized endfeet contacts with endothelial cells of the vasculature. Disruption of the interaction between astrocytes and the CNS vasculature leads to reactive astrogliosis. Conditionally deleting beta 1-integrin in astrocytes, a protein at the interface between endfeet and the basement membrane of the BBB, led to hypertrophy of astrocytes as characterized by upregulation of GFAP and vimentin, as well as increased secretion of CSPGs (Robel et al., 2009), suggesting a possible role for this receptor in mediating partial activation of astrocytes in response to injury. Disruption of the BBB also allows for the influx of the soluble plasma protein, fibrinogen, which induces TGFβ signaling and leads to activation of astrocytes, as well as scar formation (Schachtrup et al., 2010, see below). It should also be noted that astrogliosis itself may disrupt the interaction between astrocytes and CNS vasculature, which may further exacerbate the injury response.

4.2 Role in synaptogenesis and synaptic function

Astrocyte processes, together with neuronal pre- and post-synaptic regions, form the tripartite synapse. Astrocytes play an active role in modifying synaptic strength and function through their expression of neurotransmitter receptors and release of various neurotransmitters, such as glutamate, GABA, ATP and D-serine. Neuronal activity results in neurotransmitter release, which signals through neurotransmitter receptors expressed on astrocytes to trigger calcium signals within these cells, a phenomenon known as astrocyte excitability. Ultimately, this signaling leads to the release of different gliotransmitters such as prostaglandins, allowing them to alter synaptic function (Shigetomi et al., 2008). The glutamate transporters expressed by astrocytes, including GLAST and GLT-1, are important for removing glutamate from the synaptic cleft and reducing excitotoxicity (Rothstein et al., 1996). Neurons activate nuclear factor kappa B (NFκB) signaling in astrocytes, leading to upregulation of GLT-1 expression (Ghosh et al., 2011). Brain expression of glutamine synthase is found exclusively in astrocytes (Norenberg and Martinez-Hernandez, 1979). This enzyme is responsible for converting glutamate to glutamine, maintaining glutamate homeostasis (Rose et al., 2013). Disruption of this astrocyte function has critical consequences in injury and disease, as discussed below.

Astrocytes also facilitate synaptogenesis. Work from Ben Barres's lab has demonstrated that astrocytes are necessary for the formation of mature, functional synapses in the CNS and are required for the maintenance of these synapses (Christopherson et al., 2005; Ullian et al., 2001, 2004). These findings translate to a variety of neuronal subtypes, including spinal

motor neurons (Ullian et al., 2004). Follow-up work found that synaptogenesis was mediated by the astrocyte-secreted factor, thrombospondin (Christopherson et al., 2005), an important matrix molecule which is induced by purinergic signaling (Tran and Neary, 2006). Astrocytes are also able to mediate the formation of inhibitory synapses (Elmariah et al., 2005). While synaptogenesis ends in development, reactive astrocytes can help to restore synapses after injury (Emirandetti et al., 2006; Tyzack et al., 2014) and may provide a target for promoting plasticity and recovery.

In addition to their constructive role at the synapse, astrocytes also play a role in synaptic plasticity and pruning. Astrocytes have been found to be important in presynaptic muting of hippocampal neurons, again through their expression of thrombospondins (Crawford et al., 2012). Another astrocyte-secreted protein, hevin, has been implicated in regulating cortical connectivity during development by refining dendritic spines (Risher et al., 2014). They also play a role in targeting synapses for elimination (Stevens et al., 2007).

5. ASTROCYTE RESPONSE TO INJURY

Injury to the CNS causes a cascade of cellular and molecular changes that alter the local environment and impede regeneration. The most immediate effects of CNS injury are bleeding, followed by intense local inflammation that leads to progressive cavitation of the lesioned area (Fitch et al., 1999; Horn et al., 2008). The response of astrocytes varies by location in relation to the severity of the injury (described below), but those in the vicinity of the injured tissue become hypertrophic and begin to form a dense scar tissue to wall off the area of damage from the surrounding healthy tissue (Cregg et al., 2014). Although there is an abundance of astrocytes in scar tissue and they have traditionally been thought to be the major scar-forming component, recent work from the Frisen and Jae Lee labs demonstrates that fibroblasts actually outnumber astrocytes in the scar and play a critical role in its formation as well (Göritz et al., 2011; Soderblom et al., 2013). Soon after a crush injury of the spinal cord, astrocytes near the lesion had elongated morphologies with overlapping processes, whereas astrocytes more distant from the lesion maintained their stellate morphology and non-overlapping domains, suggesting a heterogeneity in reactive astrogliosis based on the proximity to the lesion center (Wanner et al., 2013). Later on, processes of the elongated reactive astrocytes near the lesion edge adjacent to the fibroblast-like pericyte population form mesh-like structures that lead to scar formation. The scar itself contains two distinct regions: the lesion core, which is comprised mostly of NG2 glia (Busch et al., 2010; Filous et al., 2014), fibroblasts/pericytes (Zhu et al., 2015), and macrophages (Busch et al., 2009; Horn et al., 2008) and the penumbra, which is formed primarily by reactive astrocytes and activated microglia (Evans et al., 2014). NG2 glia are also found immediately adjacent to the lesion core, with the ability to form a bridge into the center of the lesion (Busch et al., 2010; Cregg et al., 2014; Filous et al., 2014). Within the first week after spinal cord injury, microglia/macrophages and NG2+ cells proliferate in the injured white matter and begin to occupy the lesion core (Zai and Wrathall, 2005). The density of astrocytes and astrocyte proliferation in the penumbra of the lesion nearly doubles compared to that of uninjured tissue (Wanner et al., 2013). Traditionally, the glial scar has been viewed primarily as a major impediment to regeneration, but more recent evidence suggests that this structure is necessary to prevent the spread of injury (Faulkner et al., 2004). The exact role

of astrocytes after injury may be better characterized by their distance from the site of injury and the severity of the insult.

The protein expression pattern of astrocytes also changes in response to injury. It is well-established that astrocytes near the site of injury upregulate their expression of GFAP (Vijayan et al., 1990). They also increase their expression of S100β (Rothermundt et al., 2003). Some reports suggest they increase their expression the glutamate transporters, GLT-1 and GLAST (Vera-Portocarrero et al., 2002), while other studies have found that GLT-1 expression is actually reduced after injury (Lepore et al., 2011). Injury also induces astrocytes to re-express their developmental filament decorating proteins vimentin (Miyake et al., 1988) and nestin (Clarke et al., 1994). The altered protein expression in astrocytes after injury may help their motility away from the lesion core into the penumbra and allow the cells to assume a variety of shapes as they undertake specific mechanical as well as biochemical roles during their attempt to wall off the lesion.

5.1 Mild, Moderate, Severe Astrogliosis

The degree of astrogliosis has recently been defined as mild, moderate, or severe, based on the molecular, cellular, and functional changes that occur in the astrocytes, as well as the severity of the insult (Sofroniew and Vinters, 2010). Astrocyte responses are not all-or-none phenomena. The severity of reactive astrogliosis may determine its effects on regeneration and recovery.

Less severe injuries result in mild to moderate reactive astrogliosis. Although astrocytes upregulate expression of GFAP, they do not proliferate in response to minor insults nor do they overlap neighboring astrocytes (Sofroniew, 2009). Astrocytes distant from the lesion environment may be defined as mildly activated. Many of the changes induced by minor insults are reversible. However, severe insults, such as focal lesions, infections, or chronic neurodegeneration, cause astrocytes to upregulate GFAP and other genes, as well as to proliferate and overlap neighboring astrocyte domains (Sofroniew and Vinters, 2010). These changes lead to long-term changes in the tissue structure and over time lead to extremely dense accumulations of cells that appear to be mechanically obstructive to axon regeneration (Silver and Miller, 2004).

5.2 Glial Scar Formation

The molecular triggers of reactive astrogliosis vary by the type of insult and are incompletely understood (for review see Sofroniew, 2009). Injury-induced cytokines, such as ciliary neurotrophic factor (CNTF), interleukin-6, transforming growth factor alpha, and fibroblastic growth factor-2, together with epidermal growth factor have been reported to enhance astrocyte proliferation, potentially contributing to glial scar formation (Levison et al., 2000). Using a brain injury mouse model, Vartak-Sharma and Ghorpade found that GFAP and astrocyte-elevated gene 1 (AEG-1) colocalized at the site of injury and that knocking down AEG-1 reduced astrocyte migration and proliferation in the lesion (Vartak-Sharma and Ghorpade, 2012). Another factor implicated in triggering astrogliosis is endothelin-1 (ET-1). ET-1 is upregulated along the same time course as astrocyte proliferation and GFAP expression in the corpus callosum after lysolecithin-induced focal

demyelination and is able to induce astrocyte proliferation in culture (Gadea et al., 2008). Inhibiting matrix metalloproteinase 9 activity prevents the migration of astrocytes through the disruption of actin cytoskeleton dynamics (Hsu et al., 2008). LPS and other Toll-like receptor ligands (Farina et al., 2007), as well as neurotransmitters such as glutamate (Bekar et al., 2008) may also play a role in signaling for reactive astrogliosis. Purinergic signaling through protein kinase cascades has also been implicated in stimulating astrocyte proliferation in response to injury (Neary et al., 2006). Several studies have also shown a correlation between TGFβ signaling and astrocyte activation after SCI (Kohta et al., 2009; O'Brien et al., 1994). More recently, TGFβ has been linked to the blood protein fibrinogen in signaling for glial scar formation. After disruption of the BBB, fibrinogen enters the CNS, where it signals through Smad2 and TGFβ in astrocytes to cause CSPG deposition into the extracellular matrix, leading to inhibition of neurite outgrowth (Schachtrup et al., 2010). Depleting fibrinogen or inhibiting TGFβ signaling blocked glial activation and CSPG expression, providing convincing evidence of the role of these molecules in triggering reactive astrogliosis. TGFβ has also been shown to activate Smad3, leading to glial scar formation after a cortical stab injury. Inhibiting Smad3 signaling reduced the number of immune cells, as well as NG2+ cells, and astrocytes around the lesion area after traumatic brain injury, while also reducing laminin and fibronectin expression (Wang et al., 2007). Conditional deletion of Smad3 reduced expression of CSPGs, collagens, and GFAP one week after contusive spinal cord injury in mice (McKillop et al., 2013). Together, these molecules provide potential targets for altering astrocyte proliferation and migration in response to injury.

Neuroinflammation may play a major role in triggering astrogliosis. Inflammation is one of the earliest responses to injury, occurring within minutes, and is later followed by reactive astrogliosis (Evans et al., 2014). A strong correlation also exists between the appearance of astrogliosis and the accumulation of reactive microglia/macrophages (Balasingam et al., 1996). To demonstrate the importance of inflammatory cytokines in astrogliosis, Balasingam *et al*. utilized a neonatal mouse model system, in which astrogliosis does not normally occur and the immune system is still developing. A stab wound into the neonatal cortex, immediately followed by microinjection of a variety of cytokines, including interferon-γ, interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor-α, and macrophage colony stimulating factor, resulted in a significant increase in astrocyte reactivity, as assessed by upregulation of GFAP expression (Balasingam et al., 1994). Blocking interleukin-6 signaling immediately following contusive spinal cord injury in rats prevented the differentiation of neural stem/progenitor cells into astrocytes, while also reducing the number of invading inflammatory cells and the formation of the glial scar (Okada et al., 2004). Similar results using double transgenic mice (Brunello et al., 2000) and interleukin-6 deficient mice (Klein et al., 1997) implicate interleukin-6 in the selective activation of astrocytes. Interleukin-1 also has the ability to induce GFAP upregulation and astrocyte hypertrophy when injected directly into the cerebral cortex of adult rats. It has also been reported that activated macrophages stimulate upregulation of inhibitory CSPGs after injury (Fitch and Silver, 1997). Conversely, anti-inflammatory cytokines such as interleukin-10 (Balasingam and Yong, 1996) and type 1 interferon β (Ito et al., 2009) are able to reduce astrocyte reactivity, further suggesting that neuroinflammation plays a major role in modulating astrogliosis.

5.3 Scar Inhibition of Regeneration

Reactive astrocytes have a well-established role in inhibiting neurite outgrowth and regeneration after injury (Cregg et al., 2014; Silver and Miller, 2004). Much of the inhibitory nature associated with the glial scar is attributed to the extracellular matrix CSPGs produced by mature reactive astrocytes. CSPGs, present in high concentrations around the lesioned area only in the adult CNS, are associated with reactive astrocytes. Scar tissue isolated from the lesioned adult CNS was unable to support neurite outgrowth, which correlated with the expression of CSPGs in this tissue (McKeon et al., 1991). When adult rat DRG neurons were microtransplanted directly into white matter tracts of the CNS, they were capable of extensive regeneration, unless they encountered increased concentrations of CSPGs in the extracellular matrix at the site of transplantation (Davies et al., 1997) or at a distal lesion site (Davies et al., 1999), establishing the inhibitory nature of these molecules. High concentrations of CSPGs in a gradient cause growing axons to become dystrophic and stall, preventing regeneration (Lang et al., 2015; Tom et al., 2004a). Targeting of these molecules to promote regeneration into and beyond the glial scar has been a major field of study (Bradbury and Carter, 2011; McKeon et al., 1995). One of the most common methods of degrading CSPGs experimentally has been through the use of an enzyme known as chondroitinase ABC. This enzyme cleaves the inhibitory glycosaminoglycan side chains from the protein core, removing the inhibitory portion of the CSPG molecule that binds to its receptors (Fisher et al., 2011; Shen et al., 2009) and allowing for regeneration/plasticity. As such, this enzyme has been used in a variety of studies to improve regeneration or plasticity after spinal cord injury (Bradbury et al., 2002; Massey et al., 2006; Tom et al., 2009), brain injury (Moon et al., 2001), and in combinatorial strategies (Alilain et al., 2011; Filous et al., 2010; Zhao and Fawcett, 2013; Zhao et al., 2013). Work with this enzyme demonstrates that manipulating the CSPG composition of the glial scar may be an important step in overcoming regeneration failure.

Studies ablating astrocytes or altering expression of intermediate filament decorating proteins have shown mixed results in regards to regeneration and functional recovery. Because GFAP is abundantly expressed throughout the glial scar, studies were performed using GFAP null mice to examine glial scar formation. Surprisingly, there were no differences in scar formation or the upregulation of vimentin in these mice compared to wildtype controls after a cortical needle stab injury (Pekny et al., 1995). Therefore, although GFAP upregulation is a hallmark of astrogliosis, its elimination alone is insufficient to totally disrupt formation of a glial scar. However, GFAP upregulation does play a role in the ability of astrocytes to respond to beta amyloid, since GFAP null astrocytes in culture upon beta amyloid substrates responded more slowly and were unable to form tight bundles (Xu et al., 1999), suggesting that certain aspects of tight wall formation do appear to be dependent on GFAP levels.

A study using a knife wound to the dorsal funiculus of the spinal cord found that mice lacking two of the major proteins of the astrocyte cytoskeleton, GFAP and vimentin, form less dense scars in response to CNS injury (Pekny et al., 1999). Knocking out just one of these intermediate filaments did not affect scar formation, suggesting both are necessary for this process to occur. Because knocking out both proteins has major effects on astrocyte

reactivity in response to injury, these mice have been used in a variety of studies to explore the role of astrogliosis. Using aged GFAP(−/−)Vimentin(−/−) mice, lacking the major proteins of the astrocyte cytoskeleton, Larsson *et al.* demonstrated that cell survival and neurogenesis in the hippocampus were enhanced compared to their age-matched controls, suggesting that astrocyte reactivity may limit hippocampal neurogenesis (Larsson et al., 2004). Other studies using these mice found that astrocyte hypertrophy was reduced after a lesion of the entorhinal cortex, allowing for enhanced synaptic regeneration in the hippocampus (Wilhelmsson et al., 2004). Similar results were found using these same mice to explore the effects of reducing astrogliosis after a hemisection of the spinal cord. GFAP(−/−)Vimentin(−/−) mice had reduced astrocyte reactivity, which was associated with increased sprouting of supraspinal fibers and increased functional recovery (Menet et al., 2003), suggesting that reactive astrocytes may play a role in limiting plasticity after spinal cord injury. However, complete ablation of astrocytes has been reported to worsen the outcome after mild to moderate SCI or after a major stroke (discussed below; Faulkner et al., 2004). Therefore, simply depleting reactive astrocytes to improve recovery after CNS insult may deprive the system of valuable astrocyte functions important for neuroprotection and repair.

5.4 Beneficial Effects of Astrocytes in the Glial Scar

Although extensive research has focused on the glial scar as a physical and molecular impediment to axonal regeneration, research over the last decade has confirmed what evolutionary conservation suggests, that the glial scar is essential for preventing the spread of damage to neighboring tissue. Studies ablating astrocytes or markedly inhibiting the formation of the glial scar have convincingly demonstrated that the scar is necessary to contain the injury and spare the fragile surrounding tissue. By conditionally ablating dividing reactive astrocytes after either stab or crush injuries, Faulkner *et al.* demonstrated that without these cells, the effects of mild to moderate SCI were exacerbated, leading to persistent blood-brain barrier disruption, more pronounced leukocyte infiltration into the lesioned area, and more pronounced cellular death of neighboring neurons and oligodendrocytes resulting in more severe demyelination and ultimately leading to increased functional deficits (Faulkner et al., 2004). Similar studies were performed to confirm these results in traumatic brain injury. Selectively ablating astrocytes in the vicinity of a forebrain stab injury prevented the repair of the BBB, chronically increased the infiltration of leukocytes, and enhanced neuron degeneration. However, neurite outgrowth was somewhat increased at the site of injury, confirming the dual role of the glial scar in preventing the spread of damage, while also inhibiting regeneration (Bush et al., 1999). Ablating astrocytes after moderate cortical contusion caused a greater loss of cortical tissue, more neuronal degeneration, and increased inflammation, again suggesting that astrocytes are necessary for tissue preservation after CNS injury (Myer et al., 2006). Using mice with a selective deletion of protein signal transducer and activator of transcription 3 (Stat3) under the control of the Nes promoter-enhancer, Stat3 has been implicated as a key regulator of reactive astrocytes and their beneficial role in wound healing after CNS injury (Okada et al., 2006). Ablating Stat3 in astrocytes prevented their migration in response to injury, and also caused demyelination, pronounced immune cell infiltration, and exacerbated functional deficits.

Together, these data strongly suggest that astrocytes are necessary to promote wound repair, even though their presence in the scar may also contribute to regeneration failure.

Many studies suggest that reactive astrocytes are also neuroprotective after stroke (Liu et al., 2014). Not only do astrocytes upregulate GFAP and vimentin, but they also begin to re-express nestin in response to stroke or brain injury (Li and Chopp, 1999). Mice lacking both GFAP and vimentin saw a 2.1–3.5 increase in infarct volume compared to WT controls following middle cerebral artery occlusion (Li et al., 2008). Astrocytes cultured from GFAP(−/−)Vimentin(−/−) mice were more susceptible to apoptosis and less supportive of neurons in co-culture compared to WT controls in an oxygen-deprivation/reperfusion model of stroke *in vitro*, suggesting reactive astrocytes may be necessary to provide neuroprotection (de Pablo et al., 2013). Because of the reports that astrocytes may play a crucial role in neuroprotection, they have become model cells to target to improve functional recovery after ischemia (Li et al., 2014).

The astrocyte response to injury is multifaceted and may promote neuroprotection and repair through a variety of mechanisms. Reactive astrocytes upregulate expression of a variety of molecules that act to support the injured neurons directly. In addition to their production of inhibitory CSPGs, reactive astrocytes produce growth permissive extracellular matrix molecules as well, such as laminin (Canning et al., 1996; Frisén et al., 1995) and fibronectin (Tom et al., 2004b). These molecules provide a supportive substrate for injured neurons as they attempt to regenerate. Reactive astrocytes also upregulate the glutamate transporters GLAST and GLT-1 (Rothstein et al., 1996), which helps protect spared tissue from excitotoxicity. Evidence from co-cultures of astrocytes and neurons suggests that astrocytes produce glutathione, which protects neurons from nitric oxide neurotoxicity (Chen et al., 2001). The neurotrophic factors produced by astrocytes, such as CNTF, (Lee et al., 1998) and brain-derived neurotrophic factor (BDNF, Ikeda et al., 2001) also help support the survival of neurons. A recent study demonstrated that astrocyte conditioned media containing glial derived neurotrophic factor (GDNF) was able to abolish Zymosan-induced activation of microglia, in turn promoting neuron survival by reducing neuroinflammation (Rocha et al., 2012). Therefore, astrocytes may provide crucial support for neurons which helps in the survival of tissue surrounding an injury. It is also important to stress that while reactive astrocytes are largely inhibitory to the passage of axons in vivo due to their mesh-like configuration as well as the production of inhibitory extracellular CSPG containing matrices, the membrane surface of intensely reactive astrocytes (excluding or lacking CSPGs) when presented as a 2 dimensional substrate can be growth supportive (Canning et al., 1996).

5.5 Astrocyte Effects on Other Glia

In addition to affecting neurons, astrocytes play an important role in the regulation of other glial cell types after injury. Understanding their effects on these cells is important for understanding their complex role after injury or disease.

5.5.1 Oligodendrocytes and NG2+ cells/OPCs—Under normal conditions, astrocytes have been shown to promote myelination *in vitro* (Sorensen et al., 2008). *In vivo*, astrocytes

have been shown to release the cytokine leukemia inhibitory factor (LIF) in response to ATP released from active neurons, and LIF is able to promote myelination by mature oligodendrocytes (Ishibashi et al., 2006). During development, expression of tissue inhibitor of metalloproteinases 1 (TIMP-1) is high and promotes both astrocyte proliferation and oligodendrocyte progenitor cell (OPC) differentiation (Moore et al., 2011). Expression of TIMP-1 increases in response to CNS insult, where it may influence astrocyte behavior once again. The importance of astrocytes in myelination is further demonstrated by altering GFAP expression. GFAP-null mice had disrupted white matter architecture and abnormal myelination, as observed in the optic nerve and spinal cord (Liedtke et al., 1996), providing strong evidence that normal astrocyte function is necessary for proper myelination to occur. GFAP mutations are also associated with Alexander disease, which leads to myelination deficits and loss of oligodendrocytes (Alexander, 1949). In Alexander disease, GFAP mutations cause a disruption in glutamate transport in astrocytes, leading to oligodendrocyte death (Tian et al., 2010). Together, these data demonstrate that astrocytes play a key role in regulating oligodendrocyte behavior.

Reactive astrocytes play an important role in regulating oligodendrocyte behavior and myelination after injury as well. Mild astrogliosis may be beneficial to myelination and oligodendrogenesis (White and Jakeman, 2008). Nash and colleagues used an *in vitro* model to compare myelination of neuronal fibers grown on a monolayer of quiescent astrocytes to myelination when grown on a monolayer of mildly reactive astrocytes. Astrocytes plated with CNTF to mimic a reactive state were able to promote myelination in culture, whereas quiescent astrocytes were not (Nash et al., 2011), suggesting that mildly reactive astrocytes may play a crucial role in promoting remyelination after injury. A study using ethidium bromide-induced demyelination of the adult spinal cord found that although OPCs were successfully recruited to the lesion area, they were unable to successfully remyelinate axons in areas devoid of astrocytes (Talbott et al., 2005). A study using a contusive spinal cord injury model found that reactive astrocytes secrete bone morphogenetic proteins (BMPs) which actually inhibit OPC differentiation into oligodendrocytes, but rather promotes their differentiation into astrocytes (Wang et al., 2011). Inhibiting the expression of NFκB specifically in astrocytes, using GFAP-IκBα-dn mice, enhanced the proliferation of oligodendrocytes and the expression of myelin-associated proteins after spinal cord injury (Bracchi-Ricard et al., 2013), further supporting the idea that intensely reactive astrocytes in the spinal cord may inhibit remyelination after injury. Astrocytes have also been shown to play a role in models of multiple sclerosis (MS). There is increasing evidence that the extracellular matrix and particularly astroglial or OPC-produced CSPGs play a critical role in regulating OPC re-myelinating capabilities (Lau et al., 2012, 2013). Astrocyte expression of the chemokine CXCL10 in experimental autoimmune encephalomyelitis (EAE), serves as a chemoattractant for immune cells during disease progression (Omari et al., 2005; Ransohoff et al., 1993) leading to demyelination. Reactive astrogliosis has also been reported to cause a loss of gap junctions and a disconnection of oligodendrocytes from astrocytes in a model of MS, leading to myelination deficits (Markoullis et al., 2014). Therefore astrogliosis may have varying effects on oligodendrocyte behavior based on the severity of the insult (Franklin and Ffrench-Constant, 2008).

5.5.2 Neuroinflammation—As described above, neuroinflammation plays a major role in signaling for astrocyte reactivity in response to injury. However, astrocytes play a role in regulating inflammation as well. Culturing blood-derived monocytes on a monolayer of astrocytes caused the monocytes to deactivate and take on microglial-like properties, such as a ramified morphology and microglia related membrane currents (Schmidtmayer et al., 1994; Sievers et al., 1994a, 1994b), suggesting that astrocytes play a role in modulating immune cell behavior. It is much more difficult to determine the direct effects of astrocytes on microglia and macrophages *in vivo*, because both cell types act on one another and it is difficult to distinguish the source of various cytokines. Astrocytes have been shown to dramatically alter microglial behavior in response to amyloid plaques (DeWitt et al., 1998a). When astrocytes respond vigorously to aggregated amyloid, they surround the plaque and further seclude it by synthesizing a CSPG rich matrix (Canning et al., 1993; DeWitt and Silver, 1996; DeWitt et al., 1993, 1994, 1998b). Such reactive astrocyte activity, in turn, helps to shield the plaque from an aggressive engulfment by microglia, which increases the presence of plaque material within the brain. This data suggests that astrocytes may play a role in Alzheimer's disease by altering the immune response. Reactive astrocytes secrete other factors in response to injury that play a role in modifying immune cell behavior. ATP released from astrocytes in response to local injury has been shown to dramatically affect the morphology of infiltrating microglia, acting as a chemoattractant (Davalos et al., 2005). Astrocyte-released ATP was able to stimulate microglia through purinergic receptor P2X(7), causing their rapid migration toward the lesion, followed by an increase in membrane permeability and ultimately microglial apoptosis, suggesting that ATP secreted from astrocytes in response to CNS injury may alter microglial function and number (Verderio and Matteoli, 2001). Stimulating ATP release from astrocytes was also able to induce vesicle shedding and the release of interleukin-1β from microglia in culture (Bianco et al., 2005). Glutamate released from astrocytes in a Ca2+-dependent fashion has also been shown to affect microglial activation. Reactive astrocytes are known to secrete various neurotrophic factors, such as IGF, NGF, BDNF, CNTF, and NT-3, which can support surrounding cells (Escartin and Bonvento, 2008) and alter immune cell behavior. Recently, it has been suggested that zinc released from astrocytes under hypo-osmotic conditions can alter microglial activation as well, as defined by morphology (Segawa et al., 2014). The transcription factor NFκB upregulates a variety of genes in response to trauma and disease, in astrocytes in particular, and has a well-established role in regulating inflammation. Transgenic mice in which NFκB translocation into the nucleus is blocked in astrocytes showed significant functional recovery after a contusive SCI, which correlated with reduced proinflammatory cytokines and reduced expression of CSPGs (Brambilla et al., 2005). There is even some evidence to suggest that CSPGs and other extracellular matrix molecules produced by reactive astrocytes may affect immune cells by binding the chemoattractants and growth factors necessary for recruitment and activation of macrophages (Hayashi et al., 2001; Rolls et al., 2008) and dendritic cells (Kodaira et al., 2000), thereby causing a focal concentration of these factors to enhance immune cell infiltration at the site of injury.

6. ASTROCYTES IN NEUROPATHOLOGIES

6.1 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the presence of extracellular amyloid beta (Aβ) plaques, intracellular neurofibrillary tau tangles, and the decline of cognitive function. As a major homeostatic cell type in the CNS, astrocytes have been implicated in AD pathology. Although they are far less efficient at clearing amyloid than are microglia and they mostly tend to allow for amyloid deposition rather than its removal (see discussion above, DeWitt et al., 1998a), astrocytes are able to phagocytose and accumulate small amounts of Aβ-42, and the level of Aβ-42 accumulation correlates with the severity of AD pathology (Nagele et al., 2003). Similar results were found when astrocytes were cultured on Aβ-plaque burdened brain slices from an AD mouse model (Wyss-Coray et al., 2003), suggesting that restoring astrocyte deficits in Aβ clearance may help provide a possible treatment for AD; however, improving microglial clearance capacity will be more effective (Cramer et al., 2012). Low-density lipoprotein receptor (LDLR), a cell surface receptor for apolipoprotein E (apoE), mediates Aβ uptake and degradation by astrocytes (Basak et al., 2012; Koistinaho et al., 2004). Therefore, reactive astrocytes serve to protect neurons from plaques through this phagocytosis (Mathur et al., 2015). Fluorescently labeled astrocytes from adult, but not neonatal, mice transplanted into an AD mouse brain were able to migrate and aggregate near Aβ plaques in the hippocampus, where they were able to internalize Aβ (Pihlaja et al., 2008). However, astrocytes often lyse as a result of Aβ accumulation, resulting in the formation of astrocyte-derived Aβ-plaques in the cortical molecular layer, contributing smaller plaques to the overall plaque load in the AD brain (Nagele et al., 2003). In addition to deficits in Aβ clearance, glutamate excitotoxicity may also lead to neurodegeneration. Using cultured rat brain astroctyes, Matos *et al.* found that glutamate uptake, particularly through GLT-1 is reduced in astrocytes cultured in the presence of Aβ1–40 peptide (Matos et al., 2008). A recent study looked to see if glutamate uptake or glutamate metabolism were altered in an AD mouse model. Researchers found that expression of the glutamate transporter GLT-1 was unaltered, suggesting that glutamate uptake from the synaptic cleft was unabated. Conversely, expression of glutamine synthase was reduced over time, leading to a gradual decline in astrocyte-dependent glutamate homeostasis. This disruption in glutamate levels results in failed synaptic connectivity and ultimately cognitive and memory deficits (Kulijewicz-Nawrot et al., 2013). Calcium homeostasis in reactive astrocytes may also be altered in AD. Using a mouse model of AD, Kuchibhotla *et al.* used multiphoton fluorescence microscopy to image calcium homeotstasis in astrocytes and found that these astrocytes exhibited elevated resting calcium, as well as intracellular calcium waves in astrocytes near plaques, suggesting that the astrocyte network could contribute to AD pathology (Kuchibhotla et al., 2009). Additionally, gap junctions between astrocytes are altered in AD, as evidenced by increased expression of the gap junctional protein connexin 43 (Nagy et al., 1996). Altered gap junction expression has also been linked to increased glutamate and ATP release, leading to neuronal death (Orellana et al., 2011), suggesting that blocking hemichannels on neurons could be neuroprotective in AD. These studies provide multiple approaches for restoring astrocyte function in AD to protect neurons.

6.2 ALS

Amyotrophic lateral sclerosis (ALS) is another chronic progressive neurodegenerative disorder, primarily causing the death of motor neurons in the cerebral cortex and spinal cord. Astrocytes play a major role in ALS pathology (for review see Vargas and Johnson, 2010). Patients with ALS have been reported to have impaired glutamate metabolism, caused by reduced glutamate uptake by astrocyte-associated glutamate transporters (Rothstein et al., 1992). A recent study found that the inflammatory cytokine TNF-α is able to increase the expression of GLT-1 in astrocytes cultured from wild-type rats, but not those cultured from a rat model of ALS (Dumont et al., 2014). Another study has linked astrocytes, inflammation, and ALS pathology, reporting that in both mouse and human ALS, astrocytes have upregulated expression of the anti-inflammatory cytokine transforming growth factor-β1 (TGF-β1), which prevents microglial and T cell production of IGF-1, leading to accelerated disease progression due to the loss of inflammatory-mediated neuroprotection (Endo et al., 2015). Astrocytes from both familial and sporadic ALS patients postmortem have been shown to be toxic to motor neurons (Haidet-Phillips et al., 2011). This may in part be due to upregulation of iNOS and other markers of oxidative stress by reactive astrocytes in ALS and ALS models (Almer et al., 1999; Sasaki et al., 2001). Additionally, a recent study found that astrocytes from ALS mice had a reduced ability to support neurons, similar to what is seen in aged astrocytes (Das and Svendsen, 2015), suggesting that their functions could be targeted for therapeutic intervention to reduce motor neuron death. Finally, over 95% of ALS cases present with aggregations of transactive response DNA binding protein (TDP-43), which leads to cellular toxicity and, importantly, the TDP-43 dysfunction has recently been linked to astrocytes (Yang et al., 2014).

6.3 Parkinson’s Disease

Loss of dopaminergic neurons in the substantia nigra leads to progressive neurodegeneration known as Parkinson’s disease (PD). PD is characterized by the presence of Lewy bodies (intranuclear aggregates of α-synuclein). Like the other neurodegenerative diseases described so far, astrocytes are able to take up α-synuclein, which ultimately disrupts astrocyte function. It has been suggested that affected cortico-striatal and cortico-thalamic neurons release α-synuclein from their axon terminals, where the protein is then taken up by surrounding astrocytes (Braak et al., 2007). Astrocyte endocytosis of neuron-released α-synuclein activates expression of inflammatory genes, leading to upregulation of pro-inflammatory cytokines and chemokines (Lee et al., 2010). Immunohistochemistry of different regions of PD brains revealed that protoplasmic astrocytes, but not fibrous astrocytes, accumulate α-synuclein and that this protein accumulation altered astrocyte reactivity (Song et al., 2009). Unlike in AD, where astrogliosis coincides with declining cognition, PD severity does not correlate with cortical astrogliosis (van den Berge et al., 2012), consistent with the finding that the accumulation of α-synuclein may hinder astrocyte reactivity and function. However, other studies selectively-expressing A53T α-synuclein in astrocytes showed increased paralysis in mice, which correlated with increased reactive astrogliosis, and impaired astrocyte function, such as reduced glutamate transport and cerebral hemorrhaging (Gu et al., 2010). Accumulation of α-synuclein in astrocytes led to microglial activation and neuron death (Gu et al., 2010), suggesting possible therapeutic opportunities for reducing this inflammation to preserve vulnerable neurons. Another study

found that astrocyte activation, through ATF6α, is crucial for neuronal survival (Hashida et al., 2012). These results suggest that a careful manipulation of astrocyte activation and function may provide therapeutic potential for PD patients.

A variety of different genes have been implicated in PD. Although a deficiency of DJ-1 has been linked to familial PD, patients with sporadic PD have been found to have abundant expression of DJ-1 in reactive astrocytes, which has been found to be a compensatory neuroprotective mechanism (Mullett and Hinkle, 2009; Mullett et al., 2013). Co-culturing neurons with astrocytes overexpressing DJ-1 protected neurons from oxidative stress caused by rotenone, a chemical known to increase the risk of PD (Mullett et al., 2013). Targeting DJ-1 may have therapeutic benefits in protecting neurons in PD patients. Expression profiling was used to identify genes affected in reactive astrocytes of the striatum after dopamine depletion (Nakagawa and Schwartz, 2004). This study identified 29 genes in astrocytes with enhanced expression and 2 genes with decreased expression, providing a variety of astrocyte-specific targets to alter PD pathology.

6.4 Huntington's Disease

Huntington's disease (HD) is caused by the mutant protein, huntington. Its accumulation in both astrocytes and neurons leads to neuronal death. A wide variety of astrocyte functions have been implicated in facilitating neuronal death in HD, including glutamate toxicity, impaired GABA release, impaired secretion of trophic factors, increased inflammatory signaling, and reduced anti-inflammatory signaling. The R6 mouse model of HD shows reduced mRNA levels of GLT-1 in the striatum and reduced glutamate uptake prior to the development of neurodegeneration, suggesting astrocyte-mediated glutamate excitotoxicity leads to neuronal death (Liévens et al., 2001). Reduced expression of glutamate transporters correlates with the accumulation of mutant huntington protein in astrocytes (Shin et al., 2005). The level of glutamate transporter expression decreased corresponding with disease severity (Faideau et al., 2010). Interestingly, the excitotoxic stress in HD has been reported to stimulate striatal astrocytes to take on a pluripotent form to become neuroblasts (Nato et al., 2015), providing a possible mechanism for neuronal replacement. In addition to reduced glutamate uptake, astrocytes in HD models also have reduced GABA release, resulting in impaired tonic inhibition (Wójtowicz et al., 2013). Both patients and mouse models of HD show increased activation of the NFκB signaling in astrocytes, leading to enhanced inflammation (Hsiao et al., 2013). Inhibition of astrocyte-mediated inflammatory signaling through TNFα enhanced motor function and reduced aggregates of mutant huntington in a mouse model of HD, suggesting anti-inflammatory treatments may help slow the progression of HD (Hsiao et al., 2014). Recent findings report that cholesterol biosynthesis by astrocytes is reduced in HD, leading to neuronal deficits (Valenza et al., 2015). Additionally, accumulation of huntington aggregates in astrocytes reduced astrocytes secretion of brain derived neurotrophic factor (BDNF) (Wang et al., 2012). Alternatively, reactive astrocytes secrete pro-NGF, which leads to apoptosis of motor neurons (Domeniconi et al., 2007).

6.5 Epilepsy

Astrocyte dysfunction also plays a crucial role in epilepsy, as demonstrated in studies of patients with temporal lobe epilepsy and epilepsy models (Coulter and Steinhäuser, 2015). Disruption of K+ homeostasis, alterations in channel expression, dysfunctional gap junctions, and deficits in glutamate uptake together lead to seizures. Breakdown of the BBB leads to albumin accumulation, which stimulates upregulation of GFAP (David et al., 2009). A recent study suggests that this reactive astrogliosis is sufficient to induce seizures in mice (Robel et al., 2015), due to impaired glutamate uptake. Conditional deletion of the glutamate receptor GLT-1 in reactive astrocytes resulted in seizures and lower body weight (Petr et al., 2015). Elevated glutamate-mediated calcium signaling in astrocytes makes them hyperexcitable, leading to enhanced excitatory neurotransmission in epileptic hippocampal slices (Álvarez-Ferradas et al., 2015). Astrocytes in hippocampal slices of human patients suffering from temporal lobe epilepsy displayed prolonged depolarization and reduced inward rectifier currents (Hinterkeuser et al., 2000), implicating K+ homeostasis as an important contributor to epilepsy. Optogenetics may provide promising therapeutic potential to correct astrocytic glutamate and K+ uptake in epilepsy (Ji and Wang, 2015). Furthermore, proper functioning of gap junctions and inter-astrocytic communication are believed to play a role in the development of epilepsy, but their exact role is still unknown. Some reports suggest that astrocyte coupling is increased in murine epileptic models (Samoilova et al., 2003; Takahashi et al., 2010), whereas others suggest that gap junctions are decreased (Bedner et al., 2015; Xu et al., 2009). Expression studies have been conducted to determine the levels of connexin 43, the major gap junction protein, in epilepsy, but the results have also been mixed. Increased, decreased, and unaltered connexin expression have been reported in human epilepsy and animal models, making the results difficult to interpret without accompanying functional coupling analysis (Coulter and Steinhäuser, 2015).

6.6 Gliomas

Astrocyte interactions with glioma cells are important for glioma invasion, leading to poor survival. An interesting study looking at miRNA transfer found that gap junction mediated miRNA transfer between a glioma cell and another glioma cell does not allow for glioma invasion. In contrast, when miRNA transfer occurs between a glioma cell and an astrocyte, it promotes invasion in an *in vitro* transwell invasion assay (Hong et al., 2015). This finding suggests that gap junctions in astrocytes could be a crucial target for manipulation in preventing glioma invasion and promote patient survival. Using co-cultures of glioma cells and astrocytes, a separate study found that normal functioning astrocytes were able to reduce the rate of proliferation of glioma cells, but if astrocytes become outnumbered by glioma cells, they are no longer able to protect neurons from glioma cell glutamate secretion and excitotoxicity (Yao et al., 2014). Unlike lower grade gliomas, where non-neural metastases are self-contained, high grade tumor cells are able to infiltrate throughout the brain. The difference in the invasiveness of these tumors can be partly attributed to differences in the CSPG environment and surrounding astrocytes. In lower gliomas, a rich CSPG environment accompanied by the presence of LAR family receptors, along with an astrocytic capsule prevents the spread of the tumor. In highly invasive glioblastoma, the CSPG matrix as well as its receptors and astrocyte encapsulation are absent, favoring tumor cell invasion (Silver et

al., 2013). A better understanding of astrocyte contribution to glioma growth and invasion could provide valuable therapeutic options for patients.

7. TARGETING ASTOCYTES FOR CNS REPAIR

7.1 Astrocytes in transplantation and bridge formation

Because of their reported benefits after injury and their important role in normal physiology, astrocytes have been used in transplantation studies to try to improve functional recovery. In particular, immature astrocytes have been used because of their growth-permissive properties without the negative effects of scar formation. In fact, transplanted immature, but not mature, astrocytes have the ability to suppress glial scar formation and thereby enhance neurite outgrowth in the mouse brain (Smith and Silver, 1988). Transplanted immature astrocytes are also more motile and associate better with blood vessels than mature astrocytes (Smith and Miller, 1991), which may account for their ability to suppress scar formation. Immature astrocytes also have a better ability to grow on high concentrations of CSPGs in an MMP-2 dependent manner (Filous et al., 2010).

In addition to promoting regeneration directly, astrocytes have been transplanted as a way to alter the behavior of other glia as well. Transplanting type-1 astrocytes into ethidium bromide lesions in the white matter of the spinal cord was able to enhance remyelination (Franklin et al., 1991).

Enhancing the beneficial neuroprotective effects of astrocytes after injury, while minimizing the negative effects on regeneration is a major interest in the field. One study used an intraparenchymal adeno-associated virus injected at the site of injury to induce overexpression TGFα (White et al., 2011). TGFα was able to transform neighboring astrocytes to a growth permissive phenotype that enhanced cell proliferation, altered their distribution, and led to increased regeneration to the rostral end of the lesion, suggesting that manipulation of astrocytes, rather than their ablation, may provide a promising avenue for therapy in the future.

Many studies have focused on the possibility of astrocytes to form bridges across the lesion core after injury. A study using a microlesion of the cingulate gyrus found that microtransplanting immature astrocytes along with the enzyme chondroitinase ABC to aid in proteoglycan degradation provided a bridge across the lesion environment that allowed for injured axons to regenerate just past the lesion (Filous et al., 2010). Suppressing the expression of phosphate and tenascin homolog (PTEN) with short hairpin RNA in mouse corticospinal neurons enabled injured fibers to cross the lesion along bridge-forming astrocytes, believed to be derived from mature astrocytes rather than ependymal cells, after spinal cord injury (Zukor et al., 2013). An earlier study suggested that adult cortical astrocytes retain the ability to revert to a more immature, even radial-glial like, state that was capable of directing the migration of transplanted immature neurons (Leavitt et al., 1999).

7.2 Modifying endogenous astrocytes to promote repair

Although in the normal CNS astrocytes are not generally thought to be neural stem cells, after injury, astrocytes have been found to de-differentiate and upregulate nestin expression

(Lang et al., 2004; Shibuya et al., 2002). When cultured, these astrocytes had the ability to generate neurons, astrocytes, and oligodendrocytes (Lang et al., 2004), suggesting these cells take on neural stem cell properties in response to spinal cord injury (Götz et al., 2015). Other studies suggest that while astrocytes are able to proliferate in response to injury *in vivo*, their ability to generate neurospheres may simply be an *in vitro* phenomenon (Buffo et al., 2008). However, more recent work suggests that more invasive injuries, such as a stab wound or cerebral ischemia, are necessary to elicit the multipotency of reactive astrocytes *in vivo*, and that sonic hedgehog is necessary and sufficient to induce astrocytes to take on these stem-cell like properties (Sirko et al., 2013). The presence of endogenous stem cells after injury holds the promise of providing therapeutic options for repair.

7.3 Targeting specific molecules to enhance repair

7.3.1 Glutamate excitotoxicity—Astrocytes are important for regulating glutamate excitotoxicity within the synaptic cleft. Deficiencies in astrocyte uptake of glutamate has been linked to various neurodegenerative disorders, such as ALS (Rothstein et al., 1992). Impairments in glutamate transport and metabolism in astrocytes has also been implicated in epilepsy (Eid et al., 2013), oligodendrocyte death (Murugan et al., 2013), tauopathies (Dabir et al., 2006), and schizophrenia (Hu et al., 2015; Toro et al., 2006), whereas stroke actually leads to an increased expression of glutamate transporters (Yatomi et al., 2013). Therefore, modifying the action or expression of these glutamate transporters may provide a therapeutic target for these conditions. Various molecules have entered clinical trials to test the feasibility of manipulating astrocyte-mediated glutamate uptake in reducing neurodegeneration in stroke and ALS. Rothstein *et al.* discovered that beta-lactam antibiotics stimulate GLT-1 expression by increasing its transcription, making these FDA-approved drugs strong candidates to target glutamate excitotoxicity (Rothstein et al., 2005). One of these antibiotics, ceftriaxone, promoted EAAT2 activation through NFκB signaling (Lee et al., 2008). Furthermore, ceftriaxone is able to reduce glutamate mediated oxidative stress through the activation of antioxidant pathways (Lewerenz et al., 2009), further suggesting the possible therapeutic benefits of this drug in reducing glutamate toxicity. Alternatively, because astrocyte excitability is mediated through calcium signaling, targeting this pathway can be used to alter glutamatergic synapses.

7.3.2 Altering gap junctions—Gap junctions connect astrocytes and allow for intracellular communication. Disruptions of this signaling has been implicated in a variety of insults, making it an attractive target for therapeutic intervention. For example, ischemia leads to improper opening of connexin43 hemichannels, which make up gap junctions, leading to apoptotic cell death. However, inhibiting this signaling by pre-treating with either Gap26 or Gap27 reduced cerebral infarct volume and enhanced functional recovery (Li et al., 2015). Loss of connexin43 has also been linked to the progression of MS (Masaki, 2015). Working to restore proper glial communication could provide valuable therapeutic options for patients with many neuropathologies, including those described above.

8. CONCLUSION

It is clear that astrocytes are not mere bystanders in the complicated network of the nervous system. Their active participation in a variety of functions and pathways makes their proper functioning crucial to survival. Enhancing their beneficial roles while minimizing their deleterious effects holds enormous therapeutic potential in many diseases and insults.

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Glossary

AD	Alzheimer’s disease
AEG-1	Astrocyte-elevated gene 1
ALS	Amyotrophic lateral sclerosis
ApoE	Apolipoprotein E
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BLBP	Brain lipid binding protein
BMP	bone morphogenetic protein
CNTF	ciliary neurotrophic factor
CSPG	Chondroitin sulfate proteoglycan
ET-1	Endothelin-1
GABA	γ-Aminobutyric acid
Gcm	Glial cell missing
GDNF	Glial derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
GLAST	Glutamate aspartate transporter
GLT-1	Glutamate transporter 1
HD	Huntington’s disease
IGF	Insulin-like growth factor
LDLR	Low-density lipoprotein receptor
LIF	leukemia inhibitory factor

NFκB	nuclear factor kappa B
NGF	Nerve growth factor
NT-3	Neurotrophin 3
OPC	Oligodendrocyte progenitor cell
PD	Parkinson's disease
PTEN	Phosphate and tenascin homolog
SCI	Spinal cord injury
TDP-43	Transactive response DNA binding protein
TGFβ	transforming growth factor
TIMP-1	Tissue inhibitor of metalloproteinases 1

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Highlights

- Astrocytes function in blood-brain barrier formation and synaptogenesis under normal physiological conditions.
- Astrocytes undergo varying degrees of astrogliosis in response to the severity of injury that has occurred.
- Astrocytes in the glial scar have both beneficial and harmful effects on regeneration.
- Astrocytes play a significant role in a variety of diseases, including Alzheimer's disease, Amytrophic lateral sclerosis, Huntington's disease, Parkinson's disease, and gliomas.
- Astrocytes can be targeted to repair the CNS after injury.