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# Reactive Astrogliosis after Spinal Cord Injury—Beneficial and Detrimental Effects

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**Abstract** Reactive astrogliosis is a pathologic hallmark of spinal cord injury (SCI). It is characterised by profound morphological, molecular, and functional changes in astrocytes that occur within hours of SCI and evolves as time elapses after injury. Astrogliosis is a defense mechanism to minimize and repair the initial damage but eventually leads to some detrimental effects. Reactive astrocytes secrete a plethora of both growth promoting and inhibitory factors after SCI. However, the production of inhibitory components surpasses the growth stimulating factors, thus, causing inhibitory effects. In severe cases of injury, astrogliosis results in the formation of irreversible glial scarring that acts as regeneration barrier due to the expression of inhibitory components such as chondroitin sulfate proteoglycans. Scar formation was therefore recognized from a negative perspective for many years. Accumulating evidence from pharmacological and genetic studies now signifies the importance of astrogliosis and its timing for spinal cord repair. These studies have advanced our knowledge regarding signaling pathways and molecular mediators, which trigger and modulate reactive astrocytes and scar formation. In this review, we discuss the recent advances in this field. We also review therapeutic strategies that have been developed to target astrocytes reactivity and glial scaring in the environment of SCI. Astrocytes play pivotal roles in governing SCI mechanisms, and it is therefore crucial to understand how their activities can be targeted efficiently to harness their potential for repair and regeneration after SCI.

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**Keywords** Astrocytes · Spinal cord injury · Glial scar · Chondroitin sulfate proteoglycans · Chondroitinase · Axonal regeneration · Cell replacement · Therapeutic targets

**Abbreviations**

| | |
|---|---|
| BBB | Blood–brain barrier |
| BSB | Blood–spinal barrier |
| BMPs | Bone morphogenetic proteins |
| ChABC | Chondroitin sulfate proteoglycans |
| CSPGs | Chondroitin sulfate proteoglycans |
| CNS | Central nervous system |
| Eph | Ephrin |
| ECM | Extracellular matrix |
| GFAP | Glial fibrillary acidic proteins |
| GAG | Glycosaminoglycans |
| IL | Interleukin |
| NPCs | Neural precursor cells |
| OPCs | Oligodendrocyte precursor cells |
| RPTP | Receptor protein tyrosine phosphatases |
| SCI | Spinal cord injury |
| Stat3 | Signal transducers and activators of transcription3 |
| TGF | Transforming growth factors |
| TNF-α | Tumor necrosis factor-alpha |
| XT | Xylosyltransferase |

## Introduction

Astrocytes are the most abundant glial cells in the central nervous system (CNS), which are essential for various structural and physiological functions [1, 2]. After spinal cord injury (SCI), local environment undergoes profound

biochemical and cellular changes that affect neurons, oligodendrocytes, and astrocytes. These changes start with immediate influx of inflammatory cells into the injured spinal cord that release a host of cytokines and chemokines causing exitotoxicity and cell damage. SCI affects astrocytes differently than neurons and oligodendrocytes. In fact, SCI triggers astrocytes to become reactive and initiate astrogliosis [3, 4]. Reactive astrogliosis is characterized by the proliferation and hypertrophy of astrocytes, which eventually leads to scar formation via the activation of signaling pathways such as STAT3 and transforming growth factors-beta (TGF-β/Smad) [5–7]. Upon an injury, astrocytes undergo phenotypic and morphologic changes. They increase their expression of intermediate filaments such as glial fibrillary acidic proteins (GFAP), nestin, and vimentin [1, 8]. Reactive astrocytes also contribute to the release of pro- and anti-inflammatory cytokines such as TGF-β, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukins (IL-1 and IL-6) that modulate inflammation and secondary injury mechanisms. Reactive astrocytes also regulate their own activities in an autocrine fashion [4, 8, 9].

After SCI, reactive astrocytes alter the composition of extracellular matrix (ECM) dramatically. Several ECM components including chondroitin sulfate proteoglycans (CSPGs) and tenascins are markedly upregulated in astrocytes [4, 8, 9]. In addition to these phenotypic changes, astrocytes increase in number and migrate to the site of injury [10–12]. In severe injuries, they surround the SCI lesion and form a glial scar that will serve as a physical barrier to contain the lesion area [7, 12–14]. Astrocyte reactivity has been therefore viewed as a part of endogenous mechanisms to limit the initial tissue damage to the spinal cord and prevent extension of injury into adjacent segments. Beneficial role of reactive astrocytes particularly at early stages of SCI is now supported by growing research evidence. Ablation of reactive astrocytes or interfering with their activation at the time of injury exacerbates the outcomes of SCI by increasing tissue degeneration and failure to reconstruct blood–spinal barrier (BSB) [8, 13, 14]. However, as time elapses after injury, inhibitory properties of reactive astrocytes evolve and overcome their constructive effects. This is mainly attributed to the upregulation of inhibitory molecules such as CSPGs that potently impede neural repair and regeneration [15–22].

Astrocytes play critical roles in the normal spinal cord, and it is therefore necessary to delineate their functional roles after SCI. This knowledge is important in designing efficient therapies for SCI. This article reviews (1) the roles of astrocytes in the spinal cord under normal and injury conditions, (2) the various mechanisms that mediate reactive astrogliosis after SCI, (3) how reactive astrocytes and their associated factors influence repair process at different stages of SCI, and (4) the current status of therapeutic strategies that have been developed to modulate the properties of reactive astrocytes and glial scar after SCI.

## Astrocyte Functions in the Normal Spinal Cord

Astrocytes are the most abundant glial cells, which play major roles in the CNS physiology. They exist in individual domains, where each astrocyte domain has at least 100,000 synaptic communications [23–25]. These synapses are controlled in a well-harmonized manner through the release of neurotransmitters [24–27]. Astrocytes are the primary regulators of homeostasis in the CNS [28, 29]. They regulate a variety of key physiological functions throughout the development and adulthood [30]. Astrocytes are involved in neurotransmitter uptake [2, 31], construction of the blood–brain barrier (BBB) and BSB [32–35], proper functioning of synaptic junctions [24, 36, 37] and synaptic plasticity [8, 37], controlling blood flow [38], homeostasis of ions and fluids such as $K^+$ and water [39, 40], providing nutrition and energy metabolites to neurons [41, 42], and cortical plasticity through cholinergic modulation [43]. Owing to their indispensable contributions, astrocytes are now viewed as active cells in the CNS rather than acting only as supportive cells for neurons [36]. In this section, we review main functions of astrocytes in the developing and adult CNS (see Table 1 for summary).

### Role in Guiding Neurons and Synapse Formation

During development, although astrocytes appear after neurons, they are involved in key developmental and

**Table 1** Summary of main functions of astrocytes in the developing and adult CNS

| Functions of Astrocytes | Molecular mediators |
|---|---|
| Process, transfer, store neuronal information | $Ca^{2+}$ glutamate [36, 37] |
| Neuronal development, migration and differentiation, function | Neurotrophic factors (VEGF), $Ca^{2+}$, glutamate [45, 47–49] |
| Synaptic functions and Plasticity | Tenasin C, CSPGs [15, 46, 61] |
| Protect from glutamate excitoxicity | Transporters of glutamate [128] |
| $\left\{\begin{matrix}\text{Vasodilation}\\ \text{Vasoconstriction}\end{matrix}\right\}$ RegulatingBloodflow | Arachidonic acid [55] |
| | Arachidonic acid, NO, PGs [55] |
| Formation and maintenance of BSB | Soluble factors [42] |
| Energy provision | Lactate [14] |
| Proton shuttling | $Na^+/H^+$ exchanger, bicarbonate transporters, monocarboxylic acid transporters, ATPase [59] |
| Fluid and ion homeostasis | Aquaporins [40] |

postnatal events in the CNS [30, 44]. Astrocytes release neurotrophic factors that modulate neuronal development, migration, differentiation, and function [45–49]. Developing astrocytes guide postmitotic neurons from the ventricular zone to their target destination in developing CNS [50]. Studies by Mittal and David [51] showed that radial glial cells, a subtype of astrocytes, guide new neurons by expressing specific cell surface glycoprotein. Recent evidence in postnatal brain also suggests that astrocytes play a critical role in migration of neurons in the rostral migratory stream (RMS) from the subventricular zone to the olfactory bulb [45]. Astrocytes secrete vascular endothelial growth factor that is necessary for the generation of new blood vessels in RMS. Recent studies show that blood vessels play a critical role in supporting the migration of neuroblasts to their final destination [45]. Astrocytes also foster formation and function of developing synapses in the CNS. In vitro, astrocytes facilitate synaptic connectivity and maintenance by multiplying the count of mature functional synapses on the CNS neurons [47]. Astrocytes establish close spatial orientation with neurons and their synapses [48]. In contrast to the previous views where neurons were believed to be the sole regulators of synaptic communications [37], it is now well-accepted that the proper functioning of CNS depends on the harmony and cross-communication between astrocytes and neurons [48, 52]. Astrocytes communicate with neurons through "tripartite synapses." These synapses are comprised of astrocytic process as well as neuronal pre- and postsynaptic regions [36, 37]. Through the tripartite synapses, astrocytes regulate the gliotransmitter environment in the synaptic region. Each astrocyte also modulates the functional groups of synapses confined within their boundaries [24]. During synaptic transmission, neurotransmitters released by neurons trigger intracellular calcium release in astrocytes, which in turn stimulate the release of gliotransmitters such as glutamate, serine, and prostaglandins that ultimately modulate synaptic functions and plasticity [36, 37, 52, 53]. Astrocytes also show the ability to process, transfer, and store information [37].

## Construction of BSB and Modulation of Blood Flow

Astrocytes are the primary mediators of blood flow as they can respond to various changes in neuronal activities and are important in signaling within neurovascular unit [54]. Astrocytes connect to blood vessels via their end-feet. They mediate vasoconstriction or vasodilation through different factors such as arachidonic acid, nitric oxide, or prostaglandins [55]. Astrocytes play a pivotal role in coupling neuronal organization to signaling circuits. Interactions between astrocytes and neurons involve the hemodynamic responses between them in which astrocytes relate neuronal activity to blood flow [56]. This was shown in the visual cortex by noninvasive brain imaging where the blockade of glutamate transporters in astrocytes changed the magnitude and duration of adjacent visually driven neuronal responses [56].

Astrocytes significantly contribute to the formation and maintenance of BBB and BSB in the CNS [33, 57]. Their processes are linked to the abluminal surface of the microvascular endothelium. It appears that astrocytes secrete soluble factors, which regulate the development of intercellular tight junctions between the endothelial cells, thus contributing to the maintenance and integrity of the BBB or BSB [58]. In transgenic adult mice that astrocytes were ablated, repair of the BBB failed after a cortical injury which in turn led to vasogenic edema [13].

## Maintaining CNS Homeostasis

Astrocytes have a critical role in regulation of pH in normal and pathological conditions [59]. They regulate proton shuttling through various proteins such as $Na^+/H^+$ exchanger, bicarbonate transporters acting in a sodium-dependent or sodium-independent mode, monocarboxylic acid transporters, carbonic anhydrase in both intra- and extracellular spaces, and the vacuolar-type proton ATPase [59]. Through various neurotransmitter up-takers, astrocytes also clear GABA, glycine, and glutamate from the synaptic clefts and facilitate normal synaptic transmission [2, 24]. This function also protects neurons from excitotoxicity and cell death [31]. Astrocytes are actively involved in water homeostasis. Extracellular fluid is maintained in dynamic equilibrium through Aquaporins that present abundantly on astrocytes [2, 31]. Aquaporins contact blood vessels and control edema, thus maintaining fluid and ion homeostasis. Astrocytes also play immunomodulatory roles in the CNS by their ability to produce chemokines and cytokines [28]. They are shown to express class II major histocompatibility complex antigens and therefore are also implicated in antigen presentation and T-cell activation [28].

## Astrocyte-Associated Extracellular Matrix Molecules

Astrocytes are actively involved in the synthesis and maintenance of the ECM in the CNS. They produce a number of ECM components with both growth promoting and inhibitory properties [5]. Fibronectin and laminin are examples of promoting factors that facilitate axonal growth and regeneration in the normal and injured spinal cord [60]. Astrocytes also express tenascin-C and various CSPGs with growth inhibitory properties. At the time of neuronal maturation in the normal CNS, CSPGs are concentrated abundantly in the perineuronal nets where they are crucial for stabilizing synapses and restricting unwanted plasticity [15, 46, 61]. Interestingly, tenascin-C and CSPGs

are markedly upregulated in reactive astrocytes after SCI and impede axonal plasticity and regeneration [5, 62].

Collectively, astrocytes possess unique cellular properties, which are crucial for normal functioning of the CNS [36]. Any alterations in their cell properties would therefore have pronounced consequences on the function and integrity of CNS.

### Reactive Astrogliosis in SCI

Similar to their structural and functional impact in the normal CNS, astrocytes also play critical roles in brain and spinal cord pathology. After SCI, astrocytes undergo significant cellular, molecular, and functional changes along with profound alterations in their gene expression [4, 5, 63–65]. These reactions include hypertrophy of astrocytic processes and soma and increased proliferation and upregulation of intermediate filaments GFAP, vimentin, and nestin in the astrocytes that are located close to the site of SCI. These modifications are the hallmarks of a phenomenon known as reactive astrogliosis [8, 66, 67]. Reactive astrogliosis is also accompanied with increased production of CSPGs, various cytokines, and chemokines such as TGF-β, IL-1β, IL-6, ciliary neurotrophic factor (CNTF), adhesion/recognition molecules, and proteins such as cyclooxygenase 2, inducible NO synthase, and calcium-binding protein S100β. These factors are considered as the functional markers of astrocyte reactivity whose levels are upregulated following CNS injuries [8, 21, 22, 68, 69].

Reactive astrogliosis is a gradual process after SCI. The degree of astrocyte reactivity varies based on the severity of injury, the time after injury, and the distance of astrocytes to the site of insult [8, 9]. Astrogliosis is categorized from moderate changes in astrocytes to intense reactivity associated with scar formation [1, 22]. In initial stages of astrogliosis, there is aberrant hypertrophy of astrocytes with slight increase in GFAP levels [8]. However, astrocytes maintain their individual territories with no apparent breaching of their processes into the adjacent astrocytes domains. No significant proliferative activities usually occur in cases of mild astrogliosis. This type of reactivity is known as "isomorphic gliosis" that is seen in the cases of chemical lesions, axotomy, or mild injury where astrocytes are distal to the site of injury [1, 22, 68, 70]. hese changes can be reversed by attenuating the triggering effects of upstream signaling molecules. As time elapses, reactive astrocytes show intense GFAP expression, substantial hypertrophy, and some degree of proliferation. These significant expansions lead to disruption of individual territories of astrocytes and cause tissue distortion [8]. In severe injuries, these phenotypic changes are also accompanied by pronounced astrocyte proliferation. Astrocytic processes overlap and appear to be densely packed [1]. At this stage, a glial scar is formed that encircle the epicentre of spinal cord lesion. Glial scar that is formed after local disruption of parenchyma is irreversible and is termed as "anisomorphic gliosis" [22, 68].

Although astrogliosis is an early hallmark of SCI in rodents, astrocyte reactivity is not a prominent feature of human SCI at acute/subacute phases [71–73]. In humans, astrogliosis seems to evolve over the time and become more evident at intermediate and chronic stages of SCI [72]. Immunohistochemical examination of human SCI tissues at various time points after injury has shown the presence of dense astrogliosis at 11 days after injury that was still evident after 1 year post-SCI [72]. Further investigations are necessary to delineate the impact and timing of astrogliosis in human SCI. This is particularly important when translating therapeutic strategies that target astrogliosis from rodent models to human SCI.

Scar formation after SCI is not solely attributed to reactive astrocytes. Meningeal fibroblasts also contribute to this process [7, 74]. Evidence suggests that the formation of glial scarring is regulated by a cell–cell contact mechanism between reactive astrocytes and meningeal fibroblasts at the lesion site. Signaling between ephrin-B2 on reactive astrocytes and EphB2 receptors on meningeal fibroblasts appears to play a role in this process [74].

At the molecular level, reactive astrogliosis can be triggered through various key signaling pathways such as signal transducers and activators of transcription (STAT) and TGF-β/Smad as well as Sox9 transcription factor [8, 22, 63]. Depending on the involved signaling pathways and timing after SCI, astrogliosis can exert both beneficial and detrimental effects. Understanding the underlying mediators and mechanisms that control the activities of astrocytes in pathologic conditions will allow us to strategize therapeutic approaches that would harness the repair potential of astrocytes after SCI [5, 7, 75–77].

## Molecular Mediators of Reactive Astrogliosis and Glial Scar Formation After SCI

Transition from normal to a reactive phenotype in astrocytes involves multiple inter- and intracellular signaling mechanisms that act temporally to trigger and maintain astrocytes reactivity. Over the past years, a number of cytokines, chemokines, growth factors, and transcription factors have been identified as the mediators of astrogliosis. These mediators are mainly produced by astrocytes, microglia, leukocytes, and endothelial cells. Among the long list of mediators are TNF-α, IL-1β, IL-6, IL-10, TGF-α, TGF-β CNTF, fibroblast growth factor-2, platelet-derived growth factor, insulin-like growth factor (IGF), leukemia inhibitory factor, monocyte chemoattractant protein-1, endothelin-1, erythropoietin, fibrinogen, matrix metalloproteinase-9, and Sox9 [41, 63, 78–82]. Evidence suggests that proinflammatory cytokines TNF-α, IL-1β,

and IL-6 are the initial triggers of reactive astrocytes in the acute phase of SCI [83, 84]. At later stages, other mediators maintain astrocytes reactivity [85–87]. Interestingly, reactive astrocytes release the majority of these triggering molecules themselves, which in turn activate more astrocytes and maintain the glial scar through self-sustaining mechanisms [68, 88–91]. Activated microglia and leukocytes play a modulatory role in astrogliosis [68, 92]. The similarities that exist between the properties of reactive astrocytes and activated macrophages/microglia have made it difficult to precisely define and differentiate the impact of these cell populations in governing the secondary SCI mechanisms.

A number of signal transduction pathways and receptors have been implicated in astrogliosis including STAT, JNK/c-Jun, Smads, cAMP, nuclear factor kB (NF-kB), IGF1-calcineurin, SOCS, RhoA, and mitogen-activated protein kinase (MAPK) [1, 7, 22, 93–101], epidermal growth factor receptor (EGFR), ephrin receptor, IL-6R, IL-2R, IL-4R, and bone morphogenetic protein receptors [102–105]. STAT3 signaling has been implicated as a key mediator of astrocytic scar formation after SCI [7, 100]. STAT3 conditional knockout mice failed to form a glial scar after SCI that led to a widespread lesion and poor recovery of function. Lack of STAT3 activation particularly resulted in the inability of astrocytes to migrate to the lesion site and contain the injured area. This resulted in exacerbated influx of inflammatory cells at the site of SCI [7, 100]. This evidence emphasized the impact of STAT3 activation in astrocytes and the importance of reactive astrogliosis in restraining leukocyte infiltration and reducing the initial tissue damage after SCI.

TGF-β signaling is another mediator of reactive astrogliosis in SCI [63, 98, 106]. In fact, TGF-β has been identified as a key upstream trigger of CSPGs formation in the glial scar [63, 98]. In experimental models of SCI, blockade of TGF-β signaling is shown to attenuate scar formation [98, 106–108]. Interestingly, blood fibrinogen is a factor that activates TGF-β signaling after traumatic CNS injury [98]. After vascular disruption and hemorrhage, blood fibrinogen is released into the CNS tissue that can then induce reactive astrogliosis and CSPGs formation through the activation of TGF-β Smad2 pathway [98]. In brain injury, when fibrinogen was ablated genetically or depleted pharmacologically by ancrod, it decreased TGF-β activation and attenuated glial scar formation [98]. When fibrinogen was injected into the cortex of mouse, it was sufficient to trigger astrogliosis. In vitro and in vivo, when TGF-β/Smad2 signaling was inhibited by a TGF-β blocking antibody or a TGF-β receptor inhibitor, it also abolished the effects of fibrinogen on CSPGs formation and glial scarring [98]. Vascular injury and hemorrhage are early events after SCI, and it is therefore anticipated that fibrinogen likely contributes to CSPG upregulation and scar formation after SCI.

Activation of NF-kB transcription factor has been implicated in astrogliosis, although with some conflicting results. In SCI, one study showed that elevated level of NF-kB was detected in microglia/macrophages and endothelial cells but not in astrocytes [109]. However, in another study, reactive astrocytes were shown to express NF-kB [96]. Interestingly, studies in transgenic mice expressing IkBα, an inhibitor of NF-kB, under hGFAP promoter showed that inactivation of astroglial NF-kB attenuated the expression of TGF-β2 and CSPGs as well as other chemokines involved in the formation of glial scar such as CXCL10 and CCL2 [96]. Moreover, blockade of NF-kB activation in astrocytes has resulted in white matter sparing and improved functional recovery after SCI [96].

Similar to their importance in normal astrocyte physiology, Aquaporins may play a role in the activities of astrocytes after injury. In particular, Aquaporin-4 is important in glial scar formation [110]. In a cortical brain injury, Aquaporin-4 null mice showed decreased migration of astroglia towards the injury site and less glial scarring [110]. However, evidence from rat SCI revealed biphasic changes in astrocytic Aquaporin-4 levels with early downregulation after SCI and a subsequent long-lasting upregulation in subacute and chronic stages of injury [111]. Nonetheless, changes in Aquaporin-4 expression were not correlated with astrocytic activation after SCI as the increased expression of Aquaporin-4 was detected at 2 weeks post-SCI when the formation and migration of reactive astrocytes to the lesion area was already well underway [111]. Further elucidation is needed to understand the impact of Aquaporin-4 in scar formation after SCI.

Endothelins (ET) are vasoactive peptides that appear to modulate reactive astrogliosis in several CNS pathologies [9, 112, 113]. ET-1 and its receptors are particularly elevated in astrocytes after injury and seem to be one underlying cause of astrogliosis [114–116]. In a stab wound injury, ET-1 receptor antagonist BQ788 attenuated the activation and proliferation of astrocytes [117]. ET-1 stimulates astrocyte proliferation through the activation of JNK/c-Jun signaling pathway in vitro [99, 118].

Components of ECM significantly influence astrocytes functions with differential effects within the CNS regions. Majority of the ECM proteins such as laminin and fibronectin exert their action through integrin receptors [5]. Genetic evidence shows that the presence of β1-integrin is required to maintain a normal phenotype in astrocytes [10, 119–122] as its deletion in astrocytes results in a reactive phenotype and onset of astrogliosis. This evidence was recently confirmed when deletion of β1-integrin or their down-stream effectors Rho GTPase Cdc42 [120] and glycogen synthase kinase-3

[10] resulted in impaired migration of reactive astrocytes to the site of injury. Lack of β1-integrin signaling led to pronounced inflammation and tissue degeneration in CNS injuries.

MAPK and its downstream cascades mediate astrogliosis in a cell-autonomous fashion [123]. It is shown that *c-mos* proto-oncogene, which triggers the activation of MAPK signaling, stimulates astrogliosis. This was in agreement with other studies that implicated the phosphorylation of extracellular signal-regulated kinase/MAPK in reactive astrocytes in mice and humans [124, 125].

Altogether, accumulating evidence has identified several key signaling pathways involved in astrogliosis after SCI. This complexity reflects the broad range of interactions that astrocytes make with their neighboring cells within the spinal cord tissue. Given the multifactorial and temporal nature of astrogliosis, it is crucial to delineate the impact of reactive astrocytes at different time points after SCI in order to identify effective therapeutic targets.

## Beneficial Effects of Reactive Astrogliosis and Scar Formation in SCI

Although astrocytes are the most studied glial cells of the spinal cord, their functions in SCI are less understood. For a number of years, they were known to be solely detrimental in SCI, and their inhibition or ablation was thought to be a therapeutic strategy. Recent studies have provided strong evidence that reactive astrocytes play essential roles in SCI repair with protective nature [1, 8, 13, 68, 126].

Reactive astrogliosis is considered as a defence mechanism of astrocytes to injury [7, 13, 68, 100]. Activated astrocytes initiate a repair response by reconstructing the damaged BSB and limiting the infiltration of peripheral leukocytes and activation of resident microglia [8, 9, 92]. Reactive astrocytes also modulate blood flow by the release of vasoconstrictors and regulating blood vessels diameter [38, 127]. One of the early consequences of SCI is nonspecific release of glutamate to extracellular environment. By up-taking excess glutamate, astrocytes protect neurons and oligodendrocytes from glutamate excitotoxicity [13, 128, 129]. They also release adenosine and clear amyloid beta peptides and ammonium ions [1]. By producing antioxidants such as glutathione, astrocytes also defend against oxidative stress [13, 130]. The beneficial impact of astrogliosis in CNS repair has been supported by genetic ablation of reactive astrocytes [13, 14]. In animals that reactive astrocytes were ablated, reconstruction of BBB or BSB was compromised after brain or spinal cord injury, respectively. Moreover, ablation of reactive astrocytes caused substantial vasogenic edema and widespread inflammation and tissue degeneration after SCI [14]. Thus, astrocyte activation is now believed to be indispensable for minimizing the extent of SCI lesion at initial stages of injury.

Early after SCI, reactive astrocytes upregulate the expression of intermediate filaments, GFAP, vimentin, and nestin [8, 9]. The impact of these cellular components in astrogliosis is not fully understood due to conflicting reports in literature. In hemisection model of SCI, double GFAP and vimentin knockout mice showed beneficial outcomes [131], whereas knockout of only GFAP resulted in more pronounced lesion after SCI [14]. As mentioned earlier, astrocytes are known to become reactive through STAT3 and suppressor of cytokine signaling 3 (SOCS3) pathways [7, 14, 100]. Knockout of SOCS3 or STAT3 in GFAP-Cre or nestin-Cre transgenic models caused limited migration of astrocytes to the site of lesion and interfered with the formation of glial scar after SCI [7, 14, 100]. Failure of scar formation in these animals resulted in widespread lesion, increased neuronal and oligodendroglial cell death, and exacerbated motor deficits after SCI compared to wild-type injured animals [7, 14, 100]. In addition to their role as a physical barrier, reactive astrocytes can potentially promote tissue repair and regeneration as they upregulate their expression of FGF-2 and S100β in the injured spinal cord [132]. Interestingly, upregulation of FGF-2 and S100β was exclusive to reactive astrocytes and not activated microglia/macrophages.

## Detrimental Roles of Reactive Astrocytes After SCI

Although current evidence suggests critical neuroprotective and reparative roles for reactive astrocytes at initial stages of SCI, they are also well-known for their inhibitory influence on axonal regeneration and functional recovery at later time points after injury. Following section will review the inhibitory effects of reactive astrocytes on endogenous repair mechanisms after SCI.

### Impact of Reactive Astrocytes on Axonal Regeneration

Following SCI, a plethora of inhibitory factors is upregulated in the ECM that substantially modify the milieu of spinal cord tissue into a nonpermissive environment for repair and regeneration. Reactive astrocytes contribute significantly to the release of these inhibitory ECM components after SCI [133]. Together, reactive astrocytes and the ECM components, generate a dense glial scar around the SCI lesion that has long been recognized to pose physical and chemical barriers on axonal regeneration [5, 17, 64, 134, 135]. As axons come in close contact with the glial scar, they form dystrophic end-bulbs and retract [17]. ECM components such as CSPGs, tenascins, and collagen are among the main inhibitory factors that are dramatically upregulated in the glial scar after SCI and

obstruct axonal elongation and sprouting [136–143]. The impact of CSPGs on spinal cord repair and regeneration was established by pioneering work that showed degradation of CSPGs using chondroitinase ABC (ChABC) enhanced axonal regeneration through the glial scar after SCI [18, 64]. ChABC is a bacterial enzyme that cleaves glycosaminoglycan (GAG) side chain of CSPGs from their central protein core [18]. Over the past decade, ChABC treatment has been used extensively either as a solitary treatment or in combinatorial approaches to create a more permissive environment for axonal growth and plasticity after SCI [143–146]. Recently, it was discovered that CSPGs exert their inhibitory effects on axons and neurons primarily by signaling on two members of receptor protein tyrosine phosphatases, namely, PTP-σ and leukocyte common antigen-related phosphatase (LAR) [19, 20, 147]. Targeted gene disruption of PTP-σ or LAR was able to overcome the inhibitory effects of CSPGs and promoted axon regeneration in corticospinal tract after SCI [19, 20, 147]. In a spinal cord lesion, Shen and colleagues showed that injured *PTP*σ−/− axons grew into the lesion area with CSPG deposits; however, they failed to regenerate substantially beyond the glial scar. This observation supports the involvement of other factors such as myelin inhibitory molecules or other glial-associated receptors in regeneration failure after SCI [20, 148] .

EGFR is also thought to modulate CSPGs activation. Studies by He's group suggested that EGFR activation is necessary to mediate the inhibitory properties of CSPGs on neurite outgrowth in the CNS [149]. Subsequent studies also showed that blockade of EGFR after SCI improves functional recovery by myelin sparing and improving axonal plasticity in the injured spinal cord [150]. Interestingly, a recent study revealed that acute upregulation of EGFR by astrocytes after SCI is indeed required to mediate the effects of TGF-α in inducing reactive astrogliosis. A mutant mouse with defective EGFR activity failed to form a normal glial scar and exhibited more secondary tissue damage and impaired recovery of function. These findings suggest the essential role of endogenous EGFR activation in spontaneous recovery after SCI. Although further investigations are needed to elucidate the impact of EGR signaling in SCI, current evidence suggest the importance of timing in targeting EGFR after SCI.

At the intracellular level, Rho-ROCK signaling pathway is involved in CSPG-mediated inhibition of axon regeneration after SCI [148, 149, 151–153]. Activation of Rho-ROCK pathway stabilizes actin polymerization and cause growth cone collapse [148]. Administration of specific inhibitors of RhoA activation afforded to overcome the inhibitory effects of CSPGs on neurons and facilitated neurite outgrowth and axonal regeneration in vitro and in SCI [151–153]. CSPGs appear to also activate protein kinase C (PKC) by a $Ca^{2+}$-mediated mechanism [17, 151]. In a rat dorsal hemisection model of SCI, pharmacological and genetic approaches to inhibit PKC activity were able to reduce the ability of CSPGs to activate Rho and inhibit axonal growth [154]. Importantly, these studies indicated that targeting Rho or PKC signaling also attenuates the inhibitory influence of myelin-associated molecules on axons [148, 154, 155]. Therapeutic strategies that could potentially reverse the inhibitory effects of damaged myelin and CSPGs simultaneously would potently facilitate repair and regeneration after SCI.

Astrocytes also exert their inhibitory effects on axonal growth by expressing EphA4, a receptor for ephrin B3 [156, 157]. Ephrins, members of the Eph receptor tyrosine kinase family and their ligands, are developmental axon guidance molecules that are upregulated and activated following SCI [157, 158]. Mice lacking EphA4 showed decreased scar formation with enhanced corticospinal and rubrospinal tract regeneration, which resulted in significant functional recovery following SCI [105, 159].

## Inhibitory Influence of Reactive Astrocytes on Cell Replacement Activities After SCI

Astrocytes are known to play a modulatory role in cell migration, differentiation, and maturation in the developing CNS [1, 160, 161]. They are in close contact with neural precursor cells (NPCs) in the brain and spinal cord and can modulate their properties through various cell-cell interactions or paracrine communications [161]. Recent studies suggest that astrocytes modulate fate specification of NPCs in the CNS, and interestingly, these effects are spatially and developmentally regulated [160–163]. Astrocytes present in the adult spinal cord secrete factors such as insulin-like growth factor binding protein 6 (IGFBP6) and decorin (a form of CSPG) that inhibit neuronal differentiation of adult NPCs [162]. Of note, IGFBP6 and decorin block IGF and TGF-β signaling, respectively [162]. Conversely, astrocytes harvested from neurogenic niche of the brain or newborn spinal cord promote neurogenesis [162]. Therefore, astrocytes residing inside the adult spinal cord seem to block neurogenesis. Recent studies have supported this view by showing the failure of transplanted or endogenous multipotent NPCs to give rise to neurons in the environment of normal or injured adult spinal cord [143, 164–168]. Thus, this evidence strongly suggests the differential properties of astrocytes in different CNS regions and at different developmental stages.

In vitro and in vivo studies indicate that CSPGs influence the properties of oligodendrocyte precursor cells (OPCs) [169, 170]. Availability of CSPGs inhibited the outgrowth of OPC processes and their differentiation into mature oligodendrocytes, thus preventing myelination in vitro [169]. Phosphocan and neurocan were found to be the main CSPGs with inhibitory effects on OPCs [169]. These in vitro observations have been confirmed by in vivo studies that showed ChABC treatment enhanced

the migration and differentiation of OPCs after SCI [170]. Furthermore, reactive astrocytes in a contused spinal cord blocked the differentiation of adult OPCs into oligodendrocytes by upregulation of bone morphogenetic proteins (BMPs) after SCI [171]. Activation of BMPs led to poor remyelination of injured axons and had detrimental effects on the functional recovery after SCI [171]. Conversely, blockade of BMP signaling by BMP receptor antagonists enhanced differentiation of OPCs to mature myelinating oligodendrocytes and attenuated astrocyte differentiation [171].

Our recent transplantation studies have revealed the inhibitory influence of CSPGs on the survival and migration of engrafted NPCs in SCI [143, 164]. We found a strong correlation between the upregulation of CSPGs in the glial scar and poor integration and migration of transplanted NPCs in chronic SCI. Degradation of CSPGs by ChABC treatment prior to NPC transplantation optimized the survival, integration, and migration of transplanted NPCs within the host injured spinal cord. Combination of ChABC treatment and NPC transplantation enhanced remyelination and axonal sprouting associated with functional recovery in chronic SCI [143]. Altogether, modulation of reactive astrocytes in the microenvironment of SCI appears to be an effective therapeutic target to promote endogenous repair and regeneration after SCI.

## Therapeutic Approaches to Modulate Glial Scar

In contrast to the protective roles of reactive astrocytes in the acute phase of SCI [14, 100], injury evolving the inhibitory nature of astrocytic glial scar becomes a substantial barrier to the success of spontaneous regeneration and cell replacement activities [4, 5, 100, 143, 171]. Thus, therapeutic approaches should be designed to specifically target the detrimental effects of astrocyte activation while harnessing their protective effects. Over the past years, several approaches have been employed to minimize the inhibitory effects of glial scar using genetic approaches to block the onset of astrogliosis [7, 172], pharmacological treatments to neutralize inhibitory molecules associated with the glial scar [18, 143, 145, 173–176], or strategies to block the formation or activation of inhibitory factors such as CSPGs [177, 178] (see Fig. 1).

Modulation of CSPGs in the glial scar has been pursued by as a repair strategy for SCI in a number of investigations [5, 16, 18, 61, 69, 143, 144] (Fig. 1). Different approaches have been developed to target CSPGs and manipulate their expression after SCI. ChABC treatment has been commonly used to remove the inhibitory properties of CSPGs from the injured spinal cord [18, 61, 144, 145, 173, 175, 179, 180]. ChABC has been able to reduce the active form of CSPGs significantly both in acute [18, 144] and chronic [143] stages of SCI. ChABC degrades GAG side chains of CSPGs that are the main contributor to the inhibitory properties of

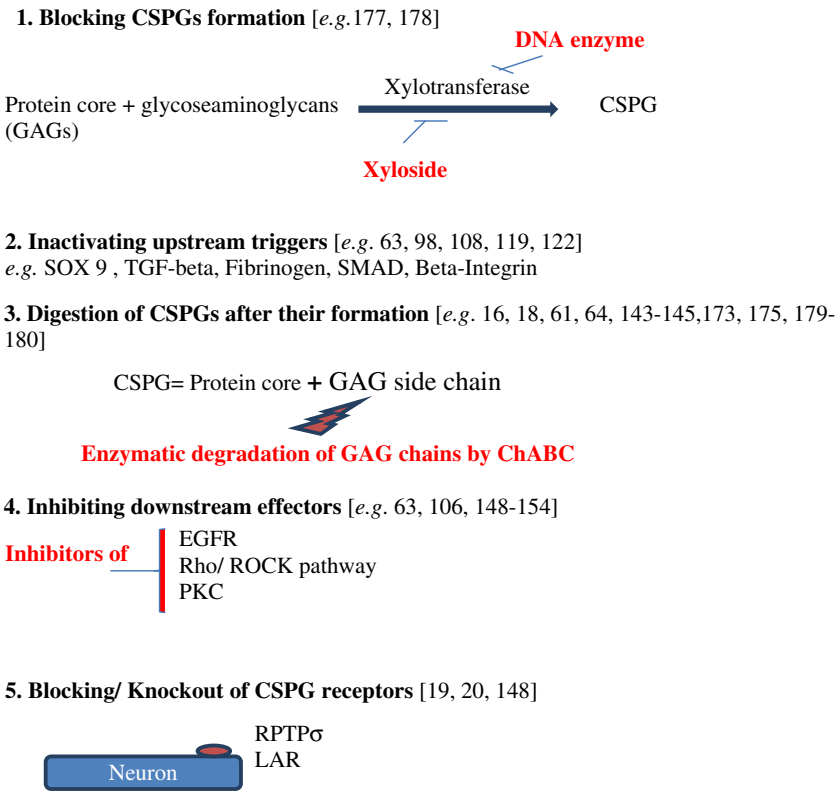


**Fig. 1** Targeting chondroitin sulfate proteoglycans (CSPGs) after spinal cord injury

CSPGs [18]. Although ChABC is effective in degrading CSPGs deposits, it does not entirely remove CSPGs from ECM since its biosynthesis is an ongoing process after SCI. Therefore, other therapeutic approaches have been developed to block CSPGs biosynthesis after SCI [177, 178]. Grimpe and Silver [177] used a DNA enzyme to xylosyltransferase-1 (XT-1) to block the formation of CSPGs after SCI. XT-1 is an enzyme required for the formation of GAG chains of CSPGs. The team showed that reducing CSPGs biosynthesis at the time of SCI enhanced the regeneration of transplanted sensory neurons through the spinal cord lesion [177]. In another strategy, using xyloside, a compound that interferes with proteoglycan synthesis, Rolls and colleagues [178] studied the impact of CSPGs in post-SCI repair mechanisms at different time points after SCI. Interestingly, the team showed the importance of timing in targeting CSPGs expression after injury. When CSPGs were inhibited acutely, the reduced availability of CSPGs significantly modified the inflammatory response after SCI. Acute inhibition of CSPGs increased the release of proinflammatory cytokine TNF-α and decreased the production of growth factor IGF-1 by macrophages/microglia [178]. This approach exacerbated the recovery of function after SCI. In contrast, subacute blockade of CSPGs led to improved recovery of function. Authors suggested that CSPGs play an immunomodulatory role in acute phase of SCI that is essential for wound healing. This evidence further supports the current view that activation of astrocytes is beneficial for repair process in early stages of injury [14, 100] while it becomes inhibitory at later stages [100].

At the transcriptional level, transcription factor Sox9 is shown to modulate the composition of ECM by astrocytes [63]. Evidence suggests that overexpression of Sox9 is required for formation of CSPGs in ECM with no apparent effects on other ECM components such as laminin and fibronectin [63]. Sox9 seems to regulate the expression of XT-I and XT-II in CSPG biosynthesis by astrocytes.

Modulation of cytokines, which trigger reactive astrogliosis and CSPG formation, has been also pursued as therapeutic strategies for SCI. Tyor and colleagues [181] showed that acute treatment with anti-inflammatory cytokine TGF-β decreased lesion volume after SCI by reducing the influx of macrophages at the injury site. However, as time elapses, TGF-β stimulates astrocytes and fibroblasts to form CSPGs and scarring, thus, hindering regeneration in subacute stages [182, 183]. Anti-TGF-β treatments or decorin as a potential blocker of TGF-B receptor–ligand interaction was shown to reduce scar formation and promote regeneration in the CNS [107, 108]. Conversely, proinflammatory cytokine IL-6 induce inflammation in an acute phase of injury, but promotes migration of astrocytes and substantial repair in a subacute phase [100]. Collectively, this evidence suggests the importance of timing in tailoring therapeutic strategies for SCI repair.

## Conclusions and Prospects

As discussed, reactive astrogliosis is a complex and multifactorial phenomenon after spinal cord injuries. Astrogliosis minimizes secondary tissue damage by restraining the lesion, providing growth factors, restoring BSB and tissue structure, revascularization, and maintenance of homeostasis and removal of tissue debris from the injured area. However, as SCI evolves, the detrimental effects of reactive astrocytes surpass their beneficial effects and impede repair and regeneration. Current findings suggest that modulation of glial scar by targeting its upstream and downstream mediators is an effective strategy for endogenous repair and improving neurological functions after SCI. However, emerging evidence signifies the impact of timing in modulating different aspects of reactive astrocytes after SCI. Hence, careful consideration should be made when developing repair strategies to target astrogliosis. More importantly, in addition to the components of glial scar, other SCI mechanisms such as neuroinflammation and myelin damage also substantially contribute to the secondary tissue degeneration and regeneration failure. Given this, it is now increasingly recognized that successful treatments of SCI requires a multifaceted approach to target various aspects of the secondary mechanisms of SCI.

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