NEURAL REGENERATION RESEARCH
December 2017, Volume 12, Issue 12
www.nrronline.org

INVITED REVIEW

Environmental cues determine the fate of astrocytes after spinal cord injury

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How to cite this article: *Nathan FM, Li S (2017) Environmental cues determine the fate of astrocytes after spinal cord injury. Neural Regen Res 12(12):1964-1970.*
Funding: *This work was supported by research grants to SL from NIH (1R01NS079432 and 1R01EY024575) and Shriners Research Foundation (SHC-86300-PHI, SHC-86200-PHI-16 and SHC-85100).*

Abstract
Reactive astrogliosis occurs after central nervous system (CNS) injuries whereby resident astrocytes form rapid responses along a graded continuum. Following CNS lesions, naïve astrocytes are converted into reactive astrocytes and eventually into scar-forming astrocytes that block axon regeneration and neural repair. It has been known for decades that scarring development and its related extracellular matrix molecules interfere with regeneration of injured axons after CNS injury, but the cellular and molecular mechanisms for controlling astrocytic scar formation and maintenance are not well known. Recent use of various genetic tools has made tremendous progress in better understanding genesis of reactive astrogliosis. Especially, the latest experiments demonstrate environment-dependent plasticity of reactive astrogliosis because reactive astrocytes isolated from injured spinal cord form scarring astrocytes when transplanted into injured spinal cord, but revert in retrograde to naive astrocytes when transplanted into naive spinal cord. The interactions between upregulated type I collagen and its receptor integrin β1 and the N-cadherin-mediated cell adhesion appear to play major roles for local astrogliosis around the lesion. This review centers on the environment-dependent plasticity of reactive astrogliosis after spinal cord injury and its potential as a therapeutic target.

Key Words: *astrogliosis; astrocyte fate; scar formation; spinal cord injury; axon regeneration; environment cue; collagen I; integrin β1*

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doi: *10.4103/1673-5374.221144*

Accepted: *2017-11-22*

Introduction
Astrocytes are the most abundant non-neuronal, highly differentiated cells that span the entire central nervous system (CNS) (Tower and Young, 1973). They have many important physiological functions in the CNS, including maintaining extracellular ion, transmitter and fluid balance, regulating blood flow, influencing synaptic plasticity and contributing to many other essential functions (Nedergaard et al., 2003; Seifert et al., 2006; Pellerin et al., 2007). Astrocytes are classified into different subtypes principally based on their locations and functions. Fibrous astrocytes populate the white matter and encompass of dense glial filaments with cylindrical processes. Protoplasmic astrocytes reside in the gray matter with fewer glial filaments and irregular processes in comparison (Vaughn and Pease, 1967). In contrast, radial astroglia are the Bergmann glia in cerebellum and Müller cell in retina (Molofsky et al., 2012).

Astrocytosis is a pathological process involved in excessive generation of astrocytes in response to CNS damages following trauma and in different neurological diseases. Because of destruction to the brain-blood barrier, leakage of serum and plasma, increased inflammatory reactions (such as activation of microglia and generation of various cytokines), and enhanced activation of transforming growth factor β (TGF-β) and SMAD2 signaling pathways, CNS injuries usually induce proliferation and migration of reactive astrocytes (RAs) at and around injury site and thus an increase in their number. Reactive astrocytes often exhibit characteristic structural changes, including marked hypertrophy and substantial overlap of astrocytic domains (Karimi-Abdolrezaee and Billakanti, 2012). Reactive astrocytes highly upregulate a large number of molecules, including different intermediate filaments, nestin, signaling proteins and many other molecules (Ridet et al., 1997; Sofroniew, 2009). In addition to the featured reactive astrocytes around lesion, injury site consists of NG2-expressing glia (including oligodendrocyte precursor cells), meningeal and vascular derived fibroblasts, pericytes, ependymal cells and phagocytic macrophages (Cregg et al., 2014).

Astrogliosis may result in both beneficial and maladaptive effects mainly depending on its time course and dynamic features (Sofroniew, 2014). Reactive astrogliosis occurs after various CNS lesions, including spinal cord injury (SCI). The primary benefits of glial scars include separation of inflammation of injury area from the intact tissues and minimize the extent of secondary damage after CNS injury. Several studies demonstrated that elimination of astrogliosis early after CNS injury resulted in greater lesion area and worse functional outcomes (Bush et al., 1999; Sofroniew, 2009; Burda and Sofroniew, 2014; Anderson et al., 2016). In response to injury, local naïve astrocytes (NAs) display sequential changes in phenotypes, initially as RAs and then as scar-forming astrocytes (SAs) (Bushong et al., 2002; Wilhelmsson et al., 2006). In contrast to individual, finely branched processes of NAs, which occupy non-overlapping domains, RAs are distinguished by hypertrophy of cell body and overlap of processes. At acute stage after CNS injury, RAs have various beneficial effects because the overlapped processes of RAs and incorporation of newly proliferated cells around the lesion separate damaged areas from healthy tissues and limit the spread of inflammatory cells (Faulkner et al., 2004; Herrmann et al., 2008). At subacute phase (4–14 days after SCI in mouse model), migrated RAs to the lesion epicenter isolate inflamma-

tory cells and repair the lesion area for functional enhancement (Okada et al., 2006). However, at chronic phase (> 14 days after SCI in mice), RAs gradually convert into SAs and form scarring tissues, the major barrier for CNS axon regeneration (Silver and Miller, 2004; Pekny and Nilsson, 2005; Karimi-Abdolrezaee and Billakanti, 2012; Ohtake and Li, 2015).

With various genetic approaches, a group recently reported the determining role of environmental conditions for reactive astrocytes (Hara et al., 2017). Isolated RAs from injured spinal cord reverted to NAs when transplanted into non-injured spinal cord, while formed SAs when transplanted into injured spinal cord. Moreover, pharmacologically blocking interactions between type I collagen and its integrin receptor prevented astrocytic scar formation and improved axonal regrowth and functional recovery. Astrogliosis has long been considered a major barrier to axon regeneration, although RAs are able to support neurite extension under certain conditions and corticospinal axons could sprout in adult injured spinal cord during reactive gliosis (Li and Raisman, 1995; Sivron and Schwartz, 1995). The recent advance in better understanding molecular control of scar genesis may lead to development of new approaches for overcoming scar-based regeneration failure.

Gene Expression Profile and Marker Proteins in Various Subtypes of Astrocytes after SCI

It is extremely important to identify the gene expression profile and molecular markers for various subtypes of astroglia, including NAs, RAs and Sas (Ridet et al., 1997). Glial fibrillary acidic protein (GFAP) has been recognized as an astrocyte specific intermediate filament (IF) protein necessary for maintaining CNS function and blood-brain barrier integrity (Liedtke et al., 1996; Kakinuma et al., 1998). A great number of studies have employed GFAP as a primary marker for astrocytic scars by detection of its immunoreactivity. Before altering expression of various other proteins, reactive glia upregulate the IF proteins GFAP, vimentin and nestin (Eddleston and Mucke, 1993; Hernandez et al., 2002), which contribute to IF network formation (Barrett et al., 1981). Mice deficient in GFAP showed reduced IF formation and altered neuronal activities (Pekny et al., 1995; McCall et al., 1996). Astrogliosis appeared normal after CNS injuries in $GFAP^{-/-}$ or $vimentin^{-/-}$ mice, but deletion of both significantly impaired scar formation frequently accompanied by bleeding around the lesion (Pekny et al., 1999).

Several groups studied the gene expression profiling of purified astrocyte populations and made progress in revealing potential new markers (Doyle et al., 2008; Fu et al., 2009; Rowitch and Kriegstein, 2010), including identification of Aldh1L1 and fibroblast growth factor (FGF) receptor 3 as the markers (Pringle et al., 2003; Cahoy et al., 2008). However, Okada's group further characterized the gene expression profile in different subtypes of astrocytes and defined the potential use of some genes as respective markers (Hara et al., 2017). It is crucial to distinguish diffident subtypes of astrocytes (NAs, RAs and SAs). As a conventional method, histological analysis has long been used to differentiate them. Because both RAs and SAs express various hallmark proteins (such as glial fibrillary acidic protein (GFAP), nestin, β-catenin, N-cadherin and sex determining region Y-box 9 (SOX9)) and their expression levels are highly dynamic with time, it is difficult to differentiate them primarily based on histological analysis of characteristic expression (Cregg et al., 2014). Many groups also employed fluorescence activated cell sorting and translating ribosomal affinity purification to analyze cell types after separating solid organ tissues into individual cells (Doyle et al., 2008; Kumamaru et al., 2012). In contrast, by using laser microdissection combined with immunohistochemistry, Hara et al. (2017) selectively isolated NAs, RAs and SAs from contused mouse spinal cord at different stages and recognized clear distinctions among three astrocyte subtypes based on the expression profile of marker genes (**Figure 1**). Because of the graded continuum of gene expression and structural alterations during astrogliosis, it seems advantageous to combine marker gene profiling and morphological definitions for identifying various astrocyte phenotypes (Yokota et al., 2015; Hara et al., 2017).

Several genes are appropriate as the RA markers, including nestin (a type VI IF protein), Ctnnb1 (a gene encoding β-catenin), Plaur (encoding urokinase receptor, also known as urokinase-type plasminogen activator receptor, uPAR), MMP2 (encoding matrix metalloproteinase 2), MMP13 (encoding matrix metalloproteinase 13) and Axin2 (also known as axin-like protein) (Hara et al., 2017). Plaur binds both precursor and mature forms of urokinase plasminogen activator and activates the receptor-bound pro-enzyme by plasmin, including the matrix metalloproteinases, thus promoting cell-surface plasminogen activation, plasmin formation and degradation of the extracellular matrix (ECM) molecules. RAs upregulate GFAP, nestin, vimentin and Ctnnb1 comparing to NAs, but out of these 4 genes, only Ctnnb1 and nestin are suitable gene markers for RAs because SAs also upregulate GFAP and vimentin. Comparing to both NAs and SAs, RAs also uniquely upregulate Plaur, MMP2 and MMP13 and Axin2 (a negative feedback regulator for β-catenin). Therefore, the six genes of nestin, Ctnnb1, Plaur, MMP2, MMP13 and Axin2 are selectively expressed by RAs and may serve as the RA specific markers (**Figure 1**).

In addition to serving as the RA marker, β-catenin related genes appear important to mediate RA migration in the lesioned spinal cord (Hara et al., 2017). The highly expressed β-catenin in cytosol could bind T cell factory lymphoid enhancer factor (Tcf/Lef) and form the protein complex, which increases expression of uPAR (Lengyel et al., 1996). Upregulation of uPAR then accelerates cell surface plasmin formation, results in extracellular matrix proteolysis by activating MMPs (Ellis et al., 1991), and thus regulates migration of cells, including RAs. RA migration appears essential for promoting tissue repair and functional recovery after SCI (Okada et al., 2006).

Comparing to NAs and RAs, SAs selectively upregulate SOX9, N-cadherin (also known as cadherin-2 and CDH2), and chondroitin sulfate proteoglycan (CSPG) related genes (Xylt1, Chst11, Csgalnact1, Acan and Pcan). SOX9 is expressed as a HMG box transcription factor by neural stem cells in embryonic spinal cord (Molofsky et al., 2012) and its deletion in conditional knockout mice by nestin-Cre predisposed to extend neurogenesis period and to delay gliogenesis onset in developing spinal cord (Stolt et al., 2003). SOX9 upregulates CSPGs in astrocyte cultures and conditional SOX9 deletion promotes axon regrowth by reducing CSPG levels (Gris et al., 2007). CSPGs encompass a diverse group of extracellular matrix proteins (*i.e.*, neurocan, aggrecan, brevican, versican, phosphocan, and NG2) and experience posttranslational alterations with complex glycosaminoglycan chains differing in sulfation patterns and length (Margolis and Margolis, 1994). CSPGs could block axon elongation during development and after CNS injury (Brittis et al., 1992; Wu et al., 1998). SOX9 deficiency downregulated certain chondroitin sulfate synthesizing enzymes, such as Xylt1/2 and C4st1 (McKillop et al., 2013; Takeuchi et al., 2013). SOX9 deletion also increased immunoreactivity puncta for synaptophysin several weeks after SCI and enhanced synaptic reconnections, resulting in improved recovery (McKillop et al., 2013). Therefore, upregulation of SOX9 by SAs probably correlates with axon growth failure mediated by CSPG overexpression after SCI.

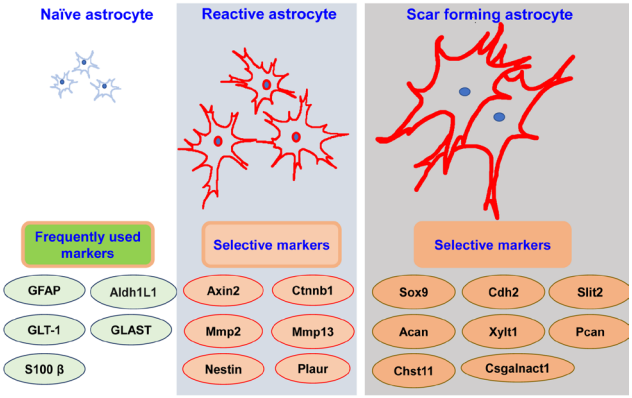

Figure 1 Schematic of three subtypes of astrocytes, the frequently used markers for astrocytes, and the selective marker genes for reactive and scar-forming astrocytes.
GFAP: Glial fibrillary acidic protein; GLT-1: glutamate transporter-1; GLAST: glutamate A spartate transporter; Axin2: axis inhibition protein 2; Ctnnb1: Catenin beta 1; Mmp2: matrix metalloproteinase 2; Mmp13: matrix metalloproteinase 13; Plaur: plasminogen activator urokinase receptor; Sox9: sex determining region Y-box 9; Cdh2: cadherin 2; Acan: aggrecan; xylt1: xylosyltransferase 1; Chst11: carbohydrate sulfotransferase 11; Csgalnact1: chondroitin sulfate N-acetylgalactosaminyltransferase 1.

Slit2, a repellant axon guidance cue, may also be a proper SA marker gene. Slit proteins are generally repulsive for axon growth and are essential for axon guidance and cell migration (Hagino et al., 2003; Silver and Miller, 2004). Slits are elevated along with their receptors (such as glypican1) after cortical injury (Ronca et al., 2001). Among them, Slit2 is co-localized with its receptor glypican1 in the spinal cord, hippocampus and cortex, and functions as a chemorepellent for hippocampal and spinal motor axons by binding glypican 1 with high affinity (Brose et al., 1999; Liang et al., 1999). Co-expression of Slit2 with glypican1 in the scar tissues indicates their potential molecular interactions after CNS injury (Hara et al., 2017).

Lesion Environment Determines Astrocytic Fate and Scar Formation after SCI

Both extracellular and intrinsic factors are important in controlling axon growth failure after CNS injury in adult mammals (Silver and Miller, 2004; Liu et al., 2011). For the former, an inhibitory environment due to scar formation at lesion site is critical for regenerative failure (Fawcett, 2006). However, the overall roles of reactive astrogliosis are complicated and reactive astrocytes may have numerous beneficial functions. Scar tissues have repairing roles after CNS damage by generating many ECM components with growth-promoting properties, such as fibronectin and laminin (Silver and Miller, 2004). In addition to acting as an accommodating bridging support for regeneration, RAs express polysialylated neuronal cell adhesion molecule and facilitate axon growth by interacting with other positive molecules, such as L1 (Aubert et al., 1995; Rutishauser and Landmesser, 1996). Astrocytes and other cell types around lesion have been reported to promote axon regrowth after SCI (Kawaja and Gage, 1991; Fawcett and Asher, 1999).

Migration of a great number of astrocytes into and around the lesion areas and formation of scar tissues create both physical and chemical barriers of axon regeneration. Importantly, upregulation of suppressing substances, particularly CSPGs, strongly blocks neural repair and axon regeneration. The inhibitory properties of reactive astrocytes develop with time after injury. A great number of studies demonstrate the potent suppression of axon regrowth by glial scar sourced inhibitors (McKeon et al., 1991; Davies et al., 1997; Ohtake and Li, 2015). Adult sensory neurons robustly regenerated their axons after micro-transplantation into intact white matter tracts by minimizing scar genesis, but failed to regrowth when approaching lesioned region with scar tissues (Silver and Miller, 2004). Digestion of the glycosaminoglycan side chains by chondroitinase ABC (ChABC) improves axon regeneration and sprouting after various CNS injuries (Bradbury et al., 2002; Alilain et al., 2011). Creation of a permissive environment around the lesion by combined peripheral nerve autographs, acidic fibroblast growth factor, and chondroitinase ABC (ChABC) enhanced recovery of urination and respiratory functions after SCI (Alilain et al., 2011; DePaul et al., 2015).

Reactive astrogliosis is reversible under certain conditions and local environment plays a major role in determining the fate of astrocytes *in situ*. The molecular mechanisms for astrocytic scar formation are not well known in spite of increased number of studies in this field. To further elucidate the molecular control of astrogliosis, Hara et al. (2017) transplanted isolated green fluorescent protein (GFP)-positive NAs from primary cultures into uninjured or contusively-injured spinal cord in mice and characterized the morphological and gene expression changes of NAs at 7 and 14 days after transplantation. Surprisingly, NAs exhibited the properties and marker gene expression of RAs at 7 days and of SAs at 14 days after transplantation into the injured spinal cord. In contrast, the grafted NAs into uninjured spinal cord remained unchanged in morphology and gene expression profile. Moreover, isolated GFP-positive RAs showed properties of SAs by upregulating SA marker genes 7 days after transplantation into injured spinal cord, but reverted back to NAs with suppressed SA gene expressions 7 days after transplantation into uninjured spinal cord.

Upregulation of type 1 collagen (Col 1) and N-cadherin around the lesion plays important roles in astrogliosis. Because activated astrocytes upregulated various cell surface molecules, including ECM molecules and cell adhesion molecules (Aubert et al., 1995; Merrill and Benveniste, 1996), Hara et al. (2017) further determined the expression levels of these genes around lesion by Gene Ontology term analysis and detected enhanced ECM genes 14 days after SCI, especially Col 1 related genes (*Col1a1* and *Col1a2*). Immunostaining indicated co-localization of Col 1 with SA-forming astrocytic scars, but not with non-converting RAs even 14 days after injury. Consistently, cultured RAs showed close adhesion on Col 1 coated plates and increased GFAP expression (characteristic of SAs), but RAs retracted their processes and reduced GFAP expression when cultured on non-coated plates (Hara et al., 2017). Thus, expression of Col 1 in RAs appears to correlate with conversion of RAs into SAs and astrocytic scar tissues following SCI. Because astrocytic scars upregulated N-cadherin, which was distributed following astrocytic structures (Vázquez-Chona and Geisert, 1999; Takeichi, 2007; Tran et al., 2008), N-cadherin also appears to play a significant role of in inducing RA transformation into SAs (Hara et al., 2017).

Essential Roles of Type I Collagen-Integrin Interactions and N-Cadherin-Mediated Adhesion in Astrocytic Scar Formation

Recent experiments with time-dependent RNA-seq analysis supports that upregulation of ECM Col 1 is necessary for astrocytic scar formation (Hara et al., 2017). Following SCI, pericytes and fibroblasts generated Col 1 in the lesion epicenter (Göritz et al., 2011; Cregg et al., 2014; DePaul et al., 2015). Pericytes

attract other types of cells to the lesion area two weeks after SCI when the scar is compartmentalized and the lesion center is enclosed initially by an astrocytic layer derived from ependymal cells. Then, another astrocytic layer resulting from self-duplication of resident astrocytes further surrounds the lesion area (Barnabé-Heider et al., 2010; Göritz et al., 2011). Thus, the collagen-generating pericytes are essential in enclosing spinal cord lesions (Göritz et al., 2011). Similarly, pericytes in fibrotic kidney and dermal scars could differentiate into collagen-forming cells and also contributed to scarring formation in these organs (Sundberg et al., 1996; Humphreys et al., 2010).

As the transmembrane receptors, integrins are expressed in multiple cells in the CNS, including pericytes, neurons, glia and endothelial cells, and have multiple essential functions (del Zoppo and Milner, 2006). Integrins play important roles in regulating inflammation, growth cone motility, astrocyte proliferation, and axon guidance and regrowth after injury (Lemons and Condic, 2008). Integrins control collagen synthesis during cell proliferation (Gardner et al., 1999). Upregulation of integrins increases neuronal adhesion and outgrowth and reduces aggrecan-mediated inhibition of cell adhesion. Moreover, integrins maintain growth cone motility of neurons over a broad range of ligand concentrations and allow axons to invade different tissues during development and regeneration (Condic and Letourneau, 1997; Condic et al., 1999).

A number of studies indicate the involvement of integrins in astrocytic pathological changes. Astrocytes express various integrins, including α1β1, α2β1, α10β1 and α11β1 (Previtali et al., 1997; Yonezawa et al., 2010), and regulate cell functions by interacting with Col 1 (Hynes, 2002). Particularly, integrins contribute to induction of NAs to Ras (Avalos et al., 2002, 2004). After brain injury in mice, mRNA levels for integrins α1 and β1 and for GFAP were increased simultaneously in the endfeet of astrocytes encompassing blood vessels (Yonezawa et al., 2010). Pilocarpine-induced seizures increased integrin α1 and β1 immunoreactivity in RAs of rat brain (Fasen et al., 2003). In contrast, oxygen-glucose deprivation reduced α1 expressions in astrocytes of mice (Milner et al., 2008). In addition, integrins promote cancer cell motility and invasion with frequently altered levels by directly interacting with ECM components (Desgrosellier and Cheresh, 2010). Accordingly, altered expression of EMC molecules, including integrins, concurs with tumor advancement and elevated dissemination (Cavallaro and Christofori, 2004).

The cell adhesion molecules of cadherins are important to regulate growth of multiple cells, including astrocyte migration, scar formation and neuronal extension. Cadherins are cell surface glycoproteins that are essential to mediate cell-cell adhesion *via* calcium signaling (Takeichi, 2007). N-cadherin is an important adhesion molecule for astrocytic scar formation by stabilizing the contacts between RAs (Vázquez-Chona and Geisert, 1999). The expression levels of N-cadherin is finely tuned during reactive astrogliosis. Deletion of N-cadherin in astrocytes resulted in defects in astrocyte migration (Péglion and Etienne-Manneville, 2012; Kanemaru et al., 2013) and impaired transformation of RAs to SAs following CNS injury (Kanemaru et al., 2013). Upregulation of N-cadherin after SCI facilitates the process of reactive astrogliosis, which may isolate the damaged area from intact neural tissues (Fitch and Silver, 1997). As the neural associated glycoprotein, N-cadherin also facilitates cell interactions essential for neural growth because blockade with its antibodies substantially decreases the number of neurons initiating neurites and the length of neurites (Tomaselli et al., 1988; Dalseg et al., 1993). Moreover, N-cadherin-mediated adhesion contributes to migration behavior of cancer cells in glia-relevant tumors (Péglion and Etienne-Manneville, 2012).

The recent study by Hara et al. (2017) further supports the timing-dependent and functional relevance of Col1, integrin β1 and N-cadherin during astrogliosis after SCI. Cell adhesion of RAs concurred with regulation of N-cadherin and GFAP proteins. Treatment with an anti-β1 antibody blocked expression levels of N-cadherin and GFAP with scattered appearances. Accordingly, treatment with a N-cadherin-neutralizing antibody suppressed transformation of RAs into SAs. Moreover, the timing-dependent N-cadherin expression correlated well with observed cellular hypertrophy and process elongation of RAs and SAs (Hara et al., 2017). Because astrocytes formed N-cadherin-mediated adhesions and SAs exhibited elevated levels of N-cadherin (Vázquez-Chona and Geisert, 1999; Hara et al., 2017), the enhanced RA contacts mediated by N-cadherin appear important for astrogliosis by inducing RAs into SAs regulated through interactions between Col 1 and its receptor integrin β1.

Therapeutic Potential for CNS Regeneration by Reducing Astrogliosis

Because of complicated and sequential nature of astrogliosis, it is important to define detailed features of astrogliosis after CNS injury and to design effective therapies that target specific molecular and cellular changes at a given stage (Silver and Miller, 2004; Cafferty et al., 2008; Sharma et al., 2012). Various ligands/receptors and signaling pathways contribute to astrogliosis after CNS injury, including collagens, integrins, cadherins, JNK/c-Jun, STAT, Smads, MAPK, SOCs, and RhoA (Okada et al., 2006; Gadea et al., 2008; Herrmann et al., 2008; Sofroniew and Vinters, 2010; Kang and Hébert, 2011). This complexity indicates the vast range of interactions between reactive astrocytes and surrounding cells at acute, subacute and chronic phases. Accordingly, astrogliosis has both beneficial and detrimental functions largely depending on its dynamic structures and chemical components at different stages. Numerous studies have demonstrated the hindering effects of reactive scar tissues around lesion and attempted to promote axon regeneration by preventing scar formation with many molecular and cellular methods. However, Anderson et al. (2016) recently further studied function of reactive astrocytes after SCI using diverse cell ablation models and reported positive effects of reactive astrocytes on neural repair. By using transgenic mouse models that diminished production of reactive astrocytes and removed scar forming astrocytes at a chronic stage, Anderson et al. (2016) reported attenuated axon regeneration of descending and ascending tracts across the lesion in adult mice with SCI, indicating that the astrocytic scars around injury promoted axon regeneration, instead of blocking regrowth of injured axonal tracts.

Because a number of studies support that SAs are highly suppressive for axon elongation after CNS injury (Silver and Miller, 2004; Karimi-Abdolrezaee and Billakanti, 2012; Cregg et al., 2014), intervening transformation of RAs to SAs and minimizing scar formation can help injured axons grow and potentially improve functional recovery. Administering anti-β1 antibody 9–13 days after SCI significantly attenuated SA formation, downregulated both N-cadherin and GFAP, and reduced cell adhesion and scar formation around the lesion (Hara et al., 2017). Similarly, treatment with a N-cadherin antibody also decreased astrocytic scar formation. Importantly, anti-β1 Ab treatment increased the numbers of descending serotonin and tyrosine hydroxylase fibers in the caudal spinal cord and also appeared to improve behavioral recovery in mice with SCI. Thus, blocking Col 1-integrin β1 signaling pathway and/or N-cadherin-mediated cell adhesion may suppress scar for-

mation and become an effective approach for providing axon regeneration after CNS injury.

Because JNK (c-Jun N-terminal kinase) signaling pathway appears to link Col 1-integrin interactions to N-cadherin-mediated cell adhesion in astrocytes (Shintani et al., 2006a, b; Hara et al., 2017), targeting JNK and N-cadherin pathways may also reduce scar formation and enhance regenerated axons to cross the lesion area after CSN injury. Stimulation of Col 1-integrin axis activates JNK signaling by increasing the levels of phosphorylated-JNK and N-cadherin in astrocytes after CNS injury (Vázquez-Chona and Geisert, 1999). Spinal nerve ligation injury increased expression of c-Jun, the substrate of JNK, and levels of phosphorylated c-Jun in $GFAP^+$ cells of the ipsilateral spinal cord, indicating that peripheral axon injury activates JNK signal in spinal cord astrocytes (Raivich et al., 2004; Raivich and Makwana, 2007). In addition, JNK activation due to activating Col 1-integrin axis induced N-cadherin-dependent cell adhesion in other types of cells, including epithelial and cancer cells (Shintani et al., 2006a, b).

TGF-β/Smad signaling pathways contribute to scar formation and also appear the therapeutic targets (Lindholm et al., 1992; Gomes et al., 2005). TGF-β signaling regulates proliferation, differentiation and survival of many cells by activating Smad dependent or independent pathways. TGF-β acts as a major upstream activator of CSPG upregulation during astrogliosis. Although TGF-β treatment reduced lesion area after acute SCI by decreasing macrophage infiltration into the injury site, but TGF-β eventually stimulated CSPG production by astrocytes and fibroblasts and scarring tissue formation, inhibiting regeneration at subacute and chronic stages (Smith and Strunz, 2005; Schachtrup et al., 2010; Susarla et al., 2011). Blocking TGF-β/Smad2 signaling by TGF-β antibody and its receptor inhibitor, or inhibiting its upstream activator fibrinogen attenuated CSPGs generation and glial scar formation (Gris et al., 2007; Schachtrup et al., 2010). As the downstream signal of TGF-β, Smad2 appears to mediate scar gliosis by activating intrinsic transcriptional program in astrocytes. Inhibiting kinesin-dependent Smad2 translocation with taxol, a microtubule stabilizing agent, diminished scarring tissues around the lesion (Hellal et al., 2011).

As a transcription factor and a downstream signal for multiple cytokines and growth factors, signal transducer and activator of transcription 3 (STAT3) mediates scar formation after CNS injury and may be a molecular target for CNS repair (Fitch and Silver, 1997; Silver and Miller, 2004; Okada et al., 2006; Herrmann et al., 2008). Deletion of STAT3 in conditional knockout mice with nestin-Cre caused failed astrocytic migration to the lesion site and exacerbated infiltration of inflammatory cells around the lesion after SCI. Conditional deletion of STAT3 from astrocytes downregulated GFAP expression and prevented astrocytic hypertrophy and astroglial scar formation after SCI (Okada et al., 2006; Herrmann et al., 2008). Also, conditional deletion of STAT3 from $GFAP^+$ cells significantly blocked astrocyte development.

Several other signaling molecules also contribute to scar genesis and may become the therapeutic targets. SOX9 is essential for CSPGs expression after CNS injury probably by regulating xyloxyltransferase I and II during CSPG biosynthesis in astrocytes (Karimi-Abdolrezaee and Billakanti, 2012). As the downstream signaling molecules of integrins, focal adhesion kinase and Ras/Rho GTPases may also contribute to astrogliosis and CNS regeneration failure after CNS injury. Several studies have supported the crucial role of small GTPases in regulating neurite extension, axon regeneration and guidance (Hall and Nobes, 2000; Raftopoulou and Hall, 2004; Fu et al., 2007). In addition, the integrins-GTPases pathway may function as bi-directional signals by mediating upstream or downstream molecules during scar genesis (Schwartz and Shattil, 2000; Lemons and Condic, 2008).

Prospective

Recent studies have made tremendous progress in astrogliosis after CNS injuries, including identifying specific marker genes for different astrocyte subtypes, illustrating environment-dependent plasticity of reactive astrogliosis, and developing effective strategies for neural repair by targeting scar related mechanisms. Over the past decades, scientists have employed various approaches to minimize negative outcomes of astrogliosis (Pekny and Nilsson, 2005; Herrmann et al., 2008), to block scar-sourced inhibitory molecules genetically and pharmacologically (Bradbury et al., 2002; Fisher et al., 2011; Lang et al., 2015) to reduce upregulation of axon growth inhibitors, especially CSPGs (Grimpe and Silver, 2004; Rolls et al., 2008), to bridge lesion area with various cell/biomaterial transplants. For development of novel and highly effective therapies to repair injured CNS, it is important to further characterize diverse activities of different astrocyte subtypes, signaling control of scar formation, and the scar associated molecules, including markers, receptors and expression factors. Because astrogliosis is highly complicated and dynamic with the injury stages, it may have damaging, beneficial and mixed effects on neural recovery largely depending on the injury types, degrees, phases, location and other essential factors. It thus is important to develop specific strategies to target environment-dependent individual cellular and molecular mechanisms at a given stage, including the major signaling pathways of astrogliosis at upstream or downstream level. It is also interesting to formulate effective therapies by minimizing damaging outcomes and maximizing protective effects of reactive glial tissues by targeting individual molecules and cell types.

Author contributions: *Both FMN and SL contributed to writing the paper and making the figure.*
Conflicts of interest: *None declared.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

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