Axonal regeneration is critical for functional recovery following neural injury. In addition to intrinsic differences between regenerative responses of axons in peripheral versus central nervous systems, environmental factors such as glial cells and related molecules in the extracellular matrix (ECM) play an important role in axonal regeneration. Schwann cells in the peripheral nervous system (PNS) are recognized as favorable factors that promote axonal regeneration, while astrocytes and oligodendrocytes in the central nervous system (CNS) are not. In this review, we evaluate the roles of Schwann cells and astrocytes in axonal regeneration and examine recent evidence that suggests a dual function of astrocytes in regenerative responses. We also discuss the role of Cdc2 pathways in axonal regeneration, which is commonly activated in Schwann cells and astrocytes. Greater insight on the roles of glial cells in axonal regeneration is key to establishing baseline interventions for improving functional recovery following neural injury.

Key words: glial cell, axonal regeneration, Schwann cell, astrocyte, Cdc2
and transcription factors that direct specific cell fates [6]. For example, basic helix-loop-helix transcription factors are crucial for diversifying differentiation of neural stem cells in order to form and specify astrocytes [6, 7]. Thus, while major differences exist, certain commonalities between these two glial cells also exist, which suggests dual functionality of astrocytes resulting in beneficial and detrimental effects for axonal regeneration. Such insight on the roles of glial cells in axonal regeneration is critical for improving functional recovery following neural injury.

There have been significant advances on understanding the role of molecular factors from oligodendrocytes, such as myelin-associated glycoprotein (MAG), Nogo-66, oligodendrocyte-myelin glycoprotein, and their receptor complexes consisting of NgR1, p75, TROY, and LINGO, which has been reviewed elsewhere [8, 9] and is not examined in this paper.

**FUNCTION OF SCHWANN CELLS FOLLOWING PERIPHERAL NERVE INJURY**

Injured axons of peripheral nerves regenerate spontaneously over long distances, and various factors contribute to this regenerative ability. Following peripheral nerve injury, distal axons degenerate while dedifferentiated Schwann cells and macrophages remove debris via phagocytosis. Dedifferentiation refers to the state in which Schwann cells revert to immature states capable of re-entering the cell cycle to proliferate and assist in nerve regeneration [10]. Schwann cells also aid in the process of remyelination, which is necessary for axon protection and action potential conduction [11]. Extracellular matrix proteins such as laminin and fibronectin [12, 13], neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) [14], and hormones such as progesterone and erythropoietin [15, 16] are also important factors that regulate Schwann cells.

During peripheral nerve regeneration, ECM components are crucial for guidance, elongation, trophic support, and axonal remyelination [17, 18]. Laminin is an ECM glycoprotein and component of the Schwann cell basal lamina. It is expressed in intact nerves and upregulated in injured nerves as it stimulates neurite outgrowth and helps ensheath and remyelinate regenerating axons [19-21]. In an experiment where laminin γ1 gene expression is stopped, all other known laminin chains are also disrupted in Schwann cells [12]. As a result, axonal regeneration is poor because of partial myelination and improper ensheathment [22, 23]. It is clear that Schwann cell dedifferentiation, proliferation, and even survival are severely impaired when laminin is disrupted. In addition, when laminin is absent, cell polarity signaling pathways fail to induce axonal growth [20]. Thus, this ECM glycoprotein plays a critical role in contributing to successful axonal regeneration following peripheral nerve injury by indirectly supporting Schwann cells or acting as a substrate for axonal regeneration [1].

Without laminin, Schwann cells cannot differentiate into myelinating phenotypes. Moreover, the resulting poor myelination and regeneration between phenotypes in mice with a Schwann cell defect in β1 integrin, a component of laminin receptors, and laminin γ1 indicate that integrin plays an important role in laminin signaling [22, 24]. In response to signals from laminin-activated integrin receptors, it has been shown that growth cones integrate myosin II-dependent contraction for rapid, coordinated turning at borders of laminin stripes, indicating that laminin acts as a stimulator and guide for axonal regeneration [25].

The important role that Schwann cell responses play in successful PNS axon regeneration can be seen in the effects of fibrinogen following peripheral nerve injury. Fibrinogen first infiltrates extracellular space of injured peripheral nerves and then converts into fibrin, which inhibits Schwann cell migration and remyelination during regeneration [26]. Here, fibrin triggers ERK1/2 phosphorylation and p75 NGF receptor production, which downregulates gene expression involved with myelin production. This eventually inhibits Schwann cell differentiation because cells are held in a predifferentiation state. Yet in normal pathophysiological situations, fibrolytic plasminogen activator (PA) is induced in peripheral nerves after injury, where it converts plasminogen to plasmin that degrades ECM proteins including fibrin and assists in axonal regeneration [27, 28].

Furthermore, different types of neurotrophins are upregulated in Schwann cells following peripheral nerve injury [29, 30]. Induction of neurotrophin receptors occurs in both axons and Schwann cells and mediates axonal regeneration [31, 32]. Binding of neurotrophic factors to their selective receptors initiates entrapping of activated receptors in the axon terminal. Activated receptors are then retrogradely transported into the nucleus of cell body, where target gene expression is induced and protein factors for axonal regrowth are transported back to the growth cone [33]. In Schwann cells, while neurotrophins such as BDNF typically aid in myelination, certain in vitro and in vivo systems have also shown neurotrophins such as NT3 to act as inhibitors of myelination [31, 34]. Thus, BDNF serves as a positive modulator of myelination and motor neuron regeneration [35], while NT3 serves as a negative modulator of peripheral nerve myelination.

After peripheral nerve damage, Schwann cells and macrophages remove cell debris and inhibitory molecules in the injury area. Here, it deserves mention that the role of Schwann cells in removing myelin-associated inhibitory molecules is an important
environmental aspect to axonal regeneration of injured peripheral nerves. The removal of myelin sheaths with myelin-associated glycoprotein following neural injury creates a permissive environment for regeneration [36, 37]. The presence of laminin, a Schwann cell basal lamina component, demonstrated that effects of inhibitory molecules such as MAG may be overcome by neurite outgrowth-promoting molecules [38]. Evidently, the removal and downregulation of inhibitory molecules such as MAG from Schwann cells during Wallerian degeneration is critical to optimizing axonal regeneration following peripheral nerve injury [37]. This notion of removing myelin-associated inhibitory molecules was also supported in previous experiments as transgenic mice overexpressing Nogo-A resulted in poor regeneration [39].

FUNCTION OF ASTROCYTES FOLLOWING SPINAL CORD INJURY

In intact nerves of the CNS, astrocytes are principal macroglial cells that provide critical support including regulation of blood flow and energy metabolism [40, 41]. Moreover, astrocytes respond to any degree of CNS injury and disease via reactive astrogliosis, where astrocytes become hypertrophic, change in molecular expression and morphology, and result frequently in glial scar formation [42, 43]. Further, phagocytes produce interleukin-1, which initiates inflammatory responses in astrocytes [44]. Reactive gliosis is comprised of changes in gene expression and cellular changes regulated via inter- and intracellular signaling [45, 46]. However, because reactive astrogliosis varies in response to severity of CNS injury and disease, reactive astrocytes may also exert beneficial effects. Changes experienced by reactive astrocytes are regulated based on context via specific cascade signaling events and can result in astrocytes gaining or losing functions, which translates into beneficial or detrimental effects [46]. Various signals including cytokines, growth factors, and adhesion molecules exerted by reactive astrocytes and injured neurons play critical roles in response to CNS injury.

Astrocytes respond to CNS injury at varied degrees as evidenced by different categories of reactive astrocytes that exist as biochemically heterogeneous [42, 47]. In mild-to-moderate reactive astrogliosis, astrocytes occupy non-overlapping domains in a similar manner to non-injured tissue [48, 49]. In response to extensive CNS injury, reactive gliosis results in newly proliferated astrocytes and glial scar formation. Interestingly, these astrocytes occupy overlapping domains as opposed to non-overlapping domains as seen in non-injured tissues [50, 51]. Moreover, structural changes as a result of glial scar formation persist over long periods of time and lead to failed CNS axon regeneration [46].

Various factors induce glial scar formation. Transforming growth factor (TGF) β1, TGFβ2, and interleukin-1 are recognized as mediators of macrophage-induced glial scarring. Cytokine interactions between interferon-γ and fibroblast growth factor 2 (FGF2) have also been linked to glial scar induction [4, 52]. Additionally, FGF2 also increases astrocyte proliferation, leading to glial scar formation [8].

Glial scar formation presents major obstacles for successful axonal regeneration as microglia, oligodendrocytes, meningeal cells, and astrocytes are recruited to the injury site via glial reaction [53]. Astrocytes, which mainly compose the glial scar, become hypertrophic and release inhibitory ECM molecules called proteoglycans that largely contribute to poor CNS axon regeneration [54]. The four classes of proteoglycans produced by astrocytes include: heparan sulfate proteoglycan (HSPG), dermatan sulfate proteoglycan (DSPG), keratan sulfate proteoglycan (KSPG) and chondroitin sulfate proteoglycan (CSPG) [55]. Highly sulfated glycosaminoglycan (GAG) chains characterize proteoglycan molecules [56] and are known to be critical in mediating inhibitory action of axonal growth [54, 57]. Following SCI, reactive astrocytes upregulate CSPG expression, which is then excreted extracellularly [58, 59]. A CSPG gradient is formed along the injury site, with the highest concentration of inhibitory molecules at the center of the injury site and decreasing concentrations outwards [60, 61]. CSPGs inhibit neurite outgrowth of different neuronal populations at varied degrees. As such, growth cones can extend along a proteoglycan gradient until a threshold is reached, where the gradient is no longer tolerable for growth cone extension [62]. Regenerating axons eventually become dystrophic and fail to regenerate near the lesion epicenter as a result of extremely inhibitory and non-growth conducive environments [4, 63]. GAG chains were identified as a critical component of CSPGs responsible for inhibiting axonal growth as the potent inhibitory effects no longer persist following treatment with chondroitinase ABC (ChABC) enzymes, which remove GAG chains [64, 65].

BENEFICIAL FUNCTIONS OF REACTIVE ASTROCYTES

Recent studies suggested that, in certain circumstances, reactive astrocytes recruited to the injury site may have a permissive role for axonal regeneration and functional recovery [46, 66]. Some evidence also demonstrates the ability to regulate inflammation or even minimize cellular degeneration [53, 67]. In vivo and in vitro evidence exists in which reactive astrocytes protect the CNS via uptake of excitotoxic glutamate [68], protection from oxidative stress [69, 70] or NH4+ toxicity [71], protection via adenosine
release [72] or degradation of amyloid β peptides [73], and stabilization of extracellular fluid and ion balance [74]. In several experiments, ablation of proliferating reactive astrocytes disrupted scar formation. This led to intensified inflammatory responses, failed repairing of the blood-brain barrier, greater tissue damage and lesion site, increased neuronal loss and demyelination, and impaired functional recovery [50, 58, 75-77]. In addition, genetic depletion of Stat3 and SOC3 in astrocytes resulted in reduced migration of reactive astrocytes into the injury cavity, widespread infiltration of inflammatory cells, and failed compaction of the injury area as demarcated by glial scar formation; all of which were related to inhibition of axonal regeneration after SCI [51, 78]. The difference between permissive and non-permissive gliosis may be partly determined by expression of particular recognition molecules [45]. Astrocytes produce intercellular effector molecules or alter molecular expression with regards to cell structure, energy metabolism, intracellular signaling, and membrane transporters and pumps [42, 79-81]. These changes may dramatically influence surrounding neural cells and eventually affect axonal regeneration in a positive or negative manner.

COMMONALITIES BETWEEN SCHWANN CELLS AND ASTROCYTES

Despite differences that exist between Schwann cells and astrocytes, these two cell types share some common features in mediating regenerative responsiveness after nerve injury. As mentioned above, both Schwann cells and astrocytes have scavenger functions that remove cell debris following neural injury in normal physiological and pathological conditions. They proliferate rapidly after nerve injury, migrate into the injury area, and regulate axonal regeneration. Migration of Schwann cells toward the leading edge of regenerating peripheral axons functions to guide axonal regeneration [2, 82, 83]. Migratory responses of astrocytes after SCI restrict inflammation and preserve tissue function, and thus contributing to successful axonal regeneration as myelinated fibers are spared [78, 84]. Moreover, recent studies suggest that both astrocytes and Schwann cells are involved in synapse formation [85, 86]. We found that Cdc2, a prototypical cell cycle protein kinase, was strongly but transiently induced from Schwann cells and that phosphorylation of caldesmone by Cdc2 was linked to Schwann cell migration and axonal regeneration in the sciatic nerve [83]. Furthermore, vimentin phosphorylation by Cdc2 in Schwann cells was involved in axonal regeneration [87]. Interestingly, induction of Cdc2 and vimentin phosphorylation was similarly found in primary astrocytes, which were prepared from spinal cord tissue given injury and subjected to long-term culture (LTC) for a week [88]. These LTC astrocytes, but not short-term cultured astrocytes, appeared to facilitate neurite outgrowth of co-cultured DRG neurons, suggesting that the Cdc2 pathway may play an important role in determining phenotypic expression of astrocytes such that astrocytes provide permissive environments for axonal regeneration following SCI.

Our studies further show that the Cdc2-vimentin pathway is linked to integrin activation. Schwann cells prepared from pre-injured sciatic nerve and LTC astrocytes revealed induction of integrin protein (β1 integrin in Schwann cells versus β3 in astrocytes), and integrin activation in these cells were related to enhanced neurite outgrowth of co-cultured neurons [88]. Since integrin receptors interact with extracellular proteins such as laminin and fibronectin [89], Cdc2 activity may play a part in mediating intercellular communication between glial cells and axons undergoing regeneration (Fig. 1).

It should, however, be noted that our studies on Cdc2 activity mentioned above used in vitro cultured cells. In regenerating peripheral nerves, the endoneurium wraps around radial surfaces of Schwann cells through the interaction between integrin and laminin [24]. In the early stages of PNS axon regeneration, Schwann cells interact with regenerating axons at the leading edge, but whether the interaction between Schwann cells and growth cones involves integrin signaling remains to be explored. Unlike Schwann cells in the injured peripheral nerve, reactive astrocytes after SCI do not form basal lamina structures. Integrin function of astrocytes has been shown in polarized interaction with ECM proteins during the wound healing process [90, 91] and cerebral microvasculature [92]. Interestingly, loss of β1 integrin in reactive astrocytes facilitates astrocyte migration and contributes to glial scar compaction [84]. It is uncertain at this moment whether LTC astrocytes may provide a permissive environment for spinal axon regeneration after lesion. A pattern of interaction of LTC astrocytes with spinal axons may be examined after the implantation of LTC astrocytes into the injury cavity.

CONCLUSION

A clear understanding of the role of glial cells, specifically Schwann cells of the PNS and astrocytes of the CNS, in axonal regeneration is critical for establishing a baseline intervention toward improving functional recovery following neural injury. For instance, successful PNS axon regeneration is largely attributed to Schwann cell response via proliferation, migration, and remyelination. Further, reactive astrocytes are the most abundant
cell type found in the CNS after injury and have been regarded as detrimental toward successful CNS axon regeneration. However, emerging evidence implicates its dual role in regulation of axonal regeneration. Considering the heterogeneity of astrocyte cell types and varied biochemical and pathophysiological properties [45, 47], the diverse responsiveness of different types of astrocytes is not surprising. In our recent study, reactive astrocytes revealed phenotypic expression in terms of increased phosphorylation by Cdc2 and integrin activation, which are positively associated with facilitated neurite outgrowth of co-cultured neurons. Evidently, further studies to better understand the roles of astrocytes and compare the common features shared with Schwann cells may provide insight on how to overcome regenerative response obstacles that contribute to poor functional recovery.

ACKNOWLEDGEMENTS

Work in our laboratory is supported by the National Research Foundation (NRF) funded by the Ministry of Education, Science and Technology, Korea (2010-0023869). Dana Toy is a 2012-2013 Luce Scholar of the Henry Luce Foundation.

REFERENCES

1. Chen ZL, Yu WM, Strickland S (2007) Peripheral regeneration. Annu Rev Neurosci 30:209-233.
2. Fawcett JW, Keynes RJ (1990) Peripheral nerve regeneration. Annu Rev Neurosci 13:43-60.
3. Richardson PM, Issa VM (1984) Peripheral injury enhances central regeneration of primary sensory neurones. Nature 309:791-793.
4. Silver J, Miller JH (2004) Regeneration beyond the glial scar. Nat Rev Neurosci 5:146-156.
5. Woodhoo A, Sommer L (2008) Development of the Schwann cell lineage: from the neural crest to the myelinated nerve. Glia 56:1481-1490.
6. Muroyama Y, Fujiwara Y, Orkin SH, Rowitch DH (2005) Specification of astrocytes by bHLH protein SCL in a restricted region of the neural tube. Nature 438:360-363.
7. Kageyama R, Ohtsuka T, Hatakeyama J, Ohsawa R (2005) Roles of bHLH genes in neural stem cell differentiation. Exp Cell Res 306:343-348.
8. Schwab ME (2002) Increasing plasticity and functional recovery of the lesioned spinal cord. Prog Brain Res 137:351-359.
9. Mandemakers WJ, Barres BA (2005) Axon regeneration: it’s getting crowded at the gates of TROY. Curr Biol 15:R302-R305.
10. Harrisingh MC, Perez-Nadalog E, Parkinson DB, Malcolm DS, Mudge AW, Lloyd AC (2004) The Ras/Raf/ERK signalling
Role of Glial Cells in Axonal Regeneration

73

pathway drives Schwann cell dedifferentiation. EMBO J 23:3061-3071.
11. Horner PJ, Gage FH (2000) Regenerating the damaged central nervous system. Nature 407:963-970.
12. Yu WM, Feltri ML, Wrabetz L, Strickland S, Chen ZL (2005) Schwann cell-specific ablation of laminin gamma1 causes apoptosis and prevents proliferation. J Neurosci 25:4463-4472.
13. Reichardt LF, Tomaselli KJ (1991) Extracellular matrix molecules and their receptors: functions in neural development. Annu Rev Neurosci 14:531-570.
14. Notterpek L (2003) Neurotrophins in myelination: a new role for a puzzling receptor. Trends Neurosci 26:232-234.
15. Koenig HL, Schumacher M, Ferzaz B, Thi AN, Ressouches A, Guennoun R, Jung-Testas I, Kobel P, Akwa Y, Baulieu EE (1995) Progesterone synthesis and myelin formation by Schwann cells. Science 268:1500-1503.
16. Li X, Gonias SL, Campana WM (2005) Schwann cells express erythropoietin receptor and represent a major target for Epo in peripheral nerve injury. Glia 51:254-265.
17. Wallquist W, Patarroyo M, Thams S, Carlstedt T, Stark B, Cullheim S, Hammarberg H (2002) Laminin chains in rat and human peripheral nerve: distribution and regulation during development and after axonal injury. J Comp Neurol 454:284-293.
18. Bunge RP, Bunge MB, Elderidge CF (1986) Linkage between axonal ensheathment and basal lamina production by Schwann cells. Annu Rev Neurosci 9:305-328.
19. Luckenbill-Edds L (1997) Laminin and the mechanism of neuronal outgrowth. Brain Res Brain Res Rev 23:1-27.
20. Menager C, Arimura N, Fukata Y, Kaibuchi K (2004) PIP3 is involved in neuronal polarization and axon formation. J Neurochem 89:109-118.
21. Masaki T, Matsumura K, Saito F, Sunada Y, Shimizu T, Yorifuji H, Motoyoshi K, Kamakura K (2000) Expression of dystroglycan and laminin-2 in peripheral nerve under axonal degeneration and regeneration. Acta Neuropathol 99:289-295.
22. Chen ZL, Strickland S (2003) Laminin gamma1 is critical for Schwann cell differentiation, axon myelination, and regeneration in the peripheral nerve. J Cell Biol 163:889-899.
23. Yang D, Bierman J, Tarumi YS, Zhong YP, Rangwala R, Proctor TM, Miyagoe-Suzuki Y, Takeda S, Miner JH, Sherman LS, Gold BG, Patton BL (2005) Coordinate control of axon defasciculation and myelination by laminin-2 and -8. J Cell Biol 168:655-666.
24. Feltri ML, Graus Porta D, Previtali SC, Nodari A, Migliavacca B, Cassetti A, Littlewood-Evans A, Reichardt LF, Messing A, Quattrini A, Mueller U, Wrabetz L (2002) Conditional disruption of beta 1 integrin in Schwann cells impedes interactions with axons. J Cell Biol 156:199-209.
25. Turney SG, Bridgman PC (2005) Laminin stimulates and guides axonal outgrowth via growth cone myosin II activity. Nat Neurosci 8:717-719.
26. Akassoglou K, Yu WM, Akpinar P, Strickland S (2002) Fibrin inhibits peripheral nerve remyelination by regulating Schwann cell differentiation. Neuron 33:861-875.
27. Siconolfi LB, Seeds NW (2001) Induction of the plasminogen activator system accompanies peripheral nerve regeneration after sciatic nerve crush. J Neurosci 21:4336-4347.
28. Akassoglou K, Kombrinck KW, Degen JL, Strickland S (2000) Tissue plasminogen activator-mediated fibrinolysis protects against axonal degeneration and demyelination after sciatic nerve injury. J Cell Biol 149:1157-1166.
29. Heumann R, Lindholm D, Bandtlow C, Meyer M, Radeke MJ, Misko TP, Shooter E, Thoenen H (1987) Differential regulation of mRNA encoding nerve growth factor and its receptor in rat sciatic nerve during development, degeneration, and regeneration: role of macrophages. Proc Natl Acad Sci U S A 84:8735-8739.
30. Acheson A, Barker PA, Alderson RF, Miller FD, Murphy RA (1991) Detection of brain-derived neurotrophic factor-like activity in fibroblasts and Schwann cells: inhibition by antibodies to NGF. Neuron 7:265-275.
31. Cosgaya JM, Chan JR, Shooter EM (2002) The neurotrophin receptor p75NTR as a positive modulator of myelination. Science 298:1245-1248.
32. Chan JR, Watkins TA, Cosgaya JM, Zhang C, Chen L, Reichardt LF, Shooter EM, Barres BA (2004) NGF controls axonal receptivity to myelination by Schwann cells or oligodendrocytes. Neuron 43:183-191.
33. Harrington AW, Ginty DD (2013) Long-distance retrograde neurotrophic factor signalling in neurons. Nat Rev Neurosci 14:177-187.
34. Chan JR, Cosgaya JM, Wu YJ, Shooter EM (2001) Neurotrophins are key mediators of the myelination program in the peripheral nervous system. Proc Natl Acad Sci U S A 98:14661-14668.
35. Koliatsos VE, Clatterbuck RE, Winslow JW, Cayouette MH, Price DL (1993) Evidence that brain-derived neurotrophic factor is a trophic factor for motor neurons in vivo. Neuron 10:359-367.
36. Bedi KS, Winter J, Berry M, Cohen J (1992) Adult rat dorsal root ganglion neurons extend neurites on predegenerated...
but not on normal peripheral nerves in vitro. Eur J Neurosci 4:193-200.
37. Schafer M, Fruttiger M, Montag D, Schachner M, Martini R (1996) Disruption of the gene for the myelin-associated glycoprotein improves axonal regrowth along myelin in C57BL/Wldm mice. Neuron 16:1107-1113.
38. David S, Braun PE, Jackson DL, Kottis V, McKerracher L (1995) Laminin overrides the inhibitory effects of peripheral nervous system and central nervous system myelin-derived inhibitors of neurite growth. J Neurosci Res 42:594-602.
39. Pot C, Simonen M, Weinmann O, Schnell L, Christ F, Stoeckle S, Berger P, Rulícke T, Suter U, Schwab ME (2002) Nogo-A expressed in Schwann cells impairs axonal regeneration after peripheral nerve injury. J Cell Biol 159:29-35.
40. Barres BA (2008) The mystery and magic of glia: a perspective on their roles in health and disease. Neuron 60:430-440.
41. Pellerin L, Bouzier-Sore AK, Aubert A, Serres S, Merle M, Costalat R, Magistretti PJ (2007) Activity-dependent regulation of energy metabolism by astrocytes: an update. Glia 55:1251-1262.
42. Eddleston M, Mucke L (1993) Molecular profile of reactive astrocytes--implications for their role in neurologic disease. Neuroscience 54:15-36.
43. Pekny M, Nilsson M (2005) Astrocyte activation and reactive gliosis. Glia 50:427-434.
44. Giulian D, Woodward J, Young DG, Krebs JF, Lachman LB (1988) Interleukin-1 injected into mammalian brain stimulates astrogliosis and neovascularization. J Neurosci 8:2485-2490.
45. Ridet JL, Malhotra SK, Privat A, Gage FH (1997) Reactive astrocytes: cellular and molecular cues to biological function. Trends Neurosci 20:570-577.
46. Sofroniew MV (2009) Molecular dissection of reactive astrogliosis and glial scar formation. Trends Neurosci 32:638-647.
47. Zhang Y, Barres BA (2010) Astrocyte heterogeneity: an under-appreciated topic in neurobiology. Curr Opin Neurobiol 20:588-594.
48. Bushong EA, Martone ME, Jones YZ, Ellisman MH (2002) Protoplasmic astrocytes in CA1 stratum radiatum occupy separate anatomical domains. J Neurosci 22:183-192.
49. Wilhelmsson U, Bushong EA, Price DL, Smarr BL, Phung V, Terada M, Ellisman MH, Pekny M (2006) Redefining the concept of reactive astrocytes as cells that remain within their unique domains upon reaction to injury. Proc Natl Acad Sci USA 103:17513-17518.
50. Bush TG, Puvanachandra N, Horner CH, Polito A, Ostenfeld T, Svendsen CN, Mucke L, Johnson MH, Sofroniew MV (1999) Leukocyte infiltration, neuronal degeneration, and neurite outgrowth after ablation of scar-forming, reactive astrocytes in adult transgenic mice. Neuron 23:297-308.
51. Herrmann JE, Imura T, Song B, Qi L, Ao Y, Nguyen TK, Korsak RA, Takeda K, Akira S, Sofroniew MV (2008) STAT3 is a critical regulator of astrogliosis and scar formation after spinal cord injury. J Neurosci 28:7231-7243.
52. DiProspero NA, Meiners S, Geller HM (1997) Inflammatory cytokines interact to modulate extracellular matrix and astrocytic support of neurite outgrowth. Exp Neurol 148:628-639.
53. Yu G, He Z (2006) Glial inhibition of CNS axon regeneration. Nat Rev Neurosci 7:617-627.
54. McKeon RJ, Schreiber RC, Rudge JS, Silver J (1991) Reduction of neurite outgrowth in a model of glial scarring following CNS injury is correlated with the expression of inhibitory molecules on reactive astrocytes. J Neurosci 11:3398-3411.
55. Johnson-Green PC, Dow KE, Riopelle RJ (1991) Characterization of glycosaminoglycans produced by primary astrocytes in vitro. Glia 4:314-321.
56. Morgenstern DA, Asher RA, Fawcett JW (2002) Chondroitin sulphate proteoglycans in the CNS injury response. Prog Brain Res 137:313-332.
57. Smith-Thomas LC, Fok-Seang J, Stevens J, Du JS, Muir E, Faissner A, Geller HM, Rogers JH, Fawcett JW (1994) An inhibitor of neurite outgrowth produced by astrocytes. J Cell Sci 107:1687-1695.
58. Jones LL, Yamaguchi Y, Stallcup WB, Tuszynski MH (2002) NG2 is a major chondroitin sulfate proteoglycan produced after spinal cord injury and is expressed by macrophages and oligodendrocyte progenitors. J Neurosci 22:2792-2803.
59. Moon LD, Asher RA, Rhodes KE, Fawcett JW (2002) Relationship between sprouting axons, proteoglycans and glial cells following unilateral nigrostriatal axotomy in the adult rat. Neuroscience 109:101-117.
60. Davies SJ, Goucher DR, Doller C, Silver J (1999) Robust regeneration of adult sensory axons in degenerating white matter of the adult rat spinal cord. J Neurosci 19:5810-5822.
61. Fitch MT, Doller C, Combs CK, Landreth GE, Silver J (1999) Cellular and molecular mechanisms of glial scarring and progressive cavitation: in vivo and in vitro analysis of inflammation-induced secondary injury after CNS trauma. J Neurosci 19:8182-8198.
62. Snow DM, Letourneau PC (1992) Neurite outgrowth on a step gradient of chondroitin sulfate proteoglycan (CS-PG). J Neurobiol 23:322-336.
63. Inman DM, Steward O (2003) Ascending sensory, but not
other long-tract axons, regenerate into the connective tissue matrix that forms at the site of a spinal cord injury in mice. J Comp Neurol 462:431-449.

64. Carulli D, Laabs T, Geller HM, Fawcett JW (2005) Chondroitin sulfate proteoglycans in neural development and regeneration. Curr Opin Neurobiol 15:116-120.

65. Bradbury EF, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB (2002) Chondroitinase ABC promotes functional recovery after spinal cord injury. Nature 416:636-640.

66. Karimi-Abdolrezaee S, Billakanti R (2012) Reactive astrogliosis after spinal cord injury-beneficial and detrimental effects. Mol Neurobiol 46:251-264.

67. Rolls A, Shechter R, Schwartz M (2009) The bright side of the glial scar in CNS repair. Nat Rev Neurosci 10:235-241.

68. Rothstein JD, Dykes-Hoberg M, Pardo CA, Bristol LA, Jin L, Kuncl RW, Kanai Y, Hediger MA, Wang Y, Schielke JP, Welty DF (1996) Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. Neuron 16:675-686.

69. Chen Y, Vartiainen NE, Ying W, Chan PH, Koistinaho J, Swanson RA (2001) Astrocytes protect neurons from nitric oxide toxicity by a glutathione-dependent mechanism. J Neurochem 77:1601-1610.

70. ShihAY, Johnson DA, Wang G, Kraft AD, Jiang L, Erb H, Johnson IA, Murphy TH (2003) Coordinate regulation of glutathione biosynthesis and release by Nrf2-expressing glia potently protects neurons from oxidative stress. J Neurosci 23:3394-3406.

71. Rao KV, Panickar KS, Jayakumar AR, Norenberg MD (2005) Astrocytes protect neurons from ammonia toxicity. Neurochem Res 30:1311-1318.

72. Lin JH, Lou N, Kang N, Takan o T, Hu F, Han X, Xu Q, Lovatt D, Torres A, Willecke K, Yang J, Kang J, Nedergaard M (2008) A central role of connexin 43 in hypoxic preconditioning. J Neurosci 28:681-695.

73. Koistinaho M, Lin S, Wu X, Esterman M, Koger D, Hanson J, Higgs R, Liu F, Malkani S, Bales KR, Paul SM (2004) Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-beta peptides. Nat Med 10:719-726.

74. Zador Z, Stiver S, Wang V, Manley GT (2009) Role of aquaporin-4 in cerebral edema and stroke. Handb Exp Pharmacol (190):159-170.

75. Sofroniew MV (2005) Reactive astrocytes in neural repair and protection. Neuroscientist 11:400-407.

76. Myer DJ, Gurkoff GG, Lee SM, Hovda DA, Sofroniew MV (2006) Essential protective roles of reactive astrocytes in traumatic brain injury. Brain 129:2761-2772.

77. Voskuhl RR, Peterson RS, Song B, Ao Y, Morales LB, Tiwari-Woodruff S, Sofroniew MV (2009) Reactive astrocytes form scar-like perivascular barriers to leukocytes during adaptive immune inflammation of the CNS. J Neurosci 29:11511-11522.

78. Okada S, Nakamura M, Katoh H, Miyao T, Shimazaki T, Ishii K, Yamane J, Yoshimura A, Iwamoto Y, Toyama Y, Okano H (2006) Conditional ablation of Stat3 or Socs3 discloses a dual role for reactive astrocytes after spinal cord injury. Nat Med 12:829-834.

79. John GR, Lee SC, Song X, Riveccio M, Brosnan CF (2005) IL-1-regulated responses in astrocytes: relevance to injury and recovery. Glia 49:161-176.

80. Daginakatte GC, Gadzinski A, Emmett RI, Stark JL, Gonzales ER, Yan P, Lee JM, Cross AH, Gutmann DH (2008) Expression profiling identifies a molecular signature of reactive astrocytes stimulated by cyclic AMP or proinflammatory cytokines. Exp Neurol 210:261-267.

81. Yeh TH, Lee da Y, Gianino SM, Gutmann DH (2009) Microarray analyses reveal regional astrocyte heterogeneity with implications for neurofibromatosis type 1 (NF1)-regulated glial proliferation. Glia 57:1239-1249.

82. Torigoe K, Tanaka HE, Takahashi A, Awaya A, Hashimoto K (1996) Basic behavior of migratory Schwann cells in peripheral nerve regeneration. Exp Neurol 137:301-308.

83. Han IS, Seo TB, Kim K H, Yoon JH, Yoon SJ, Namgung U (2007) Cdc2-mediated Schwann cell migration during peripheral nerve regeneration. J Cell Sci 120:246-255.

84. Renault-Mihara F, Kato H, Ikegami T, Iwamani A, Mukaino M, Yasuda A, Nori S, Mabuchi Y, Tada H, Shibata S, Saito K, Matsushita M, Kaibuchi K, Okada S, Toyama Y, Nakamura M, Okano H (2011) Beneficial compaction of spinal cord lesion by migrating astrocytes through glycogen synthase kinase-3 inhibition. EMBO Mol Med 3:682-696.

85. Eroglu C, Barres BA (2010) Regulation of synaptic connectivity by glia. Nature 468:223-231.

86. Feng Z, Ko CP (2008) Schwann cells promote synaptogenesis at the neuromuscular junction via transforming growth factor-beta1. J Neurosci 28:9599-9609.

87. Chang IA, Oh MJ, Kim MH, Park SK, Kim BG, Namgung U (2012) Vimentin phosphorylation by Cdc2 in Schwann cell controls axon growth via β1-integrin activation. FASEB J 26:2401-2413.

88. Chang IA, Kwon KB, Park YC, Namgung U (2013) Permissive role of Cdc2 activity induced from astrocytes in neurite outgrowth. J Neurochem (in press).
89. Giancotti FG, Ruoslahti E (1999) Integrin signaling. Science 285:1028-1032.
90. Peng H, Shah W, Holland P, Carbonetto S (2008) Integrins and dystroglycan regulate astrocyte wound healing: the integrin beta1 subunit is necessary for process extension and orienting the microtubular network. Dev Neurobiol 68:559-574.
91. Etienne-Manneville S, Hall A (2001) Integrin-mediated activation of Cdc42 controls cell polarity in migrating astrocytes through PKCzeta. Cell 106:489-498.
92. del Zoppo GJ, Milner R (2006) Integrin-matrix interactions in the cerebral microvasculature. Arterioscler Thromb Vasc Biol 26:1966-1975.