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INVITED REVIEW

Stem cell therapy for central nerve system injuries: glial cells hold the key

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Abstract

Mammalian adult central nerve system (CNS) injuries are devastating because of the intrinsic difficulties for effective neuronal regeneration. The greatest problem to be overcome for CNS recovery is the poor regeneration of neurons and myelin-forming cells, oligodendrocytes. Endogenous neural progenitors and transplanted exogenous neuronal stem cells can be the source for neuronal regeneration. However, because of the harsh local microenvironment, they usually have very low efficacy for functional neural regeneration which cannot compensate for the loss of neurons and oligodendrocytes. Glial cells (including astrocytes, microglia, oligodendrocytes and NG2 glia) are the majority of cells in CNS that provide support and protection for neurons. Inside the local microenvironment, glial cells largely influence local and transplanted neural stem cells survival and fates. This review critically analyzes current finding of the roles of glial cells in CNS regeneration, and highlights strategies for regulating glial cells' behavior to create a permissive microenvironment for neuronal stem cells.

Key Words: *Neuron regeneration; stem cell therapy; glial cells; microenvironment; oligodendrocyte regeneration; CNS injury*

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Introduction

Adult mammalian central nerve system (CNS) has a difficulty in repairing injuries because it lacks the regenerative power to replace damaged neuronal cells and reconstruct dendritic connections (Bregman et al., 1995; Horner and Gage, 2000). During the past two decades, two basic strategies have been established for neuronal regeneration: endogenous self-repair and exogenous cellular replacement. Self-repair requires endogenous neural stem cells and cellular replacement needs stem cell transplantation (Cheng et al., 1996; Stichel et al., 1998a; Horner and Gage, 2000; Bradbury and McMahon, 2006; Okano, 2009; Trueman et al., 2013). It has been demonstrated that neural stem cells (NSCs) exist in the subventricular zone (SVZ), and hippocampus of brain and the central canal of the spinal cord (Temple, 1989; Reynolds and Weiss, 1992). They can migrate to the lesion site to repair the injured tissue. These endogenous NSCs could be a regenerative source for the damaged neural cells (Gage et al., 1995, 2000; Gensert and Goldman, 1997). Nevertheless, because their number and regenerative ability are limited, they cannot fully repair the damaged tissue in CNS (Picard-Riera et al., 2004). Exogenous neuronal stem cells then become an expected source for neurogenesis. Stem cell [such as embryonic stem cells (ES cells) and induced pluripotent stem cells (iPS cells)] transplantation can offer a large number of neural progenitors for introducing new neuronal cells to the damaged CNS tissue (McDonald et al., 1999; Tsuji et al., 2010; Chen et al., 2011). Moreover bone marrow mesenchymal stem cells and dental pulp stem cells are able to be differentiated into neuronal lineages both *in vivo* and *in vitro* (Jiang et al., 2002; Jin et al., 2002; Xiao and Tsutsui, 2013). However, no matter how experimental studies showed that exogenous NSCs can be effectively differentiated into mature neuronal cells *in vitro*, in most *in vivo* experiments they only showed modest recovery of the injured CNS (Tetzlaff et al., 2011; Mothe and Tator, 2012). The reason for this is considered to be that the damaged microenvironment prevents neuronal regeneration (neurogenesis) (Neumann, 2000; Imitola et al., 2006; Yiu and He, 2006; Charil and Filippi, 2007). Factors present in the injured microenvironment (such as inflammatory mediators) influence survival, self-renewal, migration and neuronal differentiation of both endogenous NSCs and transplanted exogenous stem cells (Watanabe et al., 2007; Singhal et al., 2008; Kim et al., 2012; Dooley et al., 2014). As a result, endogenous NSCs cannot efficiently perform self-repair (Singhal et al., 2008), and exogenous stem cells have difficulty to differentiate into functional neurons, but do contribute to glial scar formation (Suhonen et al., 1996). To obtain better therapeutic result for traumatic injuries of

CNS, it is essential to create a permissive microenvironment for both endogenous and exogenous neuronal stem cells and direct them to differentiate towards functional neurons and oligodendrocytes. Glial cells play key role in the maintenance and homeostasis of the local microenvironment (Walz, 1989; Gourine et al., 2010). The interaction between glial cells and neuronal stem cells is essential for functional neuronal regeneration. Here we summarize recent findings about the role of glial cells in CNS injuries as well as the possible methods to control their behavior for stem cell-based neuroregeneration.

Local microenvironment of neurons

CNS neurons are the functional cells which form neural networks using their axons to process and transmit information through synapses. There are four types of glial cells in the local microenvironment surrounding neurons: astrocyte, oligodendrocyte, microglia and NG2 glia (polydendrocytes, or oligodendrocyte progenitor cells). Astrocytes are the supporting cells which form blood-brain-barrier (BBB) or blood-spinal cord barrier (BSCB) with endothelial cells, provide nutrients to neuron, and control synapse formation and function (Abbott, 2002; Bartanusz et al., 2011). Microglia are the defensive cells which first and mainly respond to injuries. Oligodendrocytes also act as the supporting cells which provide myelin (the insulating sheath) around the axons of neurons. NG2 glia generate oligodendrocytes, astrocytes and microglia in CNS and serve as the primary source of remyelinating cells in demyelinated lesions (Raff et al., 1983; Nishiyama et al., 2009). These four types of cells are embedded in the extracellular matrix (ECM) and work together through cell-cell or cell-ECM interactions to maintain the function of neurons (**Figure 1**).

Although the pathologies among the three types of traumatic CNS injuries, traumatic brain injury (TBI), spinal cord injury (SCI) and stroke, are quite different, they all have two injury phases, primary and secondary, and the cellular and molecular responses in the local microenvironment are similar. The common cellular and molecular responses are cell death (apoptosis and necrosis), inflammation, glial cells' activation, excitotoxicity, increase in free radicals, accumulation of acid and toxic products, demyelination, axonal degeneration and glial scar formation (Hausmann, 2003; Buga et al., 2008; Veenith et al., 2009; Mothe et al., 2012; Huang et al., 2014). Particularly, after injuries neurons and oligodendrocytes die and undergo demyelination, whereas astrocytes and microglia are activated and proliferate (Vela et al., 2002; Lalancette-Hébert et al., 2007). Microglia are the first glial cells to be activated by traumatic injury. They release chemical mediators and reactive oxygen species (ROS) that promote peripheral macrophages infiltration through the BBB. Microglia and infiltrated macrophages build a defensive system to prevent pathogens and neurotoxins, and clean up the debris of dead cells (El Khoury et al., 2007). At the same time, they also produce inflammatory factors that are neurotoxic (Dheen et al., 2007). NG2 glia are then stimulated by signals from activated microglia. They proliferate to replace the dying oligodendrocytes, provide a favorable substrate for axon growth, and contribute to the reconstruction of neuroglial network (Nishiyama et al., 2005; Yang et al., 2006; Wigley et al., 2007; 2009; Wu et al., 2010). Astrocytes are the last glial cells to respond after being activated by micraoglia. The inflammatory products of microglia play important roles for activating astrocytes (such as IL-1, IL-6, and TNF-α) (Lee et al., 1993; Röhl et al., 2006; Zhang et al., 2010; Erta et al., 2012). Astrocytes rapidly proliferate and then form a glial scar to make a border between the damaged and the healthy tissues. The glial scar [which is a complex of astrocytes, NG2 glia, extracellular matrix (ECM) and other cellular compounds] reestablishes the physical and chemical integrity of the CNS (Silver and Miller, 2004). However, it also produces many inhibitory molecules (such as myelin inhibitors) that prevent the migration of endogenous NSCs as well as inhibit significant axonal regeneration (McKeon et al., 1999; Silver and Miller, 2004). As a result, the local microenvironment is reconstructed and produces various factors to influence neuronal regeneration (Fitch and Silver, 2008) (**Figure 2**). Therefore, to make a welcoming microenvironment for stem cells-based neuronal regeneration in traumatic CNS injuries, we must 1) control glial scar formation and diminish the production of harmful factors; 2) regulate microglia's behaviors; and 3) fill up NG2 glia to generate remyelinating oligodendrocytes.

Chronic neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis) share similar cellular and molecular changes with traumatic CNS injuries, but at different levels. The differences between chronic neurodegenerative diseases and traumatic CNS are summarized in **Table 1**. Although the detailed mechanism for chronic neurodegenerative disorders is not understood, a rough outline emerged as 1) The key feature is chronic inflammation, in particular of microglia activation (Nguyen et al., 2002; Amor et al., 2010). 2) Immunological challenges might be aetiological factors (Nguyen et al., 2002). 3) The permeability of the BBB is increased which allows for the entry of immune elements (Zlokovic, 2008). 4) Astrocytes are activated and release both excitotoxic and neural protective molecules (Maragakis et al., 2006). 5) Glial scar formation usually is not observed because the moderate injury severity (Sofroniew, 2009). 6) Neurons are the only victims. They undergo apoptotic cell death. 7) Olidendrocytes undergo apoptosis in multiple sclerosis whereas they are complement-activated in Alzheimer's disease and Parkinson's disease (Peferoen et al., 2014). 8) NG2 glia are specifically involved in myelin repair (Richardson et al., 2011). For these reasons, a complex regulation of glial cells might be required for preventing chronic neurodegeneration.

Directing the glial scar towards functional neuronal cells

Astrocytes have been characterized as neural stem cells in specific regions of adult CNS. Doetsch et al (1999) demonstrated that in the subventricular zone (SVZ) of mouse brain, a subpopulation of astrocytes could give rise to immature precursors and neuroblasts both *in vivo* and *in vitro*. Later, Sanai et al. (2004) showed that SVZ astrocytes in the adult human brain are clonal precursors of self-renewing multipotent neurospheres and can be differentiated into neurons in the absence of exogenous growth factors. However, in the vast majority of the CNS, such as the cortical regions, astrocytes apparently cannot produce new neurons but form glial scar (the main barrier of axonal regeneration) after an injury (Silver and Miller, 2004; Kriegstein et al., 2009). In the lesion

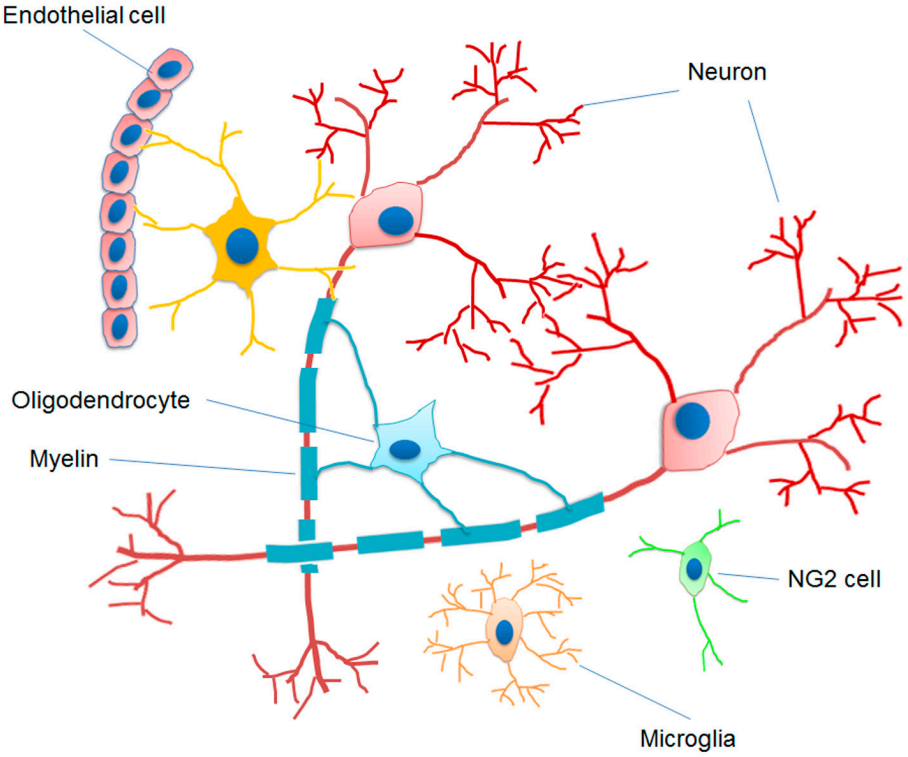

Figure 1 Glial cells and neurons in the healthy central nerve system.

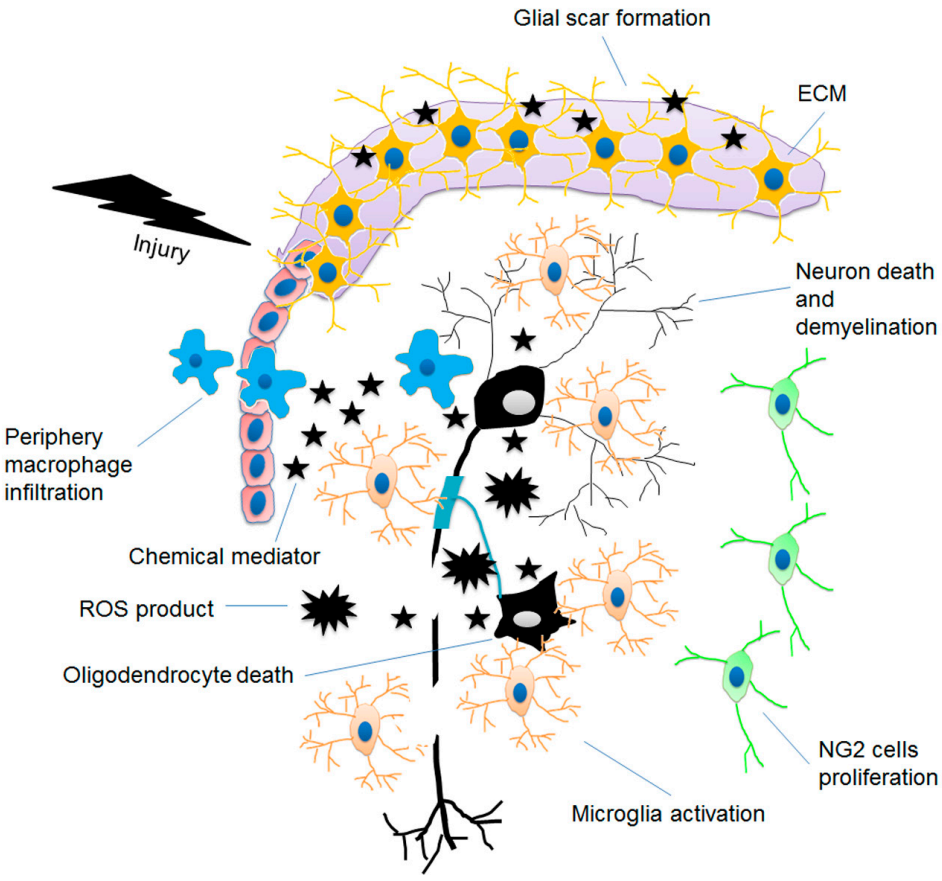

Figure 2 Damaged central nerve system microenvironment.
ECM: Extracellular matrix; ROS: reactive oxygen species; NG2: neuron-glial antigen 2.

Table 1 Differences of the microenvironment between traumatic central nerve system injuries and chronic neurodegenerative diseases

Events	Level	
	Traumatic CNS injuries	Chronic neurodegenerative diseases
Acute inflammation	+++	–
Chronic inflammation	+	+++
Microglial activation	++	+++
Astrocyte activation	+++	++
Glial scar formation	+++	–
Oligodendrocyte death	++	+++
Neuron death	++	+++
NG2 glia function	++	+
Demyelination	++	+++
Regenerative ability	+	+/–

"–": Negative; "+/–": very low; "+": low; "++": normal; "+++": strong.

sit, astrocytes play a crucial role in the healing process. They are activated by the migrated microglia through the integral membrane proteins (Volterra and Meldolesi, 2005) and offer tissue repair just like the fibroblasts in the non-CNS tissue. To repair the damaged tissue, astrocytes first proliferate and then wall off the wounded areas to form glial scar that reduces the spread and persistence of inflammatory cells. Although the glial scar serves to repair the BBB, prevent an overwhelming inflammatory response and decrease neuronal loss and demyelination, it does block axon guidance and inhibits neural regeneration (Stichel and Müller, 1998b; Sofroniew, 2005; Yiu and He, 2006; Barres, 2008). Therefore, inhibitory treatments of glial scar have been considered useful for neuronal regeneration. *In vivo* treatment with peptide amphiphile could reduce glial scar formation, increase the number of oligodendroglia at the site of spinal cord injury and resulted in significant behavioral improvements (Tysseling-Mattiace et al., 2008). IFN-β-encoding could help transplanted NSCs to inhibit glial scar formation in spinal cord injury through the stimulation of TLR4 signaling (Nishimura et al., 2013). However, as we described before, glial scar can offer wound healing, limits the inflammation and protects the healthy tissue. Inhibition of glial scar might have harmful effects. Therefore, directing astrocytes in the glial scar towards functional neurons becomes an ideal strategy for CNS regeneration. Postnatal astrocytes can be redirected toward neurons by forced expression of Pax6 or pro-neural transcription factor neurogenin-2 *in vitro* (Heins et al., 2002; Berninger et al., 2007). Astrocytes isolated from an adult cortex, reprogrammed with the pCAG-Neurog2-containing retroviral vector, could give rise to synapse-forming glutamatergic neurons (Heinrich et al., 2010). Reprogramming astrocytes with individual stem transcription factors OCT4, SOX2, or NANOG could generate NSCs. These astrocyte-derived NSCs were able to generate mature neurons *in vivo* with positive expression of synaptic proteins and neurotransmitters (Corti et al., 2012). However, since transplanted stem cells *in vivo* usually differentiate into glial cells instead of functional neurons, it is possible that these *in vitro* reprogrammed astrocyte-NSCs will have the same problems. A recent study made a breakthrough in resolving this impasse. Guo et al (2014) demonstrated that reactive glial cells, including both astrocytes and NG2 glia, in the glial scar can be reprogrammed into functional neurons in the adult mouse cortex when infected with a retrovirus-encoded single transcription factor, NeuroD1 (which plays an important role during embryonic brain development and adult neurogenesis). Astrocytes were mainly reprogrammed into glutamatergic neurons whereas NG2 glia were reprogrammed into both glutamatergic and GABAergic neurons. Although safety issues need to be resolved, this technology does open the door to functional recovery for CNS injuries.

Moreover, as the main component of glial scar, chondroitin sulphate proteoglycans (CSPGs) (a major component of the ECM) have been considered as inhibitors for neurite outgrowth (Hynds and Snow, 1999; Tan et al., 2005). Conversely, evidence has emerged that CSPGs promote proliferation and functional differentiation of neural stem cells *in vitro* (Sirko et al., 2007; Tham et al., 2010). An *in vivo* study confirmed that CSPGs have either beneficial or destructive effects in spinal cord repair. The data showed that in mice SCI model, there was an inhibition of CSPGs synthesis immediately after SCI impaired functional motor recovery and increased tissue loss. In contrast, 2 days after SCI, CSPGs inhibition improved recovery (Rolls et al., 2008). The underlying mechanism of the duo faces of CSPGs is far from being clear. Based on the above-mentioned evidence, it emerges that CSPGs are important molecules for CNS repair and endogenous neural stem cells proliferation and differentiation in the acute phase in CNS injuries, but become a barrier in the chronic phase. Since the best period for stem cell transplantation for SCI is about 2 weeks after the trauma, simultaneously using CSPGs inhibitors might be beneficial.

Microglia is a double edged sword: either exacerbating degeneration or promoting repair

In non-CNS tissues the common inflammatory response includes invasion of leucocytes, activation of fibroblasts and release of chemical mediators. However, CNS was regarded as an "immune privileged" organ, because it has intrinsic immune cells to respond to the inflammatory insults. Concretely, after injury the first and mainly activated immune cells in CNS are microglia instead of leucocytes. Microglia (the resident macrophages) proliferate and migrate to the lesion site. They produce inflammatory mediators such as IL-1, IL-6, TNF-alpha, ROS and nitric oxide (NO) (Yao et al., 1992; Erta et al., 2012; Qin and Crews, 2012; Guadagno et al., 2013). These inflammatory mediators not only act on local cells, but also recruit peripheral leukocytes to pass the BBB through the interactions between endothelial cells and astrocytes (Engelhardt and Ransohoff, 2005). Activated microglia and peripheral leukocytes eliminate pathogens and clean up the debris caused by physical trauma and inflammatory response. Cross-talk between microglia and neural stem cells (NSCs) plays a key role in neuronal regeneration (Kokaia et al., 2012). Activated microglia produce a plethora of chemical mediators ranging from neurotoxic triggers to neurontrophic factors which can impair NSCs survival and neuronal differentiation as well as beneficial effects on neu-

rogenesis. In chronic neurodegenerative diseases activated microglia can kill neurons and oligodendrocytes through the phagocyte NADPH oxidase (PHOX) and the inducible nitric oxide synthase (iNOS) (Brown and Neher, 2010; de Pablos et al., 2014). Lipopolysaccharide (LPS) has been used for triggering chronic inflammation and exacerbating neurodegeneration in animal models of chronic neurodegenerative diseases (Qin et al., 2007; Pott Godoy et al., 2008; Murray et al., 2011). LPS-activated microglia efficiently triggered apoptosis in mouse NSCs *via* TNF-α-involved mitochondrial pathway (Guadagno et al., 2013). This activation is likely controlled by caspase signaling. Knockdown or chemical inhibition of caspase signaling hindered microglia activation and consequently reduced neurotoxicity (Burguillos et al., 2011). As a tetracycline antibiotic, minocycline can permeate through the BBB or BSCB (Aronson, 1980). Minocycline is known to inhibit microglial activation. An *in vitro* study showed that minocycline significantly decreased excitotoxins (glutamate and kainite) induced neuron death (Tikka et al., 2001). In a variety of experimental models of neuron degeneration minocycline protected neurons by inhibiting microglial activation-associated chronic inflammation suggesting minocycline is a potential therapeutic reagent for chronic neurodegenerative diseases (Fan et al., 2007; Plane et al., 2010; Kobayashi et al., 2013). In an experimental rat stroke model, minocycline presented positive effects on endogenous neural stem cells' survival and activation (Rueger et al., 2012). A similar study showed that minocycline-preconditioned exogenous neural stem cells enhanced neuroprotection in a rat ischemic stroke model after transplantation (Sakata et al., 2012). These reports suggest minocycline treatment is also beneficial to both endogenous and exogenous neural stem cells. However, in some animal models (such as Parkinson's Disease), minocycline increased neuron death (Plane et al., 2010). Moreover, in a phase III randomised trial minocycline treatment showed a harmful effect on patients with amyotrophic lateral sclerosis (ALS) indicating this drug needs to be carefully investigated (Gordon et al., 2007). Natural products and hydrogen sulfide have been used to inhibit neurotoxic microglia activation that consequently achieves neuroprotection (Choi et al., 2011; Zhang et al., 2014). On the other hand, in traumatic CNS injuries activated microglia are favorable. They provide immune-related requirements for CNS self-repair. Franzen et al. (1998) demonstrated that grafted macrophages could contribute to axonal regeneration in an animal model of spinal cord injury suggesting that microglia (the local microphage in CNS) might be beneficial for neuronal regeneration. It has been demonstrated that CNS injury-activated microglia induce neuronal stem proliferation and promote functional neuronal and oligodendritic differentiation *in vitro* (Deierborg et al., 2010). Activated microglia promote the generation of neurons from white matter cells by secreting trypsinogen PRSS2 (Nikolakopoulou et al., 2013). Microglia interacted with transplanted ES cell-derived neural stem cells by fusion. The fused microglia-neural stem cells showed improvement on the functional recovery of CNS (Schwartz, 2003; Cusulin et al., 2012). These evidences suggest that for traumatic CNS injuries, such as spinal cord injury, co-transplanting microglia with neuronal stem cells might be a promising approach.

Oligodendrocyte regeneration

Oligodendrocytes are vulnerable to both physical trauma and inflammatory response after CNS injury, duo to they are the end products of neuronal lineage and have high metabolic activity, high levels of intracellular iron and low concentration of antioxidants, such as glutathione (Thorburne and Juurlink, 1996; Bradl and Lassmann, 2010; Amaral et al., 2013). In a rodent model of spinal cord injury, massive cell death of oligodendrocytes is triggered by proteolytic enzymes, chemical mediators and oxidative stress (which were produced by microglia and infiltrated macrophages) (Frei et al., 2000; Dong et al., 2003). Death of oligodendrocytes causes demyelination which impairs axon function and consequently induces neuron death (Almad et al., 2011). Moreover, fully differentiated oligodendrocytes are postmitotic and cannot repair myelin in the presence of demyelinated axons in adult CNS (Keirstead et al., 1997). Therefore, remyelination requires oligodendrocyte progenitor cells. As progenitors of oligodendrocyte, NG2 glia give rise to the majority of oligodendrocytes in CNS during development (Polito and Reynolds, 2005). NG2 glia also can produce astrocytes and neurons depending on environmental conditions (Trotter et al., 2010). In adult CNS, when the injury causes demyelination or generalized tissue destruction, NG2 glia rapidly proliferate, migrate to the lesion site (Franklin et al., 1997), and differentiate into oligodendrocytes which remyelinate neurons (Islam et al., 2009; Nishiyama et al., 2009). NG2 glia also provide an adhesive substrate for axonal growth cones and promote their growth (Yang et al., 2006). Moreover, it has been reported that NG2 glia stabilize the regenerating front of dystrophic axons in the inhibitory environment of the glial scar after spinal cord injury (Busch et al., 2010). However, evidence showed that local NG2 glia have limited ability to proliferate (Payne et al., 2013) and their population cannot be completely restored (Keirstead et al., 1998; Richardson et al., 2011). It has been demonstrated that the pleiotropic cytokine, leukemia inhibitory factor (LIF) potentiates the differentiation and survival of oligodendrocyte precursors and prevent oligodendrocyte apoptosis in response to either growth factor removal or cytotoxic challenge *in vitro* (Kerr and Patterson, 2005). *In vivo* studies confirmed that endogenous LIF production limits autoimmune demyelination and oligodendrocyte loss (Butzkueven et al., 2006). Delivery of exogenous LIF stimulates oligodendrocyte progenitor cell proliferation and enhances hippocampal remyelination (Bauer and Patterson, 2006; Deverman et al., 2012). Furthermore, LIF expands the pool of adult neural stem cells by promoting their self-renewal, thereby preventing the emergence of more differentiated progeny, both *in vivo* and *in vitro* (Pitman et al., 2004; Bauer and Patterson, 2006). LIF also promoted proliferation, survival, and differentiation in cultivated ES cells-derived neuron progenitors (Majumder et al., 2012). Hence, a combination of exogenous LIF supply and stem cell transplantation might be beneficial for remyelination and neurogenesis.

Conclusion

Regeneration of the nervous system requires not only en-

dogenous and exogenous neuronal stem cells but also an appropriate microenvironment. Glia cells are the cellular comportments of the microenvironment surrounding neurons. Microglia, astrocytes and NG2 glia play crucial roles on neuronal regeneration. Microglia have dual effects on neuronal regeneration. In chronic neurodegenerative diseases it is necessary to suppress microglial activation. Minocycline is a strong inhibitor of microglial activation that showed neuronal protection in experimental animal models of neurodegenerative diseases. But its potential harmful effects need to be carefully examined. Natural products and hydrogen sulfide might be potential therapeutic reagents for controlling microglial activation-mediated chronic inflammation in CNS. In traumatic injuries microglia are beneficial for neuronal stem cells. Co-transplanting microglia with neuronal stem cells might be a promising approach. Astrocytes produce glial scar in the lesion the sites in CNS. They also have stem cell properties. Inhibition of glial scar formation (such as peptide amphiphile treatment and IFN-β-encoding) could help neuronal regeneration. Since glial scar also has profitable effects for repair, the inhibition of glial scar might have side effects. Technologies for converting harmful glial scar into functional neurons have provided innovative approaches for the potential regeneration of CNS. NG2 glia are the progenitors of oligodendrocyte so their numbers need to be increased in CNS injured tissue. Exogenous LIF supply can maintain the rate of proliferation of NG2 glia, and promote proliferation, survival, and differentiation of neural stem cells. A combination of LIF treatment and stem cell transplantation might be permissive for remyelination and neurogenesis.

In conclusion, appropriate control of glial cells behavior can improve the local microenvironment and consequently help survival and functional differentiation of neuronal stem cells. Thus, glial cells can be an important target of future research for the treatment of CNS injuries and diseases.

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