PHYSIOLOGY 23: 296–304, 2008; doi:10.1152/physiol.00017.2008

Endogenous Neural Progenitor Cells as Therapeutic Target After Spinal Cord Injury

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Growing knowledge about the role of neural progenitor cells supports the hope that stem cell-based therapeutic approaches aimed at restoring function in the lesioned central nervous system can be established. Possible therapies for promoting recovery after spinal cord injury include stimulating the formation of neurons and glial cells by endogenous progenitor cells. This article reviews the current knowledge about the nature of adult progenitor cells in the intact and injured spinal cord and summarizes possibilities and limitations of cellular replacement strategies based on manipulations of endogenous spinal cord progenitor cells and their environment.

The characterization of adult neural stem/progenitor cells (SPCs) in mammals has been the focus of intense research with the goal of developing new cell-based regenerative treatments for central nervous system (CNS) pathologies such as spinal cord injury (SCI). Injury to the spinal cord disrupts ascending and descending axonal pathways and causes cellular destruction, inflammation, and demyelination (Ref. 90; see FIGURE 1). This results in a loss of movement, sensation and autonomic control below and at the level of the lesion. Current clinical approaches for SCI include the use of high doses of methylprednisolone to help limit secondary injury processes (19–21), surgery to stabilize and decompress the spinal cord (for review, see Ref. 16), intensive multisystem medical management (39), and rehabilitative care (9, 32–34). Although these treatment options provide some benefits (28, 38, 39), there is a critical need to develop novel approaches that account for the complex pathophysiology of SCI and optimize recovery after SCI. There are several discoveries at the preclinical level that are not only directed toward minimizing secondary damage and maximizing functionality of remaining neuronal systems but are also aimed at stimulating regeneration and repair. Prominent strategies that have been used so far include promoting regrowth of interrupted nerve fiber tracts as well as sprouting of uninjured axons by manipulation of the inhibitory spinal cord environment (25, 40, 89), bridging the lesion using peripheral nerve or diverse cell grafts (22, 26, 31, 85), and replenishment of lost cell types by stem cell-based treatments. Cell replacement strategies can be divided into two categories: *1*) transplantation of embryonic or adult SPCs into the lesioned spinal cord with or without ex vivo manipulation or *2*) reactivation and mobilization of endogenous adult spinal cord SPCs. Considering the reports published during the last decade, the transplantation of SPCs has gathered more attention. Several studies have shown functional benefits following transplantation of stem cells (for review, see Refs. 10, 29). The functional recovery is thought to be mainly mediated by the trophic factor secretion of SPCs or by remyelination of spared axons through newly formed oligodendrocytes (60), but the generation of new neurons has also been described (30, 64). However, transplantation-based approaches have several disadvantages, such as the risk of immune rejection and the need for external sources of cells. Embryonic stem cells or postnatal SPCs can be used for transplantation. Embryonic stem cells likely have a greater plastic potential than adult SPCs; however, ethical concerns and their potential for unwanted and possibly dangerous continued growth and tumor formation limit their use. Recently, the generation of autologous pluripotent stem cells from skin fibroblasts was reported (109), thus avoiding the ethical and immunorejection problems. Since these cells were manipulated using viral vectors, a therapeutic application of these converted skin cells must be initialized by thorough safety studies. Other significant challenges for stem cell transplantation include optimizing the cell characteristics before grafting, reducing risks such as tumor formation, and developing adequate commercial-scale production technologies. Given these shortcomings of exogenous stem cell application, the existence of neural progenitor cells in the adult spinal cord (3, 95, 104), and approaches to regulate their numbers and fate may provide an alternative to transplantation. This article focuses on the potential utility of endogenous neural SPCs as substrates for structural repair after SCI. We review the biology and possible function of SPCs in the normal and injured adult spinal cord as well as strategies to manipulate these cells to replace lost neurons and glia.

Neural Progenitor Cells in the Intact Adult Spinal Cord

SPCs are dispersed widely throughout the adult CNS (for review, see Ref. 45). The presence of progenitor

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cells in the spinal cord displaying self-renewal and multipotent features was demonstrated in vitro more than a decade ago (95, 104). However, we know very little about the in situ location, activity, regulation, and function of adult spinal cord SPCs. Regarding the location of these cells in the intact adult spinal cord, it has been suggested that the neural stem cells reside in the white matter parenchyma (50, 77, 107) or close to the central canal, either in the ependyma (55, 74) or subependymally (70). Two models have been proposed regarding the location of these cells in the intact adult spinal cord (50), illustrating how dividing stem cells may give rise to progenitors that migrate and proliferate. In the first model, a slowly proliferating stem cell resides in the ependymal layer of the central canal (55, 74). These cells self-renew and under certain conditions divide asymmetrically with a daughter cell migrating to the outer circumference of the spinal cord, where it matures into a proliferative glial progenitor cell or a mature spinal cord glial cell. The second, alternative model suggests that both stem cells and glial progenitors may exist in the parenchyma of the spinal cord (107) and are independent of the proliferative ependyma. Most progenitor cells in the white matter of the adult spinal cord appear rather heterogenous, expressing one or several of the partly overlapping markers such as the chondroitin sulphate proteoglycan NG2 and the transcription factors Olig2 and Nkx2.2 (50, 77). Some of these cells represent multipotent stem cells and others more restricted glial progenitors being committed to the oligodendrocyte lineage (49). Ependymal cells self-renew in vivo but do not generate appreciable numbers of other cell types in the intact spinal cord (74). In this review, we will use the term SPCs for all of these proliferative cells.

In contrast to the subgranular zone (SGZ) of the hippocampus and the telencephalic subventricular zone (SVZ), where the capacity for neurogenesis is retained in vivo, the adult mammalian spinal cord is considered a nonneurogenic region. In nonpathological conditions, the dividing spinal cord progenitor cells are glial-restricted progenitor cells and give rise to oligodendrocytes and astrocytes but not neurons (50). In vitro expansion and characterization of SPCs, however, demonstrated that in vivo proliferating cells from the adult spinal cord have the ability to give rise to neurons in culture (107). Furthermore, cell transplantation studies have demonstrated that, although SPCs derived from spinal cord will differentiate into glial cells when re-implanted into the region of origin, they are able to give rise to neurons when grafted into the neurogenic hippocampus (94). These findings indicate that the neuronal differentiation in vitro is not a tissue culture artifact but reflect the multipotent differentiation potential of these cells. In addition, these results demonstrate that adult spinal cord SPCs are not intrinsically fate restricted but that environmental cues are able to instruct their fate choice. Elucidating the mechanisms controlling the generation of different neural cell types during embryonic and postnatal stages and understanding the complex interactions between neural SPCs and their microenvironment is a big challenge in the field of stem cell research. What are the environmental and intrinsic factors that regulate proliferation, migration, and differentiation of neural SPCs? The first cellular and molecular elements of the neurogenic stem cell niche in the adult CNS (SVZ, SGZ) were identified quite recently (for review, see Refs. 35, 65, 69). In both the SVZ and SGZ, endothelial cells are an essential component of the neurogenic niche (81, 93). The endothelial cells provide attachment for SPCs and generate a variety of signals that control stem cell self-renewal and lineage commitment. The properties of local astrocyte populations seem to play a major role in the creation of a neurogenic environment (11, 53, 66, 96). Later, we discuss how the environment may influence spinal cord progenitor cells following an injury. In general, a more thorough understanding of the in vivo regulation of progenitor cells in the intact adult spinal cord is necessary and will guide strategies for manipulating SPCs after injury or disease.

"Since many inflammatory regulators have been shown to influence SPCs, manipulations of the inflammatory response will also affect SPCs."

Neural Progenitor Cells After Spinal Cord Injury: Spontaneous Reactions of Endogenous Progenitor Cells

Traumatic SCI causes damage of neuronal and glial cells in and around the lesion site leading to disruption of neuronal circuitry and neurological dysfunction. The injury evolves in two major pathological stages: The primary injury involves mechanical cell and tissue damage, and the secondary injury results in a cascade of biochemical events that produce progressive destruction of the spinal cord tissue (13–15, 36, 90). It has been demonstrated that adult spinal cord SPCs are responsive to injury (49, 59, 68, 73, 76, 107, 108, 110). The insult-induced progenitor cell response comprises division, migration, and maturation of SPCs (for review, see Ref. 80). The temporal and spatial pattern of the SPC reaction and the potential function of these cells has been assessed by several research groups: After a contusive SCI in adult rodents, proliferation of cells expressing NG2 reaches a peak at 3 days (68, 110), stays markedly increased in the epicenter of the lesion over the first 2 wk, and declines to baseline levels by 4 wk after injury (73). Using 5-bromodeoxyuridine (BrdU) labeling in the

first week after injury, some of these dividing cells were shown to have differentiated into mature oligodendrocytes or astrocytes when the tissue was examined 5 wk later. Neuronal differentiation has rarely been found after SCI and only in cases of milder lesions, such as compression injury or cervical dorsal rhizotomy (59, 92, 100). However, this rarely observed neurogenesis in the adult spinal cord seems to be abortive since mature neuronal markers have never been described. Newly formed oligodendrocytes likely contribute to remyelination. The time course of NG2-positive cell proliferation parallels the time of demyelination and remyelination. Neither NG2-positive cell proliferation nor remyelination occurred when spinal cords previously lesioned by a chemical demyelination were irradiated, suggesting that NG2-positive cells are involved in the remyelination process (60, 73). Depending on injury severity, remyelination by oligodendrocytes usually begins by 14 days after injury (41, 44, 47, 73). By 1 mo post-SCI, most axons have been remyelinated, although the new myelin sheaths are thinner and shorter than those before injury (18, 42).

The normally limited proliferation of ependymal cells increases dramatically after SCI, followed by migration of ependyma-derived progeny toward the site of injury. Moreover, ependymal cells differentiate and give rise to a substantial proportion of scar-forming astrocytes as well as to some oligodendrocytes after SCI (74).

Also, in non-human primates following a hemisection of the cervical spinal cord, a subpopulation of newly dividing cells differentiates into remyelinating oligodendrocytes and astrocytes. No BrdU-positive cells were found co-expressing neuronal markers after a spinal cord transection injury (108).

In general, these results indicate that spinal cord SPCs are able to participate in spinal cord repair by supporting and participating in remyelination and possibly by replacing lost neurons. Despite their inherent plasticity, however, it is obvious that endogenous SPCs do not lead to complete recovery in cases of severe trauma, since most of the proliferating stem and progenitor cells fail to fully differentiate into mature phenotypes. Understanding the potential and limitations of the endogenous progenitor cells stimulated by SCI is necessary to develop therapeutic interventions to enhance functional repair after SCI.

Manipulating Stem/Progenitor Cells after SCI

Since it is known that SPCs derived from the adult spinal cord produce neurons and oligodendrocytes when transplanted into neurogenic regions like the hippocampus (94), it is obvious that the environment plays a pivotal role in the fate decision made by progenitor cells. Different approaches manipulating the spinal cord environment to instruct SPCs to adopt a neuronal or glial fate have been attempted over the last few years and will be described in this chapter and are summarized in FIGURE 2. Furthermore, we will discuss new approaches for manipulating the intact

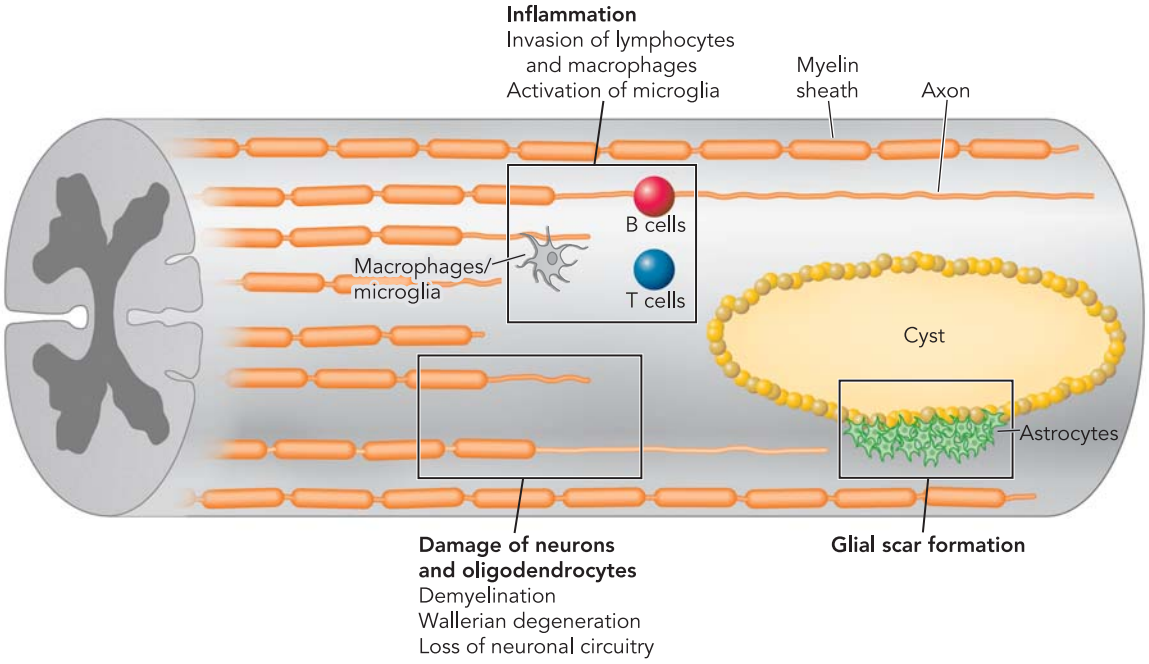

FIGURE 1. **Schematic drawing showing a SCI**
Many cells (neurons and oligodendrocytes) die immediately as well as progressively after SCI. Cysts often form after injury, and astrocytes form a glial scar. Many ascending and descending axons are interrupted by the injury and undergo Wallerian degeneration. Axons usually fail to regenerate. Inflammatory cells invade the CNS from the periphery, and resident microglia is activated. Cell debris is phagocytosed by macrophages.

Table 1. Summary of experimental approaches to modulate the behavior of neural progenitor cells

		Model	Effect	References
Cytokines	IL-6	Blockade of IL-6 receptors after SCI in adult mice	Inhibits astrogliosis and suppresses immune cell infiltration	77, 78
		TNF-α injection at the lateral ventricles of adult rats	Increases BrdU+ cells in the SVZ	104
	TNF-α	Demyelination by cuprizone in TNF-R1-/- and TNF-R2-/- adult mice	TNF-α promotes proliferation of oligodendrocyte progenitors through TNF-R2	7
		Status epilepticus in adult TNF-R1-/- and TNF-R2-/- mice	TNF-α controls neurogenesis via TNF-R1 in the hippocampus, minor effects via TNF-R2 signalling	52
	IL-1β	In vitro experiments using primary oligodendrocyte progenitors from postnatal rat	IL-1β inhibits proliferation and promotes differentiation of oligodendrocyte progenitors	98
	IL-4	Demyelination by cuprizone in IL-1β-/- adult mice	Reduced remyelination in the absence of IL-1β	71
		In vitro experiments using co-cultures of SVZ progenitors and primary microglia cultures from neonatal mice; stimulation of microglia with IL-4	IL-4 supports neuroprotection and neurogenesis; microglia stimulated with IL-4 induces a bias towards oligodendrogenesis	24
		In vitro experiments with embryonic neural mouse SPCs	LIF increases proliferation of SPCs	83
	LIF	Overexpression of LIF in the SVZ of adult mice	Increases proliferation of SPCs, reduces neurogenesis in the olfactory bulb and SVZ	12
		Systemic administration of LIF after SCI in adult mice	Increases proliferation of SPCs in the spinal cord	8
Growth factors	IGF-1	In vivo and in vitro experiments using IGF-1 in adult rat hippocampal SPCs	IGF-I increases proliferation	1, 2
			IGF-1 stimulates oligodendroglial differentiation of hippocampal SPCs via inhibition of BMP by up-regulation of Smad6, Smad7 and Noggin	51, 90
	BMP	Addition of BMP to cultured embryonic SVZ progenitors	Increases differentiation into astrocytes	43, 46
	BDNF	Overexpression of Noggin in combination with BDNF at the lateral ventricle in adult rats	Shift of astrocytic to neuronal differentiation in the striatum; new neurons also in septum, thalamus, and hypothalamus	27, 81
		In vivo and in vitro experiments with SPCs from embryonic and adult mice	BDNF stimulates production and survival of new neurons from SPCs in vitro, and in the rostral migratory stream	5, 17
		In vivo and in vitro experiments with spinal cord SPCs from adult rats	BDNF enhances neurogenesis of neurogenin2-positive spinal cord precursor cells	76
	FGF2 and EGF	Delivery of FGF-2 and EGF into lateral ventricle of adult rats	Enhances proliferation of SVZ progenitors located around the central canal of spinal cord	63, 70
		Focal demyelination of corpus callosum and overexpression of human EGF-Receptor in adult mice	Accelerated remyelination by NG2+/Mash1+/Olig2+ progenitors due to support of oligodendrocyte maturation, and functional recovery	4
	VEGF	In vitro and in vivo experiments with SVZ and hippocampal progenitors from embryonic mice and in adult rats	VEGF is involved in the induction of neurogenesis in the SVZ and the hippocampal SGZ	37, 54, 96
Transcription factors	Mash1 and Ngn2	Overexpression of Neurogenin2 (Ngn2) and Mash1, together with application of a mixture of growth factors containing BDNF, FGF2 and EGF after SCI in adult rats	Ngn2 and Mash1, together with BDNF, FGF2 and EGF, increase production of neurons and oligodendrocytes after SCI	76
	Olig2 and Mash1	Overexpression of Olig2 and Mash1 in cortical progenitor cultures from embryonic rats	Cooperation of both factors Olig2 and Mash2 is necessary for SPCs to develop into mature neurons	97
	YY-1	In vitro experiments with SVZ progenitor cultures and oligodendrocyte progenitor cultures from adult mice	Regulation of transition of oligodendrocyte progenitors from cell cycle exit to differentiation	48

and injured spinal cord environment based on reports describing factors influencing SPCs in other regions of the CNS (Table 1). The intrinsic program of the SPCs also has to be considered, especially since it became clear that diverse populations of SPCs exist, even within the same anatomical region such as the SVZ (75). The proposed factors specifying neural progenitors in a region-specific manner could be either environmental or intrinsic to the stem cells. In the last part of this review, we will evaluate approaches that target transcription factors to change the intrinsic profile of SPCs.

Manipulation of the stem cell environment

It was suggested that the properties of the local astrocyte populations play a major role in the creation of a neurogenic or gliogenic niche (11, 53, 66, 96), thus influencing differentiation of SPCs. In addition, astroglial cells may also support or restrict migration of SPCs depending on their developmental stage (62). Primary astrocytes isolated from neurogenic regions, such as the newborn and adult hippocampus as well as the newborn spinal cord, promoted neuronal differentiation of adult hippocampal SPCs, whereas astrocytes isolated from the nonneurogenic adult spinal cord did not (96). It was shown that astrocyte-derived Wnt is involved in the regulation of hippocampal neurogenesis (66). Functional characterization of candidate factors differentially expressed in neurogenesis-promoting and nonpromoting astrocytes indicated that two interleukins, interleukin-1β (IL-1β) and interleukin-6 (IL-6) promote neuronal differentiation of SPCs, whereas insulin-like growth factor binding protein 6 (IGFBP6) and the proteoglycan decorin inhibited it (11). Interestingly, these factors also play a role in the inflammatory response after SCI. Grafting SGZ astrocytes or injecting sonic hedgehog (shh) was found to be sufficient to induce neurogenesis in the nonneurogenic cortex of adult mice (53). How the environmental neural stem cell niche interacts with cytokines, growth factors, and the intracellular SPC program to influence SPC behavior remains to be investigated.

Manipulating inflammation has an influence on SPC proliferation and differentiation. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-6, IL-1α, and IL-1β are upregulated after SCI (83). Besides directing the immune response after injury, these cytokines, in particular TNF-α and IL-6, are expressed within minutes after SCI influence SPCs. In addition to its role during the immune response, TNF-α can stimulate proliferation and survival of oligodendrocyte and neuronal precursors as shown in vivo using TNF-RI and RII knockout mice (7, 52, 105). However, an aspect that has to be considered when interpreting these results is the altered immune response of TNF-RI/-II mice that lack the receptors of a key pro-inflammatory mediator. To obtain distinct information about the influence of TNF-α on neural SPCs, it is essential to create a neural SPC-specific knockdown of the TNF-α receptors in an in vivo model. Up until now, no data is available on whether TNF-α is able to directly influence SPCs after SCI.

The effects of IL-6 on SPCs after SCI have been studied by Okano and colleagues (78, 79). By inhibiting the signal transduction of IL-6 using the MR16-1 antibody against the IL-6 receptor, functional recovery in a mouse contusion injury model was improved (78). In the same study, in vitro differentiation assays showed that SPCs differentiated preferentially into astrocytes when incubated with IL-6. By blocking IL-6 using MR16-1, the differentiating process toward astrocytes was inhibited. In addition to the in vitro results, Okano and colleagues showed a decline in the number of newborn astrocytes in vivo by blocking IL-6 after SCI (78, 79). The astrogliosis-promoting effect of IL-6 in the injured spinal cord tissue and its neurogenic effect in the intact hippocampus indicates a context-dependent influence on SPCs.

IL-1β being remarkably upregulated in the adult spinal cord immediately after injury (83) is known to

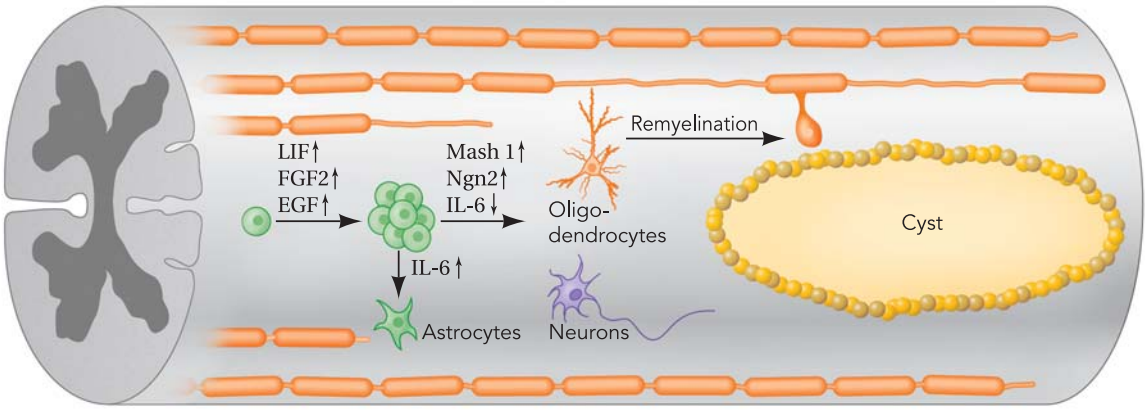

FIGURE 2. **Schematic drawing showing a SCI and published experimental manipulations influencing endogenous spinal cord progenitor cells**
The main goal of the different strategies published so far is to influence endogenous progenitors to help repair and recover after SCI by cell replacement, re-myelination, and supporting trophic factors.

be one of the key factors initiating the immune response and thereby inducing secondary neural damage. Neuroprotective approaches based on the inhibition of IL-1β have been tested in different laboratories and are extensively reviewed elsewhere (6). A direct influence of IL-1β on progenitor cells was shown by Vela and coworkers in vitro (99), suggesting that IL-1β inhibits proliferation of oligodendrocyte progenitors and promotes their differentiation. Mason and coworkers (71) suggested that IL-1β promotes remyelination after cuprizone treatment by inducing IGF-1 expression, which is known to promote the differentiation of oligodendrocyte progenitors.

The massive invasion of peripheral immune cells after SCI accompanied by the expression of proinflammatory cytokines not only induces secondary damage but has a major impact on neural SPCs. A series of reports from the group of Michal Schwartz suggests that T-cells may play a supportive role in neurogenesis. Schwartz' group showed that T-cell-mediated activation of residing microglia enhances the proliferative activity of progenitor cells in the hippocampus as well as in the SVZ (24). Depending on whether microglial cells are stimulated by the T helper cell 1 (Th1) released cytokine interferon (IFN-γ) or by IL-4 from Th2 cells, they differentially influence the fate choice of SPCs: microglia stimulated with IL-4 induced a bias toward oligodendrogenesis, whereas microglia stimulated with IFN-γ preferentially induced neurogenesis in co-cultured neural SPCs (24). Interestingly, IL-4 induced the expression of IGF-1 in microglia (23, 24), which is involved in neuroprotection and neurogenesis, as we will discuss below. T-cells with myelin specificity were shown to enhance neurogenesis in the hippocampus, SVZ, and, rather surprisingly, adult spinal cord (92). Nevertheless, a therapeutic application of autoimmune T-cells is very unlikely since T-cell-mediated autoimmune reactions have been associated with exacerbated demyelination, loss of neurons, and axonal pathology (57, 58).

Since many inflammatory regulators have been shown to influence SPCs, manipulations of the inflammatory response will also affect SPCs. To reduce the inflammatory response after SCI, the synthetic glucocorticoid methylprednisolone, having various immunosuppressive effects, is the only clinical therapy used currently (86). However, recent findings in our laboratory indicate that methylprednisolone not only affects the activation and proliferation of macrophages and microglia but also reduces the proliferation of endogenous SPCs in the injured spinal cord (our own unpublished results). The presence of the glucocorticoid and the mineralocorticoid receptor on adult spinal cord SPCs suggests a direct effect of the drug on these cells. On the other hand, as discussed above, the changed inflammatory environment also influences SPCs. Overall, the observed reduction in the amount of NG2-positive precursor cells after SCI and methylprednisolone treatment may lead to a reduced oligodendrocyte repair. These findings open the question to what extent a treatment with methylprednisolone after SCI limits the regeneration capacity of endogenous SPCs and suggest novel effects of this drug.

Activation of neural SPCs with growth factors. Different growth factors have been used to stimulate proliferation of endogenous progenitor cells and to influence their differentiation. Delivery of FGF-2 and EGF into the lateral ventricle enhanced the proliferation of progenitor cells in the SVZ (63) as well as the proliferation of endogenous progenitor cells located around the central canal of the spinal cord (70). Another candidate used for manipulation of neural SPCs is IGF-1. It was shown that IGF-I stimulates oligodendroglial differentiation of multipotent hippocampal SPCs via the inhibition of bone morphogenic protein (BMP) by upregulation of the BMP antagonists Smad6, Smad7, and Noggin (51). Furthermore, increased proliferative activity of hippocampal SPCs was demonstrated after treatment with IGF-I in vivo as well as in vitro (1, 2). In line with this observation, other groups showed a higher percentage of progenitor cells differentiating into astrocytes when BMP was experimentally increased (Table 1; Refs. 43, 46). Differentiation of neural precursor cells into neurons and oligodendrocytes after transplantation into spinal cord injured mice was demonstrated after inhibition of BMP signaling by Noggin (91). This was accompanied by functional recovery.

By overexpressing Noggin in combination with brain-derived neurotrophic factor (BDNF), the group of Goldman was able to shift the astrocytic into neuronal differentiation in the striatum, a region that is usually nonneurogenic (27, 82). It has also been demonstrated that BDNF stimulates the production and survival of new neurons from SPCs in vitro and in the rostral migratory stream (5, 17). BDNF-secreting fibroblasts grafted into SCI lesions enhance the number of BrdU-positive oligodendrocytes (72), but so far data on naive spinal cord progenitors is absent.

An acceleration of remyelination and functional recovery following focal demyelination of mouse corpus callosum has been shown by overexpression of human epidermal growth factor receptor (EGFR) in oligodendrocyte progenitors. The enhanced remyelination of the lesion by $NG2^+/Mash1^+/Olig2^+$ progenitor cells indicates that EGFR overexpression promotes oligodendrocyte maturation (4). Up until now, no data are available describing the effects of EGFR on SPCs in the spinal cord.

It has previously been reported that angiogenesis has an impact on neurogenesis in the CNS, and similar factors and mechanisms seem to be involved in both processes (67, 81, 102). Endothelial cells are likely to influence neural SPCs through the secretion of vascular endothelial growth factor (VEGF) and BDNF

(5, 11, 93, 106), and this observation has led to the hypothesis of a neurovascular niche (81, 106). VEGF as one of the components found in a neurovascular niche has been reported to influence SPCs in several ways (Table 1; Refs. 101, 111). The most important one in terms of a possible application after SCI is based on observations made in the SVZ and SGZ where VEGF was shown to be involved in the induction of neurogenesis (37, 54, 88, 97). The influence of VEGF on spinal cord SPCs has not been investigated so far.

Another factor that has been used to experimentally manipulate neural SPCs is leukemia inhibitory factor (LIF). Similar to VEGF, LIF has also been described to influence differentiation and proliferation of SPCs in various ways and in different models (Table 1; Refs. 56, 61, 87) and has been demonstrated to enhance the self renewal capacity of neural SPCs (12, 84). Evidence for a similar effect of LIF on spinal cord SPCs when administered systemically after SCI was suggested by an increased number of nestin-positive cells (8). Whether LIF can be used to increase the endogenous SPC pool in the adult spinal cord after injury followed by a directed differentiation of these cells needs to be demonstrated.

Manipulation of transcription factors involved in neural SPC behavior

As discussed above, a manipulation of the environment with its multiplicity of different factors controlling proliferation and differentiation of neural SPCs is critical for future therapeutic approaches based on endogenous stem cells. On the other hand, the manipulation of the environment may have undesired side effects, which have to be carefully assessed. Direct targeting of the intracellular program of SPCs, in addition to or instead of environmental manipulations, seems to be very promising.

Ohori and colleagues directly targeted transcription factors responsible for fate decision in SPCs after SCI (77). They show that a retroviral-mediated overexpression of the two basic helix-loop helix transcription factors, neurogenin2 (Ngn2) and Mash-1, together with the application of a mixture of growth factors containing BDNF, FGF-2, and EGF enhanced the production of new neurons and oligodendrocytes after SCI, respectively (FIGURE 2). However, the observed new oligodendrocytes and neurons disappeared after a few weeks, indicating that they have not been integrated. The role of Olig2 and Mash-1 was also analyzed in vitro demonstrating that the cooperation of both factors is necessary for SPCs to develop into mature neurons (98). The number of reports describing transcription factors responsible for directing neural SPCs into a certain lineage is constantly growing. A recently published transcription factor responsible for oligodendrocyte differentiation is Yin Yang 1 (YY-1) (48). After cell cycle exit, YY-1 regulates early stages of oligodendrocyte differentiation and, therefore, represents an attractive target for manipulating SPCs toward an oligodendrocyte fate. Another family of transcription factors involved in proliferation and differentiation of SPCs in the developing as well as in the adult CNS is the Sox family, which has been reviewed extensively elsewhere (103).

One of the remaining questions when targeting transcription factors in SPCs is which tools one can use to manipulate intrinsic factors in the correct target cells. Currently, retroviral vectors are the method of choice in experimental models. However, whether these tools can be used in a clinical setting remains to be investigated. Even if one succeeds in changing the fate of SPCs after SCI toward a neuronal and/or oligodendroglial fate, a functional integration of these newly formed cells into the spinal cord needs to be achieved. Thus we need to find out whether manipulation of transcription factors in neural SPCs eventually leads to enhanced functional recovery after SCI.

Conclusion

SCI represents a complex event with a multifaceted pathophysiology. Therefore, effective therapeutic strategies will require a combination of interventions. Here, we focus on the role stem cells may play in promoting tissue repair and behavioral recovery. Most of the present experimental approaches using stem cells in SCI models focus on SPC grafts. Transplanted SPCs may bridge the lesion site, providing a substrate for sprouting fibers, deliver trophic factors, and replace lost neurons or oligodendrocytes. Experimentally, SPC transplants can be genetically engineered to instruct a specific fate choice before grafting. Although many of these approaches have led to functional recovery in animal SCI models, they will not easily be adopted for therapies in SCI patients because of the risk of tumor formation and immune rejection. Thus the long-term goal will be to recruit endogenous SPCs after spinal cord trauma. Currently, steady progress is being made in understanding the biology of endogenous SPCs and their microenvironment. This knowledge will eventually pave the way for therapeutic applications. Combined therapies modulating the SPC niche as well as the intrinsic program of SPCs could well lead to improved recovery of SCI patients in the future. ■

We thank Drs. Dana Dodd, Michelle Starkey, Olivier Raineteau, and Sebastian Jessberger for critical comments on the manuscript.

Our work is supported by the Swiss National Foundation and the Christopher and Dana Reeve Foundation. Franz Obermair received a scholarship through EU FP6 Marie Curie Actions Early Stage Training (EST) Cooperation in Research and Training for European Excellence in the Neurosciences.

References

1. Aberg MA, Aberg ND, Hedbacker H, Oscarsson J, Eriksson PS. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. *J Neurosci* 20: 2896–2903, 2000.
2. Aberg MA, Aberg ND, Palmer TD, Alborn AM, Carlsson-Skwirut C, Bang P, Rosengren LE, Olsson T, Gage FH, Eriksson PS. IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. *Mol Cell Neurosci* 24: 23–40, 2003.
3. Adrian EK Jr, Walker BE. Incorporation of thymidine-H3 by cells in normal and injured mouse spinal cord. *J Neuropathol Exp Neurol* 21: 597–609, 1962.
4. Aguirre A, Dupree JL, Mangin JM, Gallo V. A functional role for EGFR signaling in myelination and remyelination. *Nat Neurosci* 10: 990–1002, 2007.
5. Ahmed S, Reynolds BA, Weiss S. BDNF enhances the differentiation but not the survival of CNS stem cell-derived neuronal precursors. *J Neurosci* 15: 5765–5778, 1995.
6. Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. *Nat Rev Immunol* 5: 629–640, 2005.
7. Arnett HA, Mason J, Marino M, Suzuki K, Matsushima GK, Ting JP. TNF alpha promotes proliferation of oligodendrocyte progenitors and remyelination. *Nat Neurosci* 4: 1116–1122, 2001.
8. Azari MF, Profyris C, Zang DW, Petratos S, Cheema SS. Induction of endogenous neural precursors in mouse models of spinal cord injury and disease. *Eur J Neurol* 12: 638–648, 2005.
9. Barbeau H, Rossignol S. Enhancement of locomotor recovery following spinal cord injury. *Curr Opin Neurol* 7: 517–524, 1994.
10. Bareyre FM. Neuronal repair and replacement in spinal cord injury. *J Neurol Sci* 265: 63–72, 2008.
11. Barkho BZ, Song H, Aimone JB, Smrt RD, Kuwabara T, Nakashima K, Gage FH, Zhao X. Identification of astrocyte-expressed factors that modulate neural stem/progenitor cell differentiation. *Stem Cells Dev* 15: 407–421, 2006.
12. Bauer S, Patterson PH. Leukemia inhibitory factor promotes neural stem cell self-renewal in the adult brain. *J Neurosci* 26: 12089–12099, 2006.
13. Beattie MS. Inflammation and apoptosis: linked therapeutic targets in spinal cord injury. *Trends Mol Med* 10: 580–583, 2004.
14. Beattie MS, Hermann GE, Rogers RC, Bresnahan JC. Cell death in models of spinal cord injury. *Prog Brain Res* 137: 37–47, 2002.
15. Beattie MS, Li Q, Bresnahan JC. Cell death and plasticity after experimental spinal cord injury. *Prog Brain Res* 128: 9–21, 2000.
16. Becker D, Sadowsky CL, McDonald JW. Restoring function after spinal cord injury. *Neurologist* 9: 1–15, 2003.
17. Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. *J Neurosci* 21: 6718–6731, 2001.
18. Blakemore WF. Pattern of remyelination in the CNS. *Nature* 249: 577–578, 1974.
19. Bracken MB. Methylprednisolone and acute spinal cord injury: an update of the randomized evidence. *Spine* 26: 47–54, 2001.
20. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, Eisenberg HM, Flamm E, Leo-Summers L, Maroon J, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med* 322: 1405–1411, 1990.
21. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings MG, Herr DL, Hitchon PW, Marshall LF, Nockels RP, Pascale V, Perot PL Jr, Piepmeier J, Sonntag VK, Wagner F, Wilberger JE, Winn HR, Young W. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. *J Neurosurg* 89: 699–706, 1998.
22. Bunge MB. Bridging areas of injury in the spinal cord. *Neuroscientist* 7: 325–339, 2001.
23. Butovsky O, Talpalar AE, Ben-Yaakov K, Schwartz M. Activation of microglia by aggregated beta-amyloid or lipopolysaccharide impairs MHC-II expression and renders them cytotoxic whereas IFN-gamma and IL-4 render them protective. *Mol Cell Neurosci* 29: 381–393, 2005.
24. Butovsky O, Ziv Y, Schwartz A, Landa G, Talpalar AE, Pluchino S, Martino G, Schwartz M. Microglia activated by IL-4 or IFN-gamma differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. *Mol Cell Neurosci* 31: 149–160, 2006.
25. Carulli D, Laabs T, Geller HM, Fawcett JW. Chondroitin sulfate proteoglycans in neural development and regeneration. *Curr Opin Neurobiol* 15: 116–120, 2005.
26. Cheng H, Cao Y, Olson L. Spinal cord repair in adult paraplegic rats: partial restoration of hind limb function. *Science* 273: 510–513, 1996.
27. Chmielnicki E, Benraiss A, Economides AN, Goldman SA. Adenovirally expressed noggin and brain-derived neurotrophic factor cooperate to induce new medium spiny neurons from resident progenitor cells in the adult striatal ventricular zone. *J Neurosci* 24: 2133–2142, 2004.
28. Coleman WP, Benzel D, Cahill DW, Ducker T, Geisler F, Green B, Gropper MR, Goffin J, Madsen PW 3rd, Maiman DJ, Ondra SL, Rosner M, Sasso RC, Trost GR, Zeidman S. A critical appraisal of the reporting of the National Acute Spinal Cord Injury Studies (II and III) of methylprednisolone in acute spinal cord injury. *J Spinal Disord* 13: 185–199, 2000.
29. Coutts M, Keirstead HS. Stem cells for the treatment of spinal cord injury. *Exp Neurol* 209: 368–377, 2007.
30. Cummings BJ, Uchida N, Tamaki SJ, Salazar DL, Hooshmand M, Summers R, Gage FH, Anderson AJ. Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. *Proc Natl Acad Sci USA* 102: 14069–14074, 2005.
31. David S, Aguayo AJ. Axonal elongation into peripheral nervous system "bridges" after central nervous system injury in adult rats. *Science* 214: 931–933, 1981.
32. Dietz V, Colombo G, Jensen L. Locomotor activity in spinal man. *Lancet* 344: 1260–1263, 1994.
33. Dietz V, Harkema SJ. Locomotor activity in spinal cord-injured persons. *J Appl Physiol* 96: 1954–1960, 2004.
34. Dietz V, Wirz M, Curt A, Colombo G. Locomotor pattern in paraplegic patients: training effects and recovery of spinal cord function. *Spinal Cord* 36: 380–390, 1998.
35. Doetsch F. A niche for adult neural stem cells. *Curr Opin Genet Dev* 13: 543–550, 2003.
36. Dumont RJ, Okonkwo DO, Verma S, Hurlbert RJ, Boulos PT, Ellegala DB, Dumont AS. Acute spinal cord injury, part I: pathophysiologic mechanisms. *Clin Neuropharmacol* 24: 254–264, 2001.
37. Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ, Palmer TD. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci* 18: 2803–2812, 2003.
38. Faden AI, Stoica B. Neuroprotection: challenges and opportunities. *Arch Neurol* 64: 794–800, 2007.
39. Fehlings MG, Baptiste DC. Current status of clinical trials for acute spinal cord injury. *Injury* 36, *Suppl* 2: 113–122, 2005.
40. Fournier AE, Strittmatter SM. Repulsive factors and axon regeneration in the CNS. *Curr Opin Neurobiol* 11: 89–94, 2001.
41. Gledhill RF, Harrison BM, McDonald WI. Pattern of remyelination in the CNS. *Nature* 244: 443–444, 1973.
42. Gledhill RF, McDonald WI. Morphological characteristics of central demyelination and remyelination: a single-fiber study. *Ann Neurol* 1: 552–560, 1977.
43. Gomes WA, Mehler MF, Kessler JA. Transgenic overexpression of BMP4 increases astroglial and decreases oligodendroglial lineage commitment. *Dev Biol* 255: 164–177, 2003.
44. Griffiths IR, McCulloch MC. Nerve fibres in spinal cord impact injuries. Part 1. Changes in the myelin sheath during the initial 5 weeks. *J Neurol Sci* 58: 335–349, 1983.
45. Gross CG. Neurogenesis in the adult brain: death of a dogma. *Nat Rev Neurosci* 1: 67–73, 2000.
46. Gross RE, Mehler MF, Mabie PC, Zang Z, Santschi L, Kessler JA. Bone morphogenetic proteins promote astroglial lineage commitment by mammalian subventricular zone progenitor cells. *Neuron* 17: 595–606, 1996.
47. Harrison BM, McDonald WI. Remyelination after transient experimental compression of the spinal cord. *Ann Neurol* 1: 542–551, 1977.
48. He Y, Dupree J, Wang J, Sandoval J, Li J, Liu H, Shi Y, Nave KA, Casaccia-Bonnefil P. The transcription factor Yin Yang 1 is essential for oligodendrocyte progenitor differentiation. *Neuron* 55: 217–230, 2007.
49. Horky LL, Galimi F, Gage FH, Horner PJ. Fate of endogenous stem/progenitor cells following spinal cord injury. *J Comp Neurol* 498: 525–538, 2006.
50. Horner PJ, Power AE, Kempermann G, Kuhn HG, Palmer TD, Winkler J, Thal LJ, Gage FH. Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. *J Neurosci* 20: 2218–2228, 2000.
51. Hsieh J, Aimone JB, Kaspar BK, Kuwabara T, Nakashima K, Gage FH. IGF-I instructs multipotent adult neural progenitor cells to become oligodendrocytes. *J Cell Biol* 164: 111–122, 2004.
52. Iosif RE, Ekdahl CT, Ahlenius H, Pronk CJ, Bonde S, Kokaia Z, Jacobsen SE, Lindvall O. Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis. *J Neurosci* 26: 9703–9712, 2006.
53. Jiao J, Chen DF. Induction of neurogenesis in nonconventional neurogenic regions of the adult central nervous system by niche astrocyte-produced signals. *Stem Cells* 26: 1221–1230, 2008.
54. Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. *Proc Natl Acad Sci USA* 99: 11946–11950, 2002.
55. Johansson CB, Momma S, Clarke DL, Risling M, Lendahl U, Frisen J. Identification of a neural stem cell in the adult mammalian central nervous system. *Cell* 96: 25–34, 1999.
56. Johe KK, Hazel TG, Muller T, Dugich-Djordjevic MM, McKay RD. Single factors direct the differentiation of stem cells from the fetal and adult central nervous system. *Genes Dev* 10: 3129–3140, 1996.
57. Jones TB, Ankeny DP, Guan Z, McGaughy V, Fisher LC, Basso DM, Popovich PG. Passive or active immunization with myelin basic protein impairs neurological function and exacerbates neuropathology after spinal cord injury in rats. *J Neurosci* 24: 3752–3761, 2004.

58. Jones TB, Basso DM, Sodhi A, Pan JZ, Hart RP, MacCallum RC, Lee S, Whitacre CC, Popovich PG. Pathological CNS autoimmune disease triggered by traumatic spinal cord injury: implications for autoimmune vaccine therapy. *J Neurosci* 22: 2690–2700, 2002.

59. Ke Y, Chi L, Xu R, Luo C, Gozal D, Liu R. Early response of endogenous adult neural progenitor cells to acute spinal cord injury in mice. *Stem Cells* 24: 1011–1019, 2006.

60. Keirstead HS, Levine JM, Blakemore WF. Response of the oligodendrocyte progenitor cell population (defined by NG2 labelling) to demyelination of the adult spinal cord. *Glia* 22: 161–170, 1998.

61. Koblar SA, Turnley AM, Classon BJ, Reid KL, Ware CB, Cheema SS, Murphy M, Bartlett PF. Neural precursor differentiation into astrocytes requires signaling through the leukemia inhibitory factor receptor. *Proc Natl Acad Sci USA* 95: 3178–3181, 1998.

62. Kornyei Z, Szlavik V, Szabo B, Gocza E, Czirok A, Madarasz E. Humoral and contact interactions in astroglia/stem cell co-cultures in the course of glia-induced neurogenesis. *Glia* 49: 430–444, 2005.

63. Kuhn HG, Winkler J, Kempermann G, Thal LJ, Gage FH. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. *J Neurosci* 17: 5820–5829, 1997.

64. Lepore AC, Fischer I. Lineage-restricted neural precursors survive, migrate, and differentiate following transplantation into the injured adult spinal cord. *Exp Neurol* 194: 230–242, 2005.

65. Li L, Xie T. Stem cell niche: structure and function. *Annu Rev Cell Dev Biol* 21: 605–631, 2005.

66. Lie DC, Colamarino SA, Song HJ, Desire L, Mira H, Consiglio A, Lein ES, Jessberger S, Lansford H, Dearie AR, Gage FH. Wnt signalling regulates adult hippocampal neurogenesis. *Nature* 437: 1370–1375, 2005.

67. Louissaint A Jr, Rao S, Leventhal C, Goldman SA. Coordinated interaction of neurogenesis and angiogenesis in the adult songbird brain. *Neuron* 34: 945–960, 2002.

68. Lytle JM, Wrathall JR. Glial cell loss, proliferation and replacement in the contused murine spinal cord. *Eur J Neurosci* 25: 1711–1724, 2007.

69. Ma DK, Ming GL, Song H. Glial influences on neural stem cell development: cellular niches for adult neurogenesis. *Curr Opin Neurobiol* 15: 514–520, 2005.

70. Martens DJ, Seaberg RM, van der Kooy D. In vivo infusions of exogenous growth factors into the fourth ventricle of the adult mouse brain increase the proliferation of neural progenitors around the fourth ventricle and the central canal of the spinal cord. *Eur J Neurosci* 16: 1045–1057, 2002.

71. Mason JL, Suzuki K, Chaplin DD, Matsushima GK. Interleukin-1beta promotes repair of the CNS. *J Neurosci* 21: 7046–7052, 2001.

72. McTigue DM, Horner PJ, Stokes BT, Gage FH. Neurotrophin-3 and brain-derived neurotrophic factor induce oligodendrocyte proliferation and myelination of regenerating axons in the contused adult rat spinal cord. *J Neurosci* 18: 5354–5365, 1998.

73. McTigue DM, Wei P, Stokes BT. Proliferation of NG2-positive cells and altered oligodendrocyte numbers in the contused rat spinal cord. *J Neurosci* 21: 3392–3400, 2001.

74. Meletis K, Barnabe-Heider F, Carlen M, Evergren E, Tomilin N, Shupliakov O, Frisen J. Spinal cord injury reveals multilineage differentiation of ependymal cells. *PLoS Biol* 6: e182, 2008.

75. Merkle FT, Mirzadeh Z, Alvarez-Buylla A. Mosaic organization of neural stem cells in the adult brain. *Science* 317: 381–384, 2007.

76. Mothe AJ, Tator CH. Proliferation, migration, and differentiation of endogenous ependymal region stem/progenitor cells following minimal spinal cord injury in the adult rat. *Neuroscience* 131: 177–187, 2005.

77. Ohori Y, Yamamoto S, Nagao M, Sugimori M, Yamamoto N, Nakamura K, Nakafuku M. Growth factor treatment and genetic manipulation stimulate neurogenesis and oligodendrogenesis by endogenous neural progenitors in the injured adult spinal cord. *J Neurosci* 26: 11948–11960, 2006.

78. Okada S, Nakamura M, Mikami Y, Shimazaki T, Mihara M, Ohsugi Y, Iwamoto Y, Yoshizaki K, Kishimoto T, Toyama Y, Okano H. Blockade of interleukin-6 receptor suppresses reactive astrogliosis and ameliorates functional recovery in experimental spinal cord injury. *J Neurosci Res* 76: 265–276, 2004.

79. Okano H, Okada S, Nakamura M, Toyama Y. Neural stem cells and regeneration of injured spinal cord. *Kidney Int* 68: 1927–1931, 2005.

80. Okano H, Sakaguchi M, Ohki K, Suzuki N, Sawamoto K. Regeneration of the central nervous system using endogenous repair mechanisms. *J Neurochem* 102: 1459–1465, 2007.

81. Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol* 425: 479–494, 2000.

82. Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. *J Neurosci* 21: 6706–6717, 2001.

83. Pineau I, Lacroix S. Proinflammatory cytokine synthesis in the injured mouse spinal cord: multiphasic expression pattern and identification of the cell types involved. *J Comp Neurol* 500: 267–285, 2007.

84. Pitman M, Emery B, Binder M, Wang S, Butzkueven H, Kilpatrick TJ. LIF receptor signaling modulates neural stem cell renewal. *Mol Cell Neurosci* 27: 255–266, 2004.

85. Richardson PM, Issa VM, Aguayo AJ. Regeneration of long spinal axons in the rat. *J Neurocytol* 13: 165–182, 1984.

86. Rozet I. Methylprednisolone in acute spinal cord injury: is there any other ethical choice? *J Neurosurg Anesthesiol* 20: 137–139, 2008.

87. Satoh M, Yoshida T. Promotion of neurogenesis in mouse olfactory neuronal progenitor cells by leukemia inhibitory factor in vitro. *Neurosci Lett* 225: 165–168, 1997.

88. Schanzer A, Wachs FP, Wilhelm D, Acker T, Cooper-Kuhn C, Beck H, Winkler J, Aigner L, Plate KH, Kuhn HG. Direct stimulation of adult neural stem cells in vitro and neurogenesis in vivo by vascular endothelial growth factor. *Brain Pathol* 14: 237–248, 2004.

89. Schwab ME. Nogo and axon regeneration. *Curr Opin Neurobiol* 14: 118–124, 2004.

90. Schwab ME, Bartholdi D. Degeneration and regeneration of axons in the lesioned spinal cord. *Physiol Rev* 76: 319–370, 1996.

91. Setoguchi T, Nakashima K, Takizawa T, Yanagisawa M, Ochiai W, Okabe M, Yone K, Komiya S, Taga T. Treatment of spinal cord injury by transplantation of fetal neural precursor cells engineered to express BMP inhibitor. *Exp Neurol* 189: 33–44, 2004.

92. Shechter R, Ziv Y, Schwartz M. New GABAergic interneurons supported by myelin-specific T cells are formed in intact adult spinal cord. *Stem Cells* 25: 2277–2282, 2007.

93. Shen Q, Goderie SK, Jin L, Karanth N, Sun Y, Abramova N, Vincent P, Pumiglia K, Temple S. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. *Science* 304: 1338–1340, 2004.

94. Shihabuddin LS, Horner PJ, Ray J, Gage FH. Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. *J Neurosci* 20: 8727–8735, 2000.

95. Shihabuddin LS, Ray J, Gage FH. FGF-2 is sufficient to isolate progenitors found in the adult mammalian spinal cord. *Exp Neurol* 148: 577–586, 1997.

96. Song H, Stevens CF, Gage FH. Astroglia induce neurogenesis from adult neural stem cells. *Nature* 417: 39–44, 2002.

97. Sun Y, Jin K, Childs JT, Xie L, Mao XO, Greenberg DA. Vascular endothelial growth factor-B (VEGFB) stimulates neurogenesis: evidence from knockout mice and growth factor administration. *Dev Biol* 289: 329–335, 2006.

98. Uchida Y, Nakano S, Gomi F, Takahashi H. Differential regulation of basic helix-loop-helix factors Mash1 and Olig2 by beta-amyloid accelerates both differentiation and death of cultured neural stem/progenitor cells. *J Biol Chem* 282: 19700–19709, 2007.

99. Vela JM, Molina-Holgado E, Arevalo-Martin A, Almazan G, Guaza C. Interleukin-1 regulates proliferation and differentiation of oligodendrocyte progenitor cells. *Mol Cell Neurosci* 20: 489–502, 2002.

100. Vessal M, Aycock A, Garton MT, Ciferri M, Darian-Smith C. Adult neurogenesis in primate and rodent spinal cord: comparing a cervical dorsal rhizotomy with a dorsal column transection. *Eur J Neurosci* 26: 2777–2794, 2007.

101. Wada T, Haigh JJ, Ema M, Hitoshi S, Chaddah R, Rossant J, Nagy A, van der Kooy D. Vascular endothelial growth factor directly inhibits primitive neural stem cell survival but promotes definitive neural stem cell survival. *J Neurosci* 26: 6803–6812, 2006.

102. Ward NL, Lamanna JC. The neurovascular unit and its growth factors: coordinated response in the vascular and nervous systems. *Neurol Res* 26: 870–883, 2004.

103. Wegner M, Stolt CC. From stem cells to neurons and glia: a Soxist's view of neural development. *Trends Neurosci* 28: 583–588, 2005.

104. Weiss S, Dunne C, Hewson J, Wohl C, Wheatley M, Peterson AC, Reynolds BA. Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. *J Neurosci* 16: 7599–7609, 1996.

105. Wu JP, Kuo JS, Liu YL, Tzeng SF. Tumor necrosis factor-alpha modulates the proliferation of neural progenitors in the subventricular/ventricular zone of adult rat brain. *Neurosci Lett* 292: 203–206, 2000.

106. Wurmser AE, Palmer TD, Gage FH. Neuroscience. Cellular interactions in the stem cell niche. *Science* 304: 1253–1255, 2004.

107. Yamamoto S, Yamamoto N, Kitamura T, Nakamura K, Nakafuku M. Proliferation of parenchymal neural progenitors in response to injury in the adult rat spinal cord. *Exp Neurol* 172: 115–127, 2001.

108. Yang H, Lu P, McKay HM, Bernot T, Keirstead H, Steward O, Gage FH, Edgerton VR, Tuszynski MH. Endogenous neurogenesis replaces oligodendrocytes and astrocytes after primate spinal cord injury. *J Neurosci* 26: 2157–2166, 2006.

109. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukvin II, Thomson JA. Induced pluripotent stem cell lines derived from human somatic cells. *Science* 318: 1917–1920, 2007.

110. Zai LJ, Wrathall JR. Cell proliferation and replacement following contusive spinal cord injury. *Glia* 50: 247–257, 2005.

111. Zhang H, Vutskits L, Pepper MS, Kiss JZ. VEGF is a chemoattractant for FGF-2-stimulated neural progenitors. *J Cell Biol* 163: 1375–1384, 2003.