Biochemical and Biophysical Research Communications 446 (2014) 830–835

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Sox11 promotes endogenous neurogenesis and locomotor recovery in mice spinal cord injury

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ARTICLE INFO

Article history:
Received 17 February 2014
Available online 28 February 2014

Keywords:
Sox11
Neural stem cell
Neurogenesis
Spinal cord injury
BDNF

ABSTRACT

We introduced a lentiviral vector containing the Sox11 gene into injured spinal cords of mice to evaluate the therapeutic potential of Sox11 in spinal cord injury. Sox11 markedly improved locomotor recovery after spinal cord injury and this recovery was accompanied by an up-regulation of Nestin/Doublecortin expression in the injured spinal cord. Sox11 was mainly located in endogenous neural stem cells lining the central canal and in newly-generated neurons in the spinal cord. In addition, Sox 11 significantly induced expressions of BDNF in the spinal cords of LV-Sox11-treated mice. We concluded that Sox11 induced activation of endogenous neural stem cells into neuronal determination and migration within the injured spinal cord. The resultant increase of BDNF at the injured site might form a distinct neurogenic niche which induces a final neuronal differentiation of these neural stem cells. Enhancing Sox11 expression to induce neurogenic differentiation of endogenous neural stem cells after injury may be a promising strategy in restorative therapy after SCI in mammals.

1. Introduction

In mammals, the central nervous system (CNS) is sensitive to mechanical injuries that cause permanent functional deficits. Mechanical forces imparted to the spinal cord can produce an immediate disruption of the tissue, with direct axonal and neuronal injury leading to neuronal death. Neuronal death may occur until hours or days after spinal cord injury (SCI) as a result of ensuing secondary pathological processes. Although a number of strategies have been applied to protect injured spinal cords from secondary pathological processes and promote neuronal survival and synaptic plasticity, no fully restorative therapies currently exist for mammalian SCI [1,2]. Over the past few decades, the discovery of endogenous multipotent stem cell populations in specialized niches of the adult CNS has fueled interest in regenerative therapies based on the recruitment of endogenous stem or progenitor cells [3,4]. Investigations with neural stem cells (NSCs) have revealed that endogenous adult spinal cord NSCs can facilitate functional recovery but normally fail to do so efficiently. Accordingly, information regarding the modulation of endogenous NSCs to promote functional recovery would greatly enhance the potential for optimizing regenerative neurogenesis in mammals.

The Sox family of transcription factors is well-established regulators of cell fate decisions and are expressed in a tissue-specific manner during development [5,6]. In specific, Sox11 is mainly involved in neural development and organogenesis during fetal life and functions in neural progenitor cells that have already been committed to neuronal differentiation during neural development [7,8]. With development, Sox11 expression decreases and is absent from most normal adult tissues [9]. However, it has been reported that Sox11 expression continues in neurogenic areas of the adult brain [10]. While the exact role of Sox 11 in the adult is not known, there are data demonstrating that Sox11 is up-regulated after neural injury/disease and plays an important role in regeneration [11]. Recently, it has been shown that human glioma-initiating cells lose Sox11 expression and over-expression of Sox11 suppresses tumourigenicity by inducing neuronal differentiation [12]. Based on these findings, we hypothesized that Sox11 might have a modulating role upon endogenous NSCs during regeneration after SCI of mice.

The gene transfer for therapeutic purposes offers a valuable approach for the treatment of SCI. Recombinant lentiviral vectors have proved to be superior to other vectors with regard to gene transfer as they not only provide long-term expression of the ther-

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http://dx.doi.org/10.1016/j.bbrc.2014.02.103
0006-291X/

apeutic gene, but also serve as an efficient transducer of non-dividing cells such as neurons [13]. Therefore, in the present study, we introduced a lentiviral vector containing the Sox11 gene into injured spinal cords of mice to evaluate their therapeutic potential for the treatment of SCI.

2. Materials and methods

2.1. Animals

Thirty-six female Kunming mice, weighing 30 ± 5 g, were obtained from the Laboratory Animal Center of Shandong University. Mice were bred and housed under standard laboratory conditions at 23 °C with an alternating 12 h light and dark cycle and free access to a commercial diet. All animal experiments were approved by the Shandong University Animal Care Committee.

2.2. Lentiviral vectors (LV) vector production

A CD511B (System Biosciences, San Francisco, USA) lentivirus vector expressing enhanced green fluorescent protein (GFP) was constructed to express Sox11 in mice spinal cord. The genome of the recombinant viral vector consisted of the short version (530 bp) of the murine cytomegalovirus early promoter (CMV promoter). As a control, an empty CD511B lentivirus vector expressing enhanced GFP was constructed. Vectors were transfected into 293TN cells (System Biosciences) using pPACKF1 Packaging Plasmid Mix (System Biosciences) and purified by ultracentrifugation. Genome titres were determined by UltraRapid Lentiviral Global Titering Kit (System Biosciences).

2.3. Spinal cord injury

Spinal cord hemisection was performed as described previously [14,15]. Briefly, mice were anesthetized with 10% chloral hydrate. Dorsal laminectomy was performed to expose segments T9–T11 of the spinal cord using a superficial vein at T5–T6 as a landmark. The dura was slit (1 mm) at the midline at the T10 level. A complete hemisection of the right hemicord at T10 was performed with the tip of iridectomy scissors. After surgery, the muscles and skin were sutured in layers and an antibiotic (Gentamicin, 1000u) was administered. Paralysis of right hind limb, as observed at 1d after spinal cord hemisection, indicated that the model was successful. Each mouse received manual bladder manipulation twice daily until the recovery of sphincter control. The viral constructs (LV-Sox11 or LV-GFP 8.68×10^5 transducing units in 1 μl) were injected into the lesion site [16].

The thirty-six mice were divided into two subgroups, an LV-GFP and LV-Sox11 group. At 1, 2 and 3 weeks after spinal cord hemisection, three mice for immunohistochemical staining and three mice for Western blot. The animals were assessed for motor function at specific time points post-SCI, and subsequently sacrificed for histological or biochemical measurements.

2.4. Behavioral tests

The Basso Mouse Scale (BMS) for locomotion was used to assess the degree of motor dysfunction after SCI [17]. All mice were gently handled and allowed to walk in an open-field to acclimatize them to the apparatus for several days before induction of SCI. The mice were tested before injury, to ensure that they demonstrated equivalent baseline scores. On each post-SCI day, the mice were observed for 4 min by 2 independent observers who were blind as to the treatment group. Scores were assigned for each hindlimb and averaged for each day. The data analyses were performed on these means.

2.5. Tissue processing

Mice were perfused transcardially with ice-cold 4% paraformaldehyde in 0.1 M phosphate buffer (pH = 7.2) at 1, 2 and 3 weeks after spinal cord hemisection. The spinal cords were removed and post-fixed in the same fixative. Fifteen-micrometer sections were prepared on a cryostat. Longitudinal section was made in order to show the structure of injured spinal cord well.

2.6. Immunofluorescence staining and double immunofluorescence staining

To examine the expression of Sox11 in the injured spinal cord, immunofluorescence staining was performed. Immunofluorescence staining was performed following standard methods. The sections were subjected to normal goat serum (10% in PBS, pH 7.3) with 0.2% Triton-X 100 applied for 30 min at room temperature for blocking the sections. The sections were then incubated overnight at 4 °C with rabbit anti-Sox11 (1:100, Millipore, Billerica, MA) and followed by staining with TRITC -conjugated goat anti-rabbit IgG (1:100, Sigma–Aldrich, St. Louis, MO) for 1 h at 37 °C. Nuclei were counterstained with DAPI (1:1000, Invitrogen, Carlsbad, CA).

To examine the localization of Sox11 in the spinal cord, double immunofluorescence staining was performed following standard methods. Briefly, the sections were subjected to normal goat serum (10% in PBS, pH 7.3) with 0.2% Triton-X 100 applied for 30 min at room temperature for blocking the sections. The sections were then incubated overnight at 4 °C with rabbit anti-Sox11 (1:100, Millipore) and mouse anti-Nestin (1:200, Abcam, Cambridge, MA) or mouse anti-Doublecortin (1:100, Abcam) or mouse anti-MAP2 (1:200, Millipore, Billerica, MA) and followed by staining with FITC-conjugated goat anti-rabbit IgG (1:100, Sigma–Aldrich) and TRITC-conjugated goat anti-mouse IgG (1:100, Sigma–Aldrich) for 1 h at 37 °C. Nuclei were counterstained with DAPI (1:1000, Invitrogen).

2.7. Western blot analysis

Spinal cord samples used for Western blot analysis were quickly frozen in liquid nitrogen after surgical resection and maintained at −80 °C. Tissues were washed with cold PBS and lysed in cold lysis buffer containing 10 mM Tris–HCl, pH 8.0, 240 mM NaCl, 5 mM EDTA, 1 mM dithiothreitol, 0.1 mM phenylmethylsulfonyl fluoride, 1% Triton X-100, 1 mM sodium vanadate, and 1 g/ml of leupeptin, pepstatin and aprotinin. Cell lysates were incubated on ice for 30 min and then centrifuged at 12,000 rpm for 10 min at 4 °C. The supernatant was then collected and protein content was assayed colorimetrically. Ten micrograms of total proteins were loaded onto a 10% gradient polyacrylamide gel, electrophoretically transferred to polyvinylidene difluoride membrane and probed with rabbit anti-Sox11 (1:1000, Millipore, Billerica, MA), or mouse anti-Nestin (1:1000, Abcam) or mouse anti-Doublecortin (1:1000, Abcam). Monoclonal anti-β-actin (1:1000, Sigma–Aldrich) was used as an internal control. Secondary antibodies were horseradish peroxidase conjugated to rabbit anti-mouse or goat anti-rabbit IgG (1:5000, Sigma–Aldrich). The membranes were developed using an ECL detection system (Pierce, Rockford, IL). The intensity of bands was determined using the Gel pro 4.0 software.

2.8. Statistical analysis

Data in the text and figures were expressed as the mean ± S.D. of at least three experiments. The data were analyzed using the

Student's *t* test. The differences were considered statistically significant when the *P*-value was <0.05.

3. Results

3.1. The expression of Sox11 is increased in the injured spinal cord

We established mouse spinal cord hemisection model. Check whether the right hemicord was thoroughly transected under the stereo microscope (Fig. 1A). We used thirty-six mice with successful hemi-section for subsequent experiments. Expression of Sox11 in the injured spinal cord was assessed using immunohistochemical staining at 3 week after spinal cord hemisection. Sox11 expression was more robust on the injured versus contralateral side and diminished as a function of distance from the site of injury (Fig. 1B). On the contralateral side, the expression of Sox11 was very weak (Fig. 1B).

3.2. Sox11 expression is located in ependymal cells lining the central canal and in newly-generated neurons in the injured spinal cord

To identify Sox11-positive cells in the injured spinal cord, tissues were double stained with Sox11 and Nestin/Doublecortin/MAP2 at 3 week after spinal cord hemisection. In the ependymal cells lining the central canal, immunofluorescence signals for Sox11 co-localized with the immunofluorescence signal for Nestin (Fig. 1C), suggesting that Sox11 was expressed in endogenous NSCs. Whereas, in the gray matter, immunofluorescence signals for Sox11 co-localized with the immunofluorescence signals for Doublecortin/MAP2 (Fig. 1D and E), suggesting that the Sox11-positive cells in the gray matter were newly-differentiating neuronal precursors and/or immature neurons.

3.3. LV-mediated expression of exogenous genes in the injured spinal cord

We first examined whether lentiviral vector stably transduced spinal cord tissue by injecting the lentiviral vector encoding Sox11 into the lesion site immediately after spinal cord hemi-section. GFP was detectable within 1 week after spinal cord hemi-section and this expression increased further thereafter. At 3 weeks, a strong GFP signal, extending into the cervical and lumbar spinal cord over distances of at least 4 mm from the center of the lesion site was found (Fig. 2A and B). Of all GFP-positive cells, 45% were Nestin-positive NSCs and located along the central canal (Fig. 2C), while 25.3% were Doublecortin-positive cells and located in the gray matter (Fig. 2D). Thus, for at least a 3-week period, LV-Sox11 was capable of transducing NSCs and immature neurons within the injured spinal cord.

Quantitative Western Blot analysis confirmed the immunohistochemical results regarding Sox11 expression. At 1 week after injury, Sox11 expression was increased in both LV-Sox11 and LV-GFP injected spinal cords as compared with that of intact spinal cords (data not shown). Sox11 expression was significantly increased in LV-Sox11-treated mice compared with LV-GFP-treated mice at 2–3 weeks after injury (Fig. 2E) indicating transgene Sox11 over-expression.

3.4. Over-expression of Sox11 promoted neuronal regeneration after SCI

Western blot results also showed a significant increase in the expression of Nestin and Doublecortin in LV-Sox11-treated mice compared with in LV-GFP-treated mice at 3 week after spinal cord

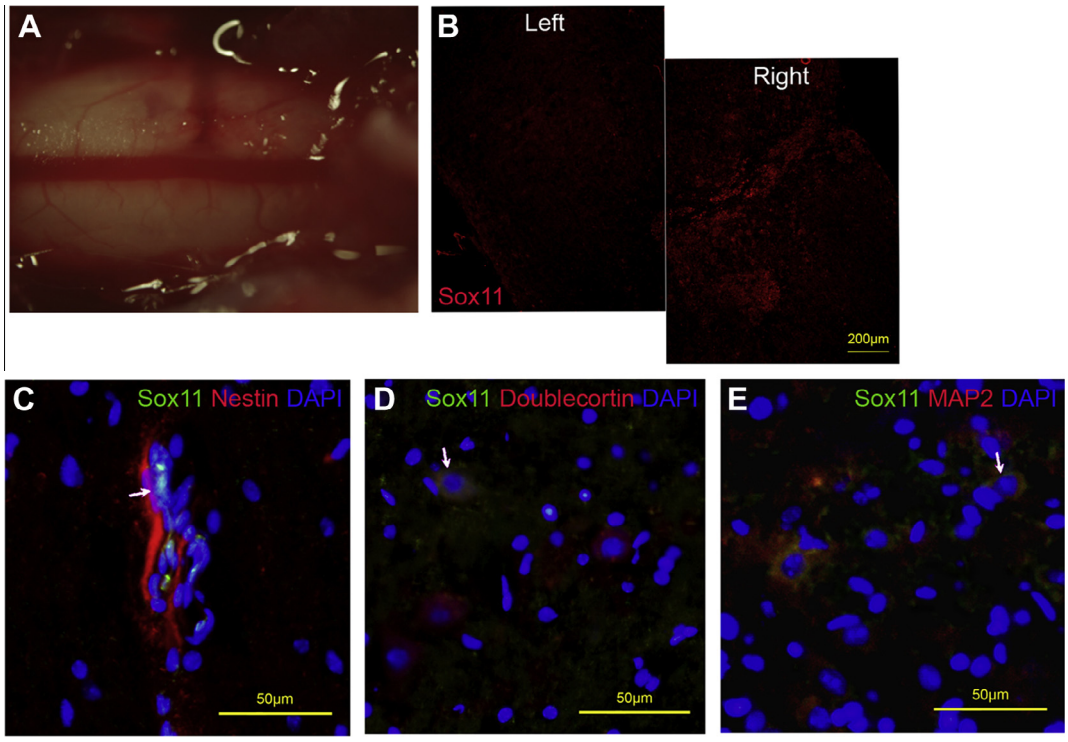

Fig. 1. Expression and localization of Sox11 within the injured spinal cord. (A) The establishment of mouse spinal cord hemi-section. Check that the right hemicord was thoroughly transected under the stereo microscope. (B) Sox11 expression was more robust on the injured versus contralateral side and diminishes as a function of distance from the injured site. On the contralateral side, the expression of Sox11 was very weak. (C) Double immunofluorescence staining of Sox11 and Nestin. The red arrows indicate the Sox11+/Nestin+ cells lining the central canal. (D) Double immunofluorescence staining of Sox11 and Doublecortin. The red arrows indicate the Sox11+/Doublecortin+ cells in the gray matter. (E) Double immunofluorescence staining of Sox11 and MAP2. The red arrows indicate the Sox11+/MAP2+ cells in the gray matter. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

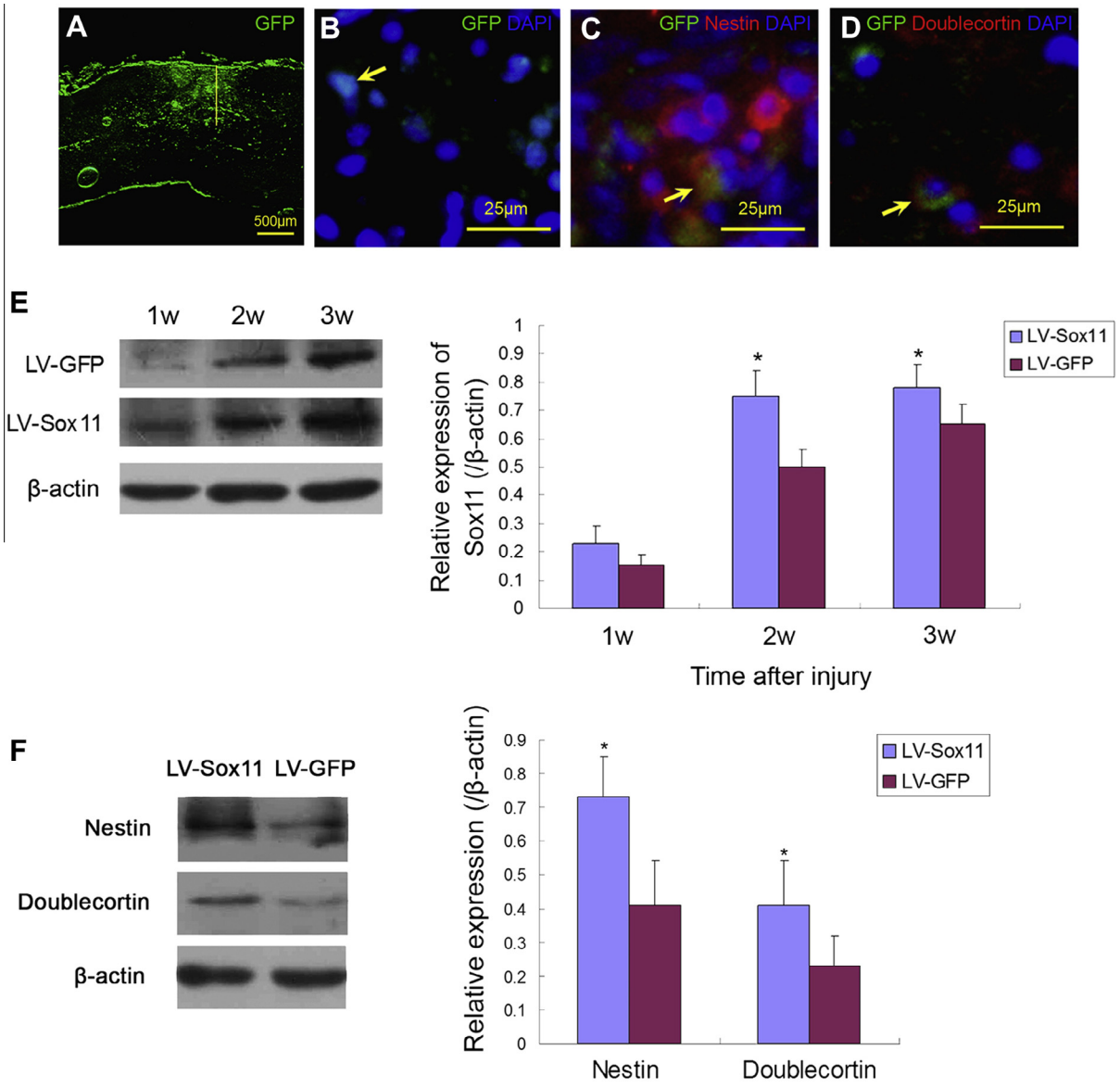

Fig. 2. Lentiviral vectors encoding Sox11 enhanced Sox11 expression and overexpression of Sox11 promoted neuronal regeneration in vivo. (A) Representative images of the LV-Sox11 group by GFP in longitudinal sections around the lesion site at 3 weeks post-injection. The GFP-positive cells were dispersed over an extended length rostrally and caudally to the injection site (performed at the level of the yellow line). (B) High-power views of GFP labeled cells in the injured spinal cord. (C) Expression of GFP in NSCs identified by immunofluorescence staining for Nestin. Individual double-labeled cells are indicated by arrows. (D) Expression of GFP in immature neurons identified by immunofluorescence staining for Doublecortin. Individual double-labeled cells are indicated by arrows. Scale bars in (A) 500 μm and scale bars in (B–D) 50 μm. (E) Western blots used to examine the effect of LV-Sox11 on Sox11 protein. Representative Western blots are shown in the left panels. Mean values and SEM of protein expression levels normalized to β-actin are shown in the right panels ($n = 3$ per group). The results indicate that Sox11 expression was enhanced at 2 and 3 weeks after spinal cord hemisection ($^*P < 0.05$). (F) Western blot analysis of Nestin, Doublecortin in LV-Sox11 and LV-GFP transduced spinal cords at 3 weeks after hemisection. Representative Western blots are shown in the left panels. Mean values and SEM of protein expression levels normalized to β-actin are shown in the right panels ($n = 3$ per group). The expressions of Nestin and Doublecortin were significantly increased after LV-Sox11 injection ($^*P < 0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hemi-section (Fig. 2F), indicating Sox11 promoted neuronal regeneration after SCI.

3.5. Over-expression of Sox11 increased expression of brain derived nerve factor after SCI

Brain-derived neurotrophic factor (BDNF) is a pleiotropic growth factor that affects neuronal survival, differentiation and regeneration. To assess the possible influence of Sox11 on expression of BDNF, double immunofluorescence staining and Western blot were performed at 3 week after spinal cord hemisection. In the gray matter of injured spinal cords, immunofluorescence signals for Sox11 co-localized with that for BDNF (Fig. 3A). Results obtained with Western blot also showed that expression of BDNF was markedly up-regulated in LV-Sox11-treated mice, as compared with its expression in LV-GFP-treated mice (Fig. 3B and C).

3.6. Effects of Sox11 over-expression on locomotor recovery after SCI

Motor function as blindly assessed with the BMS, was substantially impaired in both LV-Sox11 and LV-GFP-treated mice subjected to SCI as a consequence of the loss of right hindlimb movement at 3 days after injury. Mice treated with LV-Sox11 demonstrated a marked improvement from 1 to 3 weeks

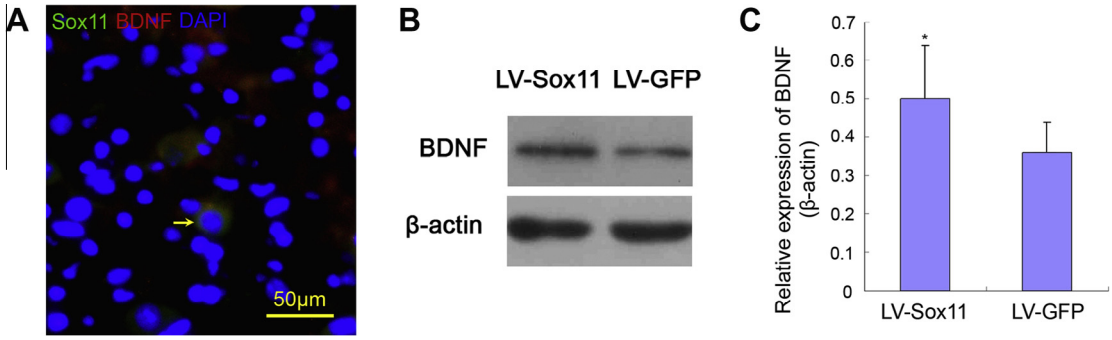

Fig. 3. BDNF expression in the injured spinal cord at 3 weeks after injury. (A) Double immunofluorescence staining of BDNF and Sox11 within the injured spinal cord. Yellow arrows indicate BDNF+/Sox11+ cells within the injured spinal cord. (B) BDNF was detected by Western blot in the injured spinal cords at 3 weeks after spinal cord hemisection. (C) Relative protein level of BDNF in the injured spinal cord after LV-Sox11/LV-GFP injection shown as histograms. Each value was normalized to β-actin. The expression of BDNF was significantly increased after LV-Sox11 injection (*$P < 0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

post-SCI, with statistically significant differences versus the LV-GFP group present at 2 and 3 weeks post-SCI (*$P < 0.05$) (Fig. 4).

4. Discussion

In the present study, we reported that the expression of Sox11 was increased after SCI and mainly located in ependymal cells lining the central canal and in newly-generated neurons in the spinal cord. There exists evidence from several sources indicating that the ependymal zone of the central canal may serve as a stem cell niche [18]. It had been reported that Sox11 expression is strictly confined to Doublecortin-expressing neuronally committed precursors/immature neurons in the adult brain and regulates adult neurogenesis [8,10,19,20]. These facts suggests that Sox11 played an important role in inducing endogenous stem cell neuronal determination after injury and initiating intrinsic repair mechanisms. Another noteworthy feature of Sox11 expression profile was that Sox11 was expressed in the cytoplasm of newly-generated neurons, whereas it was expressed in the nuclei of ependymal cells. Similar phenomenon was found in the study of the subcellular Sox11 distribution in mantal cell lymphoma [21]. For some Sox proteins (Sox2 and Sox9), nuclear import and export regulate Sox protein activity in vivo [22,23]. However, whether this is a general mechanism, of relevance for all Sox proteins including sox11, is unknown. Further studies are needed to establish the importance of Sox11 nuclear export.

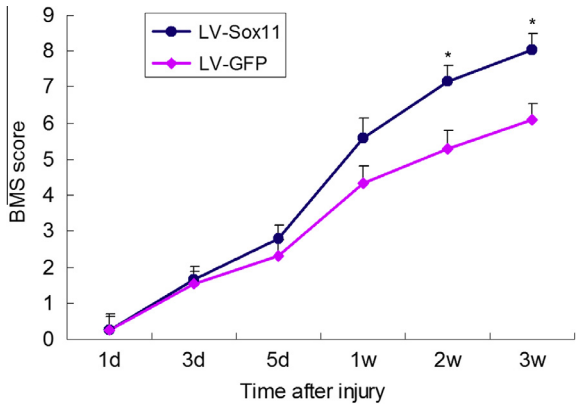

Fig. 4. Recovery of motor function after spinal cord hemi-section in mice. The degree of motor impairment was assessed in a blinded manner using the BMS protocol. Scores range from 0 (complete paralysis) to 9 (normal movement of the hindlimbs). Scores were assigned, for each of the right hindlimbs and the scores resulting from the two observers were then averaged for each mouse. Mice treated with LV-Sox11 demonstrated marked improvements from weeks 1 to 3. A statistically significant difference was found in a comparison with LV-GFP group at 2–3 weeks (*$P < 0.05$). Data are means ± S.D. of 6 mice/group.

A lentiviral vector expressing GFP containing the Sox11 gene was introduced into the injured spinal cords to evaluate the therapeutic potential of Sox11 in mice with SCI. Sox11 markedly improved locomotor recovery and this recovery was accompanied by a up-regulation of Nestin/Doublecortin expression in the injured spinal cord. Moreover, some GFP-positive cells along the central canal expressed Nestin, a neural stem cell marker and some GFP-positive cells in the gray matter of injured spinal cords expressed Doublecortin, an immature neuronal cell marker. Data from previous studies using embryonic spinal cords revealed that Nestin expression occurs in cells expressing group B1 Sox located in the ventricular zone and in those expressing Sox11 (and possibly other group C Sox) located in the subventricular zone [24,25]. Recently, it has been shown that human glioma-initiating cells lose Sox11 expression and over-expression of Sox11 prevents tumorigenesis of glioma-initiating cells by inducing neuronal differentiation [12]. In the present study, we also found that Sox11 promoted Doublecortin expression and was co-localized with Doublecortin, suggesting that Sox11 might promote neurogenesis after SCI. Based on the information presented above, we hypothesized that Sox11-dependent Nestin positive cells might represent activated NSCs, and that Sox11 induced these activated NSCs in the subventricular zone toward neuronal determination and migration for promotion of self-repair after injury.

One possibility mechanism of Sox11 effect on endogenous NSCs is that Sox11 may function as a regulator of Nestin expression. It is believed that Sox proteins cooperate with partner factors by binding to a nearby site of target DNA sequences and thus selectively regulate a cell-specific group of genes [7]. The identity of a partner factor that cooperates with Sox11 to activate Nestin expression is not known. It has been shown that a potential Sox protein binding site is present in the 258 bp mouse Nestin enhancer, immediately upstream of the POU binding site [25]. These findings raised the possibility that Sox11 could promote the expression of Nestin by interacting with POU domain transcription factors. However, more studies are needed to establish the specific partner factor of Sox11 that regulating neuronal fate.

In the present study, we also found that Sox11 promoted BDNF expression and Sox11 was co-localized with BDNF in the gray matter. It has been shown that Sox11 plays an important role in regulating injury-induced BDNF expression in an exon promoter-specific manner [26]. BDNF is known to support differentiation of NSCs to neurons as revealed under both in vitro and in vivo conditions [27,28]. High concentrations of BDNF in the injured spinal

cord have the potential to form a distinct neurogenic niche, which could then induce neuronal differentiation of endogenous NSCs. Thus, an elevation in Sox11 expression in response to SCI could lead to long-term activation of BDNF transcription and contribute to neuronal determination of endogenous NSCs.

In the adult spinal cord, endogenous NSCs exist in a quiescent state. Their capacity for constitutive proliferation and neurogenesis is limited, correlating with their ability to regenerate after injury. Enhancing Sox11 expression to induce neurogenic differentiation of endogenous NSCs after injury may be a promising strategy in restorative therapy after SCI in mammals.

Acknowledgments

This work is supported by the National Natural Science Foundation of China (Grant Nos. 81100919, 81071057, 81100849); the Scientific Research Foundation for Returned Scholars, Ministry of Education of China (21300005451001); Shangdong Province Young and Middle-Aged Scientists Research Awards Fund (BS2010YY041); Shandong postdoctoral fund (201203050).

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