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Stromal cell-derived factor-1 alpha alleviates hypoxic-ischemic brain damage in mice

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ABSTRACT

Hypoxic-ischemic brain damage (HIBD) is a major cause of acute deaths and chronic nervous system damage. There is good evidence that stromal cell-derived factor-1 alpha (SDF-1α) has been receiving much interest in its role in the treatment of ischemic diseases. Here we aim to investigate the effect of intraperitoneal delivery of SDF-1α after experimental hypoxia-ischemia (HI) and the potentially involved mechanisms. A total of 129 mice were subjected to unilateral carotid artery ligation followed by 2.5 h of hypoxia, randomly assigned to three groups: sham, HI + vehicle and HI + SDF-1α. Mice treated with SDF-1α showed recovery of spatial learning abilities and pathological conditions, decreased number of apoptotic cells, and elevated expression of SDF-1α and its cognate receptor, CXC chemokine receptor-4 (CXCR4). Meanwhile, the increased number of mesenchymal stem cells (MSCs) was found in peripheral blood after SDF-1α treatment. Taken together, the treatment of SDF-1α after HIBD contributed to an improved functional recovery, and this behavioral restoration was paralleled by a reduction of apoptosis and mobilization of MSCs via SDF-1α/CXCR4.

1. Introduction

Hypoxic-ischemic brain damage (HIBD) caused by partial or complete cerebral hypoxia, cerebral blood flow reduction or suspension, has been considered as critical factors in many human central nervous system diseases. Major sequelae of HIBD include long-term neurological disturbances such as cerebral palsy, mental retardation, seizure disorders and motor/cognitive disabilities [1,2]. Though progress has been made through the studies of pathophysiological damage after HIBD, the effective of treatments remain limited.

Chemokines are chemotactic cytokines with multiple functions that can also act in the brain to modulate our behaviors. Among the chemoattractants regulated in the brain, stromal-derived factor-1 alpha (SDF-1α) has a recognized role in brain inflammation and neuromodulation [3,4]. CXC chemokine receptor-4 (CXCR4) has been previously considered as the only receptor to mediate the transmembrane signaling of SDF-1. This chemokine system has been shown to play important roles in brain plasticity processes occurring during development but also in the physiology of the brain in normal and pathological conditions [5,6]. Furthermore, there are also good evidences that SDF-1α/CXCR4 play an important role in the mobilization of mesenchymal stem cells (MSCs) [7]. MSCs have been reported to promote repair of the remote tissue by mobilizing into peripheral blood by injury signals, and attract attention as donor cells for regenerative therapy [8].

In the present study, we therefore established an animal model of hypoxia-ischemia (HI), and focused on the mechanism by which the SDF-1α treatment induces protective effect following HIBD and provides experimental and theoretical evidence relevant to the clinical therapeutic applications of SDF-1α.

2. Materials and methods

2.1. Animals

Male Institute of Cancer Research (ICR) mice (8–10 weeks) were purchased from the Animal Center of Zhejiang Chinese Medical University, Hangzhou, China (Laboratory Animal Certificate: SCXK

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2008-0016) and housed under standardized conditions in a 12 h dark/light cycle with free access to water and food except when otherwise specified. All procedures related to care of animals were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals [9].

2.2. HI model and experimental groups

All the mice were anesthetized with 4% chloral hydrate solution (400 mg/kg). The left common carotid artery were exposed through a midline skin incision in the neck, and then maintained by unilateral left carotid artery ligation. All the animals were returned to their cages 2–3 h until being awake, and put them in a sealed glass chamber 2.5 h with mixed gas containing 92% nitrogen and 8% oxygen. Hypoxic brain injury (8% O_2 for 2.5 h) was also generated as previously described [10].

The animals were randomly divided into three experimental groups (n = 43 per group): sham group, HI + vehicle group, HI + SDF-1α group. The mice in HI + SDF-1α group were treated with SDF-1α (Peprotech, Rocky Hill, USA) at 10 μg/kg/day by intraperitoneal injection for 3 days. Other mice received the same volume of normal saline. Morris water maze test (n = 6 per group) was performed at 14 days after HI. Meanwhile, The mice were euthanized at 7, 14, and 21 days after HI for obtaining brain tissue samples, histological and immunohistochemical detection (each time point n = 3 per group), reverse transcription-polymerase chain reaction (RT-PCR) (each time point n = 3 per group) and western blotting (each time point n = 3 per group), respectively. Besides, colony-forming unit fibroblast (CFU-F) assay (each time point n = 5 per group) in vitro was performed at 3 and 7 days in vitro after HI.

2.3. Morris water maze test

The Morris water maze test, as described previously [11]. An automatic tracking system (San Diego Instruments, San Diego, CA, USA) was used to record escape latency and the swimming path. Each mouse was tested for five training days and one test day. In the task, the mouse was placed in every quadrant sequentially, facing the wall. Each trial lasted for 60 s or ended as soon as the mouse reached the submerged platform and was allowed to remain on the platform for 10 s. On the last day, the platform was removed before the test. The escape latency and the swimming time in the former platform quadrant were recorded.

2.4. Histological examination

Mice were sacrificed on day 7, 14 and 21 after HI. Brains were removed from the skull, each hippocampus was embeddedin paraffin, among which one section was stained with hematoxylin and eosin (H&E) for histological examination, the other was collected for immunohistochemical staining.

2.5. Immunohistochemical assessment

The sections were treated with primary antibody against cysteinyl aspartate specific proteinase-3 (Caspase-3, polyclonal antibody, 1:50; Multisciences, Hanzhou, China) incubated overnight at 4 °C. The sections were washed 3 times in PBS for 5 min each and incubated with secondary antiserum (EnVision Two-Step kit, DAKO 1701777A, Denmark) for 30 min at room temperature. Subsequently, the sections were washed 3 times with PBS and incubated with diaminobenzidine (DAB) for 2–3 min until a brown reaction product was observed under inverted fluorescence microscope (ECLIPSE TE2000-S, Nikon Corporation Instruments Company, Japan).

2.6. RT-PCR analysis

The hippocampal total mRNA was extracted using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. RT-PCR was performed using a BioRT Two Step RT-PCR Kit (Bioer Technology Co. Ltd., Hangzhou, China). The cycling conditions were: 5 min at 90 °C; 30 cycles of denaturation at 94 °C for 30 s, annealing at 56 °C for 30 s, and elongation at 72 °C for 3 min; final extension for 10 min at 72 °C, and held at 4 °C. Primer sequences were listed as follows: SDF-1α: F: ACGGCTGAAGAACAACAACA R: TATGCTATGGCGGAGTGTCT; CXCR4: F: GGGGACATC AGTCAGGG R: GTGGAAGAAGGCGAGGG; β-actin: F: ATCATGTTTGAGACCTTCAACA R: CATCTCTTGCTCGAAGTCCA. Aliquots of PCR products were run on a 1% agarose gel containing ethidium bromide and visualized with ultraviolet light. Signals were densitometrically quantified and results are expressed relative to β-actin mRNA levels.

2.7. Western blotting

Proteins were extracted from frozen hippocampus. Hippocampal tissues were homogenized. Homogenates were centrifuged, and the supernatants collected. Protein concentrations were determined by the method of Bradford [12], using bovine serum albumin as standard. Equal amounts of proteins (60 μg per lane) combined with 4 × loading buffer and boiled for 10 min, were size-separated by SDS-PAGE on 10% gels. Electrophoresed proteins were then transferred to polyvinylidene difluoride membranes. After being blocked with 5% nonfat dry milk for 1 h, blots were incubated overnight at 4 °C with 1:1000 rabbit polyclonal antibodies against SDF-1α, CXCR4 (Abcam Technology, Cambridge, MA, USA), and 1:3000 rabbit polyclonal antibodies against β-actin (Abcam Technology, Cambridge, MA, USA) as primary antibodies. Blots were washed three times in tris-buffered saline and tween 20 (TBST), then incubated with a second antibody (anti-rabbit IgG HRP, 1:2000; Abcam Technology, Cambridge, MA, USA) for detection using ECL (Thermo Fisher Scientific, Waltham, MA) and β-Actin was used as a loading control. The density of the bands was quantified using Image J software (National Institutes of Health).

2.8. MSCs harvest and culture

3 and 7 days after HI, MSCs from bone morrow (BM) and peripheral blood (PB) were collected separately. BM samples were obtained from mice femur and tibia. Briefly, muscles and the entire connective tissue were detached, and the epiphyses were removed. The whole BM plugs were flushed using a 25-gauge needle and a 1.0 ml syringe loaded with Dulbecco's modified Eagle's medium-low glucose (LG-DMEM, Invitrogen, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Life Technologies, Carlsbad, CA, USA) and 1% penicillin-streptomycin (HyClone Laboratories, Inc., South Logan, Utah, USA). Harvested marrow cells were centrifuged, resuspended, and counted. PB samples (1–2 ml) were collected in heparinized tubes. Mononuclear cells (MNCs) were separated by Lymphoprep (Haoyang Biological Manufacture Co., Ltd., Tianjin, China), and counted.

2.9. CFU-F assay

Total BM cells were plated in triplicate at a density of 1×10^6 (MNCs) cells per 12.5-cm2 flask in proliferation culture medium. PB MNCs were plated at a density of 3×10^6 cells per 12.5-cm^2 flask.

The culture medium was changed on day 7, and adherent colonies (>50 cells) derived from CFU-Fs were counted on day 14 for BM cells and on day 10 for PB cells.

2.10. Statistical analysis

All data are presented as mean ± standard deviation (SD). Differences between group means were assessed by analysis of variance for multiple comparisons using SPSS 19.0. A P-value of <0.05 was considered significant.

3. Results

3.1. Effects of SDF-1α on memorial and cognitive functions of mice

On day 14 after HI, the spatial performance was evaluated by Morris water maze test. Three groups of mice were able to learn to find the submerged platform; the escape latencies became shorter with increased numbers of training trials in all groups. In the place navigation test, the mice in the HI + vehicle group spent significantly more time to find the platform compared with mice in the sham group (Fig. 1A). These results suggest that the mice developed cognitive dysfunction following HI. There was a significant decrease in the escape latency of the HI + SDF-1α group compared with the HI + vehicle group on day 3, 4, and 5 (Fig. 1A). Moreover, in the spatial probe test, similar to the results from the place navigation test, mice in the HI + SDF-1α group spent less time in the target quadrant than the HI + vehicle group (Fig. 1B). These results indicated that the treatment of SDF-1α improved memorial and cognitive functions after HI.

3.2. Effects of SDF-1α on pathological changes

H&E staining provided an objective assessment on pathological changes. Examinations of the hippocampus showed that the morphological structures of the hippocampus in the sham group were normal at various time-points subsequent to HI. By contrast, the morphological structures of the hippocampus in the HI + vehicle group subsequent to HI had significant changes; the tissues were loose and intercellular edema were visible, which suggested that HI model were successfully established and could be used for further analysis. Similar results were observed in the HI + SDF-1α group subsequent to HI, i.e. the morphological structures of the hippocampus were significantly changed; however, the changes were less marked than those of the HI + vehicle group. The results illustrated that the treatment of SDF-1α ameliorated pathological changes after HI (Fig. 2A).

3.3. Effects of SDF-1α on apoptosis

Immunohistochemical determination of Caspase-3 was performed to determine whether SDF-1α treatment can decrease the number of apoptotic cells (Fig. 2B). Caspase-3-positive cell number in the HI + vehicle group was significantly increased in comparison with the sham group at each time point (Fig. 2C). The HI + SDF-1α group showed decreased number of Caspase-3-positive cells than that in the HI + vehicle group on day 14 and 21 (Fig. 2C) although difference there was no statistically significant between the two groups on day 7. Such findings suggested that SDF-1α may ameliorate pathological changes by inhibiting apoptosis after HI.

3.4. Effects of SDF-1α on the expression of SDF-1α and CXCR4 levels

The expression of RNA and protein levels of SDF-1α and CXCR4 was investigated in the sham, HI + vehicle and HI + SDF-1α groups respectively on day 7, 14, 21 after HI. In the HI + vehicle group, SDF-1α and CXCR4 expression were significantly higher than that of the sham group. Additionally, the expression of SDF-1α and CXCR4 in the HI + SDF-1α group were significantly increased in comparison with the HI + vehicle group and peaked at day 14. These results demonstrated that the treatment of SDF-1α improved functional recovery via up-regulating the expression of SDF-1α/CXCR4 (Fig. 3).

3.5. Effects of SDF-1α on MSC mobilization

CFU-F assays were performed on PB and BM samples from each group. The PB CFU-F frequency in the HI + vehicle group was significantly increased compared with the sham group, which showed HI induced autologous MSC mobilization (Fig. 4B). On day 3 after HI, although the numbers of PB CFU-Fs were increased in the HI + SDF-1α group, there were no significant differences compared with the HI + vehicle group. Meanwhile, on day 7 after HI, the PB CFU-F frequency in the HI + SDF-1α group was significantly increased than that of the HI + vehicle group. However, no significant differences in BM CFU-Fs were seen among the groups (Fig. 4A). These results suggested that the treatment of SDF-1α elevated the number of MSCs mobilized into PB after HI.

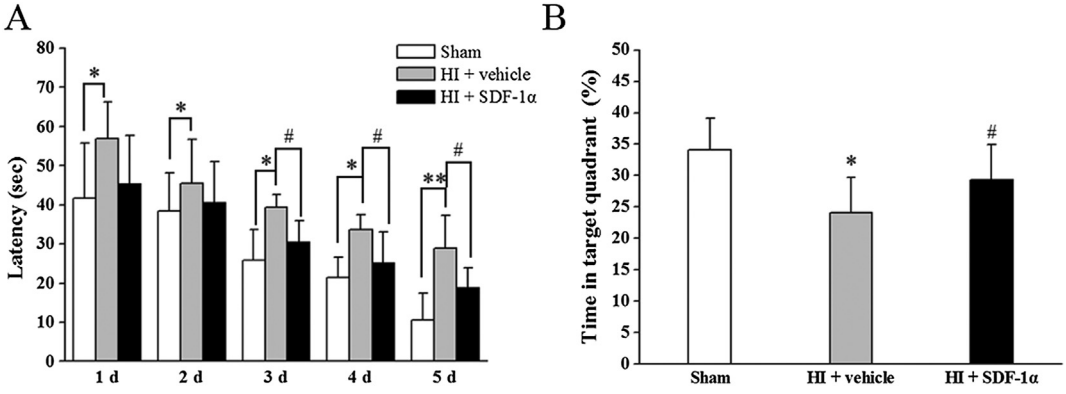

Fig. 1. Performance of the mice in the Morris water maze. (A) Latency to find the platform. (B) The percentage of swimming time in target quadrant. $^{*}P < 0.05$ and $^{**}P < 0.01$ versus the sham group; $^{\#}P < 0.05$ versus the HI + vehicle group.

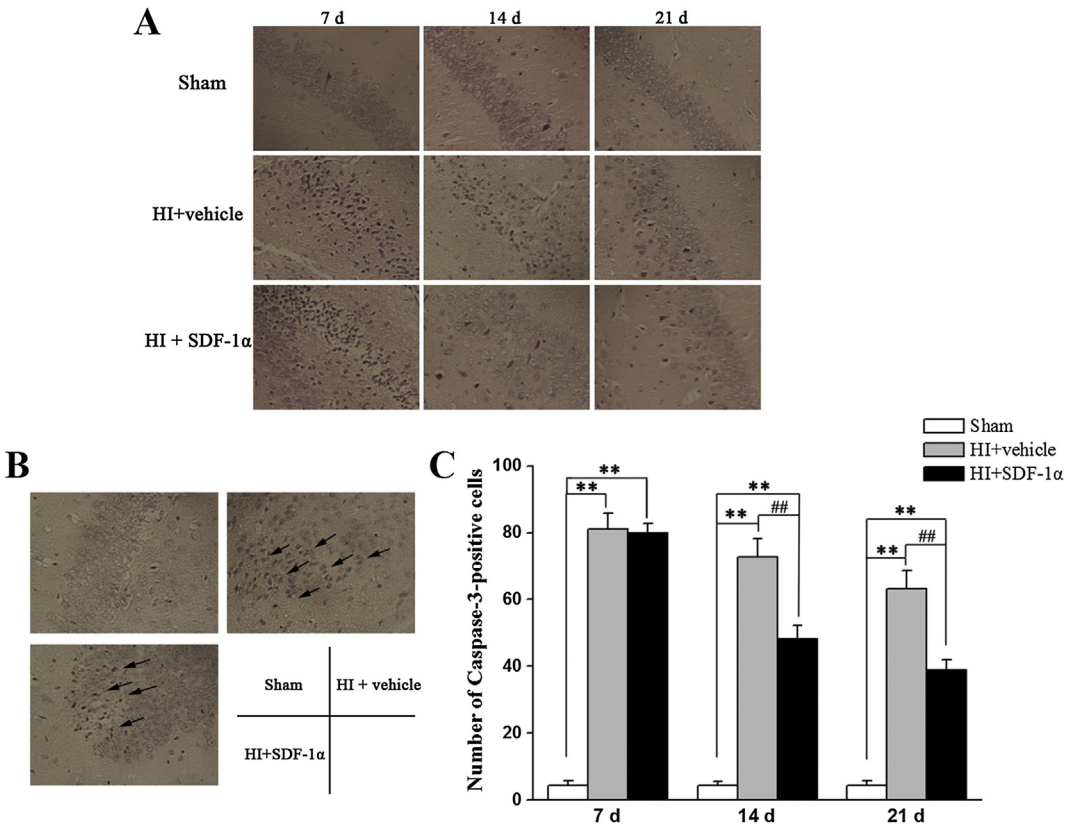

Fig. 2. Histological and immunohistochemical detection in different groups of hippocampal tissues. (A) pathological changes of hippocampal tissues by SDF-1α treatment (magnification, × 200). (B) Caspase-3 immunostained tissue in hippocampus of HI in mice (magnification, 200x). (C) The number of Caspase-3-positive cell was counted. $^{**}P < 0.01$ versus the sham group, and $^{\#\#}P < 0.01$ versus the HI + vehicle group.

4. Discussion

In the present study we established SDF-1α cerebroprotective effects 3 weeks after HIBD and demonstrated several underlying mechanisms. Using an HI mouse model, we first found the recovery of memorial and cognitive functions subjected to intraperitoneal delivery of SDF-1α for 3 days. Meanwhile the exogenous SDF-1α treatment alleviated HIBD-induced pathological changes and inhibited apoptosis in the brain. Next, SDF-1α treatment showed the elevated expression of SDF-1α and its cognate receptor CXCR4, which indicated the activation of the SDF-1α/CXCR4 axis. Furthermore, our findings also demonstrated the elevated number of MSCs mobilized into PB by SDF-1α treatment.

The Morris water maze is a test to assess spatial memory and learning of rodents, which has become one of the 'gold standards' of behavioral neuroscience [13]. The results from this experiment in the present study demonstrated that HI may cause transient deficits in water maze performance. Nonetheless, the treatment of SDF-1α in HI mice leads to improved learning and memory, manifested by the better performance in both the acquisition test and probe trials of the Morris water maze. In addition to its role in behavioral neuroscience, HIBD is also associated with pathological changes. Our findings showed that SDF-1α treatment ameliorated pathological changes after HI. These results indicated that the treatment of SDF-1α after HIBD contributes to an improved functional recovery.

Apoptosis is a physiological process that functions as an essential mechanism of tissue homeostasis. We thus investigated whether SDF-1α could exert its cerebroprotective effect by mediating cell apoptosis in the brain, with emphases on the apoptotic signaling by Caspase-3. In the present study, we found that the HI exhibited an increased number of Caspase-3-positive cells. Nonetheless, the change was significantly reversed by SDF-1α treatment. As a support to our results, Zheng et al. [14] have demonstrated that SDF-1α treatment is able to decrease cell apoptosis by reducing Caspase-3 expression. Collectively, our data indicate an anti-apoptotic effect of SDF-1α in the animal brain after HI.

A report from Ceradini et al. [15] has demonstrated that SDF-1 expression is regulated by the hypoxia responsive transcription factor HIF-1, and the level of SDF-1 expression is directly related to the degree of hypoxia such that hypoxic gradients within tissues correlate with gradients of SDF-1 gene expression. Hypoxia may leads to changes of various factors including glutamate excitotoxicity, depletion of growth factors, alteration in cellular biochemistry, etc, and the hippocampus is reported to be the most vulnerable region [16]. In order to determine the expression of SDF-1α relative to HIBD, we detected SDF-1α expression at both mRNA and protein levels in the hippocampal fissure. Our data indicate the increased SDF-1α mRNA expression occurs following HI. Additionally, the pattern of peak mRNA expression for SDF-1α we showed at 14 days after HI. Meanwhile protein expression observed in our study was consistent with mRNA expression patterns. These results are consistent with those from previous studies [17,18].

Our findings of increased numbers of MSCs in PB may be in line with the observed up-regulation of SDF-1 and CXCR4 expression [19,20]. Previous studies demonstrated that under chronically hypoxic conditions, MSCs were mobilized into the PB through up-regulation of CXCR4 [21,22]. At the same time, the level of SDF-1 was also elevated after brain damage [15]. In the current study, it demonstrated the increased number of MSCs in PB within 7 days

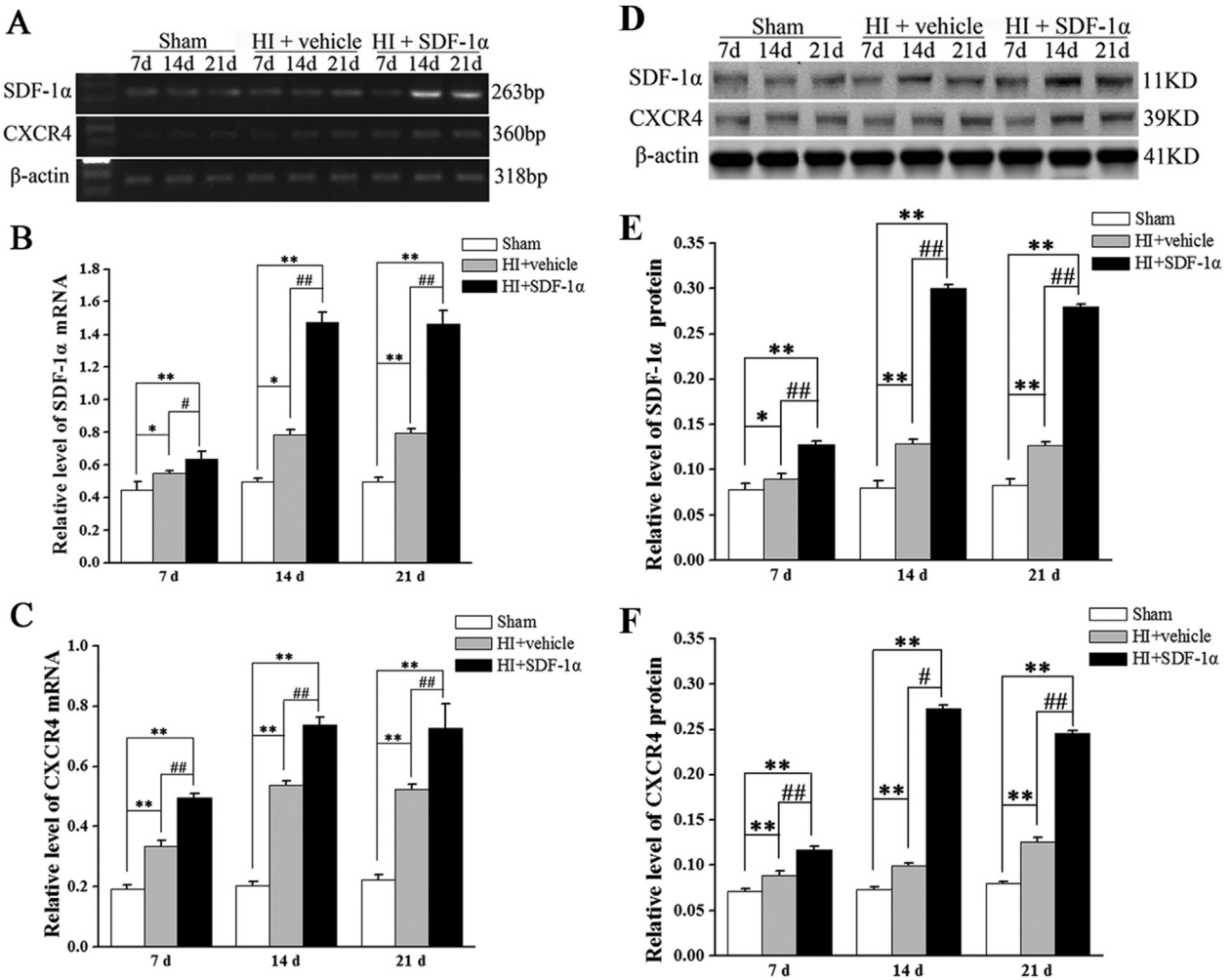

Fig. 3. Expression of SDF-1α and CXCR4 in different groups of hippocampal tissues. (A) mRNA levels of SDF-1α and CXCR4 in different groups of hippocampal tissues. β-actin was used as an inner control. (B and C) Quantification of SDF-1α and CXCR4 mRNA expression showed in (A). (D) Protein levels of SDF-1α and CXCR4 in different groups of hippocampal tissues. (E and F) Quantification of SDF-1α and CXCR4 protein expression showed in (D). $^{*}P < 0.05$ and $^{**}P < 0.01$ versus the sham group; $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ versus the HI + vehicle group.

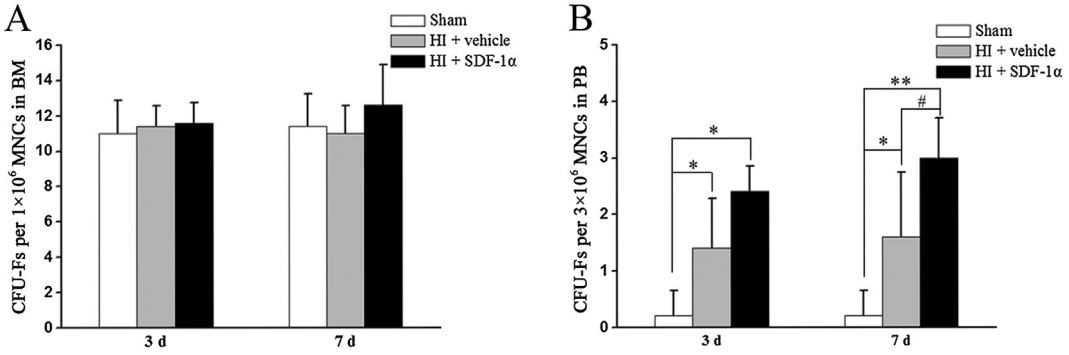

Fig. 4. Mesenchymal stem cells frequencies in PB and BM. (A) Number of CFU-Fs (mean ± SD) per 1×10^6 MNCs in BM. (B) Number of CFU-Fs (mean ± SD) per 3×10^6 MNCs in PB. $^{*}P < 0.05$ and $^{**}P < 0.01$ versus the sham group; $^{\#}P < 0.05$ versus the HI + vehicle group.

after HI, which implied that the attraction of MSCs into PB is mediated by specific regulatory mechanisms. Meanwhile we found that SDF-1α treatment up-regulated the expression of SDF-1α and CXCR4 in hippocampus. These results strongly supported that SDF-1α activates the SDF-1α/CXCR4 axis to promote MSC mobilization, and that only may be one of the mechanisms of functional recovery following HIBD.

The present study has its limitations. On the one hand, we did not use immunohistochemical evaluation with double or triple staining of markers for neurogenesis, which is better to show

neurogenesis in this study. On the other hand, the protective effect of SDF-1α against brain injury may occur through multiple pathways; therefore, further studies on the underlying associated mechanism are required to provide a theoretical basis for the future prevention and treatment of HIBD.

In summary, this study demonstrated that the treatment of SDF-1α after HIBD contributed to an improved functional recovery, and this behavioral restoration was paralleled by a reduction of apoptosis and mobilization of MSCs via SDF-1α/CXCR4.

Conflict of interest

The authors declare no conflicts of interests.

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Transparency document

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