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Original Article

CXCR4-transduced bone marrow mesenchymal stem cells contribute to liver regeneration in cirrhotic rats through the transplant microenvironment

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Abstract: Bone marrow mesenchymal stem cells (BMSCs) have multi-potential differentiation capacities and can prevent the loss of hepatic parenchymal cells and promote tissue repair. However, the poor engraftment of BMSCs is one of the primary barriers to the effectiveness of this cell therapy. A previous study indicated that CXCR4 overexpression improved the repair ability of BMSCs by increasing the homing of BMSCs. In this study, we constructed lentiviral vectors expressing CXCR4, transduced these into BMSCs, and then investigated the potential mechanism of the contribution of CXCR4-BMSCs to liver regeneration. Our results showed that the regulation of CXCR4 expression influenced the directional homing of infused BMSCs at the early stage of cell transplantation and that nearly no BMSCs localized in the injured liver 72 h post-transplant. In addition, we found more PCNA expressing hepatocytes and more EpCAM and Jagged-1 expressing biliary duct cells in the livers of cirrhotic rats that underwent transplantation of CXCR4-BMSCs. This study indicated that CXCR4-mediated engraftment of BMSCs might enhance the interactions between the BMSCs and the hepatic progenitor cells in the transplant microenvironment, thus contributing to liver regeneration.

Keywords: CXCR4, BMSCs, transplant, liver cirrhosis, microenviroment

Introduction

Liver cirrhosis (LC) is the final stage of most chronic liver diseases and, in China, is caused primarily by chronic hepatitis B infections. Liver transplantation is the only effective therapy for LC. However, the scarcity of liver donor organs has limited its widespread application. Although BMSCs have the potential to promote liver regeneration after acute or chronic liver injury through direct differentiation into hepatocyte, and/or paracrine mechanisms and immunosuppressive activities [1-5], their recruitment to the impaired liver and their survival and function are yet to be determined [6, 7]. Previous studies have shown that only a small number of transplanted BMSCs localized to injured tissues and that poor cellular engraftment is one of the primary barriers to the effectiveness of cell therapy [8-10]. Our previous study showed that bone marrow-derived monocytes contributed to the regeneration of the injured liver, but the therapeutic benefit was also limited due to the poor engraftment of transplanted cells [11]. Therefore, an effective treatment strategy aimed at enhancing the recruitment of transplanted BMSCs is essential for replenishing the pool of resident hepatic progenitor cells or for activating the progenitor cell niche, thus contributing to regeneration of the liver [12].

CXCR4 is highly expressed in BMSCs within the bone marrow; however, culture-expanded BMSCs progressively downregulate the expression of CXCR4 and lose their ability to migrate toward the SDF-1 gradient in injured tissues [13, 14].

Therefore, we hypothesized that the expression of CXCR4 in BMSCs is necessary for their homing to injured livers. In our study, we achieved a remarkable expression of CXCR4 in BMSCs by gene transfection, which was accompanied with enhanced recruitment of CXCR4-BMSCs to

the cirrhotic liver. However, our results showed that CXCR4 increased BMSCs engraftment in the cirrhotic liver only during the early stage. This result indicated that the transdifferentiation of BMSCs played a minor effect in liver regeneration. In addition, more hepatocytes with PCNA expression and more biliary duct cells with EpCAM and Jagged-1 expression were identified in the cirrhotic liver of rats following BMSCs transplantation. Furthermore, in contrast with the null-BMSCs and BMSCs groups, the transplantation of CXCR4-BMSCs further increased the proportion of Jagged-1- or EpCAM-positive cells in the cirrhotic livers. This result indicated that the expression of CXCR4 in BMSCs contributed to liver regeneration mainly through the transplant microenvironments that impacted the hepatic progenitor cells (HPCs). This study not only advances our understanding of the role of BMSCs in liver regeneration but also might improve cytokine-based therapy for liver cirrhosis.

Materials and methods

Animals

Female and male SD rats (6-8 wk old) were purchased from the Laboratory Animal Center of the Academy of Military Medical Sciences of China (Beijing). All studies were performed after approval of the Ethics Committee of the Animal Facility of Chinese PLA General Hospital and were in agreement with the Guidelines for the care of laboratory animals [15]. The rats were housed in cages in a controlled environment: 25°C and a 12-h light/dark cycle. The rats were fed standard rat chow and tap water and observed twice a week in our animal facilities before the experiments.

Lentivirus vector for pGC-FU-CXCR4

The CXCR4 gene sequence was amplified by polymerase chain reaction (PCR) from a pExpress-1 plasmid (Open Biosystems, United States), and the specific primer sequences were (Forward) 5'-GAGGATCCCCGGGTACCGGTCGCCACCATGGAAATATACACTTCGGA-3' and (Reverse) 5'-TCACCATGGTGGCGACCGGGCTTCCTCCGCCTCCGCTTCCGCCTCCGCCGCTGCCGCCACCGCCGCTGGAGTGAAAACTTGAG-3'. After digesting the pGC-FU-GFP lentivirus with AgeI (R0552v, NEB Company), the amplified PCR product was inserted into the AgeI restriction site using an In-Fusion™ PCR Cloning Kit (639626, Clontech) to produce the recombinant vector pGC-FU-CXCR4. The vector pGC-FU-CXCR4 and the viral packaging system were cotransfected into 293 cells to produce the recombinant CXCR4 lentivirus (Lv-CXCR4) and the null green fluorescent protein lentivirus (Lv-null-GFP). The lentiviral titers averaged 2×10^8 TU/mL.

Preparation of BMSCs and transduction with the CXCR4 lentiviral vector

The BMSCs were prepared from male SD rats and were characterized as described previously [16]. These cells were transduced with Lv-CXCR4 or Lv-null-GFP at passage 3. For transduction, cells were seeded at a density of 2,000 cells/cm^2 in a T-75 flask. The following day, viral particles were added at a multiplicity of infection (m.o.i.) of 100 for 16 h. Then, the cells were washed and cultured with fresh medium. Because the recombinant lentivirus expressed both GFP and CXCR4, the transfection efficiency of BMSCs with the viral system was evaluated by fluorescence microscopy and flow cytometry 96 hours after the infection.

Animal experimental design and transplant procedure

The CCl_4-induced liver cirrhosis SD rat model was established previously [17]. The BMSCs from male donor rats were infused into the tail vein of female cirrhotic recipient rats. The female rats were randomly assigned to four experimental groups (n=12 for each group): the cirrhosis model group, the BMSC group, the null-BMSC group, and the CXCR4-BMSC group. Female rats were sacrificed at 24 h, 72 h and 7 d after cell transplant. Peripheral blood samples and the median lobe of the liver were collected. The liver tissues were fixed with 4% paraformaldehyde and were analyzed by immunohistochemistry.

Engraftment assay in vivo

To determine whether CXCR4 could promote the engraftment of BMSCs in cirrhotic liver, the Sex-determining Region Y (SRY) protein was detected for tracing the location of transplanted cells by immunohistochemistry. The 4-μm liver tissue sections were deparaffinized using xylene and alcohol and rehydrated with water

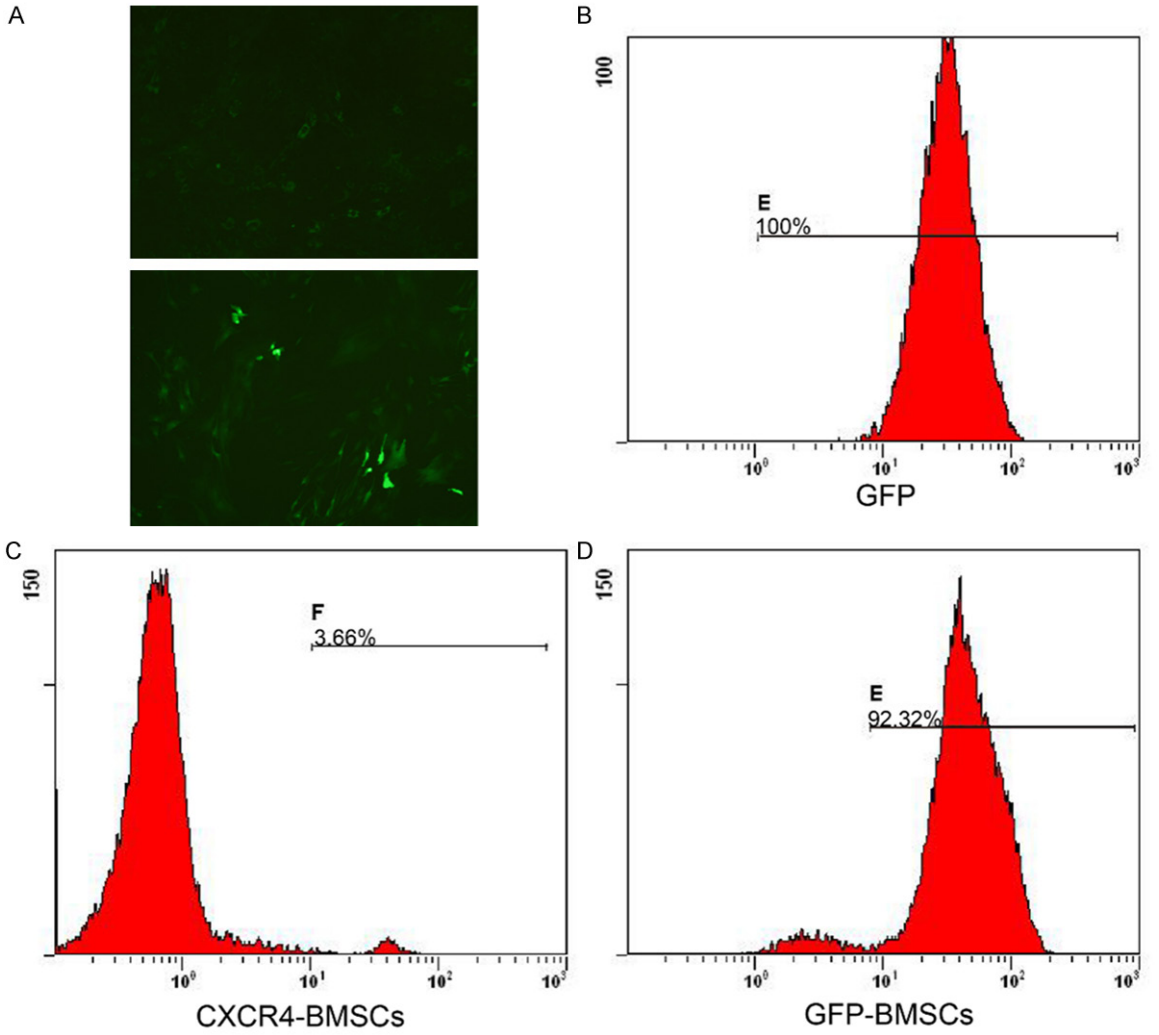

Figure 1. CXCR4 gene was highly expressed in CXCR4-transduced BMSCs. A, B: 100% of CXCR4-BMSCs were GFP-positive at 96 hours after transduction. C: 96.34% of CXCR4-BMSCs were CXCR4-positive. D: Only 7.68% of GFP-BMSCs were CXCR4-positive.

and then treated with a goat anti-rat primary antibody to SRY (1:50, sc-8233, Santa Cruz) in PBS at 4°C overnight. After 3 washes in PBS, the sections were incubated with a rabbit anti-goat second antibody (1:1000, Beijing Zhongshan Biotechnology) at 37°C for 2 hours. Finally, the immunoreactivity of the sections were visualized by incubation in 3,3'-diaminobenzidine tetrahydrochloride with 0.05% H_2O_2 (Liquid DAB+ Substrate Chromogen System; Dako) for 3 minutes to induce a color reaction. The expression and localization of SRY was examined under a light microscope (Olympus, Japan), and the presence of a brown color reaction product indicated a positive result. Immunostained sections were evaluated by two investigators in a double blind fashion. Ten non-overlapping fields of view (200× magnification) were selected, and the mean value of the proportion of SRY-positive cells for each section was used for statistical analysis.

Determination of the proliferation of hepatocytes

To determine whether CXCR4-transduced BMSCs could promote the proliferation of hepatocytes, immunohistochemical staining for PCNA (1:100, sc-7909, Santa Cruz.) was performed with an ABC staining kit (Vector Laboratories) according to the manufacturer's recommendations. PCNA-positive cells were quantified by

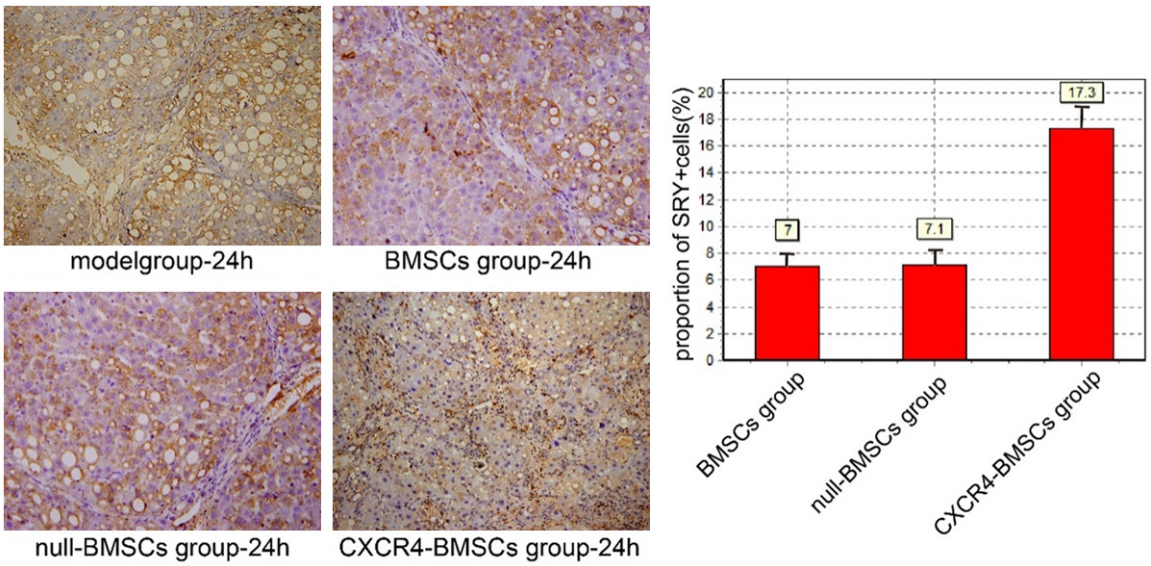

Figure 2. Effects of the overexpression of CXCR4 on the homing of BMSCs to cirrhotic liver. Left: homing of BMSCs to the cirrhotic liver of different experimental groups was observed at 24 hours after transplantation. A brown nuclear signal in some cells indicated the presence of SRY-positive cells (200× magnification). Right: quantitative analysis shows that the proportion of SRY cells in the BMSCs group and the null-BMSCs group is not significantly different ($P>0.05$). However, the proportion of SRY cells in the null-BMSCs group and the CXCR4-BMSCs group are significantly different ($P<0.05$). Results are expressed as the mean ± SD.

counting the number of positive hepatocytes in 10 random fields with a 20× objective.

Expression of the markers of hepatic progenitor cells

To determine whether the engrafted BMSCs could promote the proliferation of hepatic progenitor cells, immunohistological staining was performed for Jagged-1 (1:150, sc-6011, Santa Cruz.) and EpCAM (1:100, sc-66020, Santa Cruz.). Jagged-1- and EpCAM-positive cells were quantified by counting the number of hepatocytes in 10 random fields with a 20× objective.

Liver function assay

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin (ALB), total bilirubin (TBIL), cholesterol (CHO), and triglyceride levels were measured with an automated analyzer(Beckman DXC 600, Beckman Counter, Inc., Brea, CA).

Statistical analysis

Results are expressed as the mean ± SD. Student's *t*-test was performed to analyze the differences between two groups. Multiple-group comparisons were performed using one-way ANOVA followed by a Student-Newman-Keuls test. SPSS 17.0 statistical software was used for analysis. $P<0.05$ was considered statistically significant.

Results

CXCR4-Transduced BMSCs highly expressed the CXCR4 gene

Ninety-six hours after transduction, 100% of CXCR4-BMSCs were GFP-positive (**Figure 1A**, **1B**), and 96.34% of CXCR4-BMSCs were CXCR4-positive (**Figure 1C**). However, only 7.68% of GFP-BMSCs were CXCR4-positive (**Figure 1D**). These results showed that CXCR4-transduced BMSCs highly expressed the CXCR4 gene.

CXCR4 overexpression increases the in vivo homing of transplanted BMSCs to the cirrhotic liver

To assess the homing of BMSCs to the target tissue, the expression of the SRY gene was monitored. At 24 hour after transplantation, rats were sacrificed, and the number of SRY-positive cells in the liver tissue was counted. Some cells in the livers showed a brown nucle-

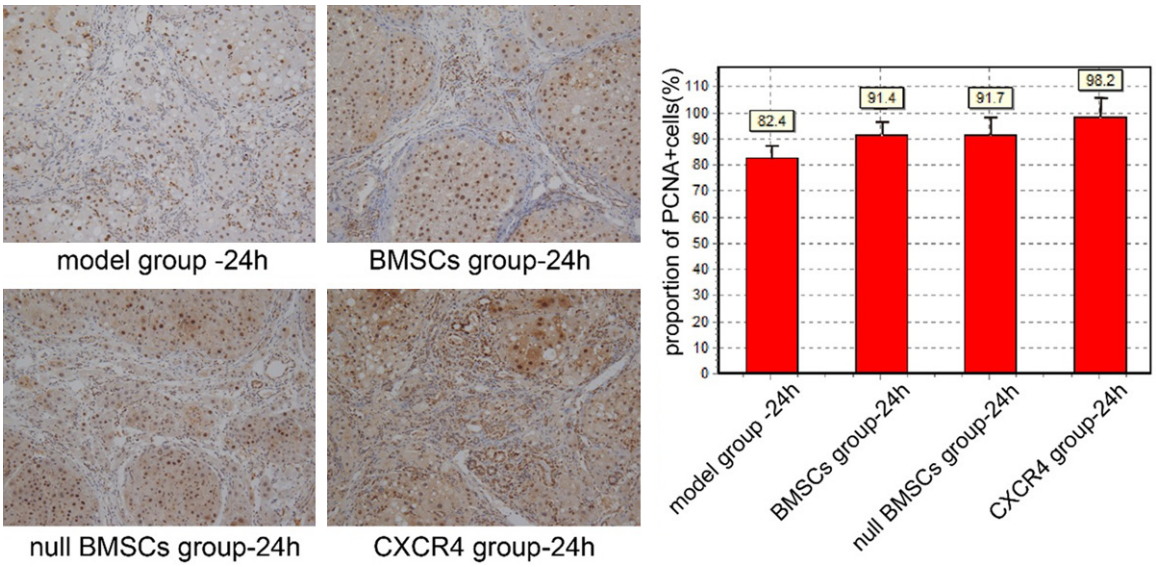

Figure 3. Determination of the proliferation of hepatocytes. Left: PCNA expression in hepatocytes was observed in different experimental groups at 24 hours after transplantation. A brown cytoplasmicsignal in some cells indicates the presence of PCNA positive cells (200× magnification). Right: quantitative analysis shows that the proportion of PCNA cells in the model group and BMSCs group is significantly different ($P<0.05$), whereas the proportion of PCNA cells in the null-BMSCs group and the BMSCs group are not significantly different ($P>0.05$). A significant difference ($P<0.05$) is observed in the null-BMSCs and CXCR4 group. The results are expressed as the mean ± SD.

ar signal in the experimental group, indicating the homing of BMSCs to the cirrhotic livers. The proportion of SRY-positive cells in the null-BMSC group was similar to that in the BMSC group. In contrast, the proportion of SRY cells in the cirrhotic livers further increased after the transplantation of CXCR4-BMSCs (**Figure 2**).

Effect of CXCR4 on the proliferation of hepatocytes of the cirrhotic liver

To evaluate the proliferation of hepatocytes, PCNA was detected using immunohistochemistry. At 24 hours after transplantation, rats were sacrificed and the PCNA-positive cells were counted. Some cells in the liver showed a brown nuclear signal in the experimental group, indicating that BMSCs could promote liver regeneration. The proportion of PCNA-positive cells in the null-BMSC group was similar to that in the BMSC group. However, the transplantation of CXCR4-BMSCs further increased the proportion of PCNA cells in the cirrhotic livers (**Figure 3**).

Effect of CXCR4 on the proliferation of HPCs of the cirrhotic liver

The Jagged-1 and EpCAM genes were identified as markers of hepatic progenitor cells (HPCs). At 24 hour after transplantation, some biliary duct cells in the portal area of the liver showed a brown nuclear stain in the experimental group, indicating that the BMSCs could promote the proliferation of HPCs. The proportion of Jagged-1-and EpCAM-positive cells in the null-BMSCs group was similar to that in the BMSC group. However, the transplantation of CXCR4-BMSCs further increased the proportion Jagged-1and EpCAM cells in the cirrhotic livers (**Figure 4A**, **4B**).

Dynamics of the liver functions of the liver cirrhosis animal model

At 24 h, 72 h and 7 d after transplantation, rats were sacrificed, and liver function tests, including ALB, CHO, TG, TBIL, ALT, and AST assays, were conducted. The liver function test results showed an improvement in cirrhotic rats that received cell transplants, in contrast with the controlled group rats. However, no significant differences were found among the groups of BMSCs, null-BMSCs and CXCR4-BMSCs (**Table 1**).

Discussion

Bone marrow-derived stem cells have been considered to have strong potential for clinical

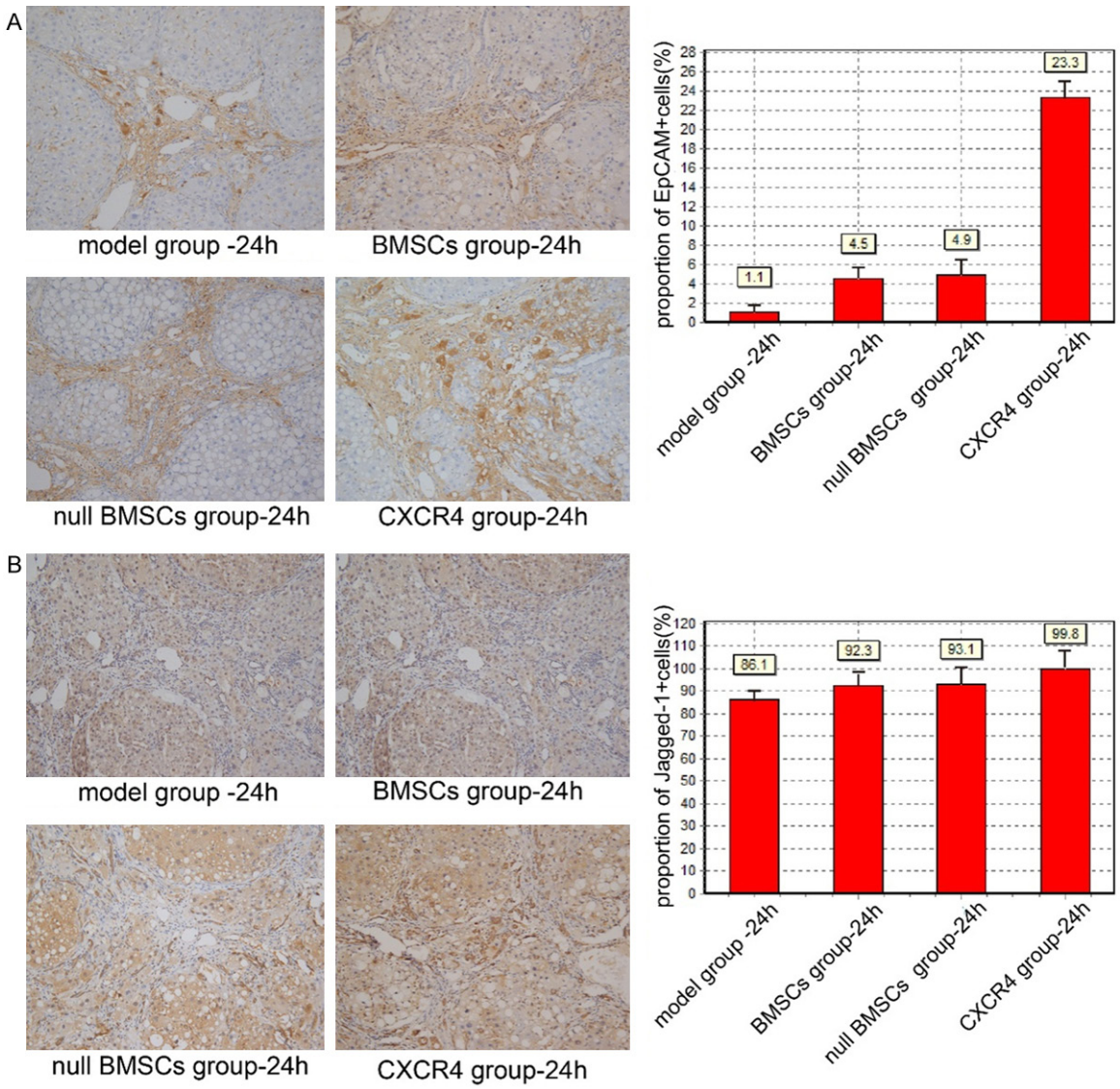

Figure 4. Effect of CXCR4 on the proliferation of the HPCs of cirrhotic liver. A. Left: EpCAM expression in the liver tissues was observe in different experimental groups 24 hours after transplantation. A brown membranous and cytoplasmic signal in some cells indicates the presence of EpCAM-positive cells (200× magnification). Right: quantitative analysis shows that the proportionof EpCAM cells in the model group and BMSCs group are significantly different ($P<0.05$), whereas the proportionof EpCAM cells in the null-BMSCs group and the BMSCs group are not significantly different ($P>0.05$). A significant difference ($P<0.05$) was observed in the null-BMSCs and CXCR4 groups. The results are expressed as the mean ± SD. B. Left: Jagged-1 expression in the liver tissues was observed in different experimental groups 24 hours after transplantation. A brown membranous signal in some cells indicates the presence of Jagged-1-positive cells (200× magnification). Right: quantitative analysis shows that the proportion of Jagged-1 cells in the model group and in BMSCs group is significantly different ($P<.05$), whereas the proportion of Jagged-1 cells in the null-BMSCs group and the BMSCs group is not significantly different ($P>0.05$). A significant difference ($P<0.05$) is observed in the null-BMSCs and CXCR4 groups. The results are expressed as the mean ± SD.

applications because of their relative ease of isolation, differentiation capacities, and paracrine and immunosuppressant activities [18-20]. Some clinical trials have been performed to examine the utility of the systemic administration of BMSCs to treat a variety of tissue damages [21, 22]. However, a significant barrier to progress has been the effectiveness of the cells' specific homing to damaged tissues [23, 24].

Table 1. Dynamics of the liver functions of the liver cirrhosis animal model (n=12)

		Pre-transplant	24 h after transplant	72 h after transplant	1 week after transplant
ALB (g/L)	CXCR4-BMSCs	30.10	32.42	45.41	52.44
	Null-BMSCs	29.96	30.67	46.60	50.89
	BMSCs	30.05	31.24	44.78	51.92
	Control	30.14	30.12	30.41	30.06
CHO (mmol/L)	CXCR4-BMSCs	0.85	1.49	1.66	2.33
	Null-BMSCs	0.91	1.33	1.70	2.45
	BMSCs	0.87	1.42	1.76	2.52
	Control	0.90	0.93	1.01	1.03
TG (mmol/L)	CXCR4-BMSCs	0.35	0.49	0.68	0.84
	Null-BMSCs	0.34	0.48	0.64	0.86
	BMSCs	0.32	0.50	0.65	0.88
	Control	0.36	0.35	0.38	0.40
TBIL (umol/L)	CXCR4-BMSCs	17.42	14.62	10.84	4.79
	Null-BMSCs	18.21	16.23	11.45	5.67
	BMSCs	17.56	15.98	12.02	5.48
	Control	18.03	17.93	18.21	17.86
ALT (U/L)	CXCR4-BMSCs	80.84	78.80	68.25	64.63
	Null-BMSCs	82.69	80.42	74.41	63.54
	BMSCs	82.06	79.90	76.53	65.24
	Control	81.76	80.79	79.97	69.90
AST (U/L)	CXCR4-BMSCs	312.12	278.24	189.32	170.95
	Null-BMSCs	300.04	286.02	176.46	172.01
	BMSCs	298.86	290.90	186.75	177.04
	Control	310.56	311.08	300.94	273.08

*$P<0.05$ was considered to have significantly differences. ALB: Albumin; CHO: Cholesterol; TG: Triglyceride; TBIL: Total Bilirubin; ALT: Alanine aminotransferase; AST: Aminotransferase aspartate.

Stromal cell-derived factor-1 (SDF-1) and its cellular receptor CXCR4 have been shown to direct the migration of stem cells associated with injury repair in many types of organ or tissue [25, 26]. In this study, we constructed a CXCR4-expressing lentivirus vector that we transduced into BMSCs and transplanted these transduced cells into cirrhotic rats. We found that CXCR4 was highly expressed in BMSCs during the early stage of BMSC transplantation but that after 72 h, the transduced BMSCs could not be detected in cirrhotic livers. This result demonstrated that the contribution of the BMSCs to liver function might depend on the differentiation of the engraftment of BMSCs. Therefore, some alternative mechanisms may be associated with the function of BMSCs in liver regeneration.

Some recent studies have hypothesized that stellate cells, portal fibroblasts, myofibroblasts, Kupffer cells, lymphocytes and some soluble factors constitute the liver progenitor cell niche and that the cross-talk between progenitor cells and myofibroblasts is essential for both fibrosis and parenchymal regeneration. Even more exciting are new data demonstrating that both resident liver cells and circulating cells from the bone marrow can function as stem cells, indicating that BMSCs might act as transplant microenvironment to impact the resident liver cells and contribute to liver regeneration [12]. In this study, we found more hepatocytes expressing the proliferation-related gene PCNA and more biliary duct cells expressing the HPC-related genes EpCAM or Jagged-1. Furthermore, in contrast with the null-BMSCs or BMSCs group, the transplantation of CXCR4-BMSCs further increased the proportion Jagged-1- and EpCAM-positive cells in cirrhotic livers. This result indicated that CXCR4 might contribute to cirrhotic liver through the transplant microenvi-

ronment, including paracrine effects, or via interact between the BMSCs and HPCs in the liver progenitor cell niche.

In summary, the present study was in partial agreement with previous studies which had shown that CXCR4 could promote BMSC engraftment in the liver at the early stage of transplantation. However, the definite mechanism of BMSCs' contribution to liver regeneration should be explored from the point of view of the dynamic microenvironment of the liver progenitor cell niche and not mainly through the direct transdifferentiation of BMSCs. In future studies, we plan to mimic the liver environment to explore the crosstalk between the CXCR4-BMSCs and HPCs, which might help improve cytokine-based therapies for liver cirrhosis.

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Disclosure of conflict of interest

None.

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