Therapeutic effect of transplanting magnetically labeled bone marrow stromal stem cells in a liver injury rat model with 70%-hepatectomy

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Summary

Background: There are only few reports about the use of bone marrow stromal stem cells (BMSCs) for the treatment of traumatic liver injury. This study aimed to study the therapeutic effect of fluorescence-labeled BMSCs administered to rats subject to traumatic liver injury.

Material/Methods: Male SD rats with a 70% resection of the liver were injected with feridex-labeled BMSCs which could be induced to functional hepatocytes in vitro. Liver function was assayed and the liver scanned by 1.5-T MRI at 12 hrs and on days 1, 3, 5, 7, and 14 post-operation. The pathological changes of liver sections were monitored.

Results: The serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, direct bilirubin, and total bilirubin in the transplantation group were significantly lower than the control group. The MRI showed rats of the transplantation group had an oval low signal area at 12 hr after operation; the low signal range gradually expanded and the signal intensity gradually decreased over 14 days after operation. The low signal range in the control group disappeared 12 hr after the operation. After Prussian blue staining, rats of the transplantation group contained blue granules with no significant hypertrophy or edema in hepatocytes, while the control group showed no blue granules with significant hypertrophy and edema.

Conclusions: The BMSCs transplanted into the injured rat liver gradually migrate to the surrounding liver tissue and partially repair the liver surgical injury in rats. BMSCs may represent an effective therapeutic approach for acute liver injury.

key words: bone marrow stromal stem cells • traumatic liver injury • cell transplantation • MRI • rat

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**Background**

Liver injury, which occurs in 62.5% of patients suffering abdominal trauma, is the most common cause of death associated with abdominal trauma. In the United States, liver trauma accounts only for 15–20% of blunt abdominal injuries, but is responsible for more than 50% of deaths from abdominal trauma [1]. A recent study reported the mortality rate of liver injury at 9%, partially due to the requirement of liver resection in 30% of liver injuries [2]. Orthotopic liver transplantation is the most effective treatment for severe liver injury, but the widespread clinical application of liver transplantation is restricted by the shortage of available donor livers and multiple postoperative complications. Stem cell therapy has been considered a viable treatment option for liver injury in the future. By eliminated the need for a donor organ, while having the potential to promote liver regeneration with fewer complications than operation, stem cell therapy has raised great hope for the improvement of liver injury treatment.

One of the hallmark features of the liver is its remarkable ability to maintain constant size despite injury. Although the precise molecular mechanisms that modulate liver regrowth are not entirely clear, the ability of the liver to quickly regain cells after injury is well documented [3]. Natural repair of liver is mainly dependent on endogenous cell pools, including hepatocytes, hepatic progenitor cells (HPCs) / oval cells (OCs), and bone marrow stromal stem cells. The role of hepatocyte replication and hepatic progenitor cells in liver regeneration has been researched in great detail. It has been shown that hepatocytes have the ability to replicate and contribute to the regrowth of the liver [4-6]. Hepatic progenitor cells (of the Canal of Hering) are the equivalent of oval cells in a rat model and have also been shown to generate large numbers of hepatocytes in liver regrowth [7-9]. Though evidence has shown differentiation of bone marrow stromal stem cells (BMSCs) into hepatocytes, the extent of the role of BMSCs in liver regeneration and repair is still uncertain. Sources of exogenous stem/progenitor cells that are currently under investigation in the context of repair of liver injury include embryonic stem cells, bone marrow-derived mesenchymal stem cells, fat-derived mesenchymal stem cells, fetal annex stem cells and endothelial progenitor cells (EPCs) [10-15].

BMSCs have been shown to differentiate into hepatocytes in vivo and in vitro under certain conditions [16-19]. MSCs are multipotent adult stem cells that are easily obtained from BM aspirates and expanded into large quantities in vitro. Primary BM-derived stem cells can undergo a process of differentiation; these differentiated cells express various hepatocyte-specific markers and have hepatocyte-specific bioactivities, including urea production, albumin secretion and glycogen storage.

There are a number of studies on the application of BMSCs for the treatment of chronic liver diseases, but only few reports about the use of BMSCs for the treatment of traumatic liver injury. AbdelAziz et al. [20] reported that injection of BMSCs into rats with CCI\textsubscript{4} induced liver injury resulted in protection against the fibrotic process through minimization of collagen deposition. In addition, this study demonstrated the ability of BMSCs to differentiate into hepatocytes. Kuo et al., reported that transplantation of different doses of BMSCs into rat spleen resulted in BMSC differentiation into functional hepatocytes, rescuing rats from liver failure [21].

This study aimed to investigate the effect of BMSCs in liver repair following traumatic injury in rats. We transplanted feridex-labeled BMSCs into rats with 70% excision of the total liver volume. Feridex-labeling of BMSCs does not alter biochemical or hemato logic measures of organ function [22]. The indicators of rat liver function were assayed and migration of BMSCs in the rat livers was monitored by 1.5-T superconducting MR imaging equipment and histological observation. Based on the literature available on the efficacy of BMSCs in chronic liver injury, we believe BMSCs will promote liver regeneration and differentiate into functional hepatocytes, thus increasing liver functionality.

**Material and Methods**

**Ethics statement**

All animal experiments were conducted by Drs Xiaowu Chen and Dajian Zhu in the Laboratory Animal Center at Southern Medical University, Guangzhou, China. The procedure was approved by the Ethics Committee of Southern Medical University, Guangzhou, China [Permit No.: SCXK (Yue) 2006-0015].

**Animals**

Male and female Sprague-Dawley (SD) rats aged 5–6 weeks (weighing 100–120 g) were used as BMSC donors (purchased from Sun Yat-sen University Experimental Animal Center, Guangzhou, China). Male SD rats aged eight weeks were used as BMSC recipients.

**Isolation and culture of rat BMSCs**

BMSCs from SD rats were isolated and cultured as per an established protocol [23]. Five week old rats were anesthetized with 8% chloral hydrate (4.0 ml/kg); the femurs and tibiae of the rats were excised and the soft connective tissue removed. The two ends of the femurs and tibiae were excised and the cells of the bone marrow were harvested by flushing the bone marrow cavity with complete culture medium. The extract was filtered with a 200 mesh filter, centrifuged for 5min at 1,000 × g, resuspended in media, and inoculated into a 25-cm\textsuperscript{2} flask containing Dulbecco’s modified Eagle’s medium with low glucose (DMEM-LG, GBICO corp., America) supplemented with 10% fetal bovine serum (FBS, BIOIND Inc., Israel) at 37°C in 5% CO\textsubscript{2}. The medium in the culture flask was replaced with the same volume of fresh 48 hrs later, then replaced every 3–5 days when adherent cells reached 70–80% confluence. Cell collection was completed with 0.25% trypsin-EDTA (GBICO) treatment and subculturing using 25-cm\textsuperscript{2} flasks.

**Feridex-labeling of rat BMSCs**

Cultured rat BMSCs were labeled with superparamagnetic nanoparticles as previously described [24,25]. BMSCs (third passage) were collected by 0.25% trypsin-EDTA and complete culture medium containing 10% FBS. The resulting mixture was centrifuged for 5 min at 1,000 × g, washed with...
phosphate-buffered saline (PBS) twice, and resuspended in 1 ml PBS. Finally, the cells were counted and separated into two aliquots of 1×10^6 cells: one for flow cytometry analysis with anti-rat CD29, CD44, CD34, or CD45 antibodies (Pharmingen Inc., San Diego, CA) and the other for feridex labeling. The other sample was centrifuged again, resuspended, and inoculated for 12 hr into a 25-cm² flask containing complete culture medium with a combination of poly-L-lysine at 0.75 µg/ml (from Sigma-Aldrich Co., St Louis, MO) and feridex at 11.2–19.6 µg/ml (from Pharmagenesis Inc., Palo Alto, CA). The feridex-labeled BMSCs were collected using the same method as described above, followed by centrifugation for 5 min at 1,000 × g, and fixation by 2.5% glutaraldehyde at 4°C for 3 days. The intracytoplasmic iron particles within the cells were evaluated with a 60-kV electron microscopy and Prussian blue staining.

Cytotoxicity assay
The cytotoxicity of feridex labeling to primary rat BMSCs was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-di-phenyltetrazolium bromide (MTT) assay. BMSCs subject to feridex labeling were incubated for 1, 2, 3, 4 or 5 weeks, and 20 µl MTT reagent (5.0 mg/ml) was added to each well after removal of medium, and cells incubated for a further 4 h at 37°C. The absorbance of formazan, a metabolite of MTT, in the resulting solution was photometrically measured at a wavelength of 595 nm using a microplate reader (Tecan Instruments Inc., Research Triangle Park, NC).

Induction of differentiation of BMSCs into hepatocyte-like cells
Feridex-labeled BMSCs were incubated with hepatocyte growth factor (HGF) at 20 ng/ml and epidermal growth factor (EGF) at 10 ng/ml for 7 days.

Construction of liver injury rat model with 70% hepatectomy
An acute liver injury rat model with 70% hepatectomy was constructed as described previously [26,27]. 40 SD rats were equally divided into transplantation group and control group randomly. All of the rats had been prohibited from eating and drinking for 12 hr, and were anesthetized by chloral hydrate (4 ml/kg) via injection into peritoneal cavity. The operation was started after tension in rats for 1 hr and on days 1, 3, 5, 7, 14 after operation. All of the rats that received cells and saline were anesthetized by chloral hydrate (2.0 ml/kg) before examination. The rats were placed in prone position in the knee coil, all the images of rat livers scanned by MRI consisted of T1-weighted images (40/15, repetition time msec/echo time msec) and T2-weighted images (4000/100, repetition time msec/echo time msec).

MRI scanning in liver injury rats with or without BMSC transplantation
We have developed an MRI method to track the BMSCs in the liver in vivo [28]. The rat livers were examined by 1.5-T MR imaging equipment (type: EXCELART/P3, Toshiba) 12 hr and on days 1, 3, 5, 7, 14 after operation. All of the rats that received cells and saline were anesthetized by chloral hydrate (2.0 ml/kg) before examination. The rats were placed in prone position in the knee coil, all the images of rat livers scanned by MRI consisted of T1-weighted images (40/15, repetition time msec/echo time msec) and T2-weighted images (4000/100, repetition time msec/echo time msec).

Assessment of hepatic function in liver injury rats with or without BMSC transplantation
Blood samples were obtained from each rat of the two groups pre-operation, at 12 hr, and on days 1, 3, 5, 7, 14 after operation. The samples were centrifuged for 10 min at 1,000 × g and 1.0 ml serum was collected, the levels of the liver function indicators, such as alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TB) and direct bilirubin (DBIL), of both the transplantation group and control group were analyzed by an Olympus AU2700 automatic biochemical analyzer (Tokyo, Japan).

Flow cytometry
For each sample, BMSCs were isolated by centrifugation at 1,000 × g for 6 min, and transferred into screw-capped tubes and stored at –80°C. Flow cytometry was performed (i.e. CD29, CD34, CD44 and CD45).

Reverse transcription-polymerase chain reaction (RT-PCR) for the detection of albumin (ALB) and α-fetoprotein (AFP)

The expression and portal vein injection and femoral vein injection). Our results showed that the local liver injection gave the best therapeutic effect compared to other two approaches (data not shown). In this study, 1.0 ml 1×10^6/ml feridex-labeled BMSCs suspension was injected into the right lobe slowly in the transplantation group within 15 min; the rats of control group were injected with 1.0 ml saline in the same position. The peritoneal cavity was flushed with metronidazole and saline. In order to close the peritoneal cavity layer by layer with 3-0 silk, the rats were given 4.0 ml of 40,000 U penicillin and 5% glucose by intravenous injection within the first 3 days after operation, twice a day, with free access to water and food for 6 hr.

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Reverse transcription-polymerase chain reaction (RT-PCR) for the detection of albumin (ALB) and α-fetoprotein (AFP)

The expression and ALB and AFP in BMSCs on days 3, 5, 7, 21 and 28 after induction with growth hormones was determined by RT-PCR amplification using Access RT-PCR System according to the manufacturer’s instructions. The housekeeping gene GAPDH was used in the same reaction as a reference for standardization of the procedure. The primer sequences for ALB were as follows: 5'-ATA CAC CCA GAA AGC ACCTC-3'; and 3'-CAC GAA TTG TGC GAATG-5'. The sequences for GAPDH were: 5'-AAC AGC AGA GTG CTG CTG CAAAC-3', and 3'-AGG TTT CGT CCC TCA GAAAG-3'. The resultant PCR products were separated by 1.0% agarose gel.
electrophoresis and visualized by means of ethidium bromide staining using a GDS8000 image analysis system (Syngene, Cambridge, the UK). The levels of ALB or AFP mRNA were normalized to that of GADPH present in the same sample.

**Histological examination**

Rat livers of the two groups were harvested on the 14th day after operation, fixed with 10% formalin, and embedded with paraffin. Histological analysis of liver tissues was conducted by serial tissue section and Prussian blue staining to identify intracytoplasmic iron particles. The liver sections were observed under the light microscopy (×40), and the blue granule cells in each field were calculated for five random fields.

**Statistical analysis**

Data is expressed as mean ±SD. All analyses were performed with SPSS13.0 software. All variables were determined by a repeated measure analysis of variance (ANOVA) between the transplantation group and the control group, followed by an F-test. Results were considered statistically significant when P<0.05.

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**RESULTS**

**Morphology of cultured rat BMSCs**

The adherent cells had a colony-like distribution in 3 days after inoculation into the flask under phase-contrast microscopy. Typically, about 70–90% confluence was reached by days 7–9. Cells of the third passage had a typical fibroblast-like morphology and good refractivity. The profile of the cells could be clearly seen, but the nuclei were not distinctly visible (Figure 1).

**Surface markers of isolated rat BMSCs and feridex labeling efficiency**

The BMSCs isolated from rat bone marrow were positive for CD29 (99.7%) and CD44 (99.4%) and negative for CD34 (1.3%) and CD45 (2.2%) by flow cytometry (Figure 2), which is in agreement with the results from a previous study [29]. The Prussian blue staining of the feridex-labeled BMSCs showed that iron particles were blue (Figure 3A). When the concentration of feridex was 11.2, 14.0, 16.8 and 19.6 µg/ml, the labeling efficiency for rat BMSCs was 71, 83, 91...
and 96%, respectively. Electron micrographs of feridex-labeled BMSCs showed that endosomal vesicles contained iron particles, the area outlined shows high-density granule aspect of endosomes (Figure 3B). Labeling of feridex at concentrations ≤16.8 µg/ml over 5 weeks did not show significant cytotoxicity towards BMSCs (P>0.05), but feridex at 19.6 µg/ml showed significant cytotoxicity to BMSCs (>25%, P<0.05).

Differentiation of rat BMSCs into functional hepatocyte-like cells in vitro

After incubation of BMSCs with HGF and EGF for 7 days, the cells became triangle-like, polygon-like, or irregular shape. After 14 days, the cells were oval-like and formed clusters (Figure 3C); after 21 days, there was increased number of oval-shaped cells.

When unlabeled and feridex-labeled BMSCs were incubated with HGF and EGF, there was no detectable AFP mRNA after 3–5 days. AFT mRNA was detectable on day 7 and enhanced on day 14 but declined on day 28. For ALB mRNA, we observed its expression on day 14 and remained until day 28. When BMSCs were labeled with feridex at 19.6 µg/ml, the expression of AFP and ALB was significantly decreased compared to those cells labeled with feridex at concentration <16.8 µg/ml.

Effect of BMSC transplantation on liver function in rats with 70% heptectomy

ALT levels of transplantation group were lower than control group significantly on days 1, 3, 5 post-operation (P<0.05, Table 1). AST and TB levels of transplantation group were lower than control group significantly at 12 hr and on days 1, 3, 5 post-operation (P<0.05). ALP and DBIL levels of transplantation group were lower than the control group significantly 12 hr and on days 1, 3, 5, 7 post-operation (P<0.05). There was no statistically significant difference between indicators of the two groups 14 days after operation (P>0.05) (Table 1).

Tracking of BMSCs in rat liver by MRI imaging technique

In rats of control group, MRI showed an oval high signal area about 2×1 mm at the site of the liver transplant 12 hr after operation, the oval high signal area was not observed after this viewing (Figure 4A, B). In rats of transplantation group, an oval low signal area of about 3×5 mm was detected by MRI in the site of the liver transplant at 12 hr after operation. The low signal area gradually expanded through the course of the study, as the area expanded to 5×7 mm 14 days post-operation (Figure 4C, D). At the same time, the signal intensity gradually decreased from 12 hr to day 14 after operation.

Effect of BMSC transplantation on liver histology and BMSC counting in rats with 70%-hepatectomy

In the sham-operated rats, the liver was red-brown with thin lobes and the edge of the liver was sharp (Figure 5A). In the BMSC-transplanted rats, the liver size was larger than before operation with enlarged lobes and stump edge (Figure 5B). No blue granule cells were observed in the liver of the control group, but significant hypertrophy and edema of the liver cells was apparent (Figure 5C). In rats of the transplantation group, cells with blue granules were distributed in the liver sinusoids, with an average of 40–50 cells in each field. No significant hypertrophy and edema of liver cells was observed (Figure 5D).

**DISCUSSION**

To track the in vivo paths and disposition of BMSCs from the donors, we labeled these cells with feridex which is often used...
in clinical settings as a magnetic resonance imaging contrast media. As aqueous colloid of superparamagnetic iron oxide associated with dextran, feridex at 19.6 µg/ml has some cytotoxicity to BMSCs as shown in our in vitro assay. Other studies have found that feridex at concentrations >22.4 or 25 µg/ml showed significant cytotoxicity towards BMSCs [30,31]. High concentrations of feridex also reduce the differentiation of BMSCs into hepatocytes [31]. Thus, we have chosen 16.8 µg/ml as the optimal concentration for feridex labeling of BMSCs.

Table 1. Effect of BMSC transplantation on serum levels of ALT, AST, ALP, total bilirubin (TB) and direct bilirubin (DBIL) in liver-resected rats (mean ±SD).

| Treatment        | Pre-transplantation | Time after operation |
|------------------|---------------------|----------------------|
|                  | 12 hr   | 1 day   | 3 days  | 5 days  | 7 days  | 14 days  |
| **ALT (U/L)**    |         |         |         |         |         |         |
| BMSC-treated     | 29±5    | 579±90  | 253±49c | 161±43c | 33±6c   | 28±7     | 32±5     |
| Sham             | 32±3    | 653±118 | 365±38  | 282±40  | 50±6    | 33±6     | 31±3     |
| **AST (U/L)**    |         |         |         |         |         |         |
| BMSC-treated     | 123±15  | 1,155±200c | 542±152c | 119±21c | 114±15c | 113±15   | 110±12   |
| Sham             | 117±12  | 1,293±166 | 879±120  | 165±17  | 127±10  | 120±14   | 119±21   |
| **ALP (U/L)**    |         |         |         |         |         |         |
| BMSCs            | 177±37  | 203±27c | 231±33c | 238±34c | 199±45c | 187±40b  | 176±43   |
| Sham             | 185±40  | 224±29  | 259±32  | 307±44  | 238±39  | 219±32   | 187±18   |
| **TB (µmol/L)**  |         |         |         |         |         |         |
| BMSC-treated     | 0.97±0.38 | 6.54±0.52c | 4.91±0.58c | 3.02±0.73c | 1.12±0.29c | 0.97±0.23c | 0.99±0.21c |
| Sham             | 1.19±0.39 | 6.87±0.53c | 5.49±0.70c | 4.70±0.67c | 1.99±0.35c | 0.90±0.13c | 0.94±0.22c |
| **DBIL (µmol/L)**|         |         |         |         |         |         |
| BMSC-treated     | 0.29±0.11 | 4.79±0.38c | 3.85±0.67c | 2.93±0.40c | 1.85±0.32c | 0.34±0.08c | 0.34±0.13c |
| Sham             | 0.28±0.07 | 5.70±0.59c | 4.68±0.63 | 3.63±0.26 | 2.66±0.26 | 1.01±0.12 | 0.32±0.09 |

* P<0.05, BMSC-transplanted vs. sham group; ** P<0.01, BMSC-transplanted vs. sham group; *** P<0.001, BMSC-transplanted vs. sham group.

Figure 4. MRI images of the rat live 12 hr and 7 days after operation. (A) sham, 12 hr after operation; (B) sham, 7 days after operation; (C) BMSC-transplanted, 12 hr after treatment; and (D) BMSC-transplanted, 7 days after treatment.
undergo symmetrical mitosis [32]. However, as suggested by the high mortality rate of liver injury, this mechanism is often not enough to regenerate the liver to functional levels. When this type of regeneration fails, a second mechanism based on stem cells from the canals of Hering can play a role [33,34]. Treatment of liver injury due with exogenous BMSCs is thought to effect liver regeneration through direct differentiation of these BMSCs into hepatocytes, as well as through delivery of growth factors that promote liver regeneration and cell fusion [35,36]. In this study, MRI scanning showed that treatment with exogenous BMSCs does in fact cause gradual BMSC migration to the surrounding liver tissue from the spot of transplantation. In addition, histological observation showed that BMSCs distribute themselves and eventually settle in the liver sinusoids.

The results support our hypothesis that BMSC treatment promotes regeneration resulting in an increase in liver function, though the exact mechanism is not fully elucidated. The levels of the liver functionality enzymes in the BMSC transplantation group were significantly lower than that of the control group at the same period, suggesting damage to liver functionality of the transplantation group was less than damage to the control group. The transplantation group’s lack of pathological changes when compared to the tightly packed, hypertrophic, and hydropic hepatocytes of the control group also indicate a healthier, better functioning rat liver in the transplantation group after treatment.

Our findings have showed that BMSCs recovered rat liver functions and ameliorated the pathological changes in traumatic liver injury. However, the mechanism of how BMSCs migrate and repair injured liver is still unknown. Our in vitro study has shown that BMSCs can be induced to functional hepatocyte-like cells in the presence of HGF and EGF. It can be anticipated that the injected BMSCs might differentiate into functional hepatocytes in vivo and thus improve the liver function. It has been reported that laminin in the liver induces transplanted cells to the hepatic parenchyma, resulting in adherence to these molecules [37]. Generally, the laminins reside in the portal and interlobular veins and would increase in number approximately 3 days after partial hepatectomy. Thus, laminin might play an important role in the biological process of migration and differentiation of BMSCs [38].

The chemokine stromal cell-derived factor-1 (SDF-1), which attracts human and murine progenitors, is expressed by liver bile duct epithelium and mediated by its receptor CXCR4, which is expressed by endothelial and various stromal cell types in the bone marrow. SDF-1 and its receptor CXCR4 participate in the homing of BMSCs [39,40], referred to as the SDF-1/CXCR4 pathway. The serum from rats with injured livers may enable BMSCs expression of a-fetoprotein and albumin mRNA [41], which we believe is closely tied to BMSC liver injury repair. Additionally, participation of hepatic mast cells the regeneration of rat liver may contribute to the overall mechanism of recovery after partial hepatectomy [42].

CONCLUSIONS

The usage of BM-derived stem cells for treatment of liver disease might sidestep many obstacles, such as ethical concerns and risks of rejection. In the future, perhaps localization of BMSCs to the canal of Hering (a stem cell “niche”) might provide even more appropriate conditions for stem cell growth and differentiation. This paper has shown the therapeutic effect of BMSC treatment on liver function in traumatic liver injury. As the mechanism behind BMSC treatment is expounded, more powerful stem cell treatments for liver injury using different delivery and targeting techniques can be developed.

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