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The role of SDF-1-CXCR4/CXCR7 axis in biological behaviors of adipose tissue-derived mesenchymal stem cells in vitro

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ABSTRACT

Numerous studies have reported that CXCR4 and CXCR7 play an essential, but differential role in stromal cell-derived factor-1 (SDF-1)-inducing cell chemotaxis, viability and paracrine actions of BMSCs. Adipose tissue-derived mesenchymal stem cells (ADSCs) have been suggested to be potential seed cells for clinical application instead of bone marrow derived stroma cell (BMSCs). However, the function of SDF-1/CXCR4 and SDF-1/CXCR7 in ADSCs is not well understood. This study was designed to analyze the effect of SDF-1/CXCR4 and SDF-1/CXCR7 axis on ADSCs biological behaviors in vitro. Using Flow cytometry and Western blot methods, we found for the first time that CXCR4/CXCR7 expression was increased after treatment with SDF-1 in ADSCs. SDF-1 promoted ADSCs paracrine, proliferation and migration abilities. CXCR4 or CXCR7 antibody suppressed ADSCs paracrine action induced by SDF-1. The migration of ADSCs can be abolished by CXCR4 antibody, while the proliferation of ADSCs was only downregulated by CXCR7 antibody. Our study indicated that the angiogenesis of ADSCs is, at least partly, mediated by SDF-1/CXCR4 and SDF-1/CXCR7 axis. However, only binding of SDF-1/CXCR7 was required for proliferation of ADSCs, and CXCR7 was required for migration of ADSCs induced by SDF-1. Our studies provide evidence that the activation of either axis may be helpful to improve the effectiveness of ADSCs-based stem cell therapy.

1. Introduction

Progenitor cells was usually administered via intracoronary infusion or transplanted directly into the ischemic region for cell therapy for the treatment of ischemic disease. Recently, there has been evidence that ADSCs hold great potential for such stem cell-based therapy [1–3]. ADSCs are readily available and easily expand, possessing multilineage differentiation potential [1]. Compared with BMSCs, ADSCs show higher ability in reconstitute hematopoiesis, and less MSC-induced toxicity [2,3]. Moreover, ADSCs have more advantage in therapy for osteoporotic fractures and cerebral ischemia than BMSCs [4,5]. So it may be an alternative for BMSCs in autologous stem cells treatment. However, after being transplanted, ADSCs face a complex hostile environment with local hypoxia, oxidative stress and inflammation that may lead to cell loss/death on a large scale. Insufficient retention and survival of transplanted stem cells will dramatically reduce therapeutic effects [6,7]. It is crucial to promote the chemotaxis and viability of implanted ADSCs in order to maintaining along-term, effective MSC-based therapy.

The ischemic tissue produces numerous cytokines, chemokines, secreted proteins and growth factors, several of which are involved in cell chemotaxis and organ-specific homing of stem cells [8,9]. Among these factors, SDF-1, also known as CXCL12, is considered to be the most important chemokines in recruitment and migration of different stem cells [10,11]. SDF-1 exerts its biological function by binding to chemokine receptors CXCR4 and CXCR7 [12–14]. It has been demonstrated SDF-1/CXCR4 axis were required for mobilization and recruitment of BMSCs [10,13]. Furthermore, it also shows potential in regulating BMSCs proliferation and survival. However, the exact role of SDF-1/CXCR4 and SDF-1/CXCR7 aix in biological behaviors of ADSCs still remains unknown.

In the present study, we evaluated the functions of SDF-1/CXCR4 and SDF-1/CXCR7 axis on biological behaviors of ADSCs. We first demonstrated that the SDF-1/CXCR4 and SDF-1/CXCR7 signaling may mediate paracrine ability of ADSCs. However, only SDF-1/CXCR4 was involved in migration of ADSCs, and CXCR7 was required for proliferation of ADSCs induced by SDF-1. To the best of our knowledge, this is the first study that demonstrating the exact role of CXCR4 and CXCR7 in ADSCs paracrine, proliferation and migration induced by SDF-1.

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2. Materials and methods

2.1. Culture of ADSCs

Human ADSCs were isolated from subcutaneous adipose tissue samples obtained from liposuction aspirates from patients undergoing cosmetic liposuction, as described by Zuk et al. [7]. One patient aged 28 from affiliated hospital of Xu Zhou Medical College were selected. This study was carried out in accordance with the Code of Ethics of the World Medical Association and all examinations were performed after obtaining written informed consents. ADSCs were maintained in DMEM containing 10% fetal bovine serum. Cells were cultured in a 37 °C humidified incubator with 95% air, 5% CO_2. Before experimental use, we confirmed that ADSCs possessed the ability to differentiate into osteoblasts.

2.2. Flow cytometry

ADSCs at passages 3 were gathered to detect surface antigens, ADSCs from passage 0 to 3 were used to detect both CXCR4 and CXCR7 expression. Before immunostaining, cells were washed twice in phosphate-buffered saline (PBS), then incubated with mouse anti-human monoclonal antibodies PE-labeled CD29, CD106 or FITC-labeled CD34, CD44 CD49d and CD80 (BD Biosciences, NJ, USA) or FITC-labeled CXCR4, CXCR7 (R&D Systems, Minneapolis, MN) at 4 °C for 45 min. After washed in PBS, cells were stained with fluorescein isothiocyanate-labeled isotype-matched antibodies (1:200) (Boster Co., Wuhan, China) for 30 min at room temperature, and rinsed with PBS. Antigens were evaluated in 1 × 104, viable cells using a FACS Calibur cytofluorometer (Becton Dickinson) and were analyzed using CELLQuest software (Becton Dickinson). Background fluorescence was assessed by control tube staining with isotype-matched antibodies.

2.3. Cell proliferation assay

ADSCs at P3 were incubated in 96-well plate and experiment was proceeded everyday after seeding. Cell numbers were determined by a standard 3-(4,5-imethylthazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Sigma, St. Louis, MO). Cells were treated with 20 μl MTT (5 mg/ml), incubated at 37 °C for 4 h, 150 μl dimethyl sulphoxide DMSO was added to each well. Finally the plates were shaken and the optical density at 490 nm was measured on ELX-800 spectrometer reader (Bio-Tek Instruments Inc., USA). Four replicate wells were tested per assay and each experiment was repeated four times. Cell viability was calculated by growth curve with time as *X* axis and optical density as *Y* axis.

2.4. Migration assay

ADSCs at P3 were collected for transwell assay. The experiment was performed using a modified two chamber plates with a pore size of 8 μm from Millipore Inc (Billerica, MA). For migration assay, 1 × 105 ADSCs cells were seeded in serum-free medium in the upper chamber. Cells were pretreated with a CXCR4 or anti-CXCR7 antibody. Then, SDF-1 (Millipore, Billerica, MA) was added in the lower chamber at a concentration of 0.5 mg/L. After 12 h incubation at 37 °C, non-migrating cells in the upper chamber were carefully removed with cotton swab, cells that had traversed the membrane were fixed in methanol, stained with hematoxylin. The number of cells was calculated by counting at least five random separate fields (200-fold magnification) as the ratio of the experimental samples to the control samples × 100.

2.5. Wound healing assay

ADSCs at P3 were used to detect cell motility. Cells were seeded onto 35 mm plates at a density of 1 × 106 and cultured as common. The experiment was proceeded after ADSCs at 80–90% of confluency. An artificial wound was carefully created using P200 pipette tip scratching on the confluent cell monolayer. Photomicrograph was taken immediately (time 0 h), then cells were incubated in DMEM containing 1% fetal bovine serum. The migration of cells and closing of scratch wound was observed and microphotographs were taken each time point. Within each assay the experiments were performed in triplicates and the whole assay was repeated three times.

2.6. Western blot analysis

P3 ADSCs were harvested from the plates. Aliquots of cell extracts were separated on a 10% SDS–polyacrylamide gel. The proteins were then transferred to nitrocellulose membrane and incubated overnight at 4 °C with following antibodies: Rabbit anti-CXCR4, CXCR7 and β-actin (Cell Signaling Technology, Beverly, MA, USA). Membranes were then washed and incubated with secondary antibody (goat anti-rabbit IgG) for 2 h, stained by coloration fluid which contains 10 ml alkaline phosphatase buffer, 33 μl BCIP, and 66 μl NBT, and finally, the membrane is scanned.

2.7. ELISA for VEGF, HGF and β-FGF

ADSCs at P4 were incubated in 96-well plates and cultured as common. The experiment was proceeded after ADSCs at 70–80% of confluency. Cells were incubated in DMEM containing 1% fetal bovine serum for 2 d. The supernatants were collected and centrifugated at 1000 rpm for 5 min, then filtered at 0.22 μm. VEGF, HGF and β-FGF concentration of the condition medium were

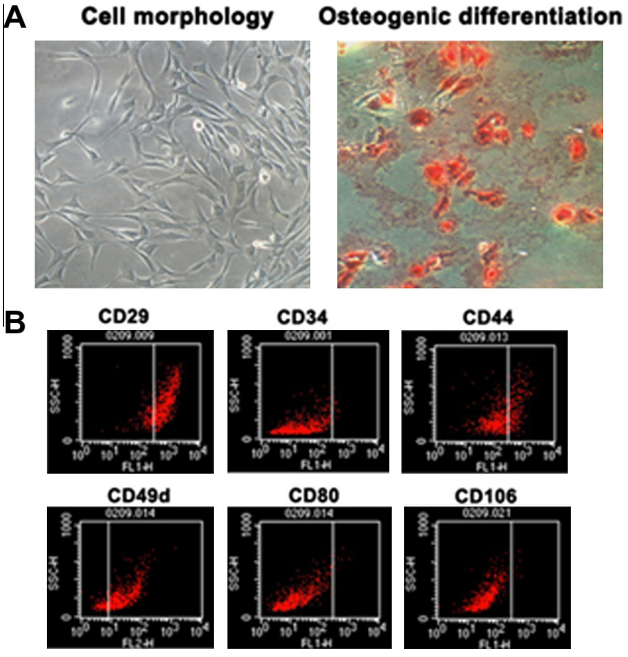

Fig. 1. Characteriation of human ADSCs. (A) Morphological characterization of ADSCs assessed by phase-contrast microscopy and osteogenic differentiation of ADSCs confirmed by alizarin bordeaux staining. (B) Flow cytometry histograms of human ADSCs.

determined by Quantikine ELISA kits according to the manufacturer's instructions (R&D Systems, Minneapolis, MN).

2.8. Statistical analysis

Numerical data are expressed as means ± SD. Statistical differences between the means for the different groups were evaluated using Student's *t*-test performed with SPSS 11.5 software (SPSS). $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Isolated cells from lipoaspirated fat displayed the properties of ADSCs

The average number of mononuclear cells isolated from lipoaspirated fat was 4.1 ± 1.6 × 106/ml ($n = 6$). Cells exhibited a elongated fibroblast-like morphology after 7 days culture (Fig. 1A). Alizarin bordeaux staining showed that cells possessed the ability of osteogenic differentiation (Fig. 1A). Flow cytometry (FCM) was used to detect the stem cell related surface markers, and our data showed that passage three (P3) cells were CD29, CD44 and CD49d positive, but CD34 CD80 and CD106 negative (Fig. 1B). These results demonstrated that mononuclear cells isolated from lipoaspirated fat were ADSCs.

3.2. CXCR4 and CXCR7 expression was up-regulated by SDF-1 stimulation

In order to detect the expression of CXCR4 and CXCR7 in different passage of ADSCs, we performed FCM and Western blot. We found that the mononuclear cells isolated from lipoaspirated fat (P0 ADSCs) expressed both CXCR4 and CXCR7 (Fig. 2A and B). However, CXCR4 or CXCR7 positive cells were significantly decreased during the process of cell culture, and almost no CXCR4 or CXCR7 positive cells in P3 ADSCs. Two days after treated with SDF-1, data from FCM and Western blot showed that both CXCR4 and CXCR7 expression was significantly upregulated in P3 ADSCs. Our results suggested that SDF-1 stimulated both CXCR4 and CXCR7 expression in ADSCs. (Fig. 2C and D).

3.3. SDF-1-CXCR4/CXCR7 axis was involved in ADSCs paracrine actions

We investigated the role of SDF-1/CXCR4 and SDF-1/CXCR7 aix in paracrine actions of ADSCs using ELISA assay. After 2 days stimulation of SDF-1, the concentration of VEGF, HGF and β-FGF in ADSCs condition medium were increased significantly. However, when we blocked CXCR4 or CXCR7 activation by corresponding antibody, the promotion of paracrine caused by SDF-1 were inhibited by either antibody. When CXCR4 and CXCR7 were blocking simultaneously, the promotion ability of SDF-1 was completely

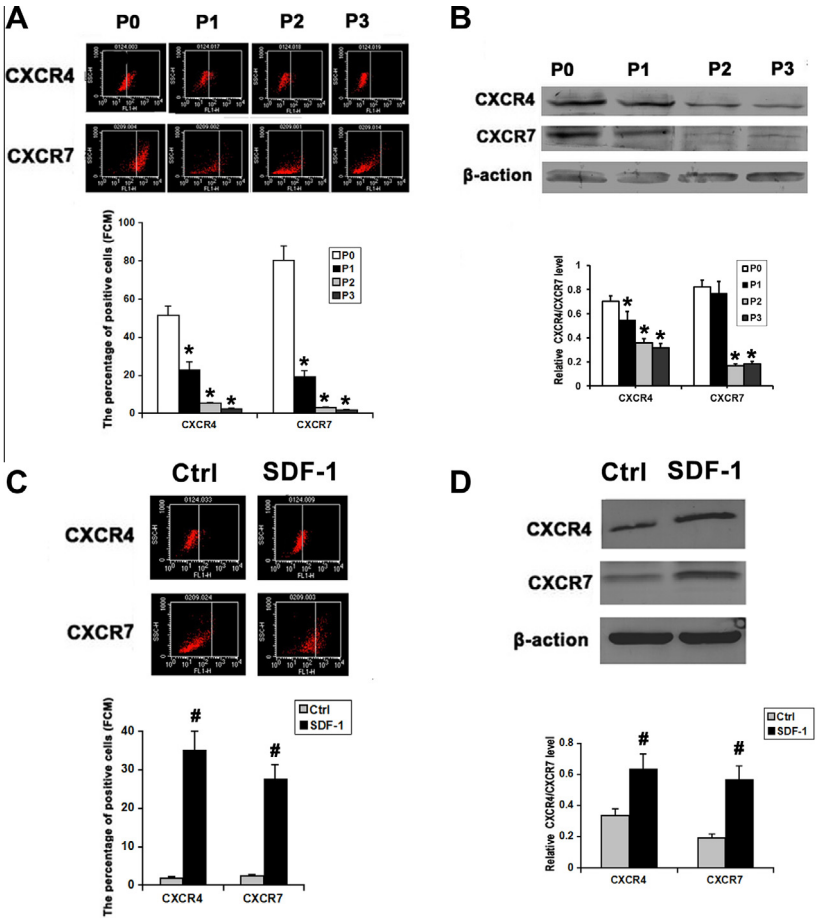

Fig. 2. SDF-1 stimulates CXCR4 and CXCR7 expression. (A) Flow cytometry were used for the analysis of CXCR4 and CXCR7 levels in ADSCs from passage 1 to 3. (B) Western blot were used for the analysis of CXCR4 and CXCR7 levels in ADSCs from passage 1 to 3. The expression of CXCR4 and CXCR7 significantly reduced from P0 to P3. $^{*}P < 0.05$ vs. P0 ADSCs. (C) Flow cytometry were used for the analysis of CXCR4 and CXCR7 levels in ADSCs exposed to 0.5 mg/L SDF-1. (D) Western blot analysis was used for the analysis of CXCR4 and CXCR7 levels in ADSCs exposed to 0.5 mg/L SDF-1. SDF-1 stimulation was able to induce both CXCR4 and CXCR7 expression in P3 ADSCs for 2 days. $^{\#}P < 0.05$ vs. P3 ADSCs. All experiments were carried out in triplicate.

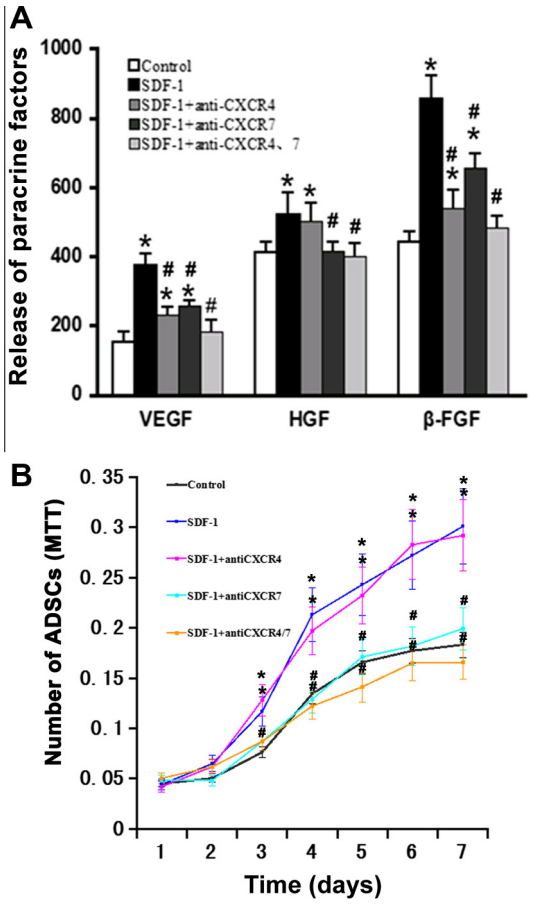

Fig. 3. SDF-1-CXCR4 /CXCR7 aix is required for ADSCs paracrine actions and proliferation. ADSCs stimulated with or without 0.5 mg/L SDF-1 were treated with 10 mg/L anti-CXCR4 or anti-CXCR7 antibody. (A) ELISA was performed to determine production of VEGF, β-FGF and HGF from ADSCs. (B) Standard MTT assay for mitochondrial viability were performed to detected cell proliferation ability. Numbers of cells were evaluated by optical density at 490 nm. $^{*}P < 0.05$ vs. control. $^{\#}P < 0.05$ vs. SDF-1 stimulating group. $n = 3$ from different groups.

abolished (Fig. 3A). Our results indicated that CXCR4 and CXCR7 were involved in ADSCs paracrine induced by SDF-1.

3.4. SDF-1/CXCR7 but not SDF-1/CXCR4 was required for ADSCs proliferation

MTT assay was performed to examine whether SDF-1 were responsible for ADSCs proliferation. We found that SDF-1 stimulated cell proliferation compared with control group (Fig. 3B). When we block CXCR4 axis, there has no significant difference in cells proliferation ability that response to SDF-1. However, after treated with anti-CXCR7 antibody, the numbers of ADSCs cultured in 3–7 days were significantly lower than cells only given SDF-1. Our data revealed that SDF-1/CXCR7 axis can function in regulating proliferation of ADSCs.

3.5. SDF-1/CXCR4 axis was required for ADSCs motility

We further investigated the role of SDF-1/CXCR4 and SDF-1/CXCR7 axis in ADSCs motility. A transwell assay was performed in our study and we found that ADSCs migration through transwell chambers significantly increased on account of chemotaxis in response to SDF-1. Such chemotactic response was blocked by an anti-CXCR4 antibody, but not CXCR7 (Fig. 4A). In wound healing assay, SDF-1 promoted ADSCs migration compared with control group. Such effect was significantly impaired when SDF-1/CXCR4 axis was blocked by anti-CXCR4 antibody, but no influence on cell migration after blocking CXCR7 (Fig. 4B). Our data suggested that SDF-1/CXCR4 axis was involved in regulating ADSCs motility.

4. Discussion

ADSCs-based regenerative strategies hold tremendous promise and may become an alternative for BMSCs in various clinical application [4,5,15,16]. Most clinical trials of cell therapy are administering stem cells via intracoronary infusion or transplanting directly into the ischemic region [17]. The mobilization and recruitment of either transplanted cells or progenitor cells from the bone marrow are usually regulated by SDF-1 [18]. However, the role of SDF-1 and its receptors CXCR4, CXCR7 in biological behavior of ADSCs has not been well understood. The present study identified for the first time that CXCR4 and CXCR7 protein expression were induced by SDF-1 in ADSCs. SDF-1 promoted ADSCs paracrine actions through CXCR4 and CXCR7 receptors. Moreover, only SDF-1/CXCR7 aix was required for ADSCs proliferation and SDF-1/CXCR4 was involved in cell migration. Our study indicated that SDF-1-CXCR4/CXCR7 pathway may play a significant role in mobilization and homing of ADSCs, thus improve the efficacy of ADSCs-based therapy.

SDF-1 is secreted by endothelial cells, reticular cells or autocrine by MSCs [19]. It is upregulated in ischemic tissue and remains elevated for several days [19,20]. SDF-1 regulates cell chemotaxis and organ-specific homing via interaction with CXCR4 and CXCR7 [21]. In order to explore the role of SDF-1-CXCR4/CXCR7 signaling in ADSCs biological behaviors, we first detect CXCR4/CXCR7 expression in ADSCs. Our data showed that CXCR4/CXCR7 were highly expressed (positive rate 51.4% for CXCR4 and 80.3% for CXCR7) in P0 ADSCs. Unfortunately, the expression of both receptors declined following a few passages in the culture (positive rate 2.54% for CXCR4 and 1.89% for CXCR7 in P3 ADSCs). This would influence the homing and repairing potentials of ADSCs, leading to the impair effect of ADSCs-based therapy in ischemic or injured tissue.

In order to overcome this limitation, Cationic liposome and lentiviral vector system are used to genetic modify stem cells for overexpressing CXCR4 and CXCR7 [19,22]. Moreover, hypoxic preconditioning also advances CXCR4 and CXCR7 expression in MSCs [23,24], consequently enhancing their therapeutic effects for renal ischemia/reperfusion injury. In the present study, we firstly demonstrated that SDF-1 pretreating increased the level of both receptors in ADSCs. It indicated that a short-term exposure of ADSCs to SDF-1 may lead to inducible expression of CXCR4 and CXCR7. This would be useful for improving engraftment of repopulating stem cells in clinical transplantation. In addition, when treated with SDF-1, the secretion of VEGF, HGF and β-FGF from ADSCs were increased, cells migration and proliferation abilities were also improved. It suggested the critical role of SDF-1 in stem cell mobilization. Pretreating ADSCs with SDF-1 before systemically administration may significantly enhance their viability, thus lead to a long-term, effective MSCs-based therapy on would healing or tissue engineering.

As two cognate receptors of SDF-1, CXCR4 and CXCR7 play a essential but differential role in therapeutic potential of stem cells. It has been verified that SDF-1 may promote proliferation and homing of transplanted BMSCs via binding with CXCR4, while CXCR7 be more involved in cell survival viability and adhesion [10,12,25,26]. So, we further evaluated whether CXCR4/CXCR7 involved in ADSCs chemotaxis, viability and paracrine induced by SDF-1.

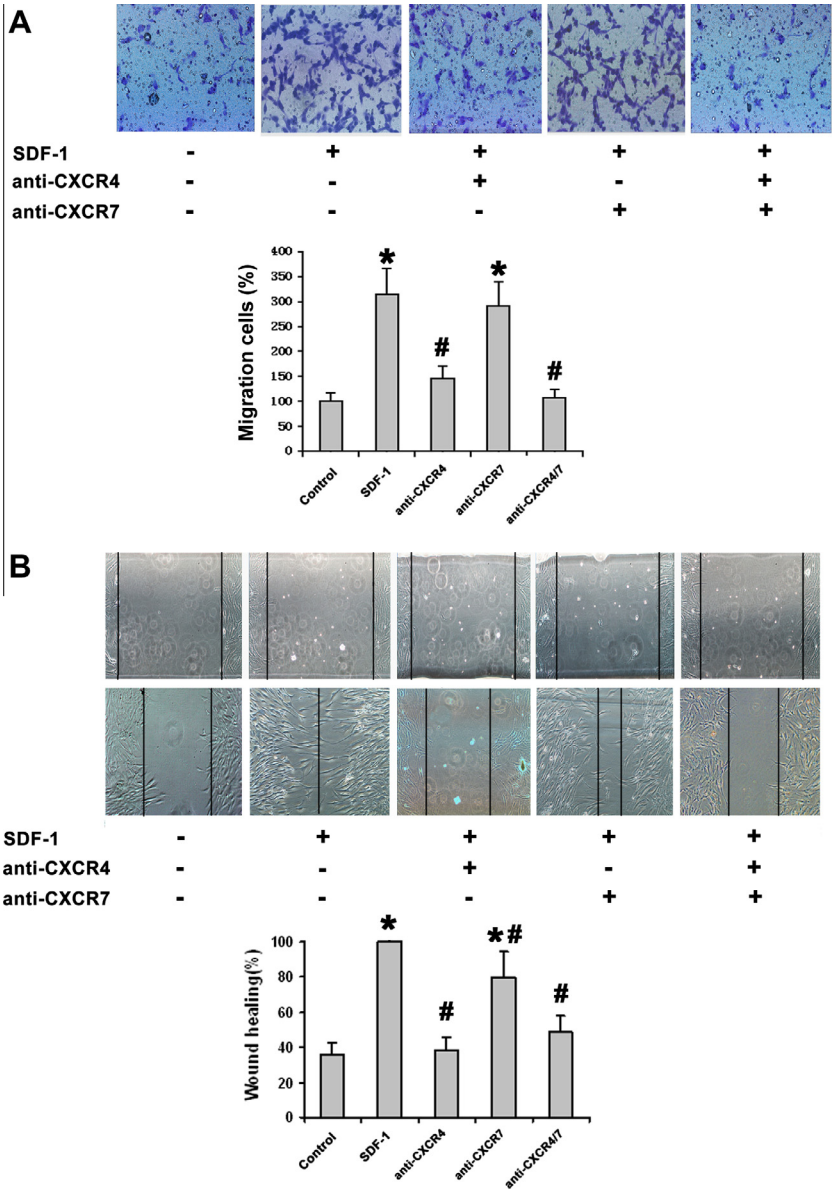

Fig. 4. SDF-1/CXCR4 promotes ADSCs motility ability. (A) Transwell assay was used to detect ADSCs migration. Cell numbers were counted in four random fields at 10 × 10 magnification, results are expressed as relative fold change compared with control value, which were given arbitrary percentage values of 100 C Data are shown as mean ± SD. $^{*}P < 0.05$ vs. control. $^{\#}P < 0.05$ vs. SDF-1 group. All experiments were carried out in triplicate. (B) Wound healing assay was preformed to detect cell motility after ADSCs stimulated with or without 0.5 mg/L SDF-1 were treated with 10 mg/L anti-CXCR4 or anti-CXCR7 antibody. The wounded spaces are reduced significantly in SDF-1 group, and such cell motility promation was partly offseted by anti-CXCR4 but not anti-CXCR7 antibody.

ADSCs are demonstrated to secrete some proangiogenic and mitogenic factors, such as VEGF, HGF and β-FGF to promote angiogenesis and wound healing [27,28]. Liu H et al. confirm that both SDF-1/CXCR4 and SDF-1/CXCR7 axis were required for BMSCs paracrine actions [23]. We pretreated ADSCs with neutralizing antibodies before stimulated by SDF-1, and found that the promotion in cell paracrine were obviously blocked by both CXCR4 and CXCR7 antibody. It supported the possibility that binding of SDF-1-CXCR4 and CXCR7 were equally important for the hematopoiesis-supporting properties of ADSCs in cell therapy.

In cell therapy, the absent of more definitive results were often attributed to poor recruitment and retention of transplanted cells [17,23]. Increasing in cell chemotaxis, transendothelial migration ability are expected to enhance therapeutic benefit [17]. Numerous studies have proved that CXCR4 is of pivotal importance in stem cell chemotaxis and migration [20,25,26,29,30]. We used transwell assay and wound healing assay to assess the role of CXCR4/CXCR7 in ADSCs motility. As expected, either cells migration through transwell chambers or scratch wound repairing ability were increased in response to SDF-1. Moreover, when pretreating cells with antibodies before stimulated by SDF-1, the promotion in cell migration was obviously blocked by CXCR4 antibody, but not CXCR7. These data suggested CXCR4 an important role in ADSCs migration and the activation of SDF-1/CXCR4 signaling maybe more important for the infused ADSCs homing to the ischemic tissue than CXCR4.

Increasing in circulating progenitor cell numbers are also expected to improve cells recruitment [17,31,32]. SDF-1 is demonstrated to have potential in regulating proliferation and survival of BMSCs through CXCR4 and CXCR7 [10,12,23,33]. In this study, we confirmed that SDF-1 increased ADSCs proliferation using MTT assay. In addition, the blocking of CXCR7 may suppress cell self-re-

newal capacity. However, inhibition of CXCR4 expression has no effect on cell proliferation increased by SDF-1. Our result suggested that the activation of CXCR7 is responsible for ADSCs self-renewal capacity. This would be helpful to elevate circulating ADSCs number and enhance the number of recruited cells, so that maximize the effectiveness of ADSCs-based therapy.

In summary, we provide novel evidence that SDF-1-CXCR4/CXCR7 axis play an essential but different role in regulating ADSCs migration, proliferation and paracrine actions in vitro. Our studies support the hypothesis that the activation of SDF-1-CXCR4/CXCR7 signaling is of crucial importance in cell mobilization and retention during clinical application.

Acknowledgments

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