Therapeutic Effect of Human Umbilical Cord Multipotent Mesenchymal Stromal Cells in a Rat Model of Stroke

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**Background.** Human umbilical cord multipotent mesenchymal stromal cells (UC-MSC) have recently been identified as ideal candidate stem cells for cell-based therapy. The present study was designed to evaluate therapeutic potentials of intracerebral administration of UC-MSC in a rat model of stroke.

**Methods.** Rats were subjected to 2-hr middle cerebral artery occlusion and received 2 × 10^3 UC-MSC or phosphate-buffered saline as a control. Neurologic function evaluation was conducted weekly after transplantation. Brain injury volume and in vivo differentiation of transplanted UC-MSC were detected 2 or 5 weeks after the UC-MSC treatment. In addition, vascular density, vascular endothelial growth factor, and basic fibroblast growth factor expression in ipsilateral hemisphere after treatment and in vitro angiogenic potential of UC-MSC were assessed.

**Results.** The transplanted UC-MSC survived for at least 5 weeks in rat brain. Compared with the phosphate-buffered saline control, the UC-MSC treatment significantly reduced injury volume and neurologic functional deficits of rats after stroke. In ischemic brain, UC-MSC widely incorporated into cerebral vasculature and a subset of them was capable of differentiating into endothelial cells. Furthermore, the UC-MSC treatment substantially increased vascular density and vascular endothelial growth factor and basic fibroblast growth factor expression in ipsilateral hemisphere of stroke. In vitro induction and tube formation assay further confirmed their angiogenic properties.

**Conclusions.** UC-MSC transplantation could accelerate neurologic functional recovery of rats after stroke, which may be mediated by their ability to promote angiogenesis.

**Keywords:** Mesenchymal stromal cells, Human umbilical cord, MCAO, Angiogenesis, Cell-based therapy.

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ment in cerebral ischemia may derive from their ability to promote angiogenesis in ischemic brain.

Recently, we have established a method to readily isolate and expand MSC from human umbilical cord (UC-MSC) and shown that these cells are biologically similar to BM-MSC (19), which is consistent with the observation of several other groups (20–22). In comparison with MSC derived from BM, UC-MSC have several advantages, including painless procedures, more abundant cell number, and lower risk of viral contamination. In addition, previous studies have reported that the application of UC-MSC could lead to an improved functional outcome in neural diseases, such as Parkinson’s disease and cerebral global ischemia (23, 24). We have also shown the therapeutic benefits of UC-MSC transplantation in rat MI and ischemic brain. Thus, the present study was designed to determine the potential of human UC-MSC in improving neurologic functional deficits in rats subjected to middle cerebral artery occlusion (MCAO), and whether UC-MSC treatment could promote angiogenesis in rat brain after stroke.

**MATERIALS AND METHODS**

**Isolation and Identification of UC-MSC**

UCs from both sexes were collected from full-term caesarian section deliveries with informed consent of the mothers. Tissue collection for research was approved by the institutional review board of the Chinese Academy of Medical Science and Peking Union Medical College. UC-MSC were isolated and expanded as described previously (19). Briefly, the cord was cut with scissor into pieces (1–2 mm³) and digested with 0.075% collagenase II (Sigma, St Louis, MO) for 30 min and with 0.125% trypsin (Gibco, Grand Island, NY) for another 30 min with gentle agitation at 37°C. After terminating the trypsin activity with serum, the digested mixture was then passed through a 100-μm filter to obtain cell suspensions. Cells were washed with phosphate-buffered saline (PBS) for three times, and then plated onto noncoated plastic flasks in Dulbecco’s minimum essential medium/F12 (1:1) (Gibco) supplemented with 10% fetal bovine serum (HyClone, Logan, UT), 100 U/mL penicillin-streptomycin (Sigma), 1% glutamine (Sigma), and 10 ng/mL epidermal growth factor (Sigma). Nonadherent cells were removed by changing the medium after 3 days. Cultures were maintained at 37°C in a humidified atmosphere containing 5% CO₂ and passed at 60% to 80% confluency. Cells of passage four to six were used in this study.

For surface phenotype analysis, cells were stained with fluorescein isothiocyanate- or phycoerythrin-conjugated monoclonal antibodies, cells surface markers included hematopoietic lineage markers (CD34, CD38, CD45, CD14), angiogenic markers (CD31, von Willebrand factor [vWF], Flk-1), adhesion integrins (CD44, CD29, CD49, CD54, CD106, CD166), human leukocyte antigen (HLA)-ABC and HLA-DR, and MSC markers of CD13, CD105(SH2), CD73(SH3), and CD90. Antibodies used were purchased from Becton Dickinson (BD, San Diego, CA) except vWF antibody was from Dako (Glostrup, Denmark). Cells were then analyzed by flow cytometry with a FACScan cytometer (BD).

In vitro osteogenic and adipogenic differentiation of UC-MSC were analyzed with the protocol as described previously (19). Von Kossa and Oil Red O (Sigma) staining were used to confirm the characteristics of osteocytes and adipocytes, respectively.

**Tube Formation Assay**

Matrigel (Sigma) was thawed on ice to prevent premature polymerization, aliquots of 50 μL were plated into individual wells of 96-well tissue culture plates and allowed to polymerize at 37°C for 30 min. The cells were washed in serum-containing medium, then resuspended at 10⁶ cells/mL. Cell suspension (100 μL) was added to each well supplemented with 10 ng/mL vascular endothelial growth factor (VEGF; Sigma), and incubated for 2 to 4 hr at 37°C before being visualized under phase contrast microscopy (Olympus, Tokyo, Japan).

**In Vitro Induction of UC-MSC into Vascular Cells**

Confluent UC-MSC were cultured in Dulbecco’s minimum essential medium/F12 medium supplemented with 2% fetal calf serum, 100 U/mL penicillin-streptomycin, 50 ng/mL VEGF, and 10 ng/mL basic fibroblast growth factor (bFGF; Sigma) for endothelial cell differentiation. For smooth muscle cell induction, 10 ng/mL platelet-derived growth factor-BB (Pepro Tech, Rocky Hill, NJ, USA) instead of VEGF and bFGF was used. Medium was changed every 3 days. Seven days after induction, immunostaining was performed to detect the expression of endothelial specific marker vWF or smooth muscle cell marker smooth muscle α-actin (ASMA; Chemicon, Temecula, CA, USA). Diaminobenzidine was used as a chromogen for light microscopy.

**Uptake of Dil-Ac-LDL** (Invitrogen, Carlsbad, CA, USA) was also conducted to verify cellular differentiation toward endothelial phenotype by incubating the postinduced UC-MSC with 10 μg/mL Dil-Ac-LDL in serum-free medium at 37°C for 4 hr. VEGF plus bFGF with or without hypoxia (3% O₂) were used as induction stimuli.

**MCAO Rat Model Establishment**

Adult male Sprague-Dawley rats weighing 230 to 260 g were used in the experiments. Briefly, rats were initially anesthetized with 10% chloral hydrate (30 mg/kg). Rectal temperature was maintained at 37°C by use of a heat blanket. MCAO was induced for 2 hr by using a previously described method of intraluminal vascular occlusion (6, 8).

**UC-MSC Labeling and Transplantation Procedure**

UC-MSC were labeled with 3 μg/mL CM-Dil (Invitrogen) at 37°C for 5 min and then at 4°C for another 15 min. The cells were washed with PBS for three times, and the labeling efficiency was detected under fluorescence microscope (Olympus). Twenty-four hours after MCAO, rats in cell-treated group (n=20) received 10 μL cell-PBS mixture with a total number of 2×10⁶ UC-MSC at the following coordinates: anterior-posterior (AP)=4.5 mm; and cortex: AP=0 mm, middle-lateral (ML)=2.0 mm, dorsal-ventral (DV)=2 mm from the bregma based on the atlas by Paxinos and Watson (27). Cells were injected at the speed of 1 μL/min and placed for another 5 min thereafter. Equal volume of PBS was administrated in the control group (n=20), and sham group (rats not subjected to MCAO except exposing the same vessels as the MCAO group) received no injection (n=16). To evaluate the immunogenicity of human UC-MSC and their angiogenic potential in normoxic condition, equal number of
cells were also injected into normal animals (n=10). In this setting, immune response was detected by CD11b (for macrophage and activated microglia; Chemicon) and myeloperoxidase (MPO, for leukocytes; Abcam, Cambridge, UK) immunostaining 3 days after injection, and angiogenic potential of MSC was analyzed at the same time point as transplantation in MCAO rats. Rats did not receive any immunosuppression medications.

2,3,5-Triphenyltetrazolium Chloride Staining and Injury Volume Measurement

Two weeks after transplantation, the rats were killed and their brains were removed carefully and dissected into coronal 2-mm sections. The fresh brain slices were immersed in a 2% solution of 2,3,5-triphenyltetrazolium chloride (TTC; Sigma) in normal saline at 37°C for 30 min. The cross-sectional area of infarction in each brain slice was examined with a dissection microscope and was measured using an image analysis software (Image-pro plus software package, Media Cybernetics, Carlsbad, CA). The total infarct volume for each brain was calculated by summation of the infarcted area of all brain slices. The ratio of injury volume expressed by the percentage of infarct volume to volume of contralateral hemisphere was used for statistical analysis.

Neurologic Evaluation

Neurologic evaluation, including modified neurologic severity score (mNSS) (7) and Morris water maze test (8), was performed before and weekly after MCAO by two individuals blinded to the experimental groups. mNSS is a composite of motor, sensory, balance, and reflex tests. Neurologic function was graded on a scale of 0 to 18 (normal score 0; maximal deficit score 18). In the severity scores of injury, one score point was awarded for the inability to perform the test or for the lack of a tested reflex; thus, the higher score, the more severe is the injury.

Morris water maze test was used to measures learning and memory. Briefly, the rat was placed in a 1.3-m diameter water tank that is visually separated into four quadrants. In the center of one quadrant, a platform is hidden 2 cm below the waterline. On the first training day, a single habituation trial was performed. If the animal fell or jumped from the platform, it was removed from the water and placed back on the platform. The temperature of the water maze was 24°C ± 0.5°C. The latency of quadrant search and path length of the rat were measured by a video tracking system interfaced to a computer.

Immunohistochemical Staining

After anesthetized, rat brains were fixed by transcardial perfusion with saline, followed by perfusion and immersion in 4% paraformaldehyde, and dehydrated with 20% sucrose in PBS overnight. A series of adjacent 10 μm thick coronal cryostat sections were cut from the brain tissue (AP = −1.0 to AP = 1.0 from the bregma). Antibodies against neuronal specific enolase (NSE; Chemicon), microtubule associated protein 2 (MAP2; Chemicon), glial fibrillary acidic protein (GFAP; Dako), vWF, ASMA, VEGF (Santa Cruz Biototechnology, Santa Cruz, CA), bFGF (Santa Cruz), CD11b (Chemicon), and MPO (Abcam) immunostaining were used, respectively. 4-,6-Diamidino-2-phenylindole (DAPI; Invitrogen) was used to identify nuclei.

Vascular Density and VEGF, bFGF Expression Analysis

To determine the effect of the UC-MSC transplantation on vascular density, rats were killed 7 days after treatment for brain tissue section, and vWF immunostaining was used to visualize vascular regions. Morphometric measurements were performed on five equidistant slices (AP = −1.0 to AP = 1.0 from the bregma) from three animals per group. Per slice, five random areas of ischemic boundary zone were photographed at a magnification of 20× and used for measurement. Vascular areas were calculated using Image-Pro Plus software package, and vascular density was expressed by the percentage of vascular areas. VEGF and bFGF expression quantitation were analyzed by the same method and expressed by the area of positive staining per square millimeter in ischemia border. The measurements were conducted by two independent examiners who were blinded to treatment assignment.

Statistical Analysis

Data are presented as mean ± SD. One-way analysis of variance was used to make comparisons of parameters among groups. If the omnibus tests among groups were significantly different, post hoc tests between groups using unpaired t tests were used. P less than 0.05 was considered significant. The SPSS (Chicago, IL, USA) software package was used for the statistical tests.

RESULTS

Isolation and Identification of UC-MSC

MSC could be isolated from UC with 100% harvesting efficiency after digested with enzyme cocktail. The cells formed a monolayer of bipolar spindle-like cells with a whirlpool-like array within 2 weeks (Fig. 1A), and in vitro expansion analysis.

**FIGURE 1.** In vitro differentiation of UC-MSC into osteocytes and adipocytes. Fibroblast-like UC-MSC grow in the growth medium (A). Positive stain of Von Kossa (B) and Oil red O (C) reflect the osteogenesis and adipogenesis of UC-MSC, respectively. Scale bar = 100 μm.
CD13, CD105 (SH2), CD73 (SH3), CD90, and adhesion molecules were positive for mesenchymal antigens, including CD14, CD45, CD38, CD34, CD166, CD54, CD49, CD29, CD133 (PECAM), CD31 (PECAM), CD13, CD90 (Thy-1), CD105 (SH2, endoglin), and CD106. These cells express HLA-ABC, MHC, HLA-DR, and vWF, indicating positive staining for neural specific markers NSE, MAP2, or GFAP (Fig. 2B). Furthermore, cultured with osteogenic or adipogenic conditional medium, UC-MSC could differentiate into osteocytes and adipocytes, as detected by positive staining of von Kossa and Oil Red O, respectively (Fig. 1B, C). The percentage of CM-Dil-labeled UC-MSC expressing NSE, for neural specific markers NSE, MAP2, or GFAP (Fig. 2B). Furthermore, cultured with osteogenic or adipogenic conditional medium, UC-MSC could differentiate into osteocytes and adipocytes, as detected by positive staining of von Kossa and Oil Red O, respectively (Fig. 1B, C).

Neurologic Function Improvement After UC-MSC Transplantation

Human UC-MSC were injected into the brain of normal rats to evaluate the host immune reaction against the transplanted human cells. The result showed that injected UC-MSC did not elicit any obvious immune response around the injection site 3 days after injection (Fig. 2A-a, b), only sparse leukocytes or macrophages/microglia accumulated around the injection site for which small number of dead cells or cell debris may be responsible.

Two-hour MCAO and reperfusion in rats caused an injury that led to neurologic functional deficits as measured by mNSS. These rats presented with high scores in sensorimotor tests during the early phase after injury. Recovery began on day 3 after injury (Fig. 2A-c) and persisted at all subsequent evaluation points in both PBS-treated and UC-MSC-treated groups. Statistically, the mNSS scores for the UC-MSC-treated group were significantly decreased compared with control group at 14, 21 days after treatment, suggesting UC-MSC transplantation fostered neurologic functional recovery after stroke.

### UC-MSC Treatment Reduces Injury Volume of Stroke

Macroscopic appearance of whole brain tissue showed reduced lesion area on the cortex surface of the UC-MSC-treated rats (Fig. 2A-f) compared with the control group (Fig. 2A-e). The extent of the infarct lesions was examined with TTC staining (8). Normal brain stains red with this method, but the cerebral infarct regions in the brains of the MCAO model rats showed no or reduced staining, clearly delineating areas of infarction. TTC staining 2 weeks after treatment showed that rats in the UC-MSC-treated group (Fig. 2A-h) had smaller injury volume of ischemic brain than those in the PBS-treated group (Fig. 2A-g). The ratio of infarct volume to contralateral hemisphere was 35.2% ± 7.7%, whereas in UC-MSC-treated group, the ratio decreased to 18.7% ± 2.9% (Fig. 2A-i, P < 0.05), suggesting a neuroprotective effect of UC-MSC.

### In Vivo Differentiation of UC-MSC Toward Neuron/Gliacyte

Five weeks after transplantation, CM-Dil-labeled MSCs were still observed in rat brain with a preferential distribution in ischemic boundary regions. By immunohistochemistry, a small number of donor cells were found positive for neural specific markers NSE, MAP2, or GFAP (Fig. 2B). The percentage of CM-Dil-labeled UC-MSC expressing NSE, MAP2, and GFAP were ~1%, ~3%, and ~2%, respectively.

### UC-MSC Treatment Increases Vascular Density and Angiogenic Factors Expression in Ischemic Rat Brain

vWF immunostaining revealed that the UC-MSC treatment significantly increased the vascular density in ischemic boundary zone 7 days after the treatment compared with the PBS-treated group (Fig. 3A). Above 90% blood vessels around ischemic region contained transplanted UC-MSC, which incorporated into cerebral vasculature or located in vessel wall (Fig. 3B). Immunostaining assay demonstrated a part of these incorporated donor cells expressed endothelial cell-specific protein vWF (Fig. 3C), whereas donor cells positive for smooth muscle cell marker AMSA were not detected.

VEGF and bFGF are well-known angiogenic factors. Treatment of UC-MSC substantially increased VEGF and bFGF expression around ischemic region (Fig. 3D, E), and a part of them were secreted by the transplanted UC-MSC (Fig. 3F). Thus, the UC-MSC treatment increased the vessel density through direct incorporation into host vasculature or up-regulation of angiogenic factors, which leads to improved circulation after ischemia.

To evaluate the influence of hypoxia on donor cells migration and their capability of promoting angiogenesis, we also intracerebrally injected UC-MSC into animals without MCAO. Seven days after transplantation, most of the UC-MSC remained in the injection regions in normoxic brain with few migrated cells adjacent to the injection regions (Fig.
4C, D). In contrast, in hypoxic brains, many more cells migrated in distance from the injection site toward the ischemic region (Fig. 4A, B). We also compared the vascular density and number of incorporated cells in vasculature around the injection regions in normoxic and hypoxic condition. Results showed that vascular density was not different between the two groups (Fig. 4G, left; $P>0.05$), but the number of incorporated donor cells in vessels was significantly higher in the MCAO group than in the normoxic group (Fig. 4G, right; $P<0.05$).

**FIGURE 2.** Neurologic function improvement after UC-MSC treatment (A) and in vivo neural differentiation of UC-MSC (B). (A) No obvious immune response of UC-MSC in rat brain (n = 5) as showed by CD11b (a) and MPO (b) immunostaining. Neurologic evaluation shows functional recovery of rats after UC-MSC transplantation (c, d: n = 6 in UC-MSC-treated group, n = 5 in PBS group, n = 6 in sham group). Representative macroscopic appearance of brain cortex (e, f: areas with black dot margin show the ischemia area) and TTC staining (g, h) in UC-MSC-treated group (f, h) and control group (e, g). Quantitative analysis of the ratio of injury volume reveals the difference is significant (i: n = 3 per group; $P<0.05$). Scale bar: a = 50 μm; e = 2 mm. (B) CM-Dil (red) labeled UC-MSC could be observed in ischemic brain 5 weeks posttransplantation (n = 6), arrows show UC-MSC colocalize with NSE, MAP2, or GFAP. DAPI (blue) staining was used to identify nuclear. Scale bar = 50 μm.
In Vitro Tube Formation Assay and Induction of UC-MSC into Vascular Cells

Tube formation assay revealed that UC-MSC were capable of forming capillary-like structure on Matrigel (Fig. 5A), whereas fibroblasts were negative for this test (Fig. 5B). In presence of 50 ng/mL VEGF and 10 ng/mL bFGF, UC-MSC could express vWF (Fig. 5C), whereas 10 ng/mL platelet-derived growth factor-BB directed UC-MSC into smooth muscle cell phenotype as UC-MSC were expressing AMSA (Fig. 5E).

Uptake of DiI-labeled ac-LDL is considered to be one of the typical functions for mature endothelial cells (28). After
culture in endothelial differentiation medium containing VEGF and bFGF for 7 days, UC-MSC were positive for ac-LDL uptake (Fig. 5G, H). Moreover, hypoxia further enhanced their capacity of ac-LDL uptake (Fig. 5I, J), whereas UC-MSC cultured in normal growth medium were negative for ac-LDL uptake (Fig. 5K, L), suggesting that the hypoxia-induced milieu is preferred for driving MSC into endothelial lineage.

**DISCUSSION**

UC tissue has recently been regarded as a rich source of stem/progenitor cells (21, 22, 29–31). The UC tissue is composite of amniotic epithelium, two arteries and one vein, and Wharton’s Jelly, and at least six distinct zones are recognized based on the structural and functional studies (32). Until today, all of the components of UC have been reported to contain stem/progenitor cells and these cells shared similar characteristics with BM-MSC based on morphology, phenotypic profile, and in vitro differentiation analysis (20–22, 29, 30), which was proposed by Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy to define human MSC (33). Recently, we isolated MSC from UC by digesting the complete tissue and found this method increased the success rate and the absolute number of colony-forming unit-fibroblast (19). Also, cells obtained using our method fulfilled the minimal criteria of MSC by International Society for Cellular Therapy. Therefore, digestion of the whole tissue may represent a more promising approach to obtain MSC from UC as compared with site-specific isolation methods, especially for the potential translation into clinic of cell-based therapy in which the cells should be in significant numbers and in the form that require little preparation. A recent study also reported the potential use of UC-derived cells by whole tissue digestion in neural diseases (34). They found that these cells showed typical MSC characteristics and genetic stability in vitro and more effectively, compared with BM-MSC, rescued photoreceptors and visual functions in a rodent model of retinal disease. Of note is the heterogeneity of these UC-derived MSC, which requires further clarification. Actually, it is a common challenge to identify MSC in regard to the lack of unique marker of them.
In the present study, we showed that UC-MSC could survive and improve neurologic function in rats after stroke. The critical question of host immune response in cell-based therapy closely relates with the survival of implanted donor cells and their therapeutic effects in transplantation. Though emerging evidence has suggested that MSC are nonimmunogenic or hypoimmunogenic because of their distinct immunophenotypic profile associated with absence of HLA-II molecule and low expression of costimulatory factors (4, 5, 19, 35), it should be cautious in regard to allogeneic and xenogeneic transplantation because immune rejection of human BM-derived cells has been reported when transplanted in rat after MI (36). The observation that UC-MSC did not elicit obvious immune response when injected into rat probably associated with the relatively immunoprivileged environment in the brain (37, 38), and this may explain the long-term survival of these cells (at least 5 weeks) in rat brain.

Previous studies have reported the benefits of MSC treatment in rats after stroke. However, the underlying mechanism of MSC therapy for ischemia animals is still unclear. Chen et al. (6) found that BM-MSC survived, migrated, differentiated into neural phenotypes, and significantly accelerated functional recovery in rats after stroke. Our work also found that exogenous UC-MSC could express neural specific markers in ischemic brain, which confirmed our previous results that UC-MSC could be induced into neural phenotype in vitro (19). However, it is hard to attribute functional improvement to cell replacement because transdifferentiation is not a common event in our study, which is consistent with other studies (6, 39). Moreover, whether these cells functionally coupled with host cells remains unknown.

We then focused on the angiogenic potential of UC-MSC in this study because accumulating data revealed that MSC were capable of promoting neovascularization in ischemic diseases (16–18), and we have previously reported that UC-MSC enhanced angiogenesis in both rat MI and mouse CLI model (25, 26). UC-MSC treatment increased vascular density after ischemia; thus, may improve the cerebral circu-
did not observe in vivo smooth muscle cell marker AMSA expression of these UC-MSC [which may attribute to our use of later passages (P4–P6) cells for treatment, see Ref. (45)], they may function as pericytes because a recent report demonstrated a close relationship of MSC with pericytes (46). In this setting, Lindolfo et al. (46) analyzed the evidence of perivascular location for MSC and proposed that MSC stabilize blood vessels and contribute to tissue homeostasis under physiological conditions and assume a more active role in the repair of focal tissue injury. Supporting evidence was that Sarugaser et al. (31) reported UC perivascular cells as a source of mesenchymal progenitors and a following study (20) further revealed these cells expressed high level of CD146, a cell marker of pericytes. These data implied that transplanted UC-MSC probably functioned as supporting cells for blood vessel maturation. In addition, MSC are capable of producing plentiful adhesion molecules, such as vascular cell adhesion molecule, cadherins and integrin (19, 23, 31), which play a crucial role in angiogenesis (44, 47).

Hypoxia is probably responsible for cell migration and the overwhelming integration of UC-MSC into vasculature in rats after stroke. UC-MSC in normoxic brain tissue predominantly stayed where they were injected and only a small number of migrated cells could be observed adjacent to the injection site. In contrast, UC-MSC transplanted in ischemic brain selectively migrated toward ischemic penumbra and frequently coupled into blood vessels. In vitro assay also revealed that hypoxia was favorable for induction of UC-MSC into endothelial cell. These observations were consistent with previous studies that hypoxic condition could enhance migration and angiogenic potential of MSC (48–50). Short-term exposure of MSC to low oxygen was shown to be able to increase their expression of migration related molecules and engraftment in vivo (48), and hypoxic preconditioning could lead to increased expression of angiogenic factors and enhance the capacity of MSC to repair infarcted myocardium (49, 50). Therefore, cerebral ischemia created a hypoxic microenvironment that may promote UC-MSC migration and provoke their angiogenic potentials through direct differentiation into vascular cells or secretion of angiogenic factors.

In conclusion, we demonstrated that UC-MSC could reduce neurologic defects after stroke in rats, and this benefit may attribute to their ability to promote angiogenesis in ischemia brain. Given the advantages of UC over BM as a source of MSC, our data suggest that UC-MSC treatment may become an ideal strategy of stem cell-based therapy for central nervous system injury and disease.

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