INTRODUCTION

Mesenchymal stem cells (MSCs) are multipotent stromal cells from many tissue sources, including the bone marrow, adipose tissue, umbilical cord and other adult tissues. MSCs are capable of differentiating into multiple lineages of tissues, such as vasculature, fat and cartilage, under lineage-specific culture conditions. Multiple studies utilizing MSCs have been conducted, being considered a promising treatment for ischaemic tissue injuries, such as hindlimb ischaemia and myocardial infarction. Due to the simplicity and reproducibility of the isolation process, adipose tissue has become an attractive source of MSCs for regenerative medicine. In recent years, multiple studies have been performed to use adipose-derived mesenchymal stem cells (ADSCs) for the revascularization and tissue engraftment in ischaemic tissue, thereby enhanced ADSCs therapeutic efficacy.
repair of ischaemic tissues. The engrafted ADSCs can favourably promote neovascularization of ischaemic limbs and effectively improve cardiac function after myocardial infarction in animal models.\textsuperscript{9,10} The benefits of ADSCs transplantation may be attributed to their multilineage differentiation ability within ischaemic tissues and paracrine secretion of growth factors produced by ADSCs, such as stromal cell-derived factor-1 and vascular endothelial growth factor.\textsuperscript{2,11,12} However, the beneficial effects observed in animal experiment have not been fully translated to patients with ischaemic injuries. The poor survival of implanted MSCs in the ischaemic environment is the main limitation of the therapeutic potential of MSCs.\textsuperscript{1,13} Therefore, overcoming this limitation by promoting the survival of MSCs or improving the local environment may improve the efficacy of MSCs therapy for ischaemic disease.\textsuperscript{14}

The interleukin-11 (IL-11) is a member of the interleukin-6 cytokine family due to their common feature of using the type I cytokine receptor glycoprotein 130 as the β-subunit in their multimeric receptor complexes.\textsuperscript{15} In 1990, IL-11 was identified from the supernatants of immortalized primate bone marrow stromal cells with the activity of plasmacytoma stimulatory.\textsuperscript{16,17} During normal homeostasis, IL-11 expression levels are usually low and therefore difficult to detect. However, it is increasingly clear that IL-11 is produced by cells within the heart, central nervous system and gastrointestinal tract.\textsuperscript{18-20} In clinical, IL-11 has been used for the prevention of chemotherapy-induced thrombocytopenia due to its megakaryocytopoiesis activity in patients with non-myeloid malignancies.\textsuperscript{21} In addition, previous studies have suggested that IL-11/receptor interaction leads to activation of JAK/STAT3 signalling pathway.\textsuperscript{22} Studies have shown that IL-11 prevents skeletal myoblasts apoptosis and endothelial cell injury under oxidant stress via STAT3 signalling pathway.\textsuperscript{23,24} Furthermore, research has shown that the expression of IL-11 significantly decreases during cerebral ischaemia-reperfusion injury, and IL-11 treatment improved neurological function and cerebral infarct volume.\textsuperscript{25} It is also shown that IL-11 is beneficial for ischaemia-reperfusion injury of kidneys, heart and intestines.\textsuperscript{26-28}

Because IL-11 plays a key role in promotion of megakaryocytopoiesis and thrombopoiesis, recombinant human IL-11 has been extensively used in patients with good clinical efficacy and safety parameters. Thus, we performed a pre-clinical study to explore the role of IL-11 as a potential pharmacological agent for improving the efficacy of stem cell therapy using a hindlimb ischaemia mouse model. In this study, we examined whether IL-11 treatment improves ADSCs therapeutic efficiency in hindlimb ischaemia tissues and explored the underlying mechanisms of IL-11 in regulating the function of ADSCs under oxidative stress.

2 MATERIALS AND METHODS

2.1 Animal study protocol

C57BL/6 male mice (8-week-old) were purchased from the Experimental Animal Center of Fudan University, China. Mice were housed in a temperature-controlled environment with 12 hour/12 hour light/dark cycles. Mice were randomly divided into three groups (n = 6): Mice were performed hindlimb ischaemia operation (hindlimb ischaemia group, HI), hindlimb ischaemia operation with control ADSCs transplantation (HI + ADSCs\textsuperscript{c00} group) or with IL-11 overexpression ADSCs transplantation (HI + ADSCs\textsuperscript{IL-11}). The Experimental Animal Ethic Committee of Fudan University approved the animal research protocol. All the animal procedures were performed in accordance with the Guiding Principles in the Use and Care of Animals (NIH Publication No. 85-23, revised 1996).

2.2 Isolation and culture of mouse ADSCs

Adipose-derived mesenchymal stem cells were isolated from inguinal subcutaneous adipose tissue as previously described.\textsuperscript{7} Briefly, adipose tissues were cut into small pieces in phosphate-buffered saline (PBS) on ice. The minced tissue was then digested with 1 mg/mL type I collagenase (Worthington-Biochem, LS004196) at 37°C for 1 hour. The digested tissue was filtered through a 70 μm mesh (Corning, 431751) to remove tissue debris. The cell suspension was then centrifuged at 600 g for 15 minutes to remove collagenase. The cell pellet was plated in 100 mm dishes and incubated with 1× lysis buffer (Beyotime, C3702) at room temperature for 10 minutes, and cells were then resuspended by centrifugation at 300 g.

2.3 Flow cytometry

Adipose-derived mesenchymal stem cells were digested by trypsinization and washed with PBS. For flow cytometry, 1 × 10\textsuperscript{6} ADSCs were stained with fluorescent antibodies at room temperature for 1 hour in PBS. The following antibodies and their non-specific negative isotype controls were employed: FITC-CD29 (Invitrogen, 11-0291-80), FITC-CD105 (Invitrogen, MA5-17945), FITC-Sca-1 (Invitrogen, 11-5981-81) and PE-CD45 (BD Pharmingen, 553081). After incubation, cells were washed three times with PBS and centrifuged at 300 g for 10 minutes, and cells were then resuspended in PBS for flow cytometry. Surface marker expression was evaluated via flow cytometry (BD LSR Fortessa\textsuperscript{TM}). FlowJo software was used for data analysis.

2.4 Adipogenesis and osteogenesis

Adipogenic and osteogenic differentiation of ADSCs were performed as previously reported.\textsuperscript{7} For adipogenesis, cells were incubated in
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adipogenic medium (Cyagen, MUBMD-90031) for 21 days. The medium was changed every three days. Adipogenesis was assessed by Oil Red O solution to stain lipids. For osteogenesis, cells were incubated in osteogenic medium (Cyagen, MUBMD-90021) for 21 days. The medium was changed every three days. Osteogenesis was evaluated by alizarin red staining solution.

2.5 | Mouse hindlimb ischaemia model and cell transplantation

Hindlimb ischaemia model was established as previously described.29 In brief, mice were anaesthetized with pentobarbital sodium (50 mg/kg) intraperitoneally. The femoral artery was separated from the femoral nerve and vein, and then, artery was ligated and excised. One day after the surgery, ADSCs (1 × 10⁶) suspended in 100 µL PBS or equal PBS was injected intramuscularly into the ischaemic hindlimb in three different sites. Hindlimb perfusion was evaluated by laser Doppler perfusion imaging (PeriScan PIM 3 system, Perimed) at 7 and 14 days. PIMsoft Software (Perimed med) was used to quantify perfusion ratio of ischaemic limb versus non-ischaemic limb by averaging relative units of flux.

2.6 | Masson’s trichrome staining

Hindlimb fibrosis was evaluated by staining with Masson Trichrome reagent (Yeasen, 60532ES58). Tissues were harvested and then fixed in formalin. Sections (5 µm thick) were prepared for Masson’s trichrome staining according to manufacturer’s instructions. Fibrosis was measured via inverted optical microscope (ZEISS Group).

2.7 | Immunofluorescence

The isolated muscular tissues were embedded in OCT, and the frozen sections were prepared and fixed in 4% paraformaldehyde. Sections were incubated with anti-GFP (CST, 2956) antibodies overnight at 4°C and then incubated with goat anti-rabbit IgG, Alexa Fluor 488 (Thermo Fisher, A-11008) for 30 minutes at 37°C. The nuclei were stained with DAPI for 10 minutes at room temperature. Sections were visualized using inverted optical microscope (ZEISS Group). The GFP-positive cells were counted with Image J software (National Institutes of Health, Bethesda, MD, USA).

2.8 | Cell viability assay

The Cell Counting Kit-8 (CCK-8) assay (Beyotime, C0037) was performed to determine cell viability. Briefly, ADSCs were seeded into a 96-well plate and treated with IL-11 or not. After 24 hours, 10 µL of CCK-8 solution was added to each well and incubated at 37°C for 2 hours. The absorbance at a wavelength of 450 nm was read using microplate reader (SpectraMax® M5, Molecular Devices).

2.9 | Cell proliferation assay

The second passage ADSCs were seeded in a 12-well plate and treated with IL-11 or not after 24 hours. Then, the cells were stained using the BeyoClick™ EdU-488 kit (beyotime, C0071S) according to manufacturer’s protocol and observed by inverted fluorescence microscope (ZEISS Group). The number of positive nuclei/the total nuclei were counted using Image J software (National Institutes of Health).

2.10 | Cell apoptosis assessment

Apoptosis of ADSCs was detected by terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling (TUNEL) staining. TUNEL Detection Kit Fluorescein (Beyotime, C1088) was employed to determine apoptosis of ADSCs according to manufacturer’s protocol. The number of TUNEL positive nuclei/the total nuclei were counted to calculate the index of apoptosis.

2.11 | Transwell assay

The Costar® Transwell® Insert (8 µm, Corning 3422) was employed in migration assay as previously described.30 ADSCs were seeded in the upper chamber in serum-free medium. The complete medium containing IL-11 or not were added in the bottom wells. 0.1% crystal violet was used to stain cells in the upper chamber. Cells in the bottom well were counted using inverted optical microscope (ZEISS Group).

2.12 | Cell transfection

1 × 10⁶ ADSCs were seeded into 6-well plates. The medium was removed after 24 hours of culture and then replaced with serum-free DMEM containing 10 µL of pLenti-EF1a-EGFP-P2A-Puro-CMV-IL11-3Flag (IL-11 overexpression group) or pLenti-EF1a-EGFP-P2A-Puro-CMV-MCS-3Flag (control group) for a further 24 hours. After transfection with pLenti-EF1a-EGFP-P2A-Puro-CMV-MCS-3Flag for 48 hours, the efficiency of transfection was determined by fluorescence microscopy. Alterations of protein were corroborated by Western blot.

2.13 | Western blotting

Proteins were isolated from ADSCs lysates, added the same amount of protein to the sodium dodecyl sulphate polyacrylamide gel and
transferred to a PVDF membrane. The membranes were incubated with primary antibody at 4°C overnight and added secondary antibody next day. Then, the membrane was visualized with enhanced chemiluminescence and quantified by densitometry. The primary antibodies included mTOR (7C10) Rabbit mAb (CST, 2983) (1:1,000), Phospho-mTOR (Ser2448) (D9C2) XP® Rabbit mAb (CST, 5536, 1:1,000), p44/42 MAPK (Erk1/2) (137F5) Rabbit mAb (CST, 4695, 1:1,000), Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) Antibody (CST, 9101, 1:1000), Stat3 (D1B2J) Rabbit mAb (CST, 30835, 1:1000) and Phospho-Stat3 (Tyr705) (D3A7) XP® Rabbit mAb (CST, 9145, 1:1000).

2.14 Statistical analysis

All data are presented as means ± standard deviation. Student’s t test (two groups) or one-way ANOVA followed by Dunnett’s post hoc test was employed for comparisons between the groups using the GraphPad Prism Software Version 5.9. Values of *P < .05 were considered statistically significant.

3 RESULTS

3.1 IL-11 promoted ADSCs growth in a dose-dependent manner

The second passage ADSCs were used for detecting the stroma-associated markers and differentiation potential. ADSCs expressed mesenchymal stem cells markers CD29 (98.9 ± 0.8%), CD105 (91.6 ± 1.1%) and Sca-1 (77.5% ± 1.7%), but few haematopoietic lineage marker CD45 (0.1 ± 0.2%) (Figure S1A,B). The adipogenic and osteoblastic potential of ADSCs demonstrated their pluripotency (Figure S1C). First, we examined the expression of IL-11 under hypoxia. Western blot analysis demonstrated that the expression of IL-11 was decreased under hypoxia compared with the control group (*P < .05, Figure 1A,B). The adipogetic and osteoblastic potential of ADSCs demonstrated their pluripotency (Figure S1C). First, we examined the expression of IL-11 under hypoxia. Western blot analysis demonstrated that the expression of IL-11 was decreased under hypoxia compared with the control group (*P < .05, Figure 1A,B).
3.2 | IL-11 promoted ADSCs proliferation, migration and protected ADSCs from hydrogen peroxide-induced cell apoptosis

To determine whether IL-11 regulated ADSCs function, we examined the proliferation, migration and apoptosis of ADSCs treated with or without IL-11 in vitro. The results indicated IL-11 increased ADSCs proliferation after 24 hours treatment compared with vehicle (P < .05, Figure 2A,B). ADSCs with H2O2 treatment increased the expression of cleaved caspase-3 and TUNEL positive nuclei. IL-11 treatment significantly attenuated these markers of apoptosis (P < .05, Figure 2C-F). The transwell assays suggested that ADSCs showed a markedly enhanced migratory capacity after IL-11 treatment (P < .05, Figure 2G,H). In addition, IL-11 has no effect on the VEGF and FGF2 secretion of ADSCs (Figure S2). These results demonstrated that IL-11 promoted ADSCs proliferation, migration and survival in vitro.

3.3 | IL-11 activated the STAT3 signalling pathway

To determine the molecular mechanisms underlying the effects of IL-11 upon ADSCs, we examined the expression of P-STAT3, P-ERK1/2 and P-mTOR in ADSCs with IL-11 treatment. Western blot analysis revealed that only the expression of P-STAT3 was significantly up-regulated after 24 hours of IL-11 treatment (P < .05, Figure 3A-D). These results suggested that IL-11 may regulate the function of ADSCs via STAT3 signalling pathway.

3.4 | IL-11 induced ADSCs proliferation, migration and anti-apoptotic effects via STAT3 signalling pathway

To further confirm that the STAT3 signalling pathway was responsible for IL-11-induced ADSCs proliferation, migration and anti-apoptotic effects, we used the inhibitor of the STAT3 (stattic) for the next experiments. The results revealed that ADSCs proliferation were decreased after IL-11 and stattic co-treatment compared with IL-11 treatment alone (P < .05, Figure 4A,B). Meanwhile, co-treatment of stattic attenuated the anti-apoptotic effects of IL-11 (P < .05, Figure 4C,D), impaired the migration capacity of ADSCs.
(P < .05, Figure 4E,F) and also decreased the phosphorylation of STAT3 in ADSCs compared with IL-11 treatment alone (P < .05, Figure 4G,H).

3.5 | IL-11 induced ADSCs proliferation, migration and anti-apoptotic effects via IL-11 alpha receptor

The classic IL-11 signalling is induced by binding to its alpha receptor, then IL-11 alpha receptor (IL-11Ra) interacted with membrane bound GP130 resulted in a trimeric complex. This trimer then associates with a second trimer to form a functional hexameric signalling complex.\(^\text{31}\) To explore whether IL-11Ra was involved in IL-11-induced ADSCs proliferation, migration and anti-apoptotic effects, we used the blocking antibody of IL-11Ra for the next experiment. After co-treatment with blocking antibody of IL-11Ra, the effect of IL-11 on ADSCs proliferation was diminished (P < .05, Figure 5A,B). Moreover, co-treatment of IL-11 and blocking antibody of IL-11Ra attenuated the anti-apoptotic effects of IL-11 (P < .05, Figure 5C,D), impaired the migration capacity of ADSCs (P < .05, Figure 5E,F) and also decreased the phosphorylation of STAT3 in ADSCs compared with IL-11 treatment alone (P < .05, Figure 5G,H).

3.6 | IL-11 enhanced the efficacy of ADSCs therapy in a mouse model of hindlimb ischaemia

To explore whether IL-11 increased the therapeutic efficacy of ADSCs in treating ischaemic diseases, we established the IL-11 overexpression ADSCs and implanted their into ischaemic mouse hindlimbs.

Expression of GFP fluorescence and the protein of flag confirmed successful construction of IL-11 overexpressing ADSCs (Figure 6A,B). Laser Doppler perfusion image assay revealed that perfusion recovery in ischaemic limbs was significantly better in the IL-11 overexpression ADSCs transplantation group than in the control group at both 7 and 14 days post-therapy (day 7, 39.4 ± 8.6% vs 28.5 ± 10.3%; day 14, 71.0 ± 9.5% vs 54.4 ± 11.4%; P < .05, Figure 6C,D). The retention of implanted ADSCs was determined using histological analysis, and the overexpression of IL-11 in ADSCs increased the ratio of cell survival in ischaemic tissues at 14 days post-therapy (P < .05, Figure 6E,F). In addition, the fibrosis of ischaemic tissues was also significantly decreased after the IL-11 over-expression ADSCs transplantation compared with implanted control ADSCs (Figure 6G). These results suggested that increased IL-11 promoted the blood perfusion recovery and contributed to improve ADSCs engraftment in ischaemic tissues.

4 | DISCUSSION

In the present study, we demonstrated that IL-11 promoted ADSCs proliferation, migration and protected ADSCs from hydrogen peroxide-induced cell apoptosis via STAT3 signalling pathway in vitro. Furthermore, we found that IL-11 increased the retention of implanted ADSCs and perfusion recovery in ischaemic limbs. These findings indicate that IL-11 may improve the therapeutic efficacy of ADSCs for the ischaemic diseases.

Adult stem cells including MSCs play key roles in the repair of damaged cells and the maintenance of tissue homeostasis.\(^\text{32}\) MSCs exist in most mammalian tissues and organs, such as the bone marrow, adipose tissue and umbilical cord. MSCs therapy has become a promising treatment for ischaemic disease, because of a large number of pre-clinical evidence supporting their reparative potential.\(^\text{4,33}\) However, poor survival of implanted MSCs and failure of stem cells engraftment in ischaemic environment occurs at early stages after delivery, raising a major challenge in the field.\(^\text{33}\) The extracellular matrices, autocrine and paracrine hormonal signals and tissues microenvironment can regulate the fate of stem cells.\(^\text{32}\) A comprehensive understanding of the mechanisms that enhance MSCs migration and survival in the injured tissues is critical for improving the repair capacity and therapeutic application of MSCs.

IL-11 is produced by a variety of tissues including the heart, central nervous system and gastrointestinal tract.\(^\text{15}\) Because of the promotion of megakaryocytopenia and thrombopoiesis, recombinant human IL-11 has been extensively used in patients for the prevention of chemotherapy-induced thrombocytopenia.\(^\text{21}\) Previous study has suggested that the expression of IL-11 mRNA and protein significantly decreases during cerebral ischaemia-reperfusion injury.\(^\text{25}\) Analogous to previous report, we found that the expression of IL-11 was decreased under hypoxia. We found that IL-11 receptor was expressed in ADSCs. In addition, ADSCs viability was increased after IL-11 treatment. IL-11 also enhanced ADSCs viability under hypoxia. These results indicate that IL-11 may play an important role under...
hypoxic conditions. Moreover, it has been found IL-11 is a critical cytokine for the development of tumours in both the colon and stomach, which is mediated by promoting cell proliferation and reducing cell apoptosis. In the colon and gastric cancer, the production of IL-11 promotes cell migration through STAT3, which is involved in metastasis of tumour cells to other organs. Additional studies have shown that IL-11 regulates cellular function mainly through three signalling pathways including JAK-STAT3, RAS-RAF-ERK and PI3K-AKT-mTORC1 pathway, which are the downstream of IL-11Rα signalling. Thus, we examined the expression of P-STAT3, P-ERK1/2 and P-mTOR in ADSCs to determine the molecular mechanisms underlying the effects of IL-11 upon ADSCs function. We found that the expression of P-STAT3 was significantly up-regulated after IL-11 treatment in ADSCs. These findings suggested that IL-11 may regulate the function of ADSCs through IL-11-IL-11Rα-STAT3 signalling pathway. Indeed, STAT3 regulates the transcription of target genes that determined various important biological functions. The phosphorylation of STAT3 leads to expression of pluripotency genes which is responsible for self-renewal and the undifferentiated state of mouse embryonic stem cells. In addition, the activation of STAT3 promotes human adult stem cells migration and survival and plays critical roles in the proliferation of adult stem cells. To further confirm our hypothesis, the inhibitor
of the STAT3 (stattic) and blocking antibody of IL-11Rα was used in our study. These results showed that both stattic and the blocking antibody of IL-11Rα impaired IL-11-induced ADSCs proliferation, migration and anti-apoptotic effects.

The poor survival of implanted MSCs in the ischaemic environment is the main impediment of the therapeutic potential of MSCs, so it is very important to explore novel ways to enhance the survival of transplanted MSCs. We found that IL-11 improved perfusion recovery and increased the retention of implanted ADSCs in ischaemic limbs. Furthermore, previous research has shown that IL-11 can promote the mobilization of CD34+/VEGFR2+ cells, induce collateral vessel regeneration and improved perfusion recovery in ischaemic limbs.43 In our study, the increasing blood perfusion may also be attributed to the direct effects of IL-11. In addition, the fibrosis of ischaemic tissues was also significantly decreased after transplantation of IL-11 overexpression ADSCs. These findings suggested that IL-11 can improve the efficacy of stem cell therapy. Our study firstly identifies the IL-11 cytoprotective effect to transplanted ADSCs, provide a new hint to interfere IL-11 in order to improve the MSC transplantation therapy outcome.

In summary, we demonstrate that IL-11 induces ADSCs proliferation, migration and anti-apoptotic effects via STAT3 signalling pathway and acts as a cytoprotective factor regulating ADSCs engraftment in ischaemic tissues.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
WLY and TTO performed the study. HJ and DLJ contributed to data acquisition and analysis. ZYQ and TTO contributed to the figures and statistical analysis. WLY and SNZ drafted the manuscript. YZZ and JYQ revised the manuscript. JBG, SNZ and AJS conceived and designed the study. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.