Article

Discovery Medicine 2026; 38(212): 2918–2930
https://doi.org/10.24976/Discov.Med.202638212.225

FGF21 Pretreatment Promotes the Cardioprotective Effects of Mesenchymal Stem Cells in Myocardial Infarction via Enhancement of Their Survival and Paracrine Effects

Xuefei Jiao[1,2,†], Jie Qiu[3,†], Chao Zhang[1], Daolai Huang[1], Jiyun Wan[1], Fang Lin[4], Kexin Ma[4], Xiaoting Liang[4,*], Xianghua Wu[1,*]

[1]Department of Gastroenterology and Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, 530021 Nanning, Guangxi, China
[2]Department of Vascular Surgery, The Affiliated Hospital of Qingdao University, 266003 Qingdao, Shandong, China
[3]Department of Emergency Medicine, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, 510080 Guangzhou, Guangdong, China
[4]Translational Medical Center for Stem Cell Therapy & Institute for Regenerative Medicine, Shanghai East Hospital, Tongji University School of Medicine, 200120 Shanghai, China
*Correspondence: liangxt@tongji.edu.cn (Xiaoting Liang); wuzhuone1@sina.com (Xianghua Wu)
[†]These authors contributed equally.
Submitted: 20 January 2026 Revised: 27 April 2026 Accepted: 15 May 2026 Published: 23 September 2026

Background: The poor engraftment of mesenchymal stem cells (MSCs) in the ischemic heart post transplantation heavily restricts their cardioprotective benefits in myocardial infarction (MI). Pretreatment has emerged as a novel approach to enhance the biological properties of MSCs and enhance their therapeutic efficacy. This study aimed to determine whether pretreatment of MSCs with fibroblast growth factor 21 (FGF21) could promote their cardioprotective effects in mice with MI and illustrate the potential mechanisms.

Methods: FGF21-pretreated MSCs (FGF21-MSCs) or MSCs were subjected to serum deprivation and hypoxia (SD/H) for 48 h. Apoptosis and proliferation of MSCs or FGF21-MSCs under SD/H were assessed using Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay and Ki67 staining, respectively. The conditioned medium (CdM) of MSCs and FGF21-MSCs was harvested by centrifugation. Left anterior descending coronary artery (LAD) ligation served to establish an MI model in mice and then MSCs or FGF21-MSCs intramyocardially injected into the peri-infarct area. Four weeks later, cardiac function, fibrosis and MSC engraftment in ischemic heart tissue were determined by echocardiography, Masson's and immunofluorescence staining, respectively.

Results: FGF21 pretreatment greatly inhibited apoptosis ($p < 0.001$) and elevated the proliferation ($p < 0.05$) of MSCs subjected to SD/H. Pretreatment with FGF21 enhanced the paracrine activity of MSCs, as evidenced by increased tube formation in HUVECs (human umbilical vein endothelial cells) ($p < 0.001$). Moreover, treatment with FGF21-MSC-CdM further alleviated SD/H-induced cardiomyocyte apoptosis ($p < 0.05$). Mechanistically, FGF21 pretreatment enhanced MSC survival under SD/H via activation of the AMPK signaling pathway by enhancing liver kinase B1 (LKB1) stability, an effect that was largely reversed by AMPK inhibitor Compound C. In the murine MI model, transplantation of FGF21-preconditioned MSCs resulted in superior cardiac recovery, accompanied by enhanced neovascularization ($p < 0.001$) and decreased cardiac apoptosis ($p < 0.001$). Importantly, FGF21 pretreatment significantly increased the persistence of human mitochondrial signaling in the infarcted heart ($p < 0.001$).

Conclusions: FGF21 pretreatment significantly improved the cardioprotective efficacy of MSCs on MI via elevation of their survival and paracrine effects, providing a novel therapeutic approach to improve MSC therapy for heart repair following infarction.

Keywords: mesenchymal stem cells; myocardial infarction; fibroblast growth factor 21; pretreatment; survival

Copyright: © 2026 The Author(s). Published by Discovery Medicine. This is an open access article under the CC BY 4.0 license.
Note: *Discovery Medicine* stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Introduction

Myocardial infarction (MI) due to coronary artery occlusion is the predominant cause of severe morbidity and mortality globally [1]. Following infarction, substantial cardiomyocytes are lost due to the absence of oxygen in the infarcted heart, leading to pathological ventricular remodeling and ultimately heart failure [2]. Although considerable pharmacological and surgical interventions have been explored for MI treatment, including angiotensin-converting enzyme inhibitors and percutaneous coronary intervention, the prognosis for MI patients has shown limited improvement [3]. It is vital to develop innovative and effective strategies for MI treatment.

Mesenchymal stem cell (MSC)-therapy has become an innovative strategy for MI treatment because of its unique advantages that include low immunogenicity, low risk of teratoma formation and differential capacity [4,5]. Nonetheless despite promising results, there remain obstacles such as their poor survival following transplantation. After MI, the presence of ischemia creates a hostile microenvironment that comprises low oxygenation, high oxidative stress and inflammation. These strongly inhibit MSC survival and their subsequent cardioprotective effects on the infarcted myocardium [6,7]. Novel strategies to enhance MSC survival post transplantation are urgently needed. There is recent accumulating evidence that pharmacological pretreatment can substantially enhance the survival and paracrine function of transplanted MSCs, thereby ameliorating cardiomyocyte apoptosis, enhancing angiogenesis, and eventually improving the therapeutic efficacy of MSCs for MI [8,9,10]. Therefore, identifying a novel pharmacologic agent to pretreat MSCs and promote their survival in the infarcted heart is vital.

Fibroblast growth factor 21 (FGF21) functions as a unique metabolic hormone that regulates the viability of multiple types of cells under stress conditions [11,12,13]. It has been reported that FGF21 treatment significantly enhances the cell viability of PC12 cells under H_2O_2 challenge via inhibition of mitochondrial apoptosis and reduced reactive oxygen species production [14]. FGF21 treatment has been shown to inhibit apoptosis of HK2 cells, induced by hypoxia/reoxygenation, via mediation of the PPARγ/NF-κB signaling pathway [15]. More importantly, several studies have revealed that FGF21 serves as a therapeutic target for cardiac repair [16]. Administration of FGF21 has been shown to attenuate diabetic cardiomyopathy via inhibition of cardiomyocyte ferroptosis by regulating the ferritin pathway [17]. Whether FGF21 pretreatment can enhance the cardioprotection afforded by MSC transplantation following MI by improving their survival has nonetheless not been investigated. We examined the effects of FGF21 pretreatment on the survival and paracrine function of MSCs and explored the potential mechanisms. We also investigated the role of FGF21 pretreatment in enhancing the protective effects of MSC transplantation in the heart following infarction.

Materials and Methods

Cell Culture

Human bone marrow–derived mesenchymal stem cells (BM-MSCs) were purchased from Lonza Bioscience (PT-2501, Walkersville, MD, USA) and maintained in Dulbecco's modified Eagle's medium (DMEM; Gibco, 11965084, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS; Life Technologies, 16000, Carlsbad, CA, USA), 5 ng/mL epidermal growth factor (EGF; PeproTech, AF-10-15, Rocky Hill, NJ, USA), and 5 ng/mL basic fibroblast growth factor (bFGF; PeproTech, 100-18B, Rocky Hill, NJ, USA) at 37 °C in a humidified incubator with 5% CO_2. MSCs at passages 4–6 were maintained at 37 °C under standard culture conditions and used for the study. Human umbilical vein endothelial cells (HUVECs) were obtained from Servicebio (STCC12103P, Wuhan, China) and cultured in RPMI 1640 medium (Gibco, C11875500BT, Thermo Fisher Scientific, Waltham, MA, USA) containing 10% FBS. Both BM-MSCs and HUVECs were authenticated by short tandem repeat (STR) profiling. Neonatal mouse cardiomyocytes (NCMs) were isolated from 0–1-day-old mouse hearts according to a previously established protocol [18] and maintained at 37 °C in Claycomb medium (Sigma, 51800, St. Louis, MO, USA) supplemented with 10% FBS. The identity of isolated NCMs had previously been validated by immunofluorescence staining for α-actinin, as reported in our earlier study [18]. All cell types used in this study, including BM-MSCs, HUVECs, and NCMs, were screened for mycoplasma contamination prior to use, and all results were negative.

CCK-8 Assay

5×10^3 MSCs were plated on 96-well plates maintained with or without different concentrations of fibroblast growth factor 21 (FGF21; Thermo Fisher Scientific, 100-42-25UG, Waltham, MA, USA) in a regular culture incubator at 37 °C (normoxia, 21% O_2 and 5% CO_2) for 24 h and then exposed for 48 h to serum deprivation and hypoxia (SD/H, 1% O_2 and 5% CO_2) in a hypoxic incubator. Viability of MSCs was evaluated using a Cell Counting Kit-8 (CCK-8; APExBIO, K1018, Houston, TX, USA) according to the protocol.

TUNEL Staining

MSCs were plated on 24-well plates and incubated with or without FGF21 for 24 h, then exposed to SD/H for 48 h. After treatment, cells were washed with phosphate-buffered saline (PBS), fixed with 4% paraformaldehyde for 30 min at room temperature, and permeabilized with 0.1%

Triton X-100 for 10 min. Apoptotic cells were detected using a TUNEL assay kit (RiboBio, C11026-1, Guangzhou, China) according to the manufacturer's instructions. Nuclei were counterstained with 4′,6-diamidino-2-phenylindole (DAPI). Fluorescence image were captured under a fluorescence microscope, and the apoptotic rate of MSCs was quantified as the percentage of TUNEL-positive cells relative to the total number of DAPI-stained nuclei.

Ki-67 Staining

MSCs were seeded in 24-well plates and incubated with or without FGF21 for 24 h, followed by exposure to SD/H for 48 h. Cells were washed with PBS, fixed with 4% paraformaldehyde for 30 min at room temperature, permeabilized with 0.1% Triton X-100 for 10 min, and blocked with 5% bovine serum albumin (BSA) for 1 h. Cells were then incubated overnight at 4 °C with anti-Ki-67 primary antibody (Abcam, ab15580, Cambridge, UK), followed by incubation with the appropriate fluorescence-conjugated secondary antibody (1:1000, Abcam, ab150079, Cambridge, UK) for 1 h at room temperature. Nuclei were counterstained with DAPI. Fluorescence images were captured under a fluorescence microscope, and the proliferative rate was quantified as the percentage of Ki-67-positive cells relative to the total number of DAPI-stained nuclei.

Conditioned Medium (CdM) Collection

The CdM was collected as previously reported [18]. MSCs were seeded on a 10-cm plate and cultured for 24 h with or without FGF21. Subsequently, the medium was discarded and changed to antibiotic - and serum-free DMEM and culture continued for 48 h. Next, MSC-CdM or FGF21-MSC-CdM underwent ultrafiltration (Millipore, UFC9050, Billerica, MA, USA). Finally, the concentration of MSC-CdM or FGF21-MSC-CdM was measured using a BCA protein kit (Beyotime, P0010, Shanghai, China).

Tube Formation

Capillary tube formation assay was used to examine the angiogenic capacity of MSC-CdM or FGF21-MSC-CdM. HUVECs were plated on 24-well plates precoated with growth factor–reduced Matrigel (Corning, 354234, Corning, NY, USA) and cultured for 6 h in the presence of MSC-conditioned medium (MSC-CdM) or FGF21-pretreated MSC-conditioned medium (FGF21-MSC-CdM). Capillary-like structures were imaged in five randomly selected fields, and total tube length quantified using ImageJ software (Version1.54, NIH, Bethesda, MD, USA).

Western Blotting

Total proteins were extracted by RIPA buffer (Beyotime, P0013B, Shanghai, China). Protein concentration was determined using a BCA assay kit (Beyotime, P0010, Shanghai, China). Equal amounts of protein were separated by 10% SDS-PAGE gel and transferred onto a PVDF membrane. Membranes were then blocked with TBST supplemented with 5% fat-free milk and incubated at 4 °C overnight with the following antibodies: FGF21 (Abcam, ab171941, Cambridge, UK), LKB1 (Immunoway, YM8389, Plano, TX, USA), p-AMPK (Affinity, AF3423, Cincinnati, OH, USA), AMPK (Proteintech, 10929-2-AP, Wuhan, China) and GAPDH (Proteintech, 60004-1-Ig, Wuhan, China). After three washes with TBST, the membranes were incubated with appropriate secondary antibodies (anti-rabbit IgG, Proteintech, SA00001-2; anti-mouse IgG, Proteintech, SA00001-1, Wuhan, China) at room temperature for 1 h. Protein bands were then visualized using an enhanced chemiluminescence (ECL) detection kit (Thermo Fisher Scientific, 32106, Waltham, MA, USA) and imaged using a chemiluminescence imaging system (Tanon Science & Technology Co., Ltd., Shanghai, China). Band intensities were quantified using ImageJ software (NIH, Bethesda, MD, USA).

RNA Sequencing Analysis

Total RNAs from MSCs were extracted by Trizol reagent (Thermo Fisher Scientific, 15596026, Waltham, MA, USA). After assessing the quantity, purity and integrity of RNAs, sequencing was determined using the BGISEQ-500 platform (BGI, Guangzhou, China) and then bioinformatics analysis performed. The differentially expressed genes (DEGs) between any two groups were evaluated using linear models with absolute fold change ≥ 1.5 and adjusted p value < 0.05 as a threshold.

Co-immunoprecipitation (Co-IP) Assay

MSCs subjected to different treatments were lysed in IP lysis buffer (Thermo Fisher Scientific, Waltham, MA, USA). After protein quantification, equal amounts of protein (1000 μg) from each group were incubated overnight at 4 °C with anti-FGF21 antibody (Abnova, H00026291-PW3) or control IgG, followed by incubation with protein A magnetic beads (Thermo Fisher Scientific, Waltham, MA, USA) overnight at 4 °C. The beads were then collected using a magnetic rack and washed three times with IP lysis buffer. Bound proteins were eluted by boiling the beads in 1× SDS loading buffer at 100 °C for 5 min and subsequently subjected to Western blot analysis using anti-LKB1 antibody (Immunoway, YM8389, Plano, TX, USA).

Establishment of an MI Model and MSC Transplantation

All study involving animals was approved by the Committee on the Use of Live Animals in Teaching and Research of Tongji University for Laboratory Animal Medicine (Approval No. TJBB04725103). Adult male C57BL/6J mice (25–30 g) were obtained from Charles River, Shanghai, China. Myocardial infarction was induced by ligation of the left anterior descending coronary artery

(LAD). Mice were anesthetized with 2% isoflurane (RWD Life Science, Shenzhen, China) and connected to a small rodent ventilator and surgical LAD ligation performed using an 8–0 Prolene suture. Following induction of MI, mice were randomly assigned to one of three groups (n = 8 per group) to receive intramyocardial injection of MSCs (3×10^5 cells), FGF21-preconditioned MSCs (3×10^5 cells), or vehicle control (30 μL PBS). Injections were administered at four sites within the peri-infarct border zone. A sham group (n = 6) underwent thoracotomy without LAD ligation. Four weeks post-surgery, cardiac function was evaluated by echocardiography (Vevo 2100, VisualSonics, Toronto, ON, Canada) and left ventricular ejection fraction (LVEF) and fractional shortening (LVFS) calculated.

Masson's Trichrome Staining

At 4 weeks post-MI, and following echocardiographic evaluation, mice were euthanized by intraperitoneal administration of pentobarbital sodium (200 mg/kg), and heart tissue harvested. Heart samples were fixed in 4% paraformaldehyde (Servicebio, Wuhan, China), embedded in paraffin, and sectioned. Masson's trichrome staining was performed using a staining kit (Sigma-Aldrich, HT15, St. Louis, MO, USA). The percentage infarct area was calculated as the ratio of the fibrotic left ventricular area to total area × 100%.

Immunofluorescence Staining

For immunofluorescence staining, heart tissue sections were incubated overnight at 4 °C with the primary antibodies: anti-CD31 (Abcam, ab7388, Cambridge, UK), anti-α-smooth muscle actin (α-SMA; Abcam, ab5694, Cambridge, UK) and anti-human mitochondria (Abcam, ab92824, Cambridge, UK). After washing with PBS, sections were incubated for 1 h at room temperature with fluorescence-conjugated secondary antibodies (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA). Nuclei were counterstained with DAPI (Beyotime, C1002, Shanghai, China). Six randomly selected fields per mouse were imaged, and the mean value from these fields used for quantification. Capillary density, arteriolar density, and human mitochondrial signals were expressed as the number of $CD31^+$ vessels, $\alpha\text{-SMA}^+$ vessels, and mitochondria-positive signals per field, respectively. Each mouse was treated as one independent biological replicate.

Statistical Analysis

Data are presented as the mean ± SEM and analyzed by GraphPad Prism software (version 10.0, GraphPad Software, San Diego, CA, USA). Data normality was assessed using the Shapiro–Wilk test before statistical analysis. Comparisons between two groups were performed using an unpaired Student's *t*-test, and comparisons among three or more groups were analyzed using one-way ANOVA followed by Bonferroni's post hoc correction. A p value < 0.05 was considered statistically significant.

Results

FGF21 Pretreatment Promoted Survival of MSCs When Subjected to SD/H Challenge

To determine whether FGF21 regulated MSC survival, we evaluated the level of FGF21 in MSCs under SD/H. The expression of FGF21 was gradually downregulated in a time-dependent manner compared with the control group (all $p < 0.05$), although no significant difference was observed between the 48 h and 60 h time points (Fig. 1A). To examine the role of FGF21 in protecting against MSC injury under SD/H, MSCs were pretreated for 24 h with 10, 20, 40 and 60 ng/mL FGF21 and then subjected to SD/H for 48 h. CCK-8 assay revealed that FGF21 treatment significantly improved MSC viability under SD/H conditions in a dose-dependent manner compared with the untreated SD/H group (all $p < 0.01$). Notably, no significant difference was observed between the 40 and 60 ng/mL groups (Fig. 1B). Therefore, 40 ng/mL FGF21 was used for further studies. Subsequently, MSCs were pretreated with FGF21 for 24 h and then subjected to SD/H for 48 h. FGF21 pretreatment greatly ameliorated MSC apoptosis under SD/H conditions ($p < 0.001$, Fig. 1C). Moreover, SD/H challenge significantly downregulated the proliferative capacity of MSCs although this effect was largely reversed by FGF21 pretreatment ($p < 0.05$, Fig. 1D). These data suggest that pretreatment with FGF21 promoted MSC survival when subjected to SD/H challenge.

FGF21 Pretreatment Promoted MSC Survival via Activation of the AMPK Pathway Under SD/H Challenge

To determine the cellular mechanisms underlying FGF21 pretreatment-enhanced MSC survival under SD/H challenge, we harvested MSCs from the normoxia, SD/H and SD/H + FGF21 group and then performed Bulk-RNA-seq analysis. As shown in Fig. 2A, the level of 2273 genes increased, and that of 1892 genes decreased in the SD/H group compared with the normoxia group. Compared with the SD/H group, the level of 529 genes was enhanced and that of 878 were reduced in the SD/H + FGF21 group (Fig. 2A). Moreover, downregulation of 427 genes in MSCs subjected to SD/H was reversed by FGF21 pretreatment (Fig. 2B). KEGG enrichment analyses revealed that the genes reversed by FGF21 pretreatment were closely associated with the HIF-, VEGF- and AMPK signaling pathways (Fig. 2C) that are known to play critical roles in cellular responses to hypoxia, angiogenesis, and metabolic stress [19,20]. Given its key role in energy homeostasis and stress adaptation, as well as its established association with FGF21 signaling [21,22], the AMPK pathway was selected for further investigation. To validate its involvement, we determined whether FGF21-mediated protection under SD/H conditions depended on AMPK activation. TUNEL staining revealed that AMPK inhibitor Compound C greatly

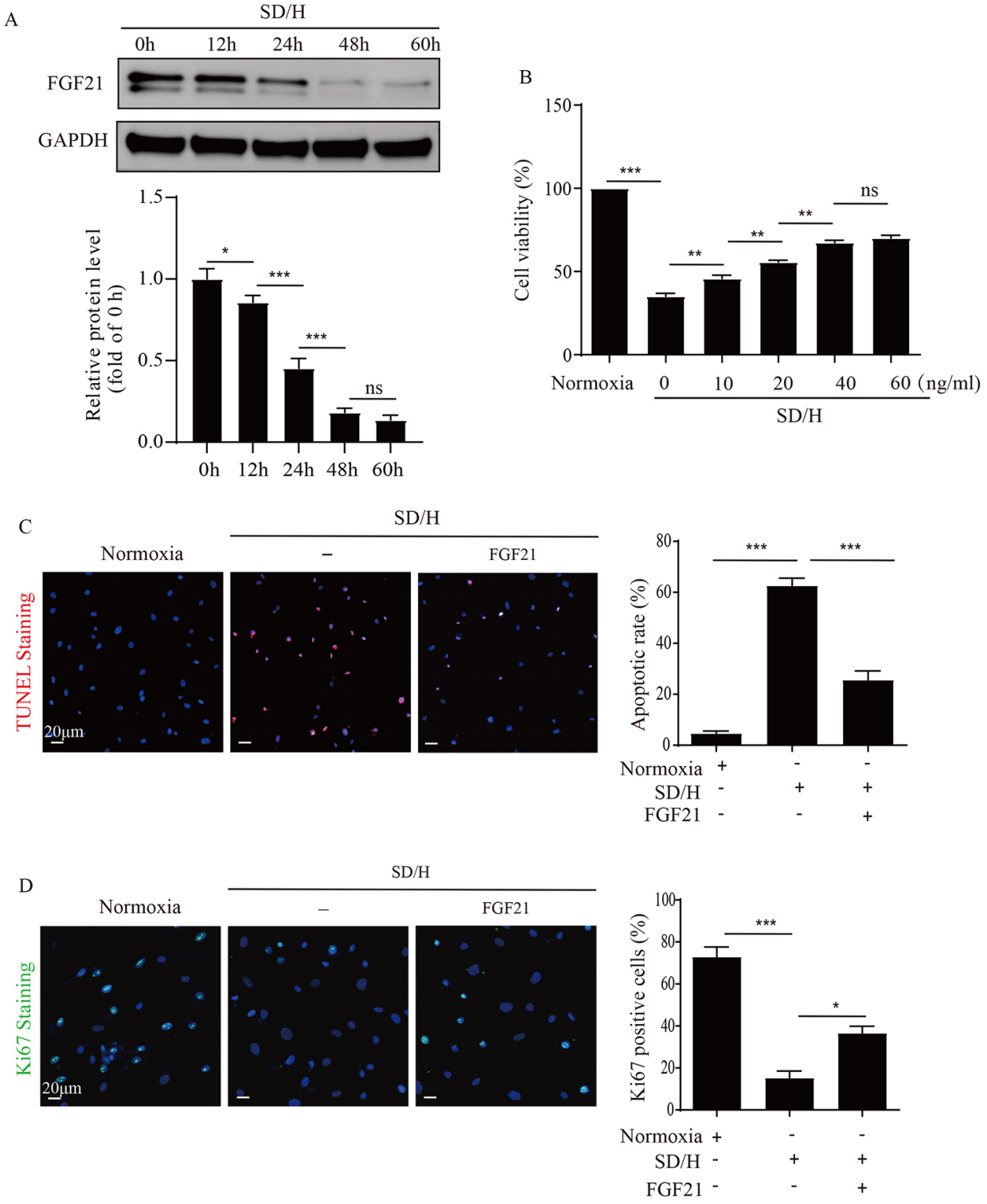

Fig. 1. FGF21 pretreatment promoted MSC survival under SD/H challenge. (A) Western blotting assay measured the level of FGF21 in MSCs under SD/H challenge at different timepoints. (B) CCK-8 assessed MSC viability with or without different concentrations of FGF21 pre-treatment under normoxic or SD/H conditions for 24 h. (C) TUNEL staining assessed the apoptotic rate of MSCs with or without FGF21 treatment under normoxic or SD/H. (D) Ki-67 staining assessed the proliferative capacity of MSCs with or without FGF21 treatment under normoxic or SD/H challenge. n = 3. ns, not significant; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. FGF21, fibroblast growth factor 21; MSC, mesenchymal stem cell; SD/H, serum deprivation and hypoxia; CCK-8, Cell Counting Kit-8; TUNEL, Terminal deoxynucleotidyl transferase dUTP nick end labeling.

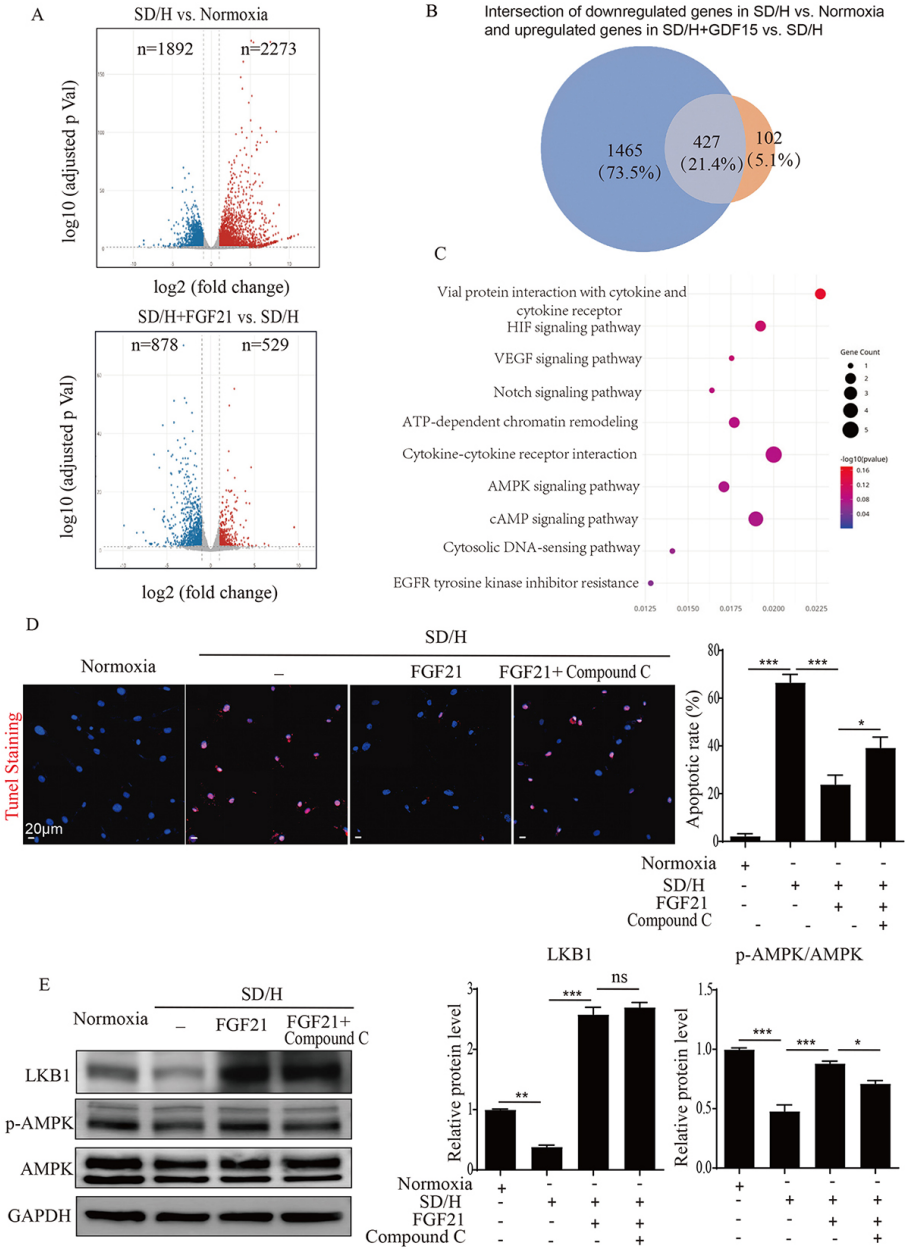

Fig. 2. FGF21 pretreatment promoted MSC survival via activation of the AMPK pathway under SD/H challenge. (A) Differentially expressed genes in SD/H vs. normoxia group and SD/H + FGF21 versus SD/H group. (B) The overlap between the downregulated genes in SD/H group vs. normoxia group and upregulated genes in SD/H + FGF21 group vs. SD/H group. (C) KEGG pathway enrichment of the overlap between downregulated genes in the SD/H group vs. normoxia group and upregulated genes in the SD/H + dFGF21 group vs. SD/H group. (D) The apoptosis of MSCs under normoxia, SD/H, SD/H + FGF21 and SD/H + FGF21 + Compound C treatment. (E) Western blotting determined the protein level of LKB1, p-AMPK, and AMPK in MSCs under normoxia, SD/H, SD/H + FGF21 and SD/H + FGF21 + Compound C treatment. n = 3. ns, not significant; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. AMPK, AMP-activated protein kinase; KEGG, Kyoto Encyclopedia of Genes and Genomes; LKB1, liver kinase B1.

mitigated the protective effect of FGF21 against SD/H-induced MSC apoptosis ($p < 0.05$, Fig. 2D). Western blotting demonstrated that FGF21 pretreatment significantly restored the decreased expression of LKB1, a key upstream kinase responsible for AMPK activation, as well as the level of p-AMPK in MSCs under SD/H ($p < 0.001$, Fig. 2E). Nonetheless Compound C co-treatment significantly downregulated the increased p-AMPK in FGF21-treated MSCs under SD/H ($p < 0.05$) but had no impact on LKB1 expression (Fig. 2E). These data collectively highlighted that FGF21 pretreatment promoted survival of MSCs subjected to SD/H via activation of the AMPK pathway and regulation of LKB1.

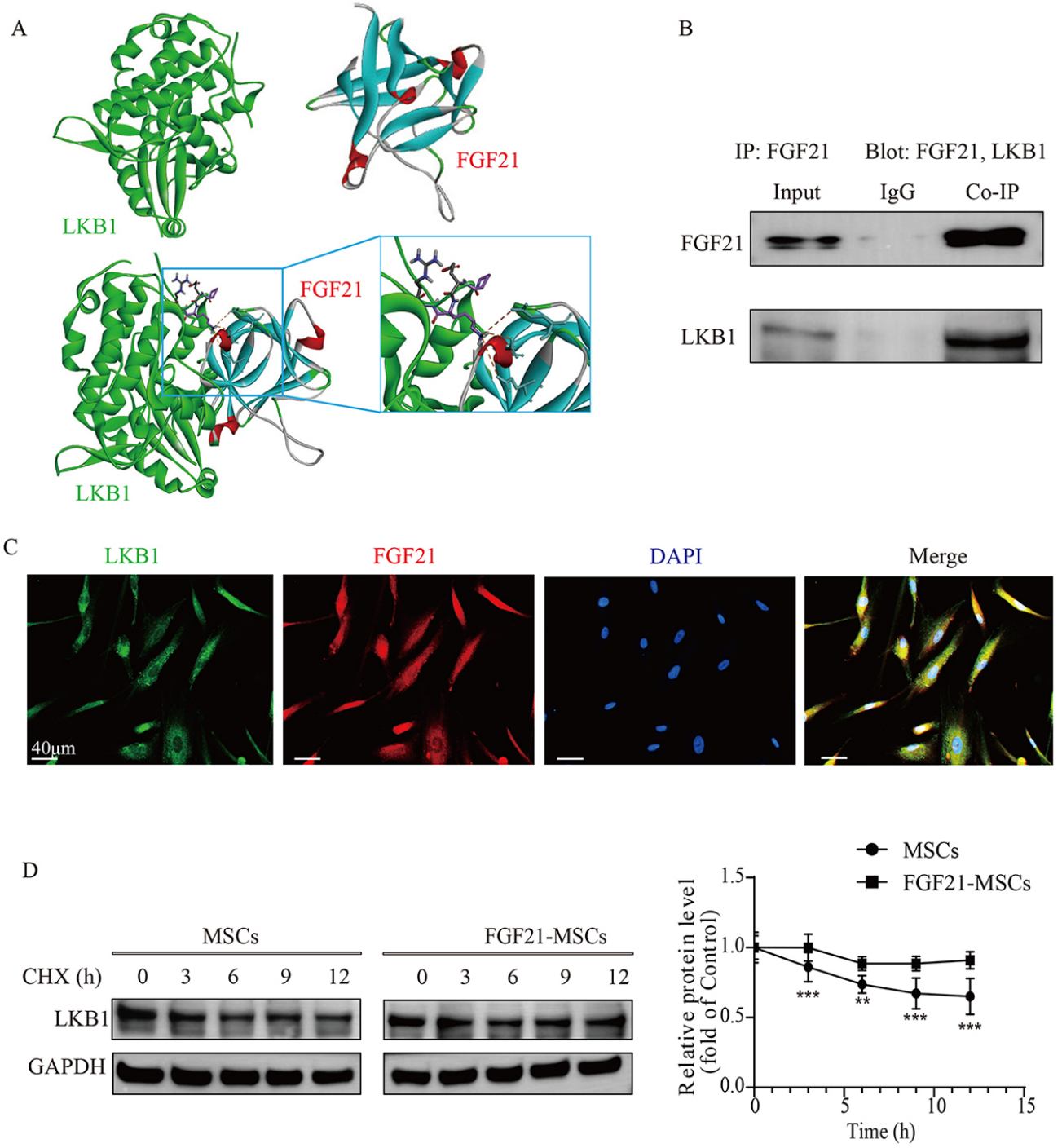

Fig. 3. FGF21 treatment stabilized LKB1 in MSCs. (A) Predicted binding interface between FGF21 and LKB1 based on molecular docking analysis. (B) Co-IP assay suggested an association between FGF21 and LKB1 in MSCs. (C) Immunofluorescence staining detected colocalization of FGF21 and LKB1 in MSCs. (D) Western blot analysis of LKB1 protein level in MSCs treated with FGF21 in the presence or absence of cycloheximide (CHX). n = 3. $^{**}p < 0.01$; $^{***}p < 0.001$ for the comparison between MSCs and FGF21-MSCs at the same time point. Co-IP, co-immunoprecipitation.

FGF21 Treatment Stabilizes LKB1 in MSCs

Subsequently, we aimed to investigate how FGF21 regulated LKB1 expression. Molecular docking analysis predicted potential binding interfaces between FGF21 and LKB1 (Fig. 3A). Co-IP assay suggested an interaction between FGF21 and LKB1 (Fig. 3B). Double immunofluorescence staining demonstrated that FGF21 was co-localized with LKB1 in MSCs, suggesting spatial proximity between the two proteins (Fig. 3C). Since FGF21 treatment could enhance the protein level of LKB1

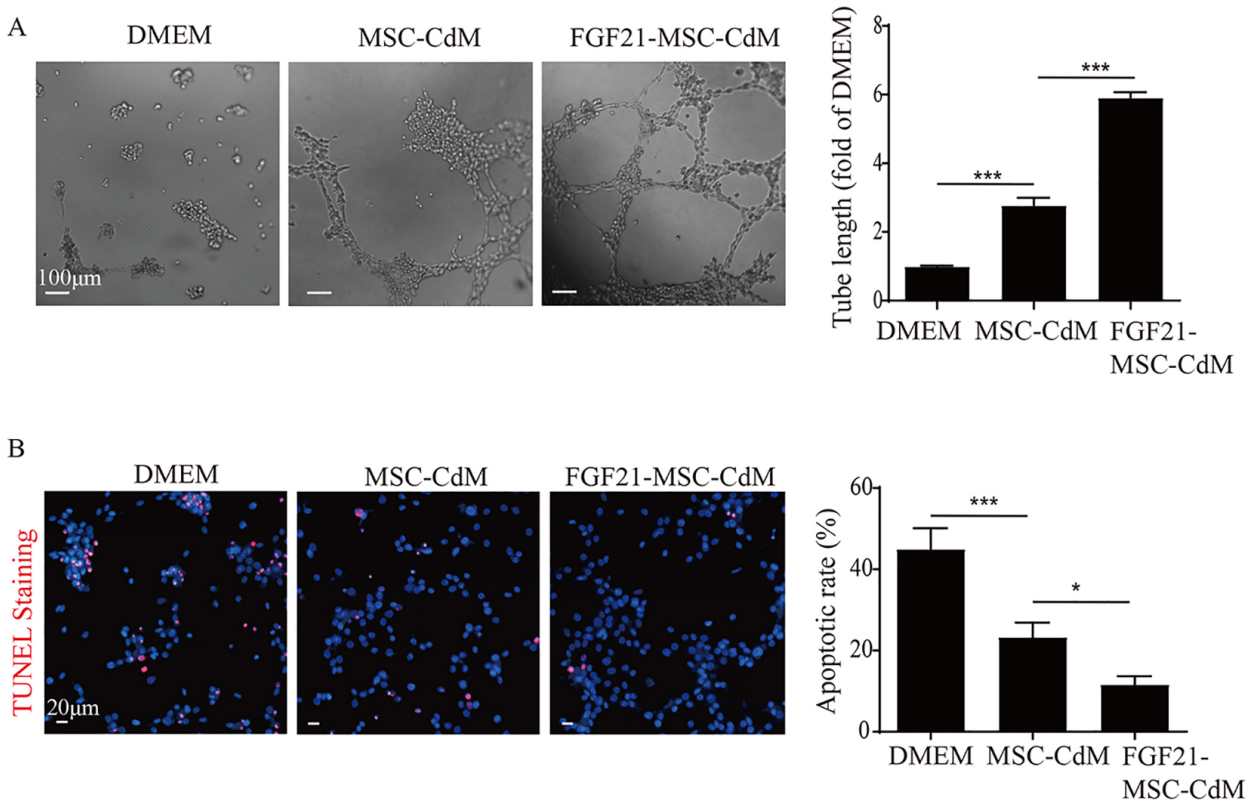

Fig. 4. FGF21 pretreatment enhanced MSC paracrine actions. (A) Representative images and quantification of HUVEC tube formation in DMEM, MSC-CdM or FGF21-MSC-CdM. (B) The apoptosis of NCMs treated with DMEM, MSC-CdM or FGF21-MSC-CdM under SD/H challenge. n = 3. *$p < 0.05$; ***$p < 0.001$. HUVEC, human umbilical vein endothelial cell; DMEM, Dulbecco's modified Eagle's medium; CdM, conditioned media; NCMs, Neonatal mouse cardiomyocytes.

in MSCs, we treated FGF21-MSCs with cycloheximide (CHX), a protein synthesis inhibitor. Results showed that FGF21 treatment prolonged the half-life of LKB1 protein under CHX challenge, indicating that FGF21 contributed to the stabilization of LKB1 ($p < 0.01$, Fig. 3D). Collectively, FGF21 treatment stabilized LKB1 in MSCs, thereby activating the AMPK pathway.

FGF21 Pretreatment Enhanced the Paracrine Actions of MSCs

To examine whether pretreatment of FGF21 could enhance MSC paracrine actions, we isolated CdM from MSCs with or without FGF21 pretreatment and incubated them with HUVECs to determine their angiogenic capacity. Compared with the DMEM control, both MSC-CdM and FGF21-MSC-CdM significantly increased tube formation in HUVECs, with the FGF21-MSC-CdM group exhibiting a markedly greater effect than MSC-CdM alone ($p < 0.001$, Fig. 4A). Under SD/H conditions, NCMs treated with MSC-CdM exhibited significantly reduced apoptosis compared with the DMEM group, and this protective effect was further enhanced by FGF21-MSC-CdM ($p < 0.05$, Fig. 4B). Taken together, these data revealed that pretreatment with FGF21 enhanced MSC paracrine actions.

FGF21-MSC Transplantation Enhanced Heart Function in Mice Following Infarction

We next investigated whether FGF21 pretreatment could enhance the reparative potential of MSCs in MI by delivering MSCs or FGF21-MSCs into the infarcted heart, followed by echocardiographic evaluation of cardiac performance (Fig. 5A). At 4 weeks post transplantation, LVEF and LVFS were greatly decreased in the MI group compared with the sham group but significantly enhanced in the MSC group and further improved in the FGF21-MSC group, indicating superior therapeutic effects of FGF21-MSC transplantation for MI ($p < 0.001$, Fig. 5B). Consistent with MI-induced remodeling, the infarcted myocardium exhibited extensive fibrosis compared with sham-operated mice; this pathological change was attenuated by MSC transplantation and further alleviated by FGF21-pretreated MSCs ($p < 0.001$, Fig. 5C). To evaluate the persistence of transplanted cell-derived signals in the infarcted myocardium, immunostaining for human mitochondria was performed 4 weeks after transplantation. Human mitochondrial signals were significantly greater in the FGF21-MSC group than in the MSC group ($p < 0.001$, Fig. 5D), suggesting enhanced persistence of transplanted cell-derived material in the infarcted heart. Collectively, these findings indicated

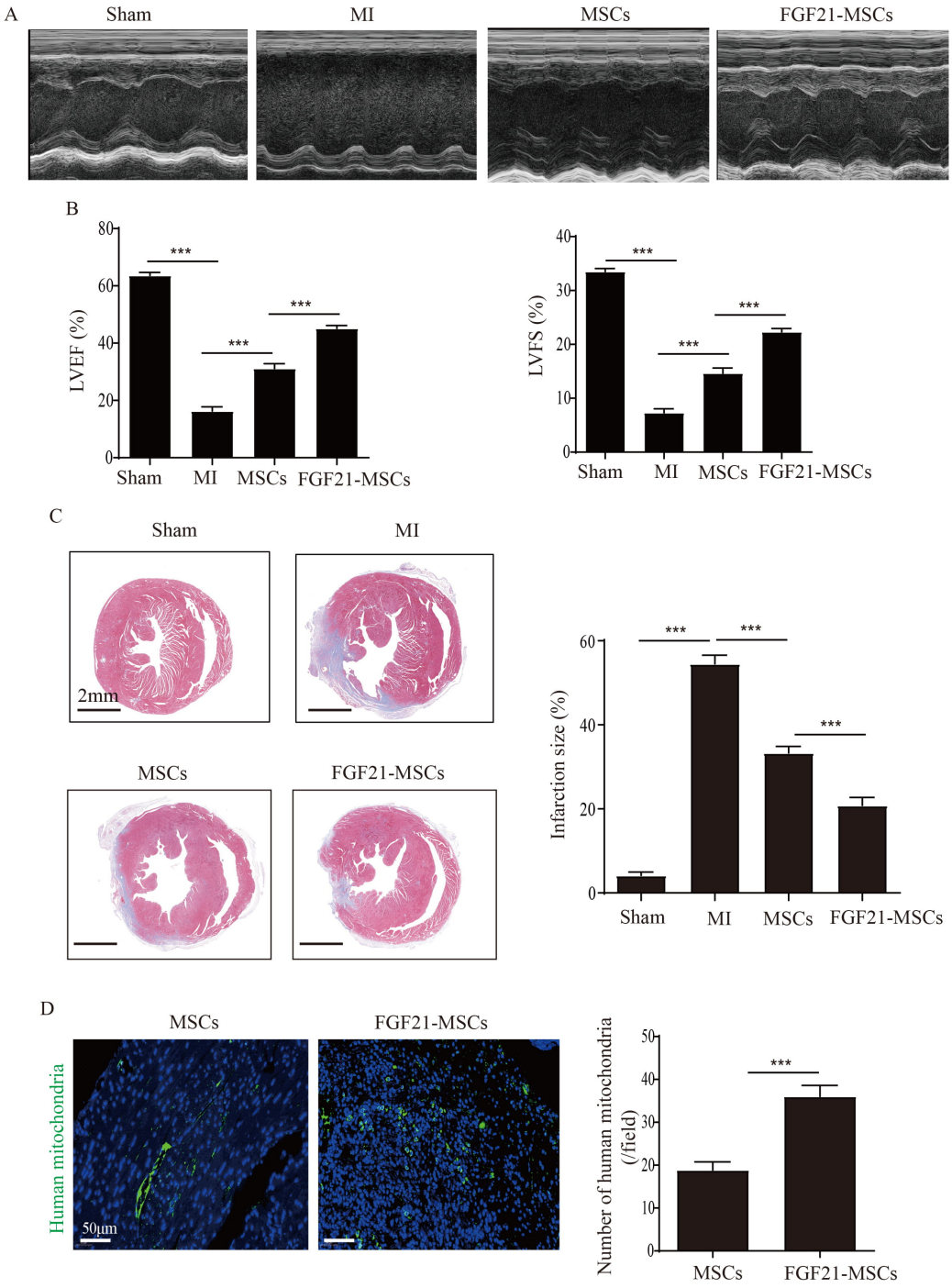

Fig. 5. Transplantation of FGF21-MSCs improved heart function in mice following infarction. (A) Echocardiographic images captured at 4 weeks in mice from different groups. (B) Quantitative analysis of LVEF and LVFS at 4 weeks in mice from different groups. (C) Masson's trichrome staining of heart tissue and measurement of infarct size at 4 weeks in mice from different groups. (D) Anti-human mitochondrial staining and measurement of the number of human mitochondria in the heart tissue from MSC group or FGF21-MSC group. n = 6. ***$p < 0.001$. LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening.

that pretreatment with FGF21 pretreatment augmented the therapeutic effects of MSC transplantation for cardiac repair following MI.

Transplantation of FGF21-MSCs Enhanced Angiogenesis and Inhibited Cardiac Apoptosis Following Infarction

As shown in Fig. 6A, cardiac apoptosis was markedly increased in MI mice compared with the sham group, whereas both MSC and FGF21-MSC treatments signifi-

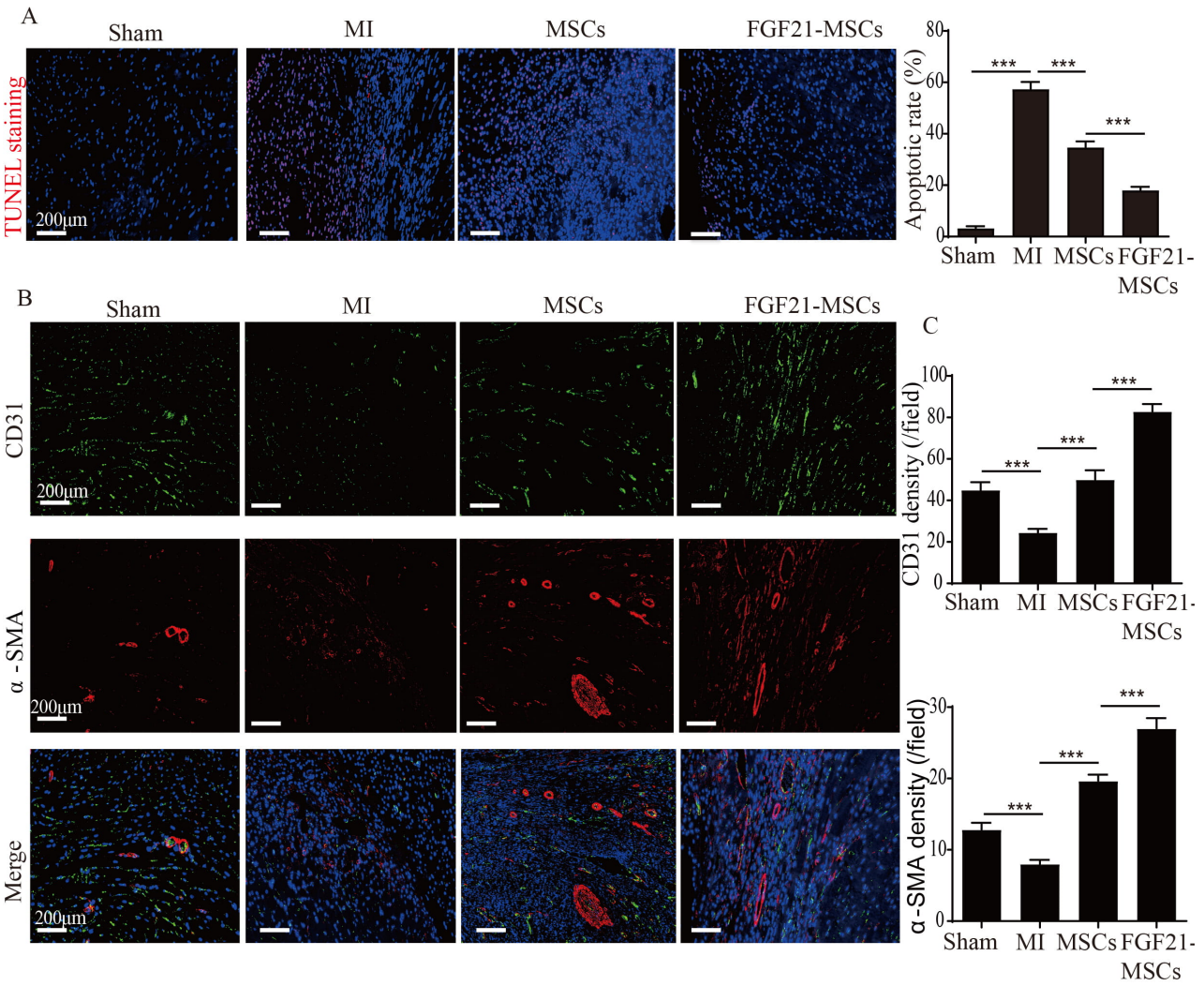

Fig. 6. Transplantation of FGF21-MSCs enhanced angiogenesis and inhibited apoptosis in the ischemic heart of mice. (A) TUNEL staining images and quantitative analysis of the degree of apoptosis in heart tissue from mice with different treatments. (B) CD31 or α-SMA staining images of the heart tissue from mice with different treatments. (C) Measurement of the capillary density and arteriolar density in heart tissue from mice with different treatments. n = 6. ***$p < 0.001$. CD31, cluster of differentiation 31; α-SMA, α-smooth muscle actin.

cantly attenuated apoptosis, with a more pronounced reduction observed in the FGF21-MSC group ($p < 0.001$, Fig. 6A). We next assessed vascular remodeling in the infarcted hearts. CD31 immunostaining demonstrated that both MSC and FGF21-MSC treatments significantly increased capillary density compared with the MI group, with a more pronounced effect observed in the FGF21-MSC group ($p < 0.001$, Fig. 6B,C). Consistently, α-SMA staining showed that MSC or FGF21-MSC transplantation greatly elevated arteriolar density in the ischemic heart tissue of mice ($p < 0.001$, Fig. 6B,C). Moreover, arteriolar density was greatly up-regulated in the FGF21-MSC group compared with the MSC group ($p < 0.001$, Fig. 6B,C). These results showed that FGF21-MSC transplantation enhanced angiogenesis and attenuated cardiac apoptosis in the heart of mice following infarction.

Discussion

This current study offers several major findings. First, FGF21 pretreatment greatly improved MSC survival via activation of the AMPK pathway under SD/H conditions. Second, FGF21 treatment activated the AMPK pathway in SD/H-treated MSCs, at least in part, by enhancing LKB1 stability. Third, FGF21 pretreatment enhanced the paracrine activity of MSCs, as evidenced by augmented angiogenesis and reduced SD/H-induced cardiomyocyte apoptosis. Fourth, FGF21-MSC transplantation greatly improved heart function in mice post infarction via both enhanced survival of MSCs and angiogenesis. Our study reveals that FGF21 pretreatment can serve as a novel means to enhance MSC-based therapy for the infarcted heart.

There is a growing body of evidence that MSC transplantation exerts beneficial effects on MI through multiple molecular mechanisms including differentiation capacity, transferred mitochondria and immunomodulation capacity [23,24]. Nevertheless their cardioprotective effects are largely restricted by the poor viability of transplanted MSCs due to the challenging microenvironment post-infarction [25,26,27]. Fewer than 2% of MSCs survive at 4 weeks after transplantation in the infarcted heart tissue of rats [28]. Similarly, only 3% of MSCs could be detected at 14 days post-transplantation in a porcine model of MI [29]. To overcome this obstacle, several approaches including genetic modification, pharmacologic pretreatment and biological patches have been explored to enhance MSC viability post transplantation in the infarcted heart [30,31,32]. Among these approaches, pretreatment has been widely used because it is an easy and economical strategy [10]. It has been reported that MSCs pretreated with haemin, a potent haem oxygenase 1 inducer, prior to transplantation exhibited significantly improved survival and thereby enhanced the cardiac function of mice with MI [33]. It is vital to identify critical biological agents to pretreat MSCs prior to transplantation. It has been reported that FGF21 treatment remarkably enhanced the viability of epidermal cells under ultraviolet B irradiation via regulation of AMPK-mediated autophagy [34]. Furthermore, FGF21 treatment was reported to alleviate hypoxia/regeneration-induced ferroptosis of pulmonary epithelial cells via activation of the FGFR1/PPARδ pathway [35]. These results encouraged us to examine whether FGF21 pretreatment could improve survival of MSCs in the infarcted heart. We first determined that FGF21 pretreatment significantly improved MSC survival as shown by decreased apoptosis under SD/H challenge *in vitro*. Treatment of CdM derived from FGF21-pretreated MSCs greatly improved endothelial tube length of HUVECs and inhibited SD/H-induced cardiomyocyte apoptosis, suggesting FGF21 pretreatment enhanced the paracrine actions of MSCs. Furthermore, in comparison to MSCs, FGF21 pretreatment greatly enhanced MSC viability in the infarcted region and improved the repair efficacy in mice with MI via promotion of angiogenesis and inhibition of apoptosis.

To address the potential cellular mechanisms underlying this protection afforded by FGF21 pretreatment against SD/H-induced MSC injury, we harvested MSCs from the normoxia, SD/H and SD/H + FGF21 group and then performed RNA-seq analysis. In comparison with the normoxia group, downregulation of 427 genes in the SD/H group was partially reversed by FGF21 pretreatment. KEGG enrichment analysis revealed these genes were primarily involved in the AMPK signaling pathway. The AMPK signaling pathway regulates cell viability under various stress conditions [36,37]. It has been reported that FOXO3 overexpression increases cell viability of human lens epithelial cells under ultraviolet B radiation via activation of the AMPK pathway [38]. Hypericin treatment has been shown to increase cardiomyocyte viability under hypoxia/reoxygenation conditions via upregulation of the AMPK/PGC-1α pathway [39]. In this study, FGF21 pretreatment significantly inhibited MSC apoptosis under SD/H challenge via upregulation of p-AMPK expression, an effect that was partially reversed by an AMPK inhibitor. This suggested that FGF21 regulated MSC viability via mediation of the AMPK pathway. To further explore how FGF21 activates the AMPK pathway, we performed molecular docking analysis that predicted a potential interaction interface between FGF21 and LKB1. Together with the Co-IP results, these findings suggest a possible association of FGF21 with LKB1. Nonetheless considering the canonical receptor-mediated mode of FGF21 signaling, it is more likely that FGF21 regulates LKB1 stability indirectly rather than through direct intracellular binding. LKB1 is an upstream kinase that phosphorylates and activates AMPK, thereby regulating diverse cellular processes [40,41]. It has been reported that liraglutide mediates lipid metabolism via regulation of the FGF21- LKB1- and AMPK pathways in white adipose tissue [42]. Nevertheless the molecular mechanisms underlying this FGF21-LKB1 interaction remain unclear. In our study, FGF21 treatment significantly increased the protein level of LKB1 in MSCs. Under CHX treatment, FGF21 prolonged the half-life of LKB1 protein, indicating that FGF21 contributed to the stabilization of LKB1.

Some limitations in the current study need to be highlighted. First, whether FGF21 pretreatment promotes MSC survival in the infarcted heart via regulation of other pathways warrants investigation. Second, MSC transplantation promoted cardiac repair following infarction via secretion of exosomes [43,44]. Whether FGF21 pretreatment improves the therapeutic efficacy of MSC-secreted exosomes for infarcted hearts has not been assessed. Third, although FGF21 pretreatment enhanced MSC paracrine effects, the critical cytokines in the CdM derived from FGF21-MSCs remain to be determined. Fourth, in addition to FGF21-MSCs, whether MSC transplantation combined with FGF21 treatment can further promote cardioprotective effects for MI was not determined.

Conclusions

Our results show that FGF21 pretreatment greatly improved the survival of MSCs under ischemic conditions as well as their paracrine effects, thus facilitating cardiac repair following infarction. Our study highlighted FGF21 pretreatment as an effective means to improve the therapeutic effects of MSCs for cardiovascular diseases and holds great potential for clinical translation.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding authors upon reasonable request.

Author Contributions

XFJ and JQ performed experiments, data analysis and wrote the original draft. CZ, DLH, JYW, FL and KXM analyzed the data. XTL and XHW conceived, designed this project and wrote the original draft. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

All studies that involved animals were conducted and approved by the Committee on the Use of Live Animals in Teaching and Research of Tongji University for Laboratory Animal Medicine (Approval No. TJBB04725103). All procedures complied with the ARRIVE Guidelines 2.0.

Acknowledgment

Not applicable.

Funding

This work was supported by a grant from the Natural Science Foundation of Shanghai (24ZR1459300).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet (London, England). 2017; 389: 197–210. https://doi.org/10.1016/S0140-6736(16)30677-8

[2] Zhongxin S, Zhijie C, Feng D, Qin GM, Ya Z, Jinxin H, et al. Astragaloside IV increases PDHA1 in mesenchymal stem cell exosomes to treat myocardial infarction. Scientific Reports. 2025; 15: 25461. https://doi.org/10.1038/s41598-025-08628-5

[3] Saha T, Soliman-Aboumarie H. Review of Current Management of Myocardial Infarction. Journal of Clinical Medicine. 2025; 14: 6241. https://doi.org/10.3390/jcm14176241

[4] Li W, Huang Y, Gao C, Zhu Z, Dai G. Mesenchymal Stem Cell (MSC) Transplantation Accompanied by Activation of Invariant Natural Killer T Cells Further Ameliorates Post-infarct Cardiac Remodeling in Mice. Discovery Medicine. 2021; 32: 51–63.

[5] Nazir S, Maqbool T, Savas S. Cardiac Repair and Mesenchymal Stem Cells: Exploring New Frontiers in Regenerative Medicine. Current Cardiology Reviews. 2026; 22: e1573403X376065. https://doi.org/10.2174/011573403X376065250728094646

[6] Zhong X, Luo L, Wu J, Li W, Liu X, Ye T, et al. Adhesion-Assisted Antioxidant-Engineered Mesenchymal Stromal Cells for Enhanced Cardiac Repair in Myocardial Infarction. ACS Nano. 2025; 19: 11412–11426. https://doi.org/10.1021/acsnano.5c00820

[7] An C, Zhao Y, Guo L, Zhang Z, Yan C, Zhang S, et al. Innovative approaches to boost mesenchymal stem cells efficacy in myocardial infarction therapy. Materials Today. Bio. 2025; 31: 101476. https://doi.org/10.1016/j.mtbio.2025.101476

[8] Du D, Wang T, Sun Y, Zhang Y, Zhang B, Shao J, et al. PRMT1 inhibition enhances the cardioprotective effect of adipose-derived mesenchymal stem cells against myocardial infarction through RUNX1. Stem Cell Research & Therapy. 2025; 16: 279. https://doi.org/10.1186/s13287-025-04409-z

[9] Hou JY, Wu H, Li SM, Li XJ, Yang SJ, Chen XX, et al. ELABELA promotes the migration and homing of bone marrow mesenchymal stem cells to myocardial injury sites through the ERK1/2/miR-299a-5p/Exo70 pathway. Frontiers in Pharmacology. 2025; 16: 1541869. https://doi.org/10.3389/fphar.2025.1541869

[10] Cai H, Han XJ, Luo ZR, Wang QL, Lu PP, Mou FF, et al. Pretreatment with Notoginsenoside R1 enhances the efficacy of neonatal rat mesenchymal stem cell transplantation in model of myocardial infarction through regulating PI3K/Akt/FoxO1 signaling pathways. Stem Cell Research & Therapy. 2024; 15: 419. https://doi.org/10.1186/s13287-024-04039-x

[11] Wang HW, Jiang X, Zhang Y, Wang J, Xie J, Wang YQ, et al. FGF21 Protects Against Hypoxia Injury Through Inducing HSP72 in Cerebral Microvascular Endothelial Cells. Frontiers in Pharmacology. 2019; 10: 101. https://doi.org/10.3389/fphar.2019.00101

[12] Ren Z, Xiao W, Zeng Y, Liu MH, Li GH, Tang ZH, et al. Fibroblast growth factor-21 alleviates hypoxia/reoxygenation injury in H9c2 cardiomyocytes by promoting autophagic flux. International Journal of Molecular Medicine. 2019; 43: 1321–1330. https://doi.org/10.3892/ijmm.2019.4071

[13] Liang P, Zhong L, Gong L, Wang J, Zhu Y, Liu W, et al. Fibroblast growth factor 21 protects rat cardiomyocytes from endoplasmic reticulum stress by promoting the fibroblast growth factor receptor 1-extracellular signal-regulated kinase 1/2 signaling pathway. International Journal of Molecular Medicine. 2017; 40: 1477–1485. https://doi.org/10.3892/ijmm.2017.3140

[14] Lin J, Wu J, Xu Y, Zhao Y, Ye S. RhFGF21 protected PC12 cells against mitochondrial apoptosis triggered by H_2O_2 via the AKT-mediated ROS signaling pathway. Experimental Cell Research. 2025; 445: 114417. https://doi.org/10.1016/j.yexcr.2025.114417

[15] Li R, Liu X. FGF21 Inhibits Hypoxia/Reoxygenation-induced Renal Tubular Epithelial Cell Injury by Regulating the PPARγ/NF-κB Signaling Pathway. Cell Biochemistry and Biophysics. 2024; 82: 909–918. https://doi.org/10.1007/s12013-024-01242-8

[16] Zhao Z, Cui X, Liao Z. Mechanism of fibroblast growth factor 21 in cardiac remodeling. Frontiers in Cardiovascular Medicine. 2023; 10: 1202730. https://doi.org/10.3389/fcvm.2023.1202730

[17] Wang R, Zhang X, Ye H, Yang X, Zhao Y, Wu L, et al. Fibroblast growth factor 21 improves diabetic cardiomyopathy by inhibiting ferroptosis via ferritin pathway. Cardiovascular Diabetology. 2024; 23: 394. https://doi.org/10.1186/s12933-024-02469-8

[18] Liang X, Ding Y, Zhang Y, Chai YH, He J, Chiu SM, et al. Activation of NRG1-ERBB4 signaling potentiates mesenchymal stem cell-mediated myocardial repairs following myocar-

dial infarction. Cell Death & Disease. 2015; 6: e1765. https://doi.org/10.1038/cddis.2015.91

[19] Marino A, Hausenloy DJ, Andreadou I, Horman S, Bertrand L, Beauloye C. AMP-activated protein kinase: A remarkable contributor to preserve a healthy heart against ROS injury. Free Radical Biology & Medicine. 2021; 166: 238–254. https://doi.org/10.1016/j.freeradbiomed.2021.02.047

[20] Liu L, Yu J, Liu Y, Xie L, Hu F, Liu H. Hypoxia-driven angiogenesis and metabolic reprogramming in vascular tumors. Frontiers in Cell and Developmental Biology. 2025; 13: 1572909. https://doi.org/10.3389/fcell.2025.1572909

[21] Zhu W, Du W, Duan R, Liu Y, Zong B, Jin X, et al. miR-873-5p Suppression Reinvigorates Aging Mesenchymal Stem Cells and Improves Cardiac Repair after Myocardial Infarction. ACS Pharmacology & Translational Science. 2024; 7: 743–756. https://doi.org/10.1021/acsptsci.3c00293

[22] Dai Q, Fan X, Meng X, Sun S, Su Y, Ling X, et al. FGF21 promotes ischaemic angiogenesis and endothelial progenitor cells function under diabetic conditions in an AMPK/NAD+-dependent manner. Journal of Cellular and Molecular Medicine. 2021; 25: 3091–3102. https://doi.org/10.1111/jcmm.16369

[23] Mori D, Miyagawa S, Kawamura T, Yoshioka D, Hata H, Ueno T, et al. Mitochondrial Transfer Induced by Adipose-Derived Mesenchymal Stem Cell Transplantation Improves Cardiac Function in Rat Models of Ischemic Cardiomyopathy. Cell Transplantation. 2023; 32: 9636897221148457. https://doi.org/10.1177/09636897221148457

[24] Zhao L, Liu X, Zhang Y, Liang X, Ding Y, Xu Y, et al. Enhanced cell survival and paracrine effects of mesenchymal stem cells overexpressing hepatocyte growth factor promote cardioprotection in myocardial infarction. Experimental Cell Research. 2016; 344: 30–39. https://doi.org/10.1016/j.yexcr.2016.03.024

[25] Xie X, Shen Y, Chen J, Huang Z, Ge J. Mineralocorticoid receptor deficiency improves the therapeutic effects of mesenchymal stem cells for myocardial infarction via enhanced cell survival. Journal of Cellular and Molecular Medicine. 2019; 23: 1246–1256. https://doi.org/10.1111/jcmm.14026

[26] Yan W, Xia Y, Zhao H, Xu X, Ma X, Tao L. Stem cell-based therapy in cardiac repair after myocardial infarction: Promise, challenges, and future directions. Journal of Molecular and Cellular Cardiology. 2024; 188: 1–14. https://doi.org/10.1016/j.yjmcc.2023.12.009

[27] Guan H, Chen Y, Liu X, Huang L. Research and application of hydrogel-encapsulated mesenchymal stem cells in the treatment of myocardial infarction. Colloids and Surfaces. B, Biointerfaces. 2024; 239: 113942. https://doi.org/10.1016/j.colsurfb.2024.113942

[28] Shan S, Liu Z, Guo T, Wang M, Tian S, Zhang Y, et al. Growth arrest-specific gene 6 transfer promotes mesenchymal stem cell survival and cardiac repair under hypoxia and ischemia via enhanced autocrine signaling and paracrine action. Archives of Biochemistry and Biophysics. 2018; 660: 108–120. https://doi.org/10.1016/j.abb.2018.10.016

[29] Freyman T, Polin G, Osman H, Crary J, Lu M, Cheng L, et al. A quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial infarction. European Heart Journal. 2006; 27: 1114–1122. https://doi.org/10.1093/eurheartj/ehi818

[30] Xu C, Xie Y, Wang B. Genetically modified mesenchymal stromal cells: a cell-based therapy offering more efficient repair after myocardial infarction. Stem Cell Research & Therapy. 2024; 15: 323. https://doi.org/10.1186/s13287-024-03942-7

[31] Maeda S, Kawamura T, Chida D, Shimamura K, Toda K, Harada A, et al. Notch Signaling-Modified Mesenchymal Stem Cell Patch Improves Left Ventricular Function via Arteriogenesis Induction in a Rat Myocardial Infarction Model. Cell Transplantation. 2023; 32: 9636897231154580. https://doi.org/10.1177/09636897231154580

[32] Yang J, Tang L, Zhang F, Yang T, Lu T, Sun K, et al. Sevoflurane preconditioning promotes mesenchymal stem cells to relieve myocardial ischemia/reperfusion injury via TRPC6-induced angiogenesis. Stem Cell Research & Therapy. 2021; 12: 584. https://doi.org/10.1186/s13287-021-02649-3

[33] Deng R, Liu Y, He H, Zhang H, Zhao C, Cui Z, et al. Haemin pretreatment augments the cardiac protection of mesenchymal stem cells by inhibiting mitochondrial fission and improving survival. Journal of Cellular and Molecular Medicine. 2020; 24: 431–440. https://doi.org/10.1111/jcmm.14747

[34] Zhao Y, Lin J, Li J, Bwalya C, Xu Y, Niu Y, et al. RhFGF21 Protects Epidermal Cells against UVB-Induced Apoptosis through Activating AMPK-Mediated Autophagy. International Journal of Molecular Sciences. 2022; 23: 12466. https://doi.org/10.3390/ijms232012466

[35] Ye X, Pei F, Li W, Xue J, Huang X, Huang J, et al. Fibroblast growth factor 21 attenuates pulmonary ischemia/reperfusion injury via inhibiting endoplasmic reticulum stress-induced ferroptosis though FGFR1/PPARδ signaling pathway. International Immunopharmacology. 2024; 143: 113307. https://doi.org/10.1016/j.intimp.2024.113307

[36] Yu Z, Wang J, Li T, Gao L. Melatonin promotes diabetic wound healing by mediating mitochondrial function in endothelial cells through the AMPK/SIRT1/HIF-1α pathway. Tissue & Cell. 2025; 95: 102884. https://doi.org/10.1016/j.tice.2025.102884

[37] Chang Y, Chou L, Zeng C, Li P, Allaf OS, Lu Y, et al. ACSL6-Mediated Cell Ferroptosis by Inhibiting AMPK Pathway in Periodontitis Stem Cells. Discovery Medicine. 2025; 37: 515–524. https://doi.org/10.24976/Discov.Med.202537194.43

[38] Sun Y, Hong Y, Ning L, Xiao B, Ainiwaer M, Jiang Y, et al. FOXO3 Protects Lens Epithelial Cells From UVB-Induced Oxidative Stress via the AMPK/FOXO3 Signaling Pathway. FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology. 2025; 39: e71039. https://doi.org/10.1096/fj.202501265RR

[39] Huihui LI, Yali B, Wanyue LI, Huitian X, Xiaofeng G, Ainiwar D, et al. Hypericin attenuates myocardial ischemia-reperfusion injury by enhancing mitochondrial energy metabolism via AMPK/PGC-1α signaling pathway. Tissue & Cell. 2025; 97: 103088. https://doi.org/10.1016/j.tice.2025.103088

[40] Shackelford DB, Shaw RJ. The LKB1-AMPK pathway: metabolism and growth control in tumour suppression. Nature Reviews. Cancer. 2009; 9: 563–575. https://doi.org/10.1038/nrc2676

[41] Trelford CB, Shepherd TG. LKB1 biology: assessing the therapeutic relevancy of LKB1 inhibitors. Cell Communication and Signaling : CCS. 2024; 22: 310. https://doi.org/10.1186/s12964-024-01689-5

[42] Zhang N, Liu C, Zhang Y, Xu D, Gui L, Lu Y, et al. Liraglutide regulates lipid metabolism via FGF21- LKB1- AMPK- ACC1 pathway in white adipose tissues and macrophage of type 2 diabetic mice. Biochemical and Biophysical Research Communications. 2021; 548: 120–126. https://doi.org/10.1016/j.bbrc.2021.02.065

[43] Ala M. The beneficial effects of mesenchymal stem cells and their exosomes on myocardial infarction and critical considerations for enhancing their efficacy. Ageing Research Reviews. 2023; 89: 101980. https://doi.org/10.1016/j.arr.2023.101980

[44] Liu Y, Wang M, Yu Y, Li C, Zhang C. Advances in the study of exosomes derived from mesenchymal stem cells and cardiac cells for the treatment of myocardial infarction. Cell Communication and Signaling : CCS. 2023; 21: 202. https://doi.org/10.1186/s12964-023-01227-9