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ORIGINAL INVESTIGATION

Human umbilical cord mesenchymal stem cells ameliorate depression by regulating Jmjd3 and microglia polarization in myocardial infarction mice

Youyang Zhang[1,2] · Xinan Wang[3] · Yuhang Li[2] · Ruiping Liu[2] · Jiangqi Pan[4] · Xiane Tang[5] · Shuifen Sun[6] · Jie Liu[6] · Wenlin Ma[1,2]

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Abstract

Rationale Microglia regulate the inflammation of the central nervous system and play a crucial role in the pathogenesis of depression. Moreover, Jmjd3 is involved in microglia polarization. Mounting studies reported the beneficial effects of human umbilical cord mesenchymal stem cells (HUC-MSCs) on myocardial infarction (MI), Unfortunately, its effects on MI-induced depression and its underlying mechanisms remain unclear.

Objectives We aimed to investigate the antidepressant effects of HUC-MSCs and their impacts on microglia polarization.

Methods In the current study, the MI model was established by ligating the left anterior descending coronary artery. Mice were injected with HUC-MSCs or PBS through the tail vein 1week after the surgery. The sucrose preference test (SPT), tail suspension test (TST), and forced swim test (FST) were performed to evaluate depression-like behavior. Cardiac function and myocardial fibrosis were evaluated at the end of the experiments. Immunofluorescence, Western blot, ELISA, and qRT-PCR were used to detect the levels of Jmjd3 and microglia-related markers and inflammatory factors.

Results HUC-MSC treatment significantly improved cardiac function, reduced the area of myocardial fibrosis, and alleviated depression-like behaviors induced by MI. HUC-MSCs inhibited the expression of Jmjd3 and promoted the switch of microglia in the prefrontal cortex, hypothalamus, and hippocampus from M1 to M2, thereby decreased the level of pro-inflammatory factors.

Conclusion HUC-MSCs have cardioprotective and potential anti-depressive effects induced by MI related to the inflammation improved by regulating Jmjd3 and microglial polarization.

Keywords HUC-MSCs · Myocardial infarction · Depression · Microglia · Jmjd3 · Inflammation

Jie Liu and Wenlin Ma shared senior authorship.

✉ Wenlin Ma
mawenlin@tongji.edu.cn

[1] Department of Cardiology, Tongji Hospital, School of Medicine, Tongji University, Shanghai 200092, China

[2] Department of Geriatrics, Tongji Hospital, School of Medicine, Tongji University, Shanghai 200092, China

[3] Department of Urology, Tongji Hospital, School of Medicine, Tongji University, 389 Xincun Rd, Putuo District, Shanghai 200092, China

[4] Department of Cardiology, Gongli Hospital, Navy Military Medical University, Shanghai, China

[5] Department of Clinical Medicine, School of Medicine, Hubei University for Nationalities, Enshi, China

[6] Regenerative Medicine Research Center, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, Kunming, Yunnan, China

Introduction

It is now been widely acknowledged that the high incidence of depression post-myocardial infarction (MI) and the prevalence can be as high as 35% (DiSante et al. 2017; Lauzon et al. 2003; Thombs et al. 2006). Depression following MI has been associated with fatal and non-fatal cardiovascular events, increased mortality (Meijer et al. 2011), impaired long-term quality of life (Benyamini et al. 2013), and high costs (Frasure-Smith et al. 2000). However, the traditional antidepressants just alleviated symptoms to a certain extent but had no improvement on mortality (Smolderen et al. 2017; Sweda et al. 2020). It is necessary and urgent to find an effective treatment.

MI and depression are both inflammatory-related diseases, and the inflammatory immune mechanism was considered one of the most important mechanisms of depression post-

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MI (Headrick et al. 2017; Ma et al. 2016; Yan et al. 2019). Our previous study has shown that coronary heart disease (CHD) patients with depression have higher levels of IL-1β and NF-κB (Ma et al. 2016). Jmjd3, a histone demethylase, regulates the methylation of key pro-inflammatory gene promoter site H3K27me3, and mediates the expression of inflammatory factors in macrophages and microglia (Przanowski et al. 2014; Yan et al. 2014). Treatment with GSK-J4, a specific antagonist of Jmjd3, alleviated brain inflammation induced by lipopolysaccharide (LSP) and improved depression-like behavior (Przanowski et al. 2014). These results suggested that Jmjd3 was involved in the susceptibility to depression.

Furthermore, recent literature reported that Jmjd3 might regulate the activation polarization of microglia (Tang et al. 2014; Wang et al. 2020). Accumulated evidence has indicated that microglia, as the primary immune regulatory cells of the central nervous system (CNS), plays a key role in the pathogenesis of depression (Jia et al. 2020; Troubat et al. 2021). The density of glial cells in hippocampal subfields of CA and dentate gyrus increased in patients with depression (Rajkowska and Miguel-Hidalgo 2007). Microglial activation mediates the chronic mild stress-induced depression-like behavior and hippocampal neuro-inflammation (Wang et al. 2018b). Exogenous fibroblast growth factor 2 inhibited the hippocampal microglia activation and reversed the depression-like behavior induced by LPS (Tang et al. 2018b).

Microglial activation can be classified into two major phenotypes defined as M1 (classical, pro-inflammatory) and M2 (alternative, anti-inflammatory) polarization types (Colton 2009). Studies have shown that different types of microglia activation may have different regulatory behaviors on the CNS and induce conflicting phenotypes (Butovsky and Weiner 2018; Tang et al. 2018a). Switching of the microglia activation phenotype is a possible treatment for depression (Zhang et al. 2018).

It is well known that mesenchymal stem cells (MSCs) have potential immunomodulatory and anti-inflammatory properties (Baraniak and McDevitt 2010). It has been established that MSC therapy improved left ventricular function and adverse remodeling in mice with MI through its anti-inflammatory effects (Luger et al. 2017). And a recent study showed that human umbilical cord MSCs (HUC-MSCs) ameliorated chronic unpredictable mild stress induced depression by modulating microglial polarization (Li et al. 2020). However, the effect of HUC-MSCs on MI-induced depression is currently unclear.

The purpose of this study was (1) to determine whether HUC-MSCs can ameliorate depression-like behavior in MI mice, and (2) to explore whether its effect was caused by regulating Jmjd3 and the activation of microglia to improve inflammation.

Methods

Animals

Seven-week-old male C57BL/6J mice, weighing 20–25g (n=80), were purchased from the Experimental Animal Center of Tongji University. All animals were housed under standard laboratory conditions (22 °C, 40–50% humidity, and 12/12 light/dark cycle) and had free access to food and water (except during the sucrose preference test). Ethics Committee in Tongji Hospital of Tongji University approved animal experiments.

Experimental design and MI model

Mice were randomly divided into 3 groups: MI+HUC-MSCs group (n=30), MI+PBS group (n=30), and Sham+PBS group (n=20). The experimental design was shown in Fig. 1. MI mouse model was constructed by ligating the left anterior descending coronary artery (LAD) as previously reported (Liu et al. 2019). Briefly, mice were anesthetized by the intraperitoneal injection of pentobarbital sodium and then were tracheotomy and intubated artificial mechanical ventilation. An 8-0 nylon thread was passed 2–3 mm below the tip of the left pinna for permanent ligation of LAD. Ligation was considered successful when the anterior wall of the LV turned pale. The same procedure was performed on the Sham + PBS group except for the ligation.

HUC-MSCs

HUC-MSCs were provided by the Stem Cell Center of Tongji Hospital and have been authenticated by flow cytometry (Figure S1). HUC-MSCs were seeded and made adherent in serum-free Dulbecco's Modified Eagle's Medium (DMEM)/F12 medium (HyClone) supplemented with 10% fetal bovine serum (FBS; Hyclone) overnight. 2×10^6 HUC-MSCs in 0.2 mL were injected in each mouse into the lateral tail vein 1week after MI; the dose selection was in accordance with a previous study (Luger et al. 2017).

Depression-like behavior tests

Sucrose preference test

Sucrose preference test (SPT) was performed according to the procedure described previously with minor modifications (Misrani et al. 2019; Willner et al. 1987). The adaptation consists of three stages. All mice were given two bottles of 1% sucrose solution for 24 h, then one of the bottles of 1% sucrose solution was changed to pure water for 24 h, and finally, all water and food were deprived for 24 h. During the formal test, mice were given a bottle of 1% sucrose solution and a bottle of

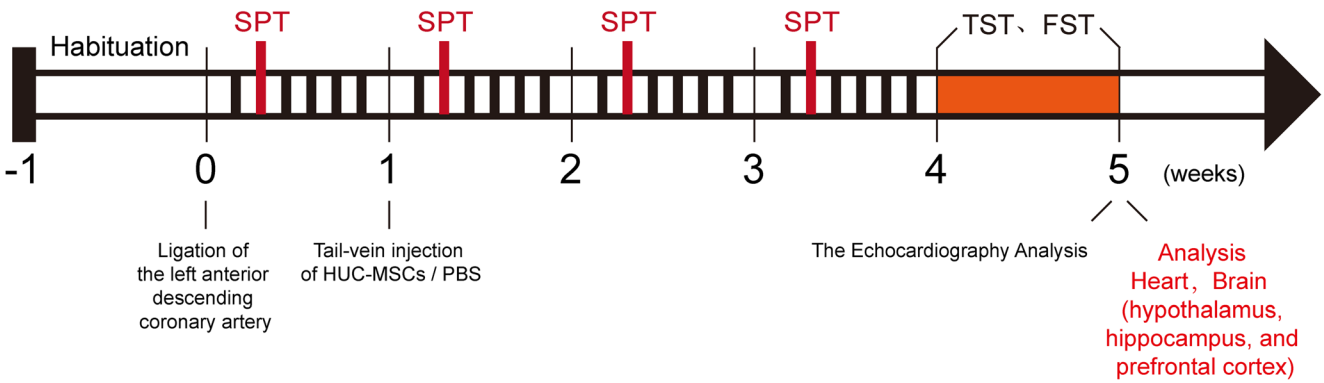

Fig. 1 The experimental design. All mice were performed LAD ligation or sham surgery (0 week) after adaptive feeding for 1 week, and the first SPT was conducted 3 days after surgery, and then once a week, a total of 4 times. HUC-MSCs or PBS were injected into the tail vein after 1 week. TST and FST were conducted after 4 weeks. All mice were evaluated by echocardiography after 5 weeks, and then sacrificed. SPT sucrose preference test, TST tail suspension test, FST forced swim test

pure water freely ingested for 1 h, and the bottles before and after the test were weighed to calculate the sucrose preference percentage (sucrose consumption/all fluid consumption).

Tail suspension test

Tail suspension test (TST) was performed according to the procedure described by Can et al. (2012b). Briefly, after the mice were acclimatized in the test room for 1 h, the tail of the mice was fixed and suspended in a suspension box (55cm height × 60cm width × 11.5cm depth) with tape. The mobility time in the 6-min test was recorded to calculate the immobility time.

Forced swim test

The mice were placed in a transparent cylindrical container (30 cm height × 20 cm diameter) containing water (15 cm in-depth, 23–25°C). The mobility time in the last 4-min test was recorded to calculate the immobility time (Can et al. 2012a).

Echocardiograms

The cardiac function of the mice in each group was evaluated by echocardiography (Vevo 2100 Imaging system; VisualSonics Inc) under isoflurane anesthesia. Evaluation indicators of cardiac function include left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS).

Masson's staining

After the mice were euthanized, the hearts of different groups were collected, fixed with 4% paraformaldehyde, embedded in paraffin, and cut into 4μm thick sections. Sections were stained according to Masson's Tricolor Staining Kit (Beijing Leagene Biological Technology Co., Ltd, China) and then examined by light microscopy. Image J software was used to calculate the percentage of fibrosis.

Immunofluorescence

The brain sections obtained by the same method as Masson staining were used for antigen retrieval using boiled citrate solution, incubated with 0.2% and 0.5% Triton and blocked with 5% BSA for 1 h. Then, the sections were incubated with primary antibody of anti-Iba1 (1:200, Abcam, USA), anti-iNOS (1:200, Abcam, USA), and anti-CD206 (1:200, Abcam, USA) at 4°C overnight and secondary antibody (CY3, 1:1000, Abcam, USA; FITC, 1:1000, Abcam, USA) for 2 h. After staining the nucleus with DAPI, the sections were observed and photographed using a confocal microscope (Nikon DS-U3, Japan).

Western blot

Tissues were lysed in radioimmunoprecipitation assay (RIPA) buffer containing phenylmethyl sulfonylfluoride (PMSF), and centrifuged at 13000 rpm at 4°C for 25 min. BCA protein detection kit (Beyotime, China) was used to detect the protein concentration in the supernatants. Then, supernatants were mixed with loading buffer and boiled for 15 min at 100 °C. Protein was separated on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene fluoride (PVDF) membrane which was then blocked with 5% skim milk in TBST. After that, the membranes were incubated with primary antibody: anti-Jmjd3(1:1000, Active Motif, USA), anti-Iba1 (1:1000,

Abcam, USA), anti-Arg-1(1:1000, Abcam, USA), anti-CD86(1:1000, Santa Cruz, USA), anti-β-Actin (1:3000, Proteintech, USA) at 4°C overnight, and then incubated with secondary antibody: HRP-labeled goat anti-rabbit or mouse IgG (1:1000, Beyotime, China) for 1.5 h at room temperature. Finally, the ECL system was used for imaging.

Quantitative real-time-PCR

Total RNA was extracted from the tissue by TRIzol reagent (Invitrogen, USA), and then was reverse-transcribed to synthesize the cDNA using a PrimeScript™ RT Master Mix (TaKaRa, Japan). The reaction conditions were 37°C for 15 min, 85°C for 5 s, and then held at 4°C. The cDNA was subjected to real-time PCR assays with PrimeScript™ RT Master Mix (TaKaRa, Japan). The reaction conditions were 95°C for 30 s, 95°C for 5 s, and 60°C for 34 s. This process was finished using a Thermo Fisher QuantStudio 5 Real-Time PCR machine. mRNA quantification was processed using the $2^{-\Delta\Delta Ct}$ method and normalized to -β-Actin as an endogenous control. The primers designed are listed in Table 1.

Enzyme-linked immunosorbent assay

The tissues were added into PBS, grinded, and centrifuged at 3000 rpm for 20 min to obtain the supernatant. The serum was obtained by centrifuging the whole blood at 5000 rpm for 15 min. All steps were performed according to the ELISA kit's protocol (Jiangsu Jingmei Biological Technology Co., Ltd, China). Finally, the optical density at 450nm was analyzed with a microplate reader.

Statistical analysis

All values were exhibited as mean ± standard deviation and analyzed by SPSS statistical software (version 23, IBM Inc.). One-way ANOVA was used for comparison of multiple groups and Student's test for comparison of two groups. Difference was considered statistically significant at $p < 0.05$.

Results

Effects of HUC-MSCs on myocardial fibrosis and cardiac function

Masson staining was performed 5 weeks after the coronary ligation. Compared with the Sham + PBS group, the ventricular wall of the MI+PBS group was significantly thinner and more blue-stained collagen fibers proliferated. Compared with the MI + PBS group, the percentage of myocardial fibrosis in the MI+HUC-MSCs group was reduced by 14.1% ($p<0.001$) (Fig. 2A and C).

The results of echocardiography showed that compared with the Sham + PBS group, the LVEF and LVFS in the MI + PBS group were significantly reduced after 5 weeks of ligation, but they were noticeably improved after treatment with HUC-MSCs (all $p < 0.01$). These results indicated that HUC-MSCs could improve left ventricular ejection function and myocardial contractility of MI mice (Fig. 2B, D and F).

HUC-MSCs ameliorated MI-induced depression-like behavior

There was a similar trend in FST and TST; that was, depression-like behavior (longer immobility time in despair) induced by MI was relieved after HUC-MSCs treatment ($F = 5.109$, $p=0.013$; $F = 19.419$, $p<0.001$, respectively) (Figure. 2F and G). Through SPT for 4 consecutive weeks, we can see that before treatment, there was no significant difference in the percentage of sucrose preference in each group. After 1 week, lack of pleasure was observed in the MI group, and the efficacy of HUC-MSCs was reflected after 2 weeks (Fig. 2H).

HUC-MSCs reduced the expression of Jmjd3 in the heart and brain

Western blot was applied to detect the expression of Jmjd3 in the heart, prefrontal cortex (PFC), hypothalamus, and hippocampus (HIP) (Fig. 3A–D). Highly consistent results were obtained in the four regions. As expected, Jmjd3 increased after MI, and significantly decreased in MI+HUC-MSC group. We further verified the mRNA level through qRT-

Table 1 Primer sequences used for qRT-PCR analysis

Gene	Forward primer sequence	Reverse primer sequence
CD86	TAGGGATAACCAGGCTCTAC	CGTGGGTGTCTTTTGCTGTA
iNOS	GCAGAATGTGACCATCATGG	ACAACCTTGGTGTTGAAGGC
CD206	AGTTGGGTTCTCCTGTAGCC CAA	ACTACTACCTGAGCCCACAC CTGCT
Arg-1	TCACCTGAGCTTTGATGTCG	TTCCCAAGAGTTGGGTTCAC
jmjd3	AAGCTGTGGCGTGATGGCCG	TGGGCCCTCAGATGCCTGCT

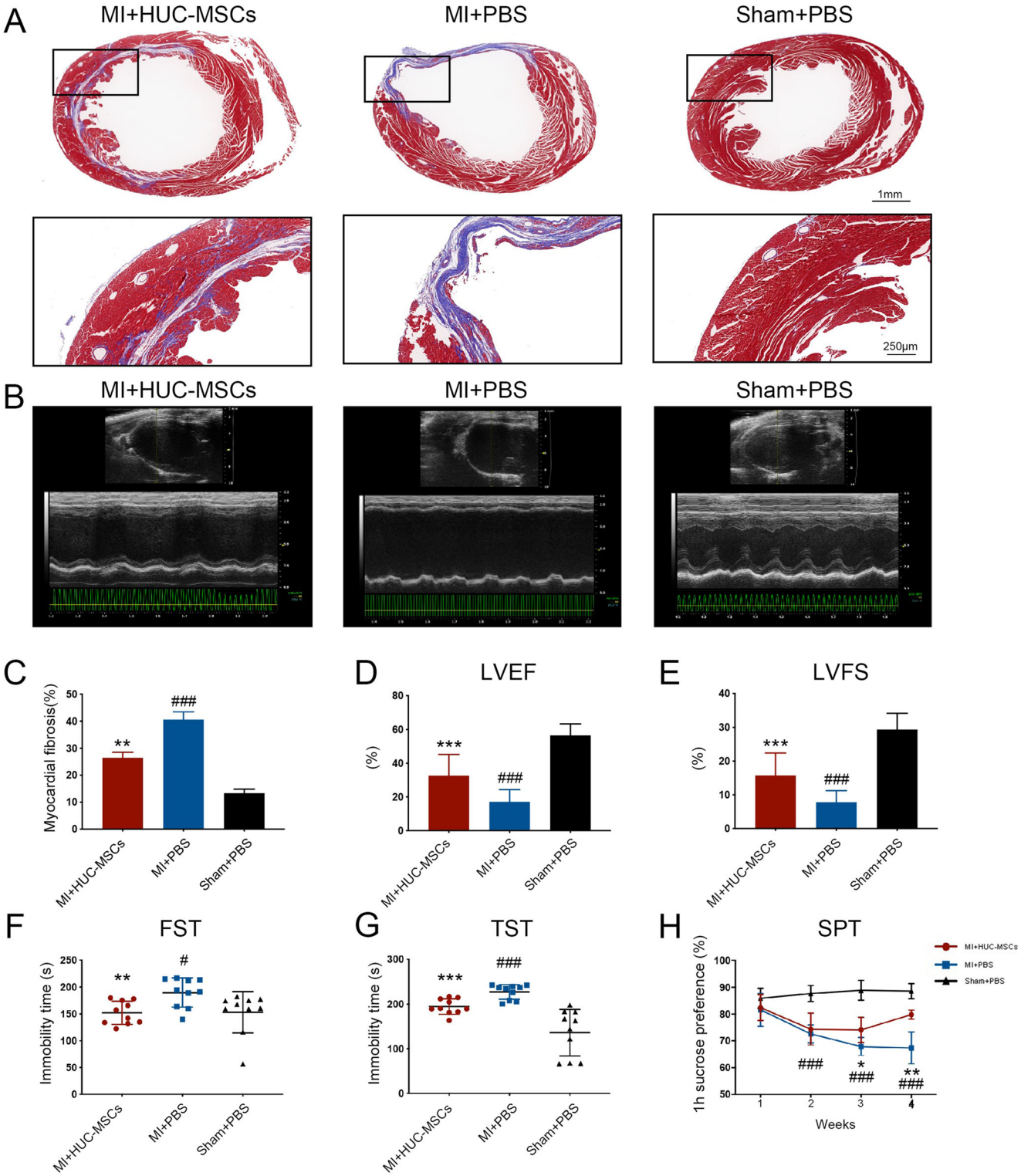

Fig. 2 HUC-MSC treatment improved cardiac function and depression-like behavior in MI mice. **A** Representative images of Masson's staining and (**B**) representative images of echocardiogram 5 weeks after ligation; **C** quantitative analysis of myocardial fibrosis (n=3); **D** LVEF and (**E**) LVFS were evaluated by echocardiography (n=20); the immobility time in (**F**) FST and (**G**) TST (n=10); **H** sucrose preference percentage in SPT (n=7). LVEF left ventricular ejection fraction, LVFS left ventricular fractional shortening, SPT sucrose preference test, TST tail suspension test, FST forced swim test. Results were shown as mean ± SD. *$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$ versus MI+PBS group, #$p < 0.05$, ## $p < 0.01$, ###$p < 0.001$ versus Sham + PBS group

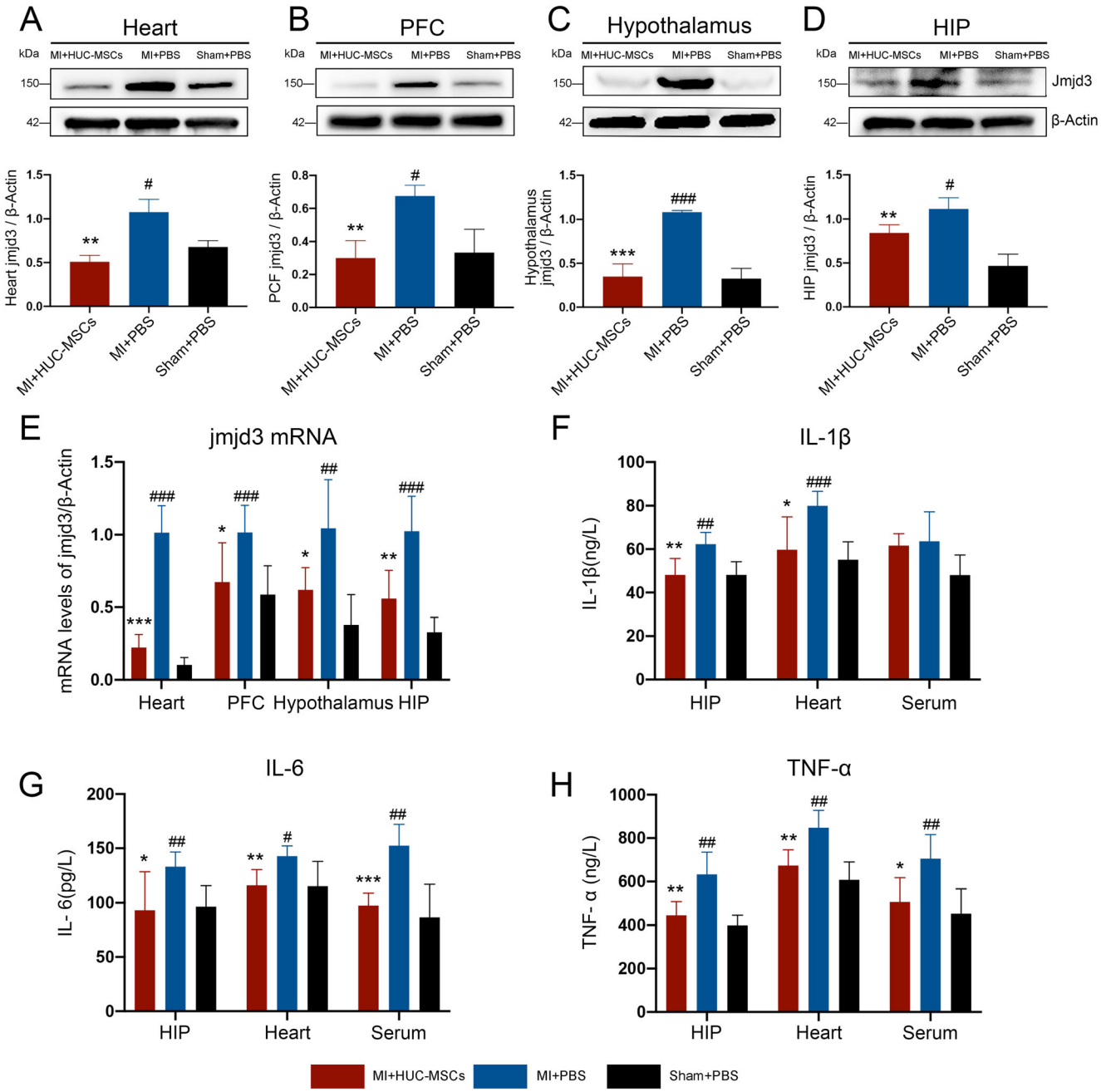

Fig. 3 HUC-MSCs downregulated the level of Jmjd3 and improved inflammation in MI mice. Levels of Jmjd3 in (**A**) heart, (**B**) PFC, (**C**) hypothalamus, and (**D**) HIP detected by Western blot (n=3); **E** quantitative analysis of Jmjd3 mRNA expression (n=6); levels of (**F**) IL-1β, (**G**) IL-6, and (**H**) TNF-α detected by ELISA (n=6). PFC prefrontal cortex, HIP hippocampus. Results were shown as mean ± SD. *p < 0.05, ** p < 0.01, ***p < 0.001 versus MI + PBS group, #p < 0.05, ## p < 0.01, ###p < 0.001 versus Sham + PBS group

PCR. As shown in Fig.3E, we can see a trend consistent with the Western blot results, particularly in the heart.

Anti-inflammatory effects of HUC-MSCs

We detected the expression of inflammatory factors IL-1β, IL-6, and TNF-α in the heart, HIP, and serum by ELISA, and found that 5 weeks after ligation, there was not only inflammation in the heart, but also increased expression of inflammatory factors throughout the body and brain. Compared with the MI+PBS group, the expression of inflammatory factors in the MI+HUC-MSCs group was significantly reduced, except for IL-1β in the serum (Fig. 3F–H).

The overall effect of HUC-MSCs on the activation of microglia

Iba-1 is a specific marker of microglia activation in the brain. Figure 4A shows the representative immunofluorescence images in the PFC, hypothalamic, and HIP (CA1 and DG) under the microscope (×400). Figure 4B shows significant differences in percentage of Iba-1-positive expression cells between groups (F=34.232, F=46.306; F=16.310, F=83.601, respectively, all $p < 0.01$). The results of Iba-1 in PFC, hypothalamus, and HIP detected by Western blot were consistent with immunofluorescence (all $p < 0.01$, Fig. 4C–E). These results indicated that HUC-MSCs could inhibit the activation of microglia after MI.

HUC-MSCs inhibited the activation of pro-inflammatory M1 microglia

iNOS and CD86 are the activation markers of M1 microglia (CNS) and macrophages (peripheral). Through the representative images of each area in Fig. 5A and the percentage of iNOS positive cells in Fig. 5B, we could see that the positive expression of iNOS in the MI+PBS group was significantly higher than that in the Sham+PBS group. However, compared with MI + PBS group, HUC-MSC treatment significantly inhibited the positive activation of iNOS. The qRT-PCR results of iNOS and CD86 and the Western blot results of CD86 also obtained consistent trend results (Fig. 5C–H). But we did not find a statistically significant difference of CD86 in the hypothalamus (F=2.046, p=0.171) (Fig. 5G).

In addition, the expression of iNOS and CD86 in the heart was the same as that in the brain, suggesting that HUC-MSCs can also inhibit the activation of M1 macrophages (Fig. 5C–E).

HUC-MSCs promoted the activation of anti-inflammatory M2 microglia

Figure 6 shows the histology, protein, and mRNA expression levels of CD206 and Arg-1 (M2 microglia/macrophage markers). Interestingly, although the levels of CD206 and Arg-1 also increased after MI, in contrast to M1 microglia, HUC-MSC treatment could further promote their expression. However, there was no statistical difference in the expression of CD206 in PFC between the groups (F=3.261, p=0.110) (Fig. 6A and B).

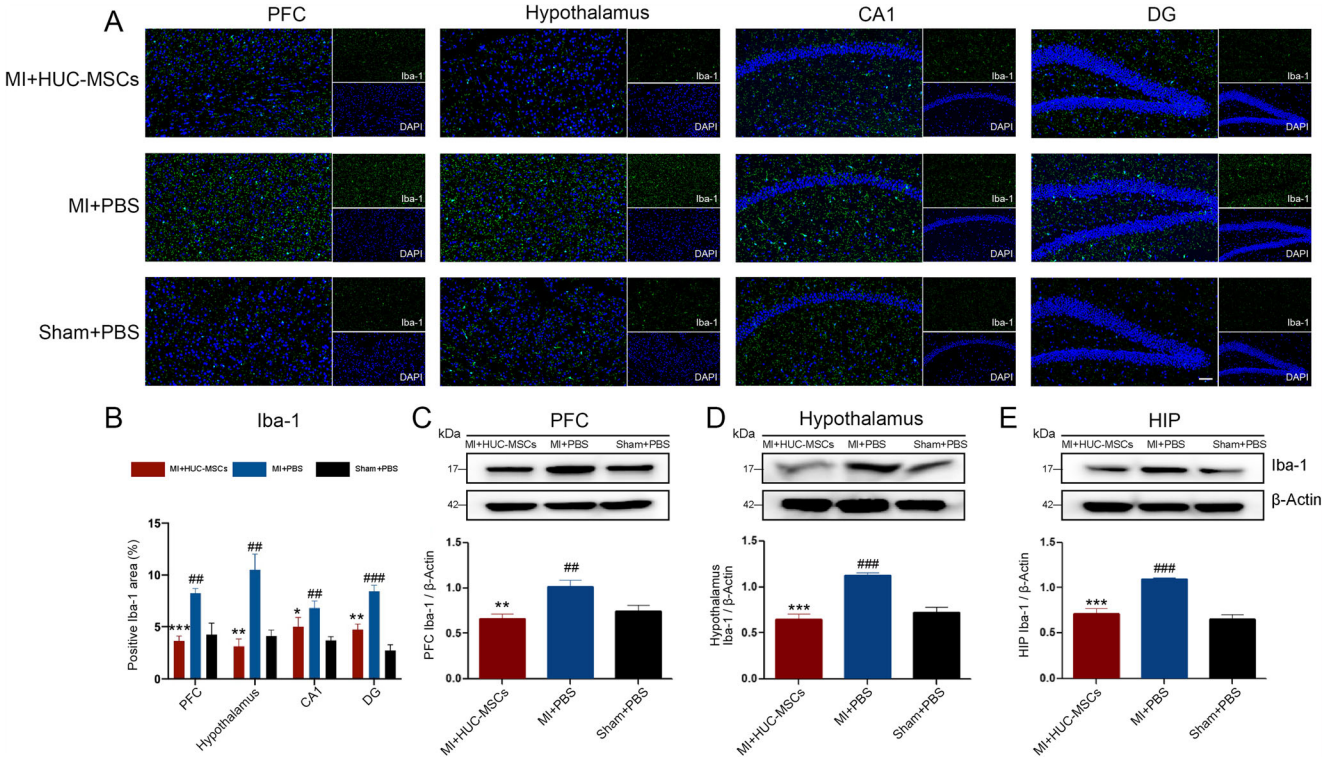

Fig. 4 The expression of Iba-1 in PFC, hypothalamus, and HIP after 5 weeks of ligation. **A** Representable images of Iba-1/DAPI (green/blue) immunofluorescence staining and (**B**) qualification of Iba-1staining in the PFC, hypothalamus, and CA1 and DG region. Scale bar 50μm (n=3); levels of Iba-1 in (**C**) PFC, (**D**) hypothalamus, and (**E**) HIP detected by Western blot (n=3); PFC prefrontal cortex, HIP hippocampus. Results were shown as mean ± SD. *p < 0.05, ** p < 0.01, ***p < 0.001 versus MI + PBS group, #p < 0.05, ## p < 0.01, ###p < 0.001 versus Sham +PBS group

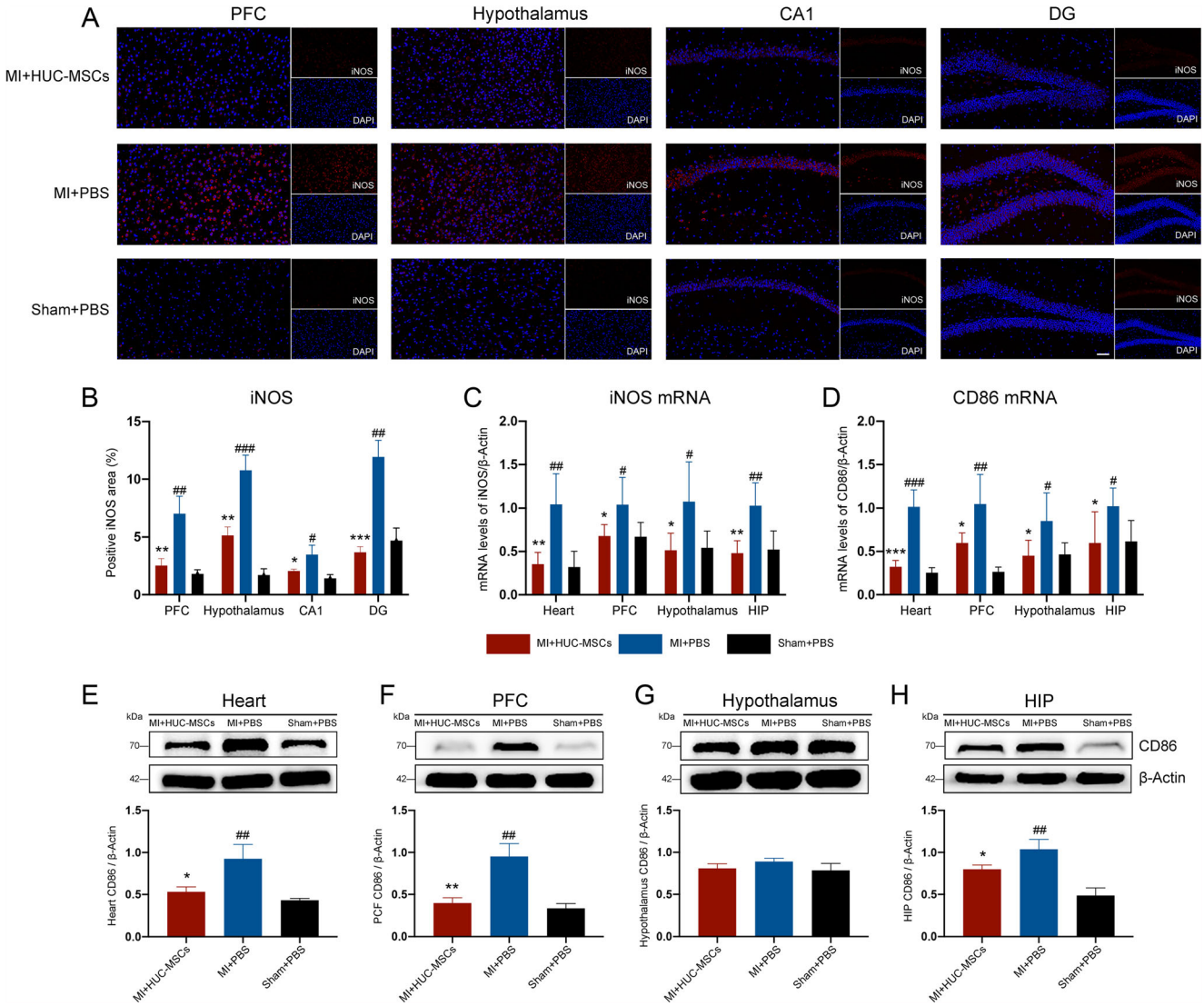

Fig. 5 HUC-MSCs inhibited the activation of M1 microglia in MI mice. **A** Representable images of iNOS/DAPI (red/blue) immunofluorescence staining and (**B**) qualification of iNOS staining in the PFC, hypothalamus, and CA1 and DG region. Scale bar 50μm (n=3); **C** quantitative analysis of iNOS mRNA expression (n=6); **D** Quantitative analysis of CD86 mRNA expression (n=6); levels of CD86 in (**E**) heart, (**F**) PFC, (**G**) hypothalamus, and (**H**) HIP detected by Western blot (n=3); PFC prefrontal cortex, HIP hippocampus. Results were shown as mean ± SD. *p < 0.05, ** p < 0.01, ***p < 0.001 versus MI +PBS group, #p < 0.05, ## p < 0.01, ###p < 0.001 versus Sham + PBS group

Discussion

In this study, a mouse model of MI by ligating the LAD of the coronary artery was established to study the treatment of MI-induced depression. As expected, cardiac function deteriorated significantly after MI. The average LVEF of MI mice was 17.08% at 5 weeks after ligation (Fig. 2C). These mice induced significant depression-like behaviors, including prolonged immobility in the desperate environment caused by TST and FST, and lack of pleasure in SPT. And we observed that a significant reduction in sucrose preference rate occurred only 1 week after MI, and it continued for 4 weeks after the ligation (Fig. 2G). Previous literature reported (Ge et al. 2020; Hoschar et al. 2019) that this model also induces depression-like behavior and may last for 8 weeks, indicating that this is an effective method for screening effective and reliable antidepressants for the treatment of MI-related depression.

HUC-MSCs seem to be an optimal choice for stem cell-based therapy because of their low immunogenicity, non-invasive harvest procedure, easy expansion in vitro, and ethical access compared with stem cells from other sources (Li et al. 2015). Luger et al. demonstrated that MSCs injected through the tail vein were distributed in various parts of the body, including the heart, liver, spleen, and kidneys, and persistent in the heart for as long as 3 weeks (Luger et al. 2017). Antidepressant effects can be exerted by implanting MSCs into the CNS of genetically susceptible rats (Kin et al. 2020;

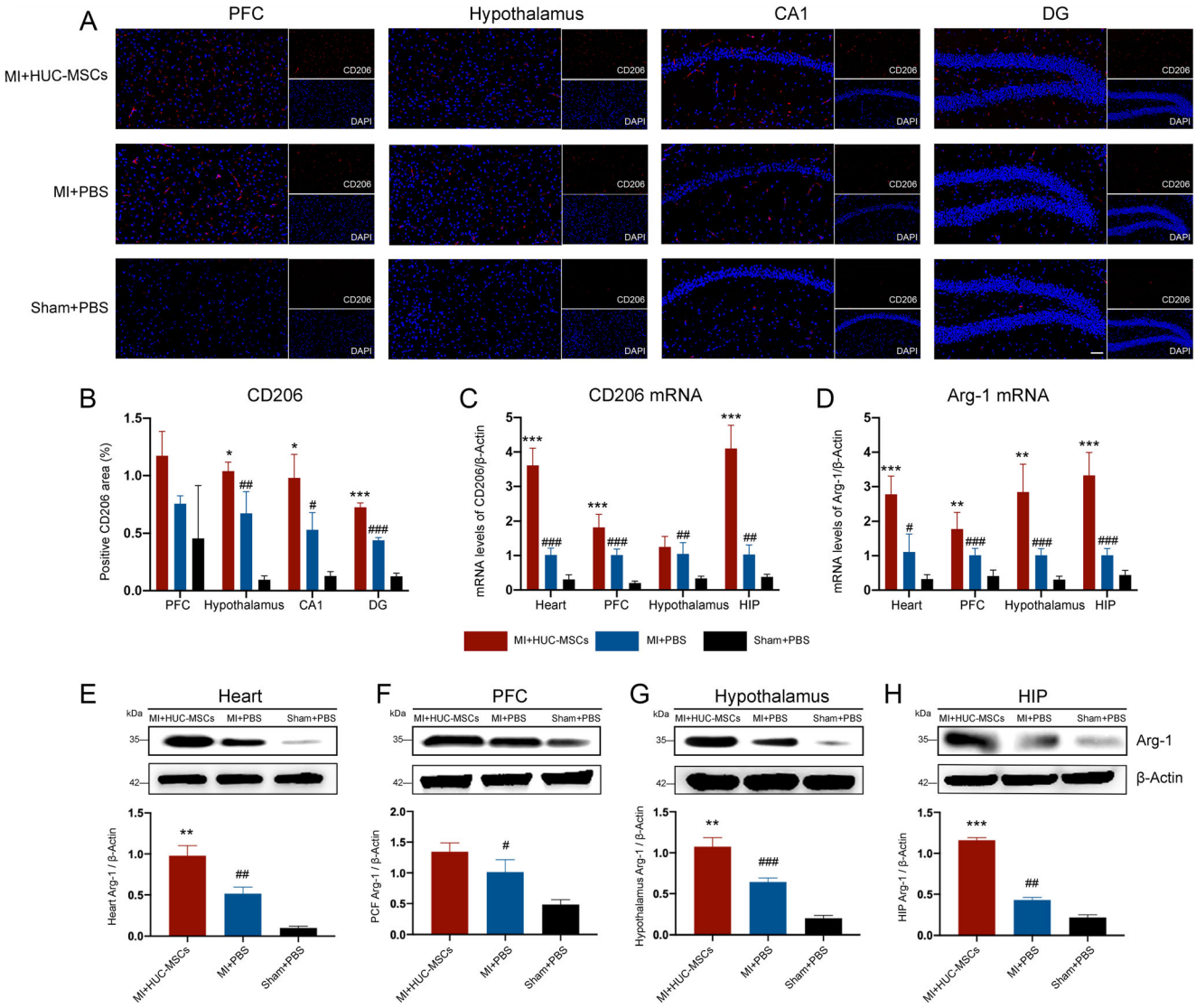

Fig. 6 HUC-MSCs promoted the activation of M2 microglia in MI mice. **A** Representable images of CD206/DAPI (red/blue) immunofluorescence staining and (**B**) qualification of CD206 staining in the PFC, hypothalamus, and CA1 and DG region. Scale bar 50μm (n=3); **C** quantitative analysis of CD206 mRNA expression (n=6); **D** quantitative analysis of Arg-1 mRNA expression (n=6); levels of Arg-1 in (**E**) heart, (**F**) PFC, (**G**) hypothalamus, and (**H**) HIP detected by Western blot (n=3); PFC prefrontal cortex, HIP hippocampus. Results were shown as mean ± SD. *p < 0.05, ** p < 0.01, ***p < 0.001 versus MI + PBS group, #p < 0.05, ## p < 0.01, ###p < 0.001 versus Sham + PBS group

Tfilin et al. 2010). Based on this, we chose tail vein infusion of HUC-MSCs, which might exert through paracrine mechanisms systemic anti-inflammatory effects, to explore its dual effects on MI and its induced depression.

Although MSCs have been reported in the treatment of depression, this study provides the first evidence of the improvement effect of HUC-MSCs treatment on MI-induced depression. We found that the level of Jmjd3 increased, and M1 and M2 microglia were activated after MI. However, HUC-MSC treatment reversed the decrease in Jmjd3 levels, inhibited M1 microglia, and promoted M2 microglia activation. M1 microglia is associated with tissue destruction—it can produce pro-inflammatory cytokines and mediators (IL-1β, IL-6, TNF-α, etc.) and induce the destruction of the blood-brain barrier, resulting in massive infiltration of surrounding inflammatory cells. On the contrary, M2 microglia is involved in promoting repair and regeneration—it can produce the anti-inflammatory cytokine IL-10, which inhibits M1 microglia-mediated neuroinflammation (Hsuan et al. 2016; Nakagawa and Chiba 2015). Previous studies reported increased inflammation and a marked increase in activated microglia after MI (Badoer 2010; Thackeray et al. 2018), which was consistent with our results. Minocycline, as an antibiotic that inhibits microglia activation and releases pro-inflammatory cytokines, significantly reduced the increase in microglial activation by at least 50% (Dworak et al. 2014) and

improved systemic inflammation and depression-like behavior caused by MI (Wang et al. 2019). These suggested that microglia activation and polarization were compelling targets for treating MI-induced depression.

Mounting previous studies have demonstrated the significant anti-inflammatory effects of MSCs (Sun et al. 2017; Luger et al. 2017). We also found that MSCs downregulated the expression of pro-inflammatory cytokines IL-1β, IL-6, TNF-α in the HIP, heart, and serum. This result showed that the MSCs injected through the tail vein played a role in the whole body. In addition, studies have also shown the role of MSCs in regulating microglia activation. Jose et al. reported that bone marrow-derived MSCs inhibit lipopolysaccharide-stimulated BV2 microglia proliferation independent of nitric oxide and IL-6 (Jose et al. 2014). MSC-induced microglial phenotype switching from M1 to M2 suppressed the production of pro-inflammatory cytokines, improved oxidative stress, and improved Alzheimer's disease (Yokokawa et al. 2019). Another study showed that MSCs exert a neuroprotective effect via the clearance of extracellular α-synuclein by controlling microglia M2 polarization (Park et al. 2016). In this study, we found that the M1 microglia markers CD86 and iNOS were simultaneously downregulated in the HIP, PFC, and hypothalamus. On the contrary, the M2 microglia markers CD206 and Agr-1 were upregulated. This trend was similar to the results of a recent study which suggested that HUC-MSCs can alter the polarization of microglia by inhibiting C3a-C3aR signaling, which had therapeutic effects on depression-like behavior caused by CUMS (Li et al. 2020). There are some differences here in that we discovered a new mechanism; that is, the improvement of HUC-MSCs to MI-induced depression seems to be related to the regulation of Jmjd3.

Limited literature reported the relationship between Jmjd3 and depression. Jmjd3 was involved in the susceptibility to depression due to early-life stress and maternal separation by enhancing neuroinflammation in the PFC and HIP of rats (Wang et al. 2018a; Wang et al. 2020). However, evidence has shown that Jmjd3 can inhibit the expression of inflammation-related genes (Salminen et al. 2014). In addition, Jmjd3 and STAT activate the transcription network together in a H3K27 demethylation-independent manner, leading to functional inflammatory activation of microglia (Przanowski et al. 2014). Unfortunately, our study did not explore whether Jmjd3 can regulate the polarization of M1/M2 microglia in MI-induced depression, which needs further research. Another limitation is that we did not track the distribution of HUC-MSCs in our study. Although a study showed that HUC-MSC distribution in heart was minima in the mouse model of acute lung injury (Liu et al. 2018), the results reported by Luger et al. showed that compared with rats without MI, the heart was engrafted preferentially after MI, and in MI heart, MSCs concentrated predominantly in regions of injury (Luger et al. 2017). This suggests that MSCs tend to gather in disease models and injured areas. The studies which suggested tail vein injection of MSCs improved depressive symptoms provided no evidence about the distribution of MSCs in the brain (Huang et al. 2020; Li et al. 2020). So, it requires more research to focus on this because it is of great significance to the potential therapeutic effects of MSCs.

In summary, our results showed that HUC-MSCs achieved a dual improvement in cardiac function and depression-like behaviors caused by MI, which may be through downregulation of Jmjd3 levels and regulation of M1/M2 microglia polarization and the level of inflammatory factors. HUC-MSCs may bring more significant benefits to patients with MI and depression compared with traditional antidepressants. The study clarified for the first time that HUC-MSCs might be related to the regulation of Jmjd3 levels in MI mice, and provided some new insights for depression during MI.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-021-05912-w.

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Declarations

Conflict of interest The authors declare no competing interests.

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