

## Review Article

# Functionally Improved Mesenchymal Stem Cells to Better Treat Myocardial Infarction

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Myocardial infarction (MI) is one of the leading causes of death worldwide. Mesenchymal stem cell (MSC) transplantation is considered a promising approach and has made significant progress in preclinical studies and clinical trials for treating MI. However, hurdles including poor survival, retention, homing, and differentiation capacity largely limit the therapeutic effect of transplanted MSCs. Many strategies such as preconditioning, genetic modification, cotransplantation with bioactive factors, and tissue engineering were developed to improve the survival and function of MSCs. On the other hand, optimizing the hostile transplantation microenvironment of the host myocardium is also of importance. Here, we review the modifications of MSCs as well as the host myocardium to improve the efficacy of MSC-based therapy against MI.

## 1. Introduction

Myocardial infarction (MI) leads to a massive loss of functional cardiomyocytes, which is a major cause of human death worldwide [1–3]. Though pharmacotherapy, thrombolysis, coronary stent implantation, and coronary artery bypass grafting have been clinically used to treat MI and improve patients' survival, these methods cannot fundamentally repair the damaged heart and restore heart function. Stem cell transplantation is considered as a promising way to treat MI, which has made significant progress in preclinical and clinical studies recently [4]. Stem cell candidates mainly include two categories: (1) pluripotent stem cells (embryonic stem cell and induced pluripotent stem cells) and their derivatives and (2) adult stem cells, including hematopoietic stem cells and mesenchymal stem cells (MSCs) [5]. MSCs are mesoderm-derived multipotent stromal cells that reside in embryonic and adult tissues, having the capacity for self-renewal, immune privilege, immunomodulation, and low tumorigenicity [6]. To date, MSCs have become the mostly practiced cell type in clinical trials for

treating MI [7], due to the safety, multidifferentiation potential, nutritional activity, immunomodulatory properties, and abundant donor sources [6, 8]. MSCs have low immunogenicity due to the low expression of MHC II as well as the lack of expression of MHC I, which lead to immune tolerance allowing allogeneic transplantation [8].

However, the therapeutic effect of MSC transplantation is unsatisfactory. The increase in left ventricular systolic function (LVSF) of MI patients is only 3–10% with MSC transplantation [9]. Implanted cells do not survive for a long time. In fact, only about 3% of MSCs appeared in the marginal area of the infarct myocardium within 24 hours after systemic administration, and less than 1% of MSCs could survive for more than a week [5]. Recent studies have concluded that MSCs are very difficult to differentiate towards cardiomyocytes, and the benefits of MSC therapy mainly depend on its paracrine mechanism [10]. The key steps of the cell therapy procedures, such as donor selection, *in vitro* amplification, survival in a hostile transplantation microenvironment, migration, differentiation, and paracrine function, need to be optimized. Here, we review the strategies

of MSC modifications for optimizing the therapeutic potential of MSCs against MI.

## 2. Therapeutic Effect of MSCs against MI Injury

MSCs have the potential of self-renewal, proliferation, and multidifferentiation in an appropriate microenvironment [11]. MSCs exert a therapeutic effect on MI through direct differentiation into vessel cells (cardiomyocyte differentiation events are rare) and paracrine mechanism (which has been proved predominant) [10]. Transplanted MSC-derived endothelial cells and vascular smooth muscle cells can contribute to the new vessel formation [12–14]. MSC paracrine factors include protein cytokines such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), miRNAs [15–17], and exosomes [18]. These factors can induce immunomodulation and anti-inflammatory effects, evidenced by inhibition of the activity of inflammatory mediators and regulation of the function of immune cells [19]. The factors can induce an antifibrosis effect by inhibiting the proliferation of fibroblasts, reducing the deposition of collagen and producing matrix metalloproteinases [20]. In addition, factors such as stromal cell-derived factor-1 (SDF-1), VEGF, and basic fibroblast growth factor (bFGF) have a strong proangiogenic effect, due not only to promotion of endothelial cell proliferation and migration but also to prevention of endothelial cells from apoptosis [8, 21].

The MSC-based treatments for MI have successfully entered phase I and phase II clinical trials. A meta-analysis comprising 34 randomized controlled trials (RCTs) with a total number of 2307 patients indicates that MI patients who received MSC transplantation showed a significantly improved cardiac function, a significant increase in the left ventricular ejection fraction (LVEF) (+3.32%), and a decrease in LV end-diastolic indexes (−4.48) and LV end-systolic indexes (−6.73) [22]. Another meta-analysis covering 28 RCTs with a total of 1938 STEMI patients shows that MSC treatment resulted in an improvement in long-term (12 months) LVEF of 3.15% [23]. A recent study also showed benefits of MSC transplantation on mechanical and clinical outcomes. The LVEF of MI patients with MSC treatment increased by 3.84%, and the effect was maintained for up to 24 months. Scar mass was reduced by −1.13, and the wall motion score index was reduced by −0.05 at 6 months after MSC treatment [24]. Clinical trials of MSC transplantation for treating MI are listed in Table 1. Though previous clinical trials have made some advances, optimizing the process of MSC transplantation is needed in preparing for the clinical phase III trials.

## 3. Strategies for Optimizing MSC-Based Therapy

MSCs can be obtained from various tissues such as bone marrow, fat, peripheral blood, lungs, muscle, placenta, umbilical cord blood, and dental pulp [40]. Bone marrow MSCs (BM-MSCs) are the most frequently investigated and tested in clinical trials. It is reported that MSCs from younger

donors are more effective than those from older donors, indicating an age-dependent effect of MSC functions. The expressions of inhibitory kappa B kinase, interleukin-1 $\alpha$ , and inducible nitric oxide synthase in the elderly donor's MSCs were significantly decreased [15]. Previous studies showed that the expression of the pigment epithelium-derived factor (PEDF) was significantly increased in MSCs of aged mice compared with young mice. Knockout PEDF in aged MSCs can improve the therapeutic effect of MSCs [41]. These data suggest that using young MSCs for treating MI might be a more advisable option.

For cell number of MSC transplantation,  $\sim 10^5$ – $10^8$  MSCs were reported in diverse studies [42], but usually  $>1 \times 10^7$  cells were required in clinical trials given the low retention rate [43, 44]. Cell expansion *in vitro* is needed for about 1–3 months before implantation to obtain enough cell numbers [5]. However, cell aging and the loss of chemokine markers during amplification could reduce the cell survival and functions of MSCs in the transplantation microenvironment. Methods such as environmental preconditioning, cytokine or drug coculture, and gene modification may overcome these problems.

### 3.1. Preconditioning MSCs in Culture before Transplantation

**3.1.1. Hypoxia Preconditioning.** The peripheral area of MI is a typical site for preclinical MSC treatment. The oxygen partial pressure in the peripheral area generally does not exceed 1%, and hypoxia is a major cause of dysfunction and death of transplanted MSCs [45]. Hypoxia preconditioning *in vitro* (2–5% oxygen) can maintain homogeneity and differentiation potential, delay cell senescence process, and increase chemokine receptor expression of MSCs [46]. Hypoxia preconditioning is also proved to increase the paracrine activity of nonhuman primate MSCs [47]. Thus, MSCs with hypoxia preconditioning is more therapeutically effective against massive myocardium injury and does not increase the incidence of arrhythmia complications [48].

**3.1.2. Hyperoxia or Hydrogen Peroxide Preconditioning.** Hyperoxia pretreatment can also improve MSC efficacy by reducing the number of apoptotic cells. BM-MSCs were implanted into hypoxic tissues after hyperoxia (100% oxygen), and the apoptotic cells were significantly reduced (apoptotic score index determined by TUNEL assays reduced from 86.6% to 11.6%) [49]. In addition, sublethal hydrogen peroxide preconditioning attenuated oxidative stress-induced cell apoptosis. Pretreatment with 200  $\mu\text{mol/L}$   $\text{H}_2\text{O}_2$  for 2 hours decreased MSC apoptosis. Compared with control MSCs, MSCs with  $\text{H}_2\text{O}_2$  pretreatment better improved cardiac function and reduced myocardial fibrosis [50].

**3.1.3. Thermal Preconditioning.** MSCs were incubated with water bath at 42°C for 2 hours before transplantation can effectively reduce the oxide-induced apoptosis of MSCs and enhance cell survival. The mechanism may be related to the expression of heat shock proteins, which act as a molecular chaperone and indirectly promote cell survival by inhibiting the apoptosis pathway and resist oxidation stress [51].

TABLE 1: Clinical trials of MSC transplantation for treating MI.

Clinical trials	Phase	Dose (*10 <sup>6</sup> )	Delivery route	Enrollment	Infarct scar	LVEF	Following up	Study	Reference
NCT00114452	Phase 1	0.5/1.6/5	IC	53	n.a.	↑**	6 m	Hare et al. (2009)	[25]
NCT00677222	Phase 1	100	IC	30	n.a.	↑*	4 m	Penn et al. (2012)	[26]
2011AA020109	Phase 1	3.08	IC	43	=	↑*	12 m	Gao et al. (2013)	[27]
UO1 HL087318-04	Phase 1	150	IC	65	↓*	↑***	12 m	Traverse et al. (2014)	[28]
NCT01234181	Phase 1	100	IC	22	↓*	↑*	12 m	Hu et al. (2015)	[29]
NCT01087996	Phase 1/2	20	IM	30	↓***	↑	13 m	Hare et al. (2012)	[30]
U54HL081028	Phase 1/2	20	IM	30	↓*	↑**	13 m	Suncion et al. (2014)	[31]
NCT02323477	Phase 1/2	20	IM	79	n.a.	n.a.	12 m	Can et al. (2015)	[32]
NCT00883727	Phase 1/2	180–220	IV	20	=	=	2 y	Chullikana et al. (2015)	[33]
NCT02504437	Phase 1/2	—	—	200	—	—	12 m	Pei (2015–2017)	ClinicalTrials.gov
NCT02503280	Phase 1/2	200	—	55	—	—	12 m	Joshua (2015–2032)	ClinicalTrials.gov
NCT02666391	Phase 1/2	—	—	64	—	—	18 m	Pei (2016–2017)	ClinicalTrials.gov
NCT01770613	Phase 2	—	—	—	—	—	12 m	Nabil (2013–2017)	ClinicalTrials.gov
NCT00684021	Phase 2	150	IC	101	n.a.	↑***	6 m	Schutt et al. (2015)	[34]
NCT00984178	Phase 2	15	IC	120	↓*	↑**	12 m	San Roman et al. (2015)	[35]
NCT00765453	Phase 2	59.8	IC	100	n.a.	↑***	12 m	Choudry et al. (2015)	[36]
NCT01291329	Phase 2	6	IC	116	↓***	↑***	18 m	Gao et al. (2015)	[37]
NCT03047772	Phase 2	—	—	124	—	—	12 m	Yang (2017–2018)	ClinicalTrials.gov
NCT00877903	Phase 2	—	IV	220	—	—	5 y	Donna (2009–2018)	ClinicalTrials.gov
NCT02013674	Phase 2	100	IM	30	↓*	↑*	12 m	Florea et al. (2013–2019)	[38]
NCT01392105	Phase 2/3	72	IC	80	n.a.	↑*	6 m	Lee et al. (2014)	[39]
NCT03404063	Phase 2/3	30	—	115	—	—	6 m	Piotr (2017–2020)	ClinicalTrials.gov
NCT01394432	Phase 3	—	IM	50	—	—	12 m	Evgeny (2012–2016)	ClinicalTrials.gov
NCT01652209	Phase 3	—	—	135	—	—	13 m	Yang (2013–2020)	ClinicalTrials.gov
NCT02672267	Phase 3	—	IM	50	—	—	6 m	Saule (2014–2016)	ClinicalTrials.gov

MSCs: mesenchymal stem cells; MI: myocardial infarction; IM: intramyocardial; IC: intracoronary; IV: intravenous; LVEF: left ventricular ejection fraction; y: year; m: month; n.a.: not analyzed; =: no statistical significance. \* $p < 0.05$ , \*\* $p < 0.01$ , and \*\*\* $p < 0.001$ .

**3.1.4. Nutritional Deprivation Preconditioning.** The transplantation microenvironment is poor in nutritional supply. Reducing energy requirements to allow MSCs to enter a relatively quiescent state helps them adapt to the upcoming low-energy environment. Serum deprivation for 48 hours could induce MSCs into a quiescent state and improve MSC survival rates. Compared with control, serum deprivation increased the survival rates by 3–4-fold after the third day and on the seventh day after transplantation [52].

**3.1.5. Transient Adaptation Preconditioning.** Although MSC itself is with low immunogenicity, the presence of

immunogenic contamination in xenogeneic serum may result in acute rejection with the host immune system after MSC transplantation [53]. A two-stage culture strategy was developed to overcome this problem. In the first phase, the MSCs were isolated and expanded in the human platelet lysate or mixed allogeneic serum medium. Then, in the second stage, the expanded MSCs were cultured in the autologous serum medium. This transient adaptation in autologous serum may contribute to the expression of chemokine receptors and tissue-specific differentiation of amplified MSCs *in vitro*, which provides an efficient method for the immunological rejection [46].

**3.2. Genetic Modification and Cytokine/Drug Treatment on MSCs.** To obtain enough cell numbers, MSC expansion in culture usually needs 1–3 months [5]. Not only is the process time-consuming and laborious but also it is difficult to maintain the multidifferentiation ability. Viral vectors or nonviral methods were used to genetically modify MSCs before transplantation. Overexpression of antiapoptotic transcription factor Akt could significantly increase MSC viability [54]. MSCs transfected with both OCT4 and SOX2 showed a strong proliferative activity [55]. Overexpressing manganese superoxide dismutase can endow cells with anoxic tolerance before transplantation then effectively increase the survival rate [56]. Studies that enhance cell engraftment via genetic modification are listed in Table 2. Pretreating MSCs with cytokines/drugs prior to transplantation can promote cell proliferation. A combination of hypoxia (5% O<sub>2</sub>) and 10 ng/mL basic fibroblast growth factor generated a significant synergistic effect. It produced highly reproducible MSCs, allowing MSCs to maintain multidifferentiation ability after the 11th generation. Besides, the cell production is 2.8 times faster than the traditional method [57]. Chemical drugs are also used for MSC pretreatment. Proline hydroxylase inhibitor DMOG-pretreated MSCs significantly reduced cell mortality after transplantation, which is associated with elevated expressions of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), VEGF, GLUT-1, and phospho-Akt were significantly increased [58]. Mitochondrial electron transport inhibitors, such as antimycin, have been used to block the activation of mitochondrial death pathways [53]. Omentin-1 promotes MSC proliferation, inhibits apoptosis, increases the secretion of angiogenic cytokines, and enhances angiogenesis via the PI3K/Akt signaling pathway [59]. Studies that enhance cell engraftment via drug/cytokine pretreatment are listed in Table 3.

**3.3. Cotransplantation MSCs with Bioactive Factors.** Multiple studies have shown that cotherapy with drugs/specific cells/cytokines/specific biomaterials can prolong the survival time of MSCs and thus improve their therapeutic efficacy [117]. MSC transplantation combined with heparin significantly reduced the retention of MSCs in the lungs. Cotransplantation of MSCs and HGF improved cardiac function and reduced infarct size of post-MI heart [118]. Encapsulating cells in an injectable biomaterial could play an antioxidant role [119]. In a rat MI model, the survival rate of MSCs was increased by about 30% after coinjection with fibrin glue [120]. In a swine MI model, cotransplantation of MSCs and cardiac stem cells was reported to be superior than transplantation of each single type of stem cells [121]. Combined therapy of MSCs and rosuvastatin reduced fibrosis, decreased cardiomyocyte apoptosis, and preserved heart function [122]. Nutrient-rich plasma containing high levels of growth factors and secreted proteins has been identified as a biological material which can promote MSC function and promote wound healing. Thus, cotransplantation of MSCs with plasma is beneficial for MSCs adapting to nutritional deficiency in the infarct myocardium, which has been applied for clinical trials [123]. When we injected the MSCs through intravenous administration, it is easy to induce

the block of vessels. Then, the use of vasodilator drugs significantly avoids the issues and contributes to the migration and homing of MSCs [53].

**3.4. Biomaterials, Scaffolds, and Tissue Engineering to Improve MSC Functions.** Long-term retention in the injection site is a necessary condition for the continued effectiveness of MSCs in the MI treatment. MSCs have multiple administration routes applied to clinical or preclinical studies. Injection routes including intravenous injection, intracoronary injection, intramyocardial injection (including transendocardial and transepical) were applied for MSC transplantation [124, 125]. Systematic intravenous injection is obviously simple and easy for dose control, but it causes massive cell redistribution into other organs such as the liver and lung. To date, intracoronary injection is the most studied technique during the time of percutaneous coronary intervention after MI, which is convenient and proved safe. Stem cells delivered through this method have been proved to improve cardiac function and reduce infarct size. Furthermore, specific studies comparing the effectiveness of different cell delivery routes showed that catheter-based transendocardial injection is superior to intracoronary injection, in terms of cell retention and cardiac function improvement [126]. Accumulating evidence supported that both transendocardial and surgical transepical injections are safe and effective in various preclinical and clinical studies [38]. Therefore, intramyocardial injection is considered to be the most efficient way for cell delivery [127]. However, even after intramyocardial delivery, the majority of transplanted cells are lost; thus, the above methods still could not guarantee the cell survival and long-term retention.

**3.4.1. Multicellular Spheres.** Cell preparations based on multicellular spheres have proved to be a promising way to enhance the therapeutic potential of MSCs [128]. Compared with the traditional two-dimensional (2D) monolayer culture, three-dimensional (3D) cell tissue can enhance the intracellular effect. Compared with the same number of MSCs in the traditional 2D monolayer culture, the MSC sphere in fibrin gel increased the level of VEGF secretion by 100 times [129] and the level of the CXCR4 receptor by 2 times [130]. The MSC sphere also obviously increases the expressions of HIF-1, FGF2, HGF, and miRNAs related to pleiotropia [17, 131]. Therefore, 3D MSCs improve the anti-inflammatory and angiogenic properties of MSCs after transplantation. In both rodent and porcine MI models, 3D MSCs were shown to be differentiated into endothelial cells and myocardium-like cells after transplantation and improve cardiac function of post-MI hearts [132, 133].

**3.4.2. Cell Sheet and Hydrogels.** Cell sheet technology has been confirmed to prolong the resident time of transplanted cells in the infarct myocardium [134]. The effect of three-layer MSC sheet administration for MI treatment is better than that of conventional intramyocardial injection [135]. The use of biomaterials, such as suspending MSCs in hydrogels or coated MSCs with hydrogel, may



TABLE 2: Gene modification in MSC transplantation for treating MI.

Gene name	Disease	Model	Modification	Gene function	Reference
Hsp27	MI	Rat	Overexpression	Viability↑; apoptosis↓	[60]
MicroRNA-133	MI	Rat	Overexpression	Survival ↑	[61]
SDF-1 $\alpha$	MI	Rat	Overexpression	Homing↑	[62]
CAMKK1	MI	Rat	Overexpression	Angiogenesis↑; infarct size↓; ejection fraction↑	[63]
eNOS	MI	Rat	Overexpression	Infarct size↓; angiogenesis↑	[64]
Akt1	MI	Rat	Overexpression	Cardiac function↑	[45]
PKG1 $\alpha$	MI	Rat	Overexpression	Survival↑; angiogenesis↑	[65]
Caspase 8	MI	Rat	Silence	Cardiac fibrosis↓; survival↑	[66]
SIRT1	MI	Rat	Overexpression	Cardiac remodeling↓; angiogenesis↑	[67]
Netrin-1	MI	Rat	Overexpression	Survival↑; migration	[68]
FGF4-bFGF	MI	Rat	Overexpression	Survival↑; microvascular density↑; cardiac fibrosis↓	[69]
MicroRNA-377	MI	Rat	Knockdown	Angiogenesis↑	[70]
PKC $\epsilon$	MI	Rat	Overexpression	Survival ↑; infarct size ↓apoptosis ↓	[71]
Trx1	MI	Rat	Overexpression	Angiogenesis↑	[72]
BCL2L1 (Bcl-xL)	MI	Rat/MSC culture	Overexpression	Apoptosis↓; angiogenesis↑	[73]
MDK	MI	Rat/MSC culture	Overexpression	Apoptosis↓; cardiac function↑	[74]
miR-23a	MI	Rat/MSC culture	Overexpression	Apoptosis↓; infarct size↓	[75]
miR Let-7b	MI	Rat/MSC culture	Overexpression	Cardiac function↓; infarct size↓; angiogenesis ↑	[76]
VEGF	MI	Rat/MSC culture	Overexpression	Survival ↑; angiogenesis ↑	[77]
HIF-1A	MI	Rat/MSC culture	Overexpression	Paracrine↑; angiogenesis↑; migration↑	[78]
KLK1 (tissue kallikrein)	MI	Rat/MSC culture	Overexpression	Apoptosis ↓; apoptosis↓	[79]
PHD2	MI	Mouse	Silence	Survival↑; apoptosis↓;scar size↓	[80]
ecSOD	MI	Mouse	Overexpression	Infarction size↓; apoptosis↓; survival.↑	[81]
MIR1-1 (miR-1)	MI	Mouse	Overexpression	Survival↑	[82]
HGF	MI	Mouse	Overexpression	Angiogenesis↑; apoptosis↓	[83]
ILK	MI	Porcine	Overexpression	Homing↑; LVEF↑; myocardial remodeling↓	[84]
IGF-1	MI	Porcine	Overexpression	Angiogenesis ↑	[85]
GLP-1	MI	Porcine	Overexpression	Angiogenesis ↑	[86]
VEGF (165)	MI	Ovine	Overexpression	Infarct size↓; left ventricular function↑	[87]
hRAMP1	MI	Rabbit	Overexpression	Infarct size↓	[88]
SOD2	—	MSC culture	Overexpression	Apoptosis↓	[56]
miR-210	—	MSC culture	Overexpression	Apoptosis↓; survival↑	[88]
CXCL12	—	MSC culture	Overexpression	Apoptosis↓; proliferation↑	[89]

MDK: midkine; Trx1: thioredoxin-1; PKC $\epsilon$ : protein kinase C  $\epsilon$ ; IGF-1: insulin-like growth factor-1; Hsp27: exogenous heat shock protein 27; SOD2: manganese superoxide dismutase; OH-1: heme oxygenase; CXCR4: CXC chemokine receptor 4; CAMKK1: calcium/calmodulin-dependent protein kinase kinase-1; eNOS: endothelial nitric oxide synthases; ILK: integrin-linked kinase; Nrf2: nuclear factor- (erythroid-derived 2-) like 2; PHD2: prolyl hydroxylase domain protein 2; GLP-1: glucagon-like peptide-1; SIRT1: silent mating type information regulation 2 homolog 1; FGF4: fibroblast growth factor 4; bFGF: basic fibroblast growth factor; ecSOD: extracellular superoxide dismutase; RAMP1: receptor activity-modifying protein 1; PKG1 $\alpha$ : protein kinase type 1 $\alpha$ .

effectively reduce the mechanical forces during injection and protect cells from damage [136].

The process of survival and retention of MSCs can be affected by various factors, such as ischemia, hypoxia, and inflammatory cell attack. The application of tissue engineering can improve this undesirable state [137]. The physical properties and microstructure of hydrogels regulate the infiltration of inflammatory cytokines and T lymphocytes *in vivo*, thereby reducing the attack of inflammatory cells on MSCs [53]. Injecting MSCs in an *in situ* cross-linked alginate hydrogel can maintain its activity and keep its paracrine with no immunogenicity [138]. Encapsulating MSCs in an

alginate hydrogel patch may also improve the retention of MSCs [139]. The collagen scaffolds (such as type I collagen scaffolds) can enhance the adhesion and proliferation of MSCs and exhibit better cytocompatibility [4].

In addition, the invention of an artificial simulated extracellular matrix based on tissue engineering has overcome many difficulties in the application of MSCs. Using hydrogels as scaffolds and adding high-affinity growth factors and chemokines may overcome the loss of chemokines via cell-scaffold interaction [4, 140]. MSCs suspended at 2% sodium alginate (a natural hydrogel) before transplanting was four times more effective [141].

TABLE 3: Drug/cytokine pretreatment in MSC transplantation for treating MI.

Drug/cytokine	Disease	Model	Dose/method	Function	Reference
Pioglitazone	MI	Rat	3 mg/kg/day/2 weeks	Cardiac function ↑	[90]
Atorvastatin	MI	Rat	1 mM/24 h	Neovascularization ↑	[91]
Sevoflurane	MI	Rat	3%/30 min	Activation of CSCs	[16]
Tadalafil	MI	Rat	1 μmol/L/2 h	Survival ↑; homing ↑	[92]
AER-ME	MI	Rat	200 mg/kg/day/30 days	Viability ↑; differentiation ↑	[93]
SRT1720	MI	Rat	0.5 μM/24 h	Survival ↑	[94]
Angiotensin II	MI	Rat	100 nM/24 h	Infarct size ↓	[95]
Salvianolic acid B	MI	Rat	10 μM/30 min	Infarct size ↓	[96]
DNP	MI	Rat	0.25 mM/20 min	Infarct size ↓; angiogenesis ↑	[97]
Edaravone	MI	Rat	500 μM	Apoptosis ↓; migration ↑	[98]
Trimetazidine	MI	Rat	2.08 mg/kg/day	Apoptosis ↓; infarct size ↓	[99]
IGF-1	MI	Rat	10 ng/mL/48 h	Survival ↑; apoptosis ↓	[100]
IL-1β, TNF-α	MI	Rat	10 ng/mL/24 h	Infarct size ↓	[101]
(EGb) 761	MI	Rat	100 mg/kg/day	Antioxidant ↑; differentiation ↑	[102]
Tβ4	MI	Rat	1 μg/mL/48 h	Proliferation ↑; retention ↑; survival ↑	[103]
Tanshinone IIA	MI	Rat	0.2 μg/mL/72 h	Migration ↑	[104]
Astragaloside IV	MI	Rat	0.4 μg/mL/72 h	Migration ↑	[104]
Melatonin	MI	Mouse	5 mM/24 h	Infarct size ↓	[105]
Apicidin	MI	Mouse	3 μM/24 h	Cardiac markers ↑	[106]
H <sub>2</sub> O <sub>2</sub>	MI	Mouse	200 μmol/L/2 h	Apoptosis ↓; angiogenesis ↑	[50]
PMSNs-siCCR2	MI	Mouse	25 μg/g/cotransplantation	Survival ↑; angiogenesis ↑	[107]
Aliskiren	MI	Mouse	15 mg/kg/day	Survival ↑; systolic function ↑	[108]
Atorvastatin	MI	Porcine	0.25 mg/kg/day	Infarct size ↓	[109]
TG-0054	MI	Porcine	2.85 mg/kg/day	LV contractility ↑	[110]
GLP-1	MI	Porcine	100 nM/48 h	Apoptosis ↓; infarct size ↓	[111]
G-CSF	MI	Rabbit	20 u/kg/day	Apoptosis ↓	[112]
Atorvastatin	MI	Rabbit	1.5 mg/kg/day	Myocardial remodeling ↓	[113]
Nicorandil	—	MSC culture	100 μM/1.5 h	Apoptosis ↓	[114]
Geraniin	—	MSC culture	20 μM/24 h	Efficacy ↑	[115]
Exendin-4	—	MSC culture	0–20 nm/L/12 h	Proliferation ↑	[116]

DNP: 2,4-dinitrophenol; GLP-1 :glucagon-like peptide-1; DMOG: dimethylxalyl glycine; AER-ME: Ailanthus excelsa Roxb. methanolic extract; PMSNs: siRNA-loaded photoluminescent mesoporous silicon nanoparticles. TG-0054: a novel CXCR4 antagonist; EGb 761: Ginkgo biloba extract; G-CSF: granulocyte colony-stimulating factor; Tβ4: thymosin β4.

**3.4.3. Nanomaterials.** Nanobiomaterial-incorporated stem cell therapy for MI has aroused much attention in recent years. The cardiac patch [142], nanofibrous scaffolds [143], and self-assembling peptides [144] appear promising in repairing the damaged myocardium. Cardiac patches consist of native collagen or synthetic polymers with a nanofibrous structure poly(lactide-co-epsilon caprolactone (PLCL)). These patches function when they are placed on the epicardial surface of the infarcted myocardium. PLCL is a highly flexible polymer which can form nanofibrous scaffolds, which significantly improves the survival rate of implanted MSCs compared to MSCs by direct injection [145]. Bioinspired self-assembling peptide nanofibers can be used as a cell carrier. MSCs that dealt with functional self-assembling peptide nanofibers RAD/PRG or RAD/KLT showed improved efficacy to treat MI [144]. Another study constructed poly(lactide-co-glycolide)-monomethoxy-poly-(polyethylene glycol) nanoparticles to encapsulate melatonin

on adipose-derived MSCs and improve the efficiency of their transplantation [146].

**3.5. Modifying Transplantation Environment of the Host Myocardium.** Modifying the target tissue prior to MSC transplantation to make the environment more conducive is a supplement approach to donor cell pretreatment. C1q/tumor necrosis factor-related protein-9 (CTRP9) is a novel pro-survival cardiokine with a significantly downregulated expression after MI, which is critical in maintaining a healthy microenvironment facilitating stem cell engraftment in infarcted myocardial tissue. Overexpression of CTRP9 in the host myocardium significantly enhanced stem cell therapeutic efficacy [147].

The process of transporting MSCs to damaged tissue is called homing, which is the result of the interaction of multiple chemokines and their receptors. CXC chemokine receptor 4 (CXCR4) and SDF-1 play a key role in the homing.

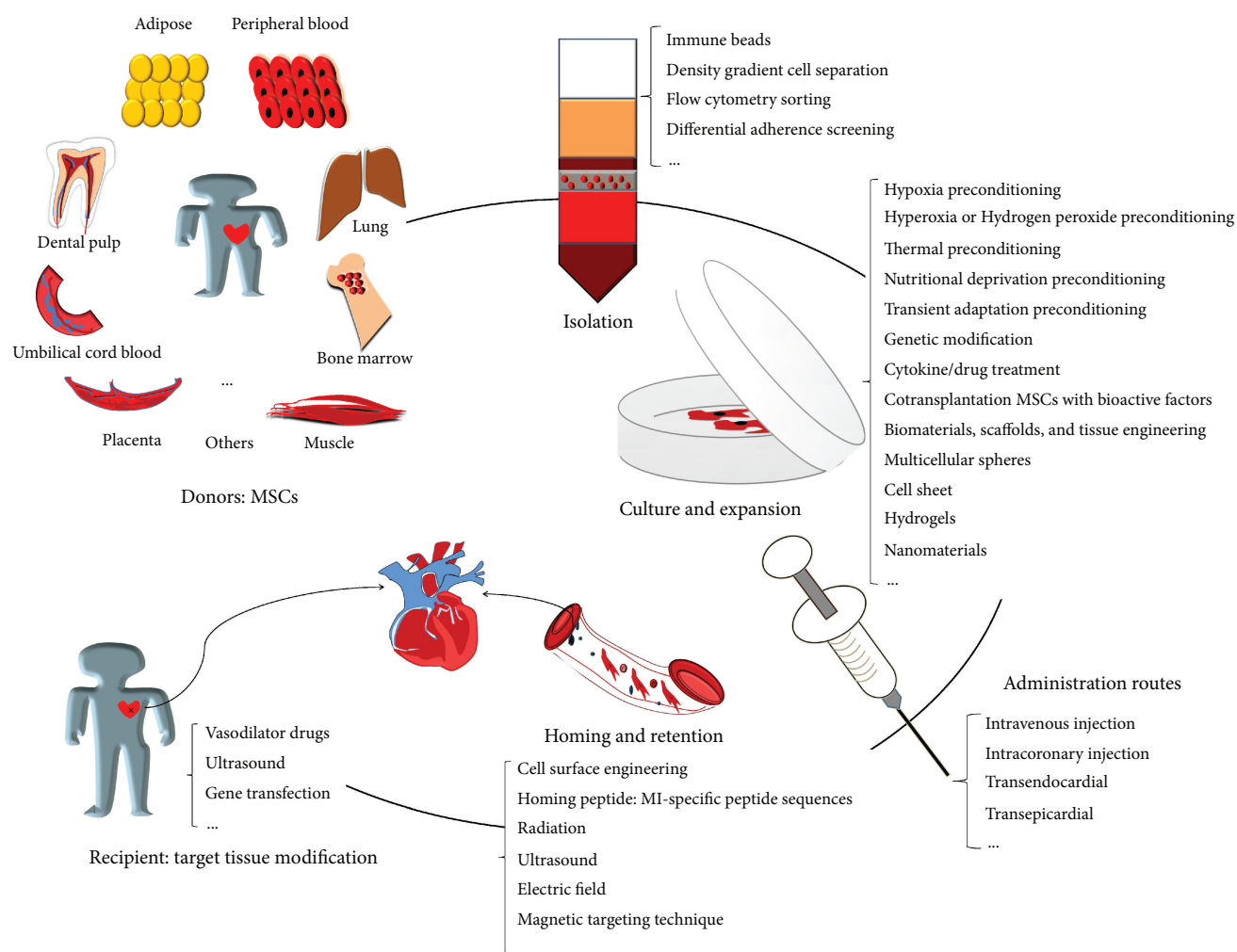


FIGURE 1: The procedures of MSC-based therapy, including donor selection, cell expansion, dosage, injection routes, homing, and target tissue modification. MSCs: mesenchymal stem cells.

MSCs are naturally capable of migrating to the injured area in the myocardium, but this feature is impaired because *in vitro* culture would induce the loss of the key homing receptor CXCR4 and other cellular signals. Releasing the adenoviruses carrying SDF-1 $\alpha$  to increase the local concentration of SDF-1 $\alpha$  in the injured myocardium could increase the homing of MSCs [90]. Combination of SDF-1 secretes from the infarct myocardium, and CXCR4 in MSCs can induce the migration of MSCs to the injured site [4]. Meanwhile, transfection of MSCs with CXCR4 overexpression vector increased the number of migrating MSCs by 3-fold [4].

**3.6. Novel Approaches to Stimulate MSC Homing.** Another intriguing method to increase the homing efficiency of MSCs is cell surface engineering, which is the temporary modification of the cell surface. These temporary changes help to improve the homing of MSCs without affecting viability, proliferation, adhesion, or differentiation of the transplanted cells [148]. In addition, the phage display

approaches were used to screen MI-specific peptide sequences. In MI mouse models, four peptide sequences (CRPPR, CRKDKC, KSTRKS, and CARSKNKDC4) were identified. The number of homing MSCs was significantly increased by injecting MSCs coated with MI-specific homing peptide in treating MI, indicating that the use of homing peptide-coated MSCs is a promising method for the treatment of MI [149].

Except for molecular modification of MSCs, it has been found that radiation, ultrasound, electric field, or magnetic field can also promote homing. Within 4 hours of MI, treating the bone marrow with 804 nm wavelength and 1 J/cm<sup>2</sup> energy density can increase the survival, proliferation, and homing of MSCs [150]. The magnetic targeting technique (MTT) is based on the premagnetization of MSCs and then MSCs move *in vivo* with the aid of a magnetic field [151]. MTT allows a wider range of transplanted cells to reach the target tissue, providing a more efficient and sustained medium release without increasing the number of MSCs [152].

#### 4. Conclusion and Future Perspectives

Many strategies were developed to modify the MSCs as well as the transplantation microenvironment, which improve the survival, retention, homing, multidifferentiation capacity, and paracrine factors, thereby enhancing the outcome of MSC-based therapy against MI (Figure 1). The combination of certain methods may exert synergistic effects to improve the efficacy of MSC transplantation. Clinical trials have shown that MSC transplantation is feasible and safe for MI, and it does not increase the risk of adverse events. Although some approaches such as supplement with rosuvastatin are clinically safe [122], whether other methods to improve the MSC functions are safe when applying to patients is currently uncertain. Further optimizing these methods to achieve clinical safety and effectiveness is of great significance for stem cell therapy.

#### Abbreviations

MI:	Myocardial infarction
MSCs:	Mesenchymal stem cells
BM-MSCs:	Bone marrow mesenchymal stem cells
LVEF:	Left ventricular ejection fraction
LVSF:	Left ventricular systolic function
VEGF:	Vascular endothelial growth factor
HGF:	Hepatocyte growth factor
IGF-1:	Insulin-like growth factor-1
SDF-1:	Stromal cell-derived factor-1
PEDF:	Pigment epithelium-derived factor
bFGF:	Basic fibroblast growth factor
RCTs:	Randomized controlled trials
HIF-1 $\alpha$ :	Hypoxia inducible factor-1 $\alpha$ .

#### Conflicts of Interest

The authors declare no potential conflict of interest.

#### Authors' Contributions

Zhi Chen and Long Chen have contributed equally to the article. Zhi Chen and Long Chen searched references, analyzed data and drafted the manuscript. Wei Eric Wang and Chunyu Zeng revised the manuscript. We apologize to the many investigators whose work in this area could not be mentioned by us because of space limitations.

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