REVIEW

Genetically modified mesenchymal stromal cells: a cell-based therapy offering more efficient repair after myocardial infarction

Congwang Xu[1], Yuanyuan Xie[2] and Bin Wang[1,2]*

Abstract

Myocardial infarction (MI) is a serious complication of coronary artery disease. This condition is common worldwide and has a profound impact on patients' lives and quality of life. Despite significant advances in the treatment of heart disease in modern medicine, the efficient treatment of MI still faces a number of challenges. Problems such as scar formation and loss of myocardial function after a heart attack still limit patients' recovery. Therefore, the search for a new therapeutic tool that can promote repair and regeneration of myocardial tissue has become crucial. In this context, mesenchymal stromal cells (MSCs) have attracted much attention as a potential therapeutic tool. MSCs are a class of adult stem cells with multidirectional differentiation potential, derived from bone marrow, fat, placenta and other tissues, and possessing properties such as self-renewal and immunomodulation. The application of MSCs may provide a new direction for the treatment of MI. These stem cells have the potential to differentiate into cardiomyocytes and vascular endothelial cells in damaged tissue and to repair and protect myocardial tissue through anti-inflammatory, anti-fibrotic and pro-neovascularization mechanisms. However, the clinical results of MSCs transplantation for the treatment of MI are less satisfactory due to the limitations of the native function of MSCs. Genetic modification has overcome problems such as the low survival rate of transplanted MSCs in vivo and enhanced their functions of promoting neovascularization and differentiation into cardiomyocytes, paving the way for them to become an effective tool for repair therapy after MI. In previous studies, MSCs have shown some therapeutic potential in experimental animals and preliminary clinical trials. This review aims to provide readers with a comprehensive and in-depth understanding to promote the wider application of engineering MSCs in the field of MI therapy, offering new hope for recovery and improved survival of cardiac patients.

Keywords Myocardial infarction, Mesenchymal stromal cell, Genetic modification, Survival, Differentiation

*Correspondence:
Bin Wang
wangbin022800@126.com
[1] Clinical Stem Cell Center, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese, Medicine321 Zhongshan Road, Nanjing 210008, People's Republic of China
[2] Clinical Stem Cell Center, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210000, People's Republic of China

Introduction

Cardiovascular disease (CVD) is a major health threat worldwide, and Myocardial infarction (MI) is included in this group of diseases characterized by high morbidity and mortality [1]. MI is pathologically characterized by the death of myocardial cells resulting from prolonged ischemia of the myocardium [2]. If left untreated, it will lead to irreversible myocardial loss, scar formation or even replacement by fibrotic tissue, ultimately resulting in heart failure [3–6]. Current clinical treatments, including pharmacological

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thrombolysis, percutaneous coronary intervention, and coronary artery bypass grafting, have significantly improved symptom relief and patients' quality of life. However, these treatments still face limitations when it comes to regenerating and repairing myocardial tissue [7–9].

Research on mesenchymal stromal cells (MSCs) transplantation for the treatment of MI has been conducted for several years, and its role in myocardial protection, immunomodulation, and promotion of angiogenesis has been gradually confirmed, showing a broad therapeutic perspectives [10–12]. Owing to unfavorable conditions within infarcted myocardium that significantly compromise survival rates of transplanted cells, primary strategies to enhance therapeutic efficacy include pretreatment of transplanted cells, optimization of myocardial microenvironment, and integration of genetic engineering with tissue engineering, among other approaches [13–17]. Among them, the optimization method based on genetically engineering cells has a number of advantages, for example, MSCs come from a wide range of sources, which are easy to obtain and expand, and do not involve the controversy of ethics and morality; and by modulating the expression of specific genes, the ability of MSCs to promote angiogenesis and anti-apoptosis can be improved, which significantly improves the transplantation effect [18–20].

This review consolidates recent advancements and future prospects of genetically modified MSCs-based therapies for MI treatment, while also examining the mechanisms and effects associated with transplantation of genetically modified MSCs in addressing this condition. Finally, the current challenges and strategies are discussed to provide reference and guidance for further advancing research and clinical applications in this field. Based on these opportunities and challenges, the prospect of clinical application of genetically modified MSCs transplantation for MI remains promising. Through continued in-depth research and constant innovation, it is believed that this treatment will bring better quality of life and therapeutic efficacy to patients with MI.

The pathophysiological process of MI and treatment

The most common type of MI is type I MI, defined as MI caused by atherosclerotic thrombotic CVD [21]. There are many risk factors that can trigger MI (Fig. 1). Initially, damage occurs to the endothelium of coronary arteries, often resulting from narrowing or rupture associated with atherosclerosis [22]. In the damaged area, platelets aggregate and form a thrombus, leading to a blockage of the coronary artery, which may be partial or complete, thus preventing blood flow to the myocardium leading to myocardial ischemia [23]. At this point, there is an
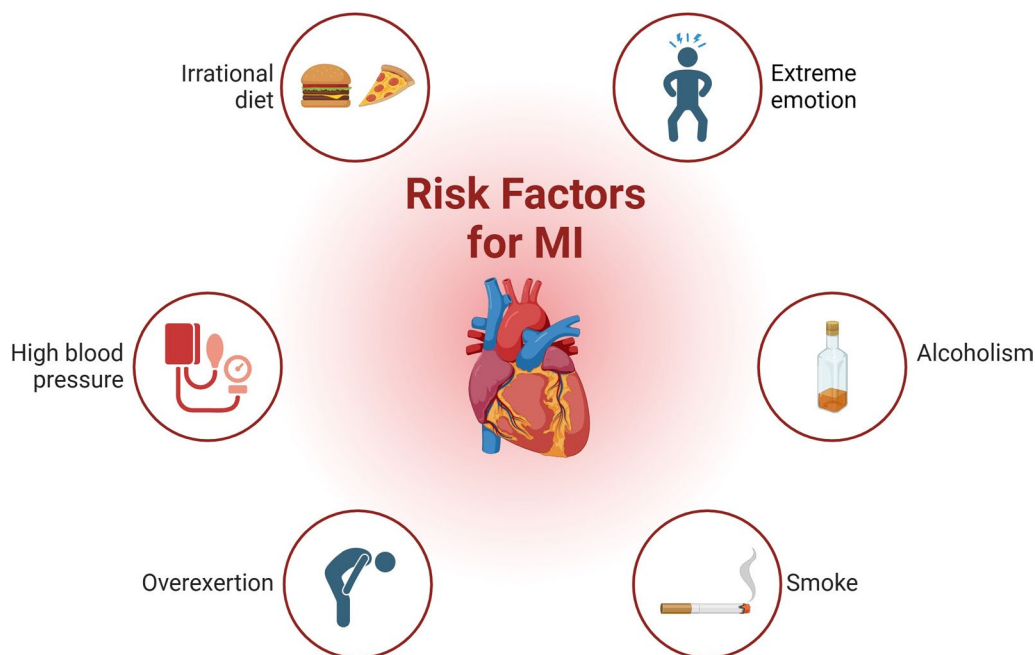
Fig. 1 Major risk factors for MI include an irrational diet, which can lead to high blood cholesterol and high blood pressure. Extreme emotions, including overexertion and sadness, can cause rapid short-term ischemia of the heart muscle, while overexertion can deprive the heart of oxygen by prolonged heavy work. Smoking is strongly associated with thrombosis, and alcohol abuse increases oxygen consumption by the heart muscle through increased heart rate and blood pressure

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inadequate supply of oxygen and energy to the cardiac muscle cells, and under ischemic conditions, these cells begin to suffer damage. Ischemia causes loss of function and structural damage to cardiomyocytes. Metabolic processes within the cells are disrupted and cell membrane permeability is increased, leading to disturbances in the exchange of substances between the inside and outside of the cell [24]. At this point, the cells may experience reversible damage, but if ischemia continues, irreversible damage develops. If ischemia persists for a longer period of time, irreversible cellular damage leads to cardiomyocyte death and the formation of an infarct zone [25]. Size and location of the infarct zone are determined by the extent and site of coronary artery obstruction. Dead cardiomyocytes release intracellular components that initiate an inflammatory response, attracting immune cells to the infarct zone, which subsequently clear away dead cells and tissue debris [26]. Over time, the inflammation subsides and collagen fibers are gradually deposited, forming scar tissue that replaces the dead cardiomyocytes [27]. This process may lead to a permanent weakening of myocardial function, affecting the heart's ability to pump blood.

The main goals of conventional drug therapy are to relieve symptoms, improve heart function, and prevent reinfarction. These include anticoagulants, antiplatelet agents, and beta-receptor antagonists [28]. Although these treatments can help patients maintain their lives and slow the progression of the disease to some extent, they cannot reverse the tissue damage and scarring caused by a heart attack to the extent that normal heart function cannot be restored and patients may continue to experience problems such as heart failure. Conventional treatments have not been effective in stopping the inflammatory response that interferes with the repair process in the infarcted area.

Many basic studies have been conducted on MSCs-based repair therapy after MI, and most of the preclinical studies have achieved good results. However, recent clinical trials have unveiled several drawbacks associated with original MSCs, revealing that their clinical efficacy is constrained by inherent native functions and falls short of anticipated levels. Based on this status quo, it is very difficult to meet the approval criteria for patented drugs and to advance the clinical translation of MSCs.

Biological properties of MSCs and MI

MSCs are adult stem cells whose biological properties make them a potential tool for repair therapy after MI [29, 30]. They are derived from a variety of tissues, such as bone marrow, adipose tissue, umbilical cord, and placenta, encompassing a wide range of sources [31]. This diversity of sources provides flexibility for clinical applications, allowing MSCs to be derived from the patient's own or other suitable sources [32]. The types of MSCs commonly investigated in human clinical trials are bone marrow-derived MSCs (BM-MSCs), adipose-derived MSCs (AD-MSCs), and umbilical cord-derived MSCs (UC-MSCs) [33]. Of these, the main ones used for post-MI cardiac repair studies are BM-MSCs and UC-MSCs. Subgroup analyses of cell sources showed that UC-MSCs improved ejection fraction of heart more significantly than BM-MSCs and AD-MSCs, indicating MSCs derived various tissues had tissue heterogeneity in therapeutic outcomes [34].

MSCs are characterized by their multidirectional differentiation potential and self-renewal capacity [35]. The multidirectional differentiation potential of MSCs allows them to differentiate into various cell types, such as cardiomyocytes and vascular endothelial cells. This characteristic is anticipated to facilitate the process of myocardial repair following MI [36–38]. MSCs not only excel in their differentiation potential, but their immunomodulatory capacity is also a distinguishing feature of their biological properties [39]. MSCs have the capability to enhance inflammation when the immune system is not sufficiently active, and they can also inhibit inflammation when the immune system is overactive, in order to prevent auto-aggression [40]. This makes MSCs a powerful tool in the treatment of autoimmune and inflammatory diseases [41]. The modulation of the inflammatory microenvironment is an important therapeutic target in post MI repair therapy, and MSCs can reduce further myocardial damage by immunomodulation through paracrine effects and by acting on immune cells [11, 36, 42].

The natural repair and regeneration capabilities of MSCs provide a solid foundation for genetic modification (Fig. 2) [18]. Firstly, they can differentiate into cardiomyocytes to fill in the damaged areas [43]. Secondly, MSCs promote repair of myocardial infarcted areas by secreting growth factors such as vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), and immunomodulatory factors in order to act as a promoter of angiogenesis, modulator of inflammatory responses, and stimulator of matrix remodelling [44]. In addition, MSCs exhibit anti-apoptotic and anti-fibrotic properties, which are important for tissue repair after MI [45]. By inhibiting apoptosis, MSCs help maintain the survival of cardiomyocytes and slow down the process of tissue damage [46]. Meanwhile, inhibition of fibrosis helps to reduce scar tissue formation and inhibit adverse remodelling [47].

Genetic engineering-based transformation of MSCs

The current challenges for MSCs cardiac therapies are to improve their survival and engraftment in injured myocardium and to enhance their ability to promote cardiac
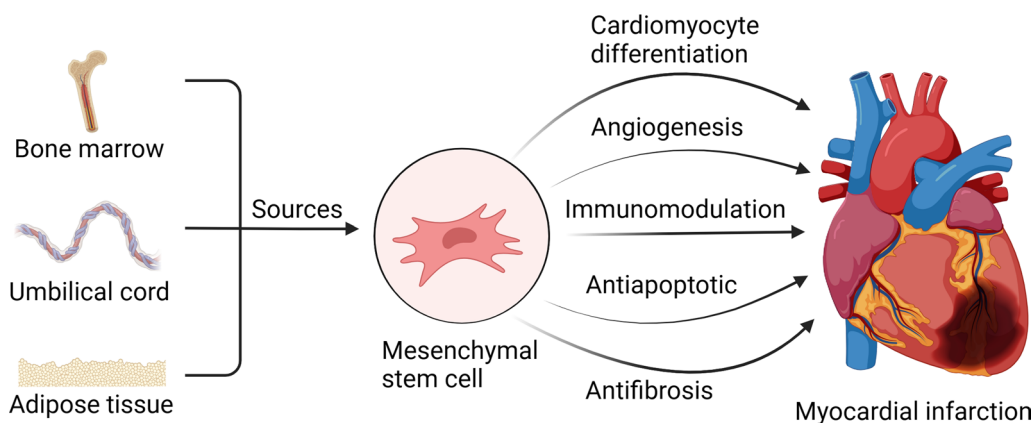
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Fig. 2 Sources of MSCs and their roles in repair therapy after MI

regeneration [48]. A variety of approaches have been used to enhance the function of naive MSCs to suit therapeutic needs (Table 1).

In recent years, genetic engineering, a cutting-edge field at the forefront of scientific and technological progress, has provided an innovative approach to repair therapy after MI [18]. The essence of this approach resides in regulating MSCs at the molecular level via genetic manipulation, which enhances cellular function and improves therapeutic outcomes in MI [56]. Genetic engineering techniques used to modify MSCs include gene editing and transgenic techniques (Table 2). In the modification of MSCs, guide RNAs can be designed to achieve precise editing of target genes by gene editing techniques, leading to gene knockout, modification or substitution. Transgenic technology, on the other hand, uses vectors such as plasmids and viruses to deliver target genes into the interior of MSCs and ensure stable delivery of exogenous genes so that MSCs can constantly express or inhibit specific proteins under specific conditions to achieve precise regulation of cellular functions, and vectors carrying specific drugs can also be introduced into MSCs so that they can become drug carriers and achieve targeted release of therapeutic substances

[57]. In addition, reverse transcription gene technology can be used to introduce specific genes to enhance myocardial tissue repair and regeneration by MSCs. Lentiviruses, retroviruses, adeno-associated viruses (AAVs), and adenoviruses can all be used as viral vectors for genetically modified MSCs [57]. Small interfering RNA (SiRNA) gene silencing and microRNA (miRNA) are also common genetic engineering techniques, where miRNA plays an important role in gene modification of MSCs by post-transcriptional inhibition of the target messenger RNA (mRNA) to alter gene expression [58].

Improving survival of grafted cells

The myocardial lesion areas of MI patients often exhibit a complex state of ischemia, hypoxia and chronic inflammation, and this poor host microenvironment is highly susceptible to induce the expression of apoptosis-related genes in transplanted MSCs, thereby adversely affecting their survival [73]. Secondly, the biological effects of MSCs from different individual sources vary widely, and MSCs from older donors tend to be more susceptible to apoptosis as a result of senescence and apoptosis due to the downregulation of biological functions caused by aging [74–76]. An increasing number of studies

Table 1 Methods used to enhance the function of MSCs and their therapeutic effects

Technique	Method	Effects
Hypoxic pretreatment	Hypoxic conditioned medium [49], etc	Wound repair↑
3D culture pretreatment	Non-adherent dishes, cell sheets, micro-fluidics and the hanging drop method [50], etc	Vascular protection↑
Inflammatory factor pretreatment	Coculture with IFN-γ [51], etc	Angiogenesis↑、Apoptosis↓
Growth factor pretreatment	Coculture with FGF-2, IGF-1, and BMP-2 [52], etc	Commitment of MSCs to CMC lineage↑
Drug pretreatment	Pretreated with TXL solution for 24 h [53], etc	Anti-apoptotic and anti-inflammatory mechanisms↑
Genetic modification	Lentiviral transfection [54], siRNA intervention [55], etc	Angiogenesis↑、Rejuvenation↑

↑ means "Up", ↓ means "down"

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Table 2 Current basic research on gene-modified cell therapy for MI

Cell type	Modification gene	Transfection method	Animal model	Result	Problem	References
BM-MSCs	FAIM↑	Lentivirus infection	Mouse	Cellular survival↑	Low practicality	[59]
BM-MSCs	Islet-1↑	Lentivirus infection	Rat	Cellular survival↑, paracrine function↑	Mechanism unknown	[60]
AD-MSCs	Farnesoid X receptor↑	Adenovirus infection	Mouse	Paracrine angiogenic↑	Limited effect	[61]
BM-MSCs	LUCAT1↑	Recombinant lentivirus transfection	Mouse	Anti-apoptotic↑	Mechanism unknown	[62]
BM-MSCs	Apelin↓, ↑	SiRNA, lentivirus transfection	Mouse	Cellular survival and angiogenic↑	Stability unknown	[63]
BM-MSCs	TPP1↑, ↓	Lentivirus infection, siRNA	Mouse	Cellular survival and heart function↑, fibrosis↓	–	[64]
BM-MSCs	FoxC1↑, ↓	Recombinant Adeno-Associated virus, siRNA	Rat	Myocardial repair↑	–	[65]
BM-MSCs	Sug1↓	ShRNA	Rat	Cellular survival↑	–	[66]
BM-MSCs	FNDC5↑	Lipofectamine and plasmid	Mouse	Engraftment and paracrine effect↑	–	[67]
AD-MSCs	IKKβ↑	Lentivirus transfection	Mouse	Myocardial repair↑	–	[68]
BM-MSCs	miR-155-5p↓	miR-155-5p inhibitors transfection	Mouse	Angiogenesis and cellular survival↑, cellular senescence↓	–	[69]
BM-MSCs	miR-206↓	miR-206 inhibitors transfection	Rat	Cellular senescence↓	–	[70]
BM-MSCs	HO-1↑	siRNA transfection	Mouse	Cellular survival↑	Mechanism unknown	[71]
BM-MSCs	HIF-1α↑	Lentiviruses infection	Rat	Angiogenesis↑, fibrosis↓	–	[54]
BM-MSCs	MIF↑	Lentiviral transduction	Rat	Cellular survival, angiogenesis↑	Mechanism unknown and long-term effects	[72]

have shown that the survival of transplanted MSCs in infarcted myocardium can be effectively improved by genetically engineering MSCs.

As early as 2003, Mangi et al. used isolated retroviral transduction of rat MSCs to overexpress the proto-survival gene protein kinase Bα (Akt1), significantly increased survival of MSCs after transplantation into rat ischemic myocardium, with inhibition of cardiac remodeling and near restoration of normal function [77]. Subsequent studies further confirmed this effect and suggested that these beneficial effects may be due to paracrine effects of MSCs, although the exact mechanism remained to be investigated [78]. Akt upregulation by stromal cell-derived Factor-1alpha (SDF-1α) prevented apoptosis and MSCs transduced by lentiviral vector have reduced apoptosis and increased survival after injection into infarcted myocardium [79]. Deng et al. also demonstrated that overexpression of cellular repressor of E1A-stimulated genes activated Akt to down-regulate the expression of p53, and the transcriptional activation of p53 led to the expression of pro-apoptotic proteins including BCL2-Associated X (Bax) and cell death proteins, and thus effectively inhibited apoptosis in MSCs under conditions of hypoxia and serum deprivation in vitro [80]. To further improve the survival of MSCs,

Chen et al. transduced MSCs using isolated AAVs to overexpress Akt1 and Wnt Family Member 11 (Wnt11), and found that the transplanted cells showed reduced apoptosis and increased survival, as well as greater cardiac differentiation and survival potential [81]. During this period, a team transfected BM-MSCs with the fibroblast growth factor-2 (FGF-2) gene and found that their secretion of FGF-2 increased under hypoxic conditions, their survival was significantly improved and the expression of the anti-apoptotic gene B-cell lymphoma/leukemia 2 was increased [82]. Secreted Frizzled-related protein 2 (sFRP2) was thought to be a key mediator of MSCs-mediated myocardial repair, and overexpression of sFRP2 enhanced the resistance to apoptosis as well as increased the implantation rate of MSCs, and these effects were achieved by inhibiting the Wnt and Bone morphogenic protein signaling pathways [83]. Overexpression of mid-range factor (MK) inhibited MSCs apoptosis induced by hypoxia and glucose deprivation in vitro, and implantation of MSCs overexpressing MK into the hearts of myocardial infarcted rats was observed to result in an increase in survival, as well as a reduction in infarct size and an improvement in cardiac function [84]. GATA binding protein 4 (GATA-4) played a regulatory role in the differentiation, growth and survival of a wide range

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of cell types, and Li et al. found that BM-MSCs overexpressing GATA-4 showed increased survival in ischemic myocardium, an effect that may be attributed to the anti-apoptotic effect of GATA-4 in addition to the upregulation of insulin-like growth factor-1 (IGF-1) levels in MSCs [85]. B-cell Lymphoma-extra-large (Bcl-xL) was an important factor in the regulation of apoptosis and belongs to the B-cell lymphoma-2 (Bcl-2) family of proteins, and overexpression of Bcl-xL in rat MSCs by gene modification improved the implantation rate of MSCs as well as their survival in the ischemic and hypoxic microenvironment, in addition to enhancing the pro-angiogenic capacity of MSCs [86]. Heme oxygenase-1 (HO-1) was an anti-apoptotic and anti-inflammatory enzyme, and Zeng et al. used recombinant adenoviruses to transfect MSCs and found that they improved the survival of MSCs in the ischemic myocardium of infarcted rats by improving the mRNA levels of inflammatory cytokines and reducing the levels of the pro-apoptotic protein Bax, mainly through the release of paracrine factors that bind to HO-1 protein [87]. In response to the upregulation of specific chemokines in infarcted myocardium and the very low expression of corresponding chemokine receptors in MSCs, Huang et al. genetically engineered MSCs to overexpress Chemokine (c–c motif) receptor 1 and observed a reduction in the number of apoptotic cardiomyocytes and infarcted area after transplantation into ischemic myocardium [88]. Integrin-linked kinase (ILK) was an important pleiotropic protein that regulated cell survival, proliferation, differentiation and angiogenesis. Mu et al. injected ILK-transfected MSCs into myocardial infarcted pigs and found that MSCs homed to the infarcted myocardium was significantly enhanced and apoptosis was effectively reduced [89]. The LIM homology cassette transcription factor islet-1 played a crucial role in the development of cardiac embryos and adult resident cardiac stem cells. Xiang et al. found that ISL1 overexpressed human mesenchymal stromal cells (HMSCs) enhanced hMSCs survival and paracrine function in hMSCs transplanted into myocardial infarcted rats, and that this effect may be mediated through insulin-like growth factor binding protein 3 [60]. Follicle suppressor-like 1 (Fstl 1) has been described as a novel cardiomyocyte survival-promoting factor. Shen et al. found that transduction of MSCs with Fstl 1 recombinant lentiviruses attenuated myocardial extracellular matrix (ECM) deposition and inflammatory cell infiltration in ischemic hearts and improved the survival of transplanted cells [90]. Irisin has anti-apoptotic, increased cell viability and antioxidative stress cardioprotective effects and was the extracellular domain of Fibronectin type III domain-containing protein 5 (FNDC5), and overexpression of FNDC5 by genetic modification of BM-MSCs

prevented hypoxia-induced increased in apoptosis and consequently improved MSCs survival after transplantation [67]. Octamer-binding protein 4 (Oct4) can promote the release of cytoprotective factors such as Basic fibroblast growth factor (BFGF), survivin and Bcl-2, and can reduce the expression of apoptosis-associated proteins Bax and caspase-3, and Huang et al. found that β-catenin was an upstream regulatory target that can be overexpressed to maintain the survival of transplanted MSCs [91]. Fas apoptosis inhibitory molecule (FAIM) was involved in the regulation of exogenous apoptotic pathways, Chen et al. found that FAIM-overexpressed MSCs improved the survival of transplanted MSCs in myocardial infarcted mice by inhibiting the C-Jun N-terminal kinase-mediated ubiquitinated proteasome-dependent Cellular-FLICE inhibitory protein degradation pathway [59].

Based on the fact that overexpression of anti-apoptotic genes can improve the survival rate of MSCs, it was suggested that silencing of pro-apoptotic genes might have the same effect. Therefore, a recombinant human caspase-8 small hairpin RNA adenovirus was prepared to transfect MSCs and transplanted into the ischemic myocardium of infarcted rats, and the results showed that it significantly reduced the activity and expression of caspase-8 in the border zone of the infarcted myocardium and also increased the survival rate of the transplanted MSCs [92]. Apoptosis signal-regulated kinase 1 (ASK1) has been implicated in the development of oxidative stress-associated pathologies in the injured heart, and Lee et al. found that hypoxia-induced activation of ASK1 signaling could be attenuated by microRNA-301a overexpression in human adipose-derived stem cells to inhibit apoptosis and improve the survival of transplanted stem cells [93]. Chen et al. found that after injection of BMSCs overexpressing microRNA-133 into the hearts of rats with MI, apoptosis of MSCs in hypoxic conditions was significantly reduced, inflammation and fibrosis in the infarcted heart were suppressed, and cardiac function was improved [94]. Mitochondrial integrity played an important role in the anti-apoptotic process of hMSCs, which prevented the release of various pro-apoptotic factors, and regulation of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway helped to maintain the integrity and function of mitochondria [80]. Leptin conferred mitochondrial integrity to hMSCs by enhancing the accumulation of Optic atrophy 1, so that leptin overexpression enhanced the survival of MSCs in an ischemic environment [95]. Ischemia and hypoxia usually led to mitochondrial dysfunction, which in turn leads to apoptosis, and it was found that ELABELA regulated Hypoxic/ischemic-induced mitochondrial dysfunction through apelin receptor, thereby improving the

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anti-apoptotic capacity and increasing the viability of MSCs [96].

Senescence has become a prominent area of investigation, where mesenchymal stromal cells were observed to transition into a senescent state due to factors such as telomere dysfunction, genomic lesions, chromatin structural irregularities, and the engagement of active mitotic signaling pathways [75, 97]. Concurrently, these cells face an inevitable diminishment in their immunoregulatory functions [98]. In addition to this, the proliferative, differentiation, and migratory capabilities of MSCs also diminished accordingly [99, 100]. Consequently, this adversely affected the survival rate and reparative capabilities of the transplanted cells [101]. Sirtuin 3 (SIRT3) was localized in mitochondria and was associated with oxidative stress and longevity, and overexpression of SIRT3 enhanced the antioxidant capacity of Old hMSCs as a mean of increasing the number of survivors after transplantation into damaged myocardium [102]. MicroRNA-10a (MiR-10a) was significantly reduced in O-hBM-MSCs, and overexpression of miR-10a increased survival of transplanted hBM-MSCs in infarcted mouse hearts by activating AKT [103]. Erb-B2 receptor tyrosine kinase 4 (ERBB4)-overexpressing aged MSCs were more resistant to oxidative stress-induced cell death, and the increased expression of their phosphorylated AKT and extracellular signal-regulated kinase (ERK) under hypoxic conditions effectively reduced apoptosis [104]. Senescent BM-MSCs have reduced autophagy levels and are less tolerant to hypoxia, so their apoptosis rate was higher under hypoxic conditions compared to the younger group. Yang et al. found that knocking down IGF-1 increased their autophagy levels, which facilitated their survival when transplanted into infarcted myocardium [105]. In conclusion, modification of MSCs by genetic engineering is a reliable way to increase their survival rate. Inverse regulation of N6-methyladenosine by ALKB homologue 5 (ALKBH5) promoted cellular senescence, so down-regulation of ALKBH5 rejuvenated aged MSCs and increased their survival in infarcted hearts [55].

Promoting angiogenesis

Myocardial perfusion was closely related to the survival of cardiomyocytes. Therefore, hemodialysis after MI played an important role in the recovery of cardiac function, and previous studies have shown that MSCs can differentiate into vascular endothelial cells for angiogenesis [106, 107].

VEGF and angiopoietin-1 (Ang1) played a therapeutic role by promoting angiogenesis, but their therapeutic effects in a mouse model of Acute myocardial infarction (AMI) were found to be weaker than in a group of transplanted MSCs [108]. One team suggested transfecting MSCs with VEGF to improve the therapeutic effect, and found that transplanting them into damaged hearts not only promoted angiogenesis, but also helped to improve post-infarction cardiac remodeling and cardiac systolic and diastolic function [109]. In the hearts of rats with MI treated with HO-1-MSCs, the expression level of VEGF was more significantly enhanced and the density of micro vessels was significantly increased [87]. In addition, autologous MSCs transplanted with angiopoietin gene transfection showed increased neointima formation and synergistic effects on cardiac perfusion and functional improvement in a porcine model of chronic ischemia [110]. Based on the fact that MSCs overexpressing the Akt gene showed improved survival and engraftment in infarcted myocardium, Jiang et al. transduced MSCs co-overexpressing Ang-1 and Akt to enhance the viability of remaining cardiomyocytes and transplanted cells by promoting angiogenesis [111]. Subsequent studies have demonstrated its long-term stable efficacy [112]. Zhang et al. to maximized the effect of SDF-1α on cell migration and regeneration, adenoviral transduction of male rat MSCs to overexpress C-X-C motif chemokine receptor type 4 (CXCR4) was transplanted into myocardial infarcted rats and found to be significantly increased in infarcted areas and peri-infarcts, effectively promoted angiogenesis and alleviated early signs of left ventricular remodelling [113]. Zhao et al. injected lentiviral engineered MSCs into the myocardium for sustained release of SDF-1α to complement transient endogenous cytokine release for enhanced angiogenesis [79]. BM-MSCs overexpressing GATA-4 also promoted angiogenesis in ischemic myocardium through paracrine effects, and several growth factors, including Vascular endothelial growth factor-A (VEGF-A) and IGF-1, may be involved [85]. Glycogen synthase kinase (GSK)-3 was a serine/threonine kinase that regulated a variety of intracellular functions by phosphorylating intracellular substrates such as glycogen synthase and GATA4, and VEGF-A was found to be upregulated in the hearts of mice injected with GSK-3β—bone marrow-derived MSCs in the study by Cho et al. It was therefore hypothesized that it was most likely through this pathway that angiogenesis was promoted [114]. The pro-angiogenic chemokine granulocyte chemotactic protein-2 (GCP-2) played a key role in angiogenesis, Kim et al. transplanted GCP-2 overexpressing human AD-MSCs into myocardial infarcted mice and found that the expression of pro-angiogenic factors, such as VEGF-A and hepatocyte growth factor (HGF), was higher, and that chemokines, such as interleukin (IL)-8 and GCP-2, were also significantly upregulated [19]. Intramyocardial injection of HGF-transfected BM-MSCs into the myocardium of a rat model of MI stimulated angiogenesis and reduced myocardial fibrosis

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[115]. Growth differentiation factor 11 promoted stem cell activity and leaded to increased survival and retention in infarcted hearts after transfection of MSCs, favoring enhanced angiogenesis [116].

Considering the effect of aging on the pro-angiogenic function of MSCs, Liu et al. ameliorated the aging phenotype of aged MSCs by overexpressing silent mating type information regulation 2 homolog 1 to recapitulated their pro-angiogenic properties [117]. Thioredoxin-1 (Trx1) has been shown to be a potent antioxidant, transcription factor and growth factor regulator, and Suresh et al. found a pro-angiogenic effect in the form of increased capillary density and better maintenance of survival and differentiation after transplantation of MSCs transfected with Trx1 into rats with MI [118]. Overexpression of miR-10a in aged BM-MSCs also increased VEGF and SDF secretion, thereby promoting angiogenesis in ischemic mouse hearts [103]. In contrast, ERBB4-age MSCs promoted angiogenesis by secreting higher levels of angiopoietin, epithelial neutrophil-activating peptide 78, VEGF and fibroblast growth factor 2 [104]. MicroRNA-335 (MiR-335) caused senescence in MSCs through its regulatory effect on mitochondrial dynamics. Hong et al. inhibited miR-335 expression in MSCs by genetic modification and enhanced their angiogenesis in a mouse model of aging MI [69].

Although IGF-1 and HGF had the potential to promote cardiac repair and MSCs overexpressing either IGF-1 or HGF enhanced neointima formation in a porcine model of AMI, simultaneous administration did not appear to exert a synergistic effect [119]. Whereas very small embryonic-like MSCs co-overexpressing hypoxia-inducible factor 2-alpha and Oct4 synergistically enhanced their angiogenesis [120]. Overexpression of β-conjugated protein-treated MSCs optimally upregulated Oct4 in ischemic cardiomyocytes and strongly contributed to the secretion of the pro-angiogenic cytokines Ang1, BFGF, HGF and VEGF [91]. Overexpression of c-Myc favored angiogenesis in cardiac-resident MSCs, but inevitably induced an inflammatory response, which was compensated by its co-expression with Oct4, resulted in a synergistic effect of enhanced angiogenesis [121].

Promoting myocardial regeneration

Previous studies have shown that MSCs can differentiate into cardiomyocytes to participate in the repair of damaged myocardium due to their multidirectional differentiation potential [122–124].

Grauss et al. found early on that forced expression of cardiac myosin by genetic modification of hMSCs prior to transplantation could increase their tendency to differentiate into cardiomyocyte-like cells in mice with MI [125]. 5-Bromo-4-chloro-3-indolyl

β-D-galactopyranoside-positive cells and upregulation of troponin T were observed after injection of MSCs overexpressing GSK-3β into mice with MI, providing strong evidence that overexpression of GSK-3β promoted the differentiation of MSCs into cardiomyocytes [114]. Compound 56 was an epidermal growth factor receptor inhibitor that promoted cardiogenic differentiation of hMSCs. MiRNA-133a also targeted EGFR to induce cardiogenic differentiation of hMSCs, and the expression of endogenous miRNA-133a was regulated by compound 56. Therefore, EGFR can be targeted by transfection of miRNA-133a to promote the differentiation of hMSCs into cardiomyocytes [126]. Co-overexpression of Akt1 and Wnt11 significantly upregulated the expression of cardiac markers Natural killer type-2 transcription factor related 5, GATA-binding protein 4, α-myosin major histocompatibility complex and brain natriuretic protein, thus contributing to myocardial differentiation in MSCs. Therefore, their promoting effect on myocardial differentiation in MSCs should not be underestimated [81]. T-Box Transcription Factor 20 (Tbx20) belonged to the T-box family of transcription factors involved in the differentiation process that regulated cardiomyocyte differentiation and may played a role in upregulating gene expression in cardiac development and cardiomyocyte homeostasis in conjunction with a variety of other cardiac transcription factors. Human AD-MSCs transduced with Tbx20 lentiviral vectors induced the expression of markers of myocardial differentiation by increasing the expression of cardiomyocyte differentiation markers at both the RNA and protein levels [127]. Pygopus Family PHD Finger 2 (PYGO2) was a core component of the canonical Wnt signaling pathway, and transfection with PYGO2 contributed to canonical Wnt signaling to promote the early differentiation of human umbilical cord-derived mesenchymal stromal cells (hUC-MSCs) into cardiomyocytes, and promoted the mid- to late-stage differentiation of MSCs into cardiomyocytes through activation of the PI3K-Akt signaling pathway [128].

Combining multiple approaches to optimize the biological functions of MSCs to enhance therapeutic efficacy after MI

In recent years, more and more optimization methods have gradually emerged based on genetic engineering to optimize the biological functions of MSCs. This included the combination of adjuvant therapies such as growth factors and anti-inflammatory drugs, which can promote cell growth and reduce the inflammatory response [129]. The use of biomaterials, such as suitable scaffolds and bio-colloids, to provide support and guidance for MSCs can promote cell colonization and differentiation in damaged areas [130]. The use of

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nanotechnology to achieve the targeted release of therapeutic agents and to improve the spatial and temporal precision of the therapeutic effect.

Medication-assisted treatment

Statins were known to protect endothelial function, inhibit inflammation and stabilize atherosclerotic plaques, among which rosuvastatin may exerted a protective effect on AD-MSCs by modulating FoxO3a induced by the PI3K/Akt and Mitogen-activated extracellular signal-regulated kinase (MEK)/ERK1/2 pathways, so that when combined with AD-MSCs, it enhanced implanted survival and proliferation and reduced myocardial fibrosis [131]. In contrast, combined treatment with atorvastatin increased SDF-1 expression in peri-infarct myocardium while suppressing inflammation [132]. NO production associated with inducible nitric oxide synthase (iNOS) overexpression impaired BMSCs transplanted into infarcted rat myocardium, ameliorated by combined use of selective iNOS inhibitors [133]. Exendin-4 modulated the PI3K/Akt-sfrp 2 pathway to reduce mitochondrial oxidative stress damage, so that AD-MSCs pretreated with exendin-4 can exert better anti-apoptotic effects after transplantation into infarcted myocardium [134]. 5-Diphosphoinositol pentakisphosphate (IP7) physiologically inhibited the production of Akt, which is generated by inositol hexakisphosphate kinases (IP6Ks); Therefore, N2-(m-trifluorobenzyl)-N6-(p-nitrobenzyl) purine (TNP), as a reversible inhibitor of IP6Ks, promoted the implantation of MSCs in the infarcted heart by inhibiting IP6Ks to downregulate the production of IP7 and enhance the activation of Akt promoted the implantation of MSCs in the infarcted heart and paracrine effects that contributed to the protection of myocardial function after MI [135]. Edaravone, a free radical scavenger that inhibited the production of reactive oxygen species (ROS), in combination with BM-MSCs attenuated hypoxia-induced apoptosis by inhibiting the accumulation of intracellular ROS and prolonged the activation of the Akt pathway to promote the paracrine potential of BM-MSCs, which promoted angiogenesis and cardiac stem cell-mediated regeneration of the cardiac muscle [136]. Traditional Chinese medicine promoted stem cell migration and survival by improving the microenvironment of the infarcted myocardium, in which Guanxin Danshen preparation, as the main prescription for clinical treatment of ischemic heart disease, can reduce apoptosis of the transplanted cells when administered in combination with MSCs and reduce angiogenesis in the infarcted area and the periphery, thus improving cardiac function after MI [137].

Biomaterials

CXCR4-overexpressing MSCs promoted neo angiogenesis in infarcted myocardium, Huang et al. designed a stem cell patch using peritoneum as a substrate, which in combination with CXCR4-overexpressing MSCs synergistically created a suitable environment to promote angiogenesis and cardiomyocyte survival, and reduced myocardial remodeling through paracrine effects [138]. Arginyl-glycyl-aspartic acid (RGD)-modified alginate microspheres encapsulate MSCs and, when injected into infarcted rat myocardium, provided myocardial structural support to prevent adverse post-MI remodeling while inducing neovascularization [139]. Collagen I was a major component of the ECM of the heart, and mixing MSCs with type I collagen solution to distribute them in collagen scaffolds and to make three-dimensional (3D) patches, their transplantation improved myocardial function by promoting reverse remodeling of the infarcted area [140]. Poly/gelatin nanofibrous patch can provide adequate mechanical support for MSCs, improved cellular interactions required for infarct repair, attenuates left ventricular remodeling and induced angiogenesis and cardiomyopoiesis in rat model of MI [141]. Hyaluronic acid (HA) was involved in many cellular processes, including proliferation and differentiation, and the use of hyaluronic acid-based hydrogel scaffolds as a vehicle for the delivery of MSCs may improve infarcted myocardial structure and function by promoting cell survival after transplantation, reducing inflammatory responses and increasing neointimal formation [142]. VEGF-loaded gelatin and alginate polyelectrolytes encapsulate MSCs by layer-by-layer self-assembly technology, which was a novel targeted delivery vehicle that can be delivered to myocardial infarcted tissues by virtue of the homing effect of MSCs and release VEGF continuously, thus promoting angiogenesis in infarcted areas and increasing perfusion to improve cardiac function [143]. Chitosan hydrogel was a slow-release carrier that protected cells from the host immune system clearance response and can effectively increase the viability of transplanted cells in the infarcted myocardium. IGF-1 had pro-proliferative, anti-apoptotic and angiogenesis-inducing effects, so chitosan hydrogel modified by the C structural domain of IGF-1 can provide a good microenvironment for the survival of human placenta-derived mesenchymal stromal cells and enhance their ability to promote angiogenesis, anti-apoptosis and inhibit fibrosis [144]. Cell sheet was a bioactive material that can prolong the retention and survival time of transplanted MSCs and improve the transplantation microenvironment. Transplanted hUC-MSCs

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cell sheets modulated inflammatory responses in infarcted myocardium and inhibited ventricular remodeling through paracrine effects. Additionally, the ECM left behind after UC-MSCs' demise served as a bioactive scaffold for host cells, fostering angiogenesis in infarcted regions. Nerve growth factor primarily facilitated the proliferation and survival of MSCs [145]. Porous microspheres produced based on Polyethylenimine$_{1.8\ k}$ and poly (lactic-co-glycolic acid) particles exhibited low toxicity, provided a large inoculum surface area for MSCs, and increased the oxygen and nutrient support required for their growth, thereby greatly enhanced the regenerative potential of MSCs after transplantation into infarcted myocardium [146]. Hydrogel systems based on gelatin methacrylate and oxidized dextran in combination with reductive graphene oxide exhibited conductivity similar to that of natural cardiac tissue, UC-MSCs encapsulated by them were well morphologically shaped and sustained release was achieved, and the efficiency of differentiation of UC-MSCs was improved with the up-regulation of Cardiac Troponin I and Connexin 43 expression [147].

Nanotechnology

Nanocarriers as an siRNA delivery strategy were less toxic and safer than viral vectors, where poly (amidoamine) dendritic polymers with precisely controlled radial symmetry and high cargo capacity in a nanoscale volume combined with the advantage of arginine residues to facilitated cell membrane penetration, and the combination of both of them can provide a highly efficient and biocompatible delivery system for siRNA-mediated silencing of the prolyl hydroxylase structural domain protein 2 in MSCs to improve the survival rate and paracrine effect of MSCs after transplantation [148].

Hollow mesoporous organosilicon nanoparticles (HMONs), after surface optimization with polyethyleneimine (PEI), had achieved enhanced gene loading capacity and protection, avoided the drawbacks of toxicity and adverse immune responses that may be associated with traditional strategies. Using HMONs-PEI as a gene carrier, HGF can be effectively transfected into BM-MSCs without affecting their migration and proliferation, and can induce enhanced expression of infarcted myocardial HGF protein after transplantation. The use of HMONs-PEI as a gene carrier can effectively transfect HGF into BM-MSCs without affecting their migration and proliferation, and can induce enhanced expression of HGF protein in infarcted myocardium after transplantation, which improved therapeutic efficacy by decreasing apoptosis and increasing angiogenesis [149]. Patch made of electro spun cellulose nanofibers can improve the post-infarction myocardial microenvironment by mimicking the heart's natural ECM and can provide a 3D scaffold for implanted AD-MSCs. Combined with the non-toxic, biodegradable, and anti-inflammatory features of chitosan/silk proteins (CS/SF), the biocompatibility of the nanofiber patch made of CS/SF assembled on electro spun cellulose nanofibers by layer-by-layer (LBL) technology was optimized. The biocompatibility of the nanofibrous patch made of CS/SF assembled onto electro spun cellulose nano patches by LBL technology was optimized, thus increasing the survival of AD-MSCs transplanted into infarcted myocardium and effectively improving ventricular remodelling [150]. Self-assembling peptide can form a hydrogel scaffold to provide a favorable microenvironment for stem cell attachment, growth and survival under specific conditions, and after modification with functional motifs glutamine-histidine-arginine-glutamic acid-aspartic acid-glycine-serine (QHREDGS) to obtain the designer self-assembling peptide (DSAP) cellular delivery system, the paracrine effect of MSCs inoculated with DSAP was up-regulated after transplantation into the infarcted myocardium, which resulted in an increase in graft cell survival and angiogenesis [151].

Clinical research and challenges

Previous studies have shown that trans endocardial injections of MSCs were safe (Table 3) [152]. Although treated patients showed transient small increases in myocardial biomarkers (Creatine Kinase Isoenzyme-MB and serum troponin I), there was a modest reduction in the size and mass of myocardial scar tissue, with no serious adverse effects of postoperative pericardial effusion and an improvement in quality of life [153]. Another study also found that scar tissue reduction and functional improvement occurred predominantly in the actual injected area, and provided strong evidence that 20 million injections of autologous MSCs produced the greatest relative gains [154]. In a subsequent clinical trial, the researchers found that the 100 million-dose injections produced superior results, with increased cardiac ejection fraction in addition to reduced scar size, due to the smaller sample size per dose and random allocation of patients to autologous or allogeneic hMSCs transplantation, as well as the effect of disease severity on cell dose [155]. During clinical trials, Gao et al. found that the function and viability of BM-MSCs declined with age and could not meet the therapeutic needs of MI patients in a timely manner, making it necessary to seek an alternative source of stem cells [156]. In a subsequent double-blind randomized controlled trial, Wharton's glial-derived MSCs showed no immune response or tumor formation in allografts and demonstrated enhanced cardiovascular differentiation, effectively improving cardiac function and preventing left ventricular remodelling [157]. Since then, Attar's

Table 3 Clinical trial of MSCs for the treatment of myocardial infarction

Trials status	Disease condition	Interventions	Ages eligible for study	Infusion time	Effect	ClinicalTrials.gov ID
Completed	ST-Elevation Myocardial Infarction	Intracoronary human umbilical WJ-MSCs transfer	18 years or older adult	4–7 days after successful reperfusion therapy	Significantly improve myocardial viability and heart function	NCT01291329 [160]
Completed	Acute Myocardial Infarction	Intravenous and intracoronary human UC-MSCs transfer	30 years to 80 years	STEMI patients within 5 days after symptom	Unknown	NCT04340609
Completed	Acute Myocardial Infarction	One single IC infusion followed by one single IV infusion of UC-MSC01	20 years to 75 years	Patients after the onset of heart attack	The effect appears to be safe, feasible	NCT04056819 [161]
Terminated	Chronic Ischemic Cardiomyopathy, Coronary Artery Bypass Surgery	HUCS-MSCs transplantation	30 years to 80 years	During CABG in chronic ischemic cardiomyopathy (EF < %45)	Display higher scores in reducing the scar tissue and restoration of ventricular wall functions	NCT02323477 [162, 163]

team conducted a single-blind, randomized, multicenter trial to compare the efficacy of one versus two transplants of Wharton's glial-derived MSCs (WJ-MSCs) after AMI, and found that the left ventricular ejection fraction of the target patients was significantly improved by intracoronary transplantation of WJ-MSCs on days 3–7, and augmented by a booster dose of transplantation 10 days later [158]. Although suitable alternative sources have been identified for the poor efficacy of BM-MSCs after transplantation, in the long term strategies such as combining drugs and engineering were needed to improve the survival and low implantation rates of BM-MSCs in the heart [159].

Current clinical trials of MSCs in the treatment of MI have shown overall safety, but efficacy has not been satisfactory. In addition, there have been no clinical trials of MSC gene modification for specific targets. Therefore, the results of animal experiments that have shown that gene modification of MSCs was more effective in the treatment of MI in basic research should be applied to clinical research in the future to achieve more satisfactory clinical therapeutic effects.

MSCs derivant-exosomes

A growing number of studies have found that MSCs-derived exosomes exert cardioprotective effects similar to those of their parent MSCs, with enhanced safety and therapeutic efficacy [164]. MSCs-derived exosomes were found to exhibit cardioprotective effects similar to those of their parents. By participating in the regulation of intercellular communication, it may play an important role in the treatment of MI as an anti-apoptotic, anti-inflammatory and anti-ventricular remodeling agent [165–167]. Exosomes were rich in a variety of biologically active molecules including proteins and miRNAs, among which proteins such as VEGF and MMP stimulated angiogenesis, and factors such as Interleukin-6 (IL-6), Interleukin-10 (IL-10), transforming growth factor-β (TGF-β) and HGF played a favorable role in immunomodulation processes [168]. In addition to this, exosomes attenuated cardiomyocyte damage after MI by inhibiting ferroptosis and mediating polarization processes in macrophages [169, 170]. MicroRNA-136 released from exosomes of young MSCs also downregulated the expression of apoptotic peptidase activating factor in receptor cells as a means to enhance the viability of senescent MSCs and improve their myocardial repair capacity [171].

Various approaches have been used to improve the low yield and low bioavailability of exosomes from MSCs in order to improve their efficacy for post-infarction repair [172]. Pharmacological pretreatment with atorvastatin and Tongxinluo (TXL) improved cardio protection of MSCs exosomes by promoting angiogenesis and other effects [173, 174]. In addition, research on engineered exosomes has also yielded results in that fusion of exosomes with the ischemic myocardium-targeting peptide CSTSMLKAC allowed exosomes to be preferentially targeted to the ischemic myocardium to exert therapeutic effects [175]. Improved stability and sustained release of exosomes using polymer-grafted nanoparticle hydrogels formed by mixing peptide amphiphile-Growth hormone-releasing peptides and naphthalene-conjugated short peptide (NapFF) [176]. Exosomes derived from iron oxide

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nanoparticles-encapsulated MSCs can be magnetically guided to increase their retention in the infarcted heart and allow the infarcted heart to advance to the repair phase, resulting in a decrease in apoptosis and fibrosis, as well as an enhancement of angiogenesis and recovery of cardiac function [177]. Nanocomplexes constructed by self-assembly of MSCs membranes on the surface of miRNA-containing mesoporous silica nanoparticles mimic exosome function with higher miRNA loading, escaped immunosurveillance, and targeted ischemic myocardium to promote cardiomyocyte proliferation by inhibiting translation of apoptosis-associated proteins [178]. A minimally invasive exosome spray cardiac patch designed by inoculating MSCs-derived exosomes in fibrin scaffolds increased the retention time of exosomes in the infarcted heart and made them more readily available for uptake, effectively reduced apoptosis and facilitates surgical procedures [179]. Injectable conductive hydrogels containing sulfhydryl CP05 peptide can both enhance the retention of hUC-MSCs-derived Exosomes in infarcted myocardium by anchoring it and exert some pro-angiogenic effects [180]. EVs released from MSCs overexpressing hypoxia-inducible factor 1-alpha could promote angiogenesis as well as anti-apoptotic effects by expressing higher levels of microRNA-221-3p, and their survival in the infarcted heart was also improved after wrapping by RGD hydrogel [181]. The short peptide thermosensitive hydrogel developed based on Ang-1 can accelerate the functional recovery of infarcted myocardium by prolonged slow release of ISL1-MSCs-Exosomes allowing it to have a high therapeutic concentration in the injected area [182]. Delivery of exosomes containing microRNA-29b mimics with biocompatible microneedle patches bound to gelatin was a novel attempt to prevent cardiac fibrosis by inhibiting pathological remodeling of the ECM through inhibition of the TGF-β signaling pathway [183]. Electro spun nanofiber cardiac patches made of mixed polycaprolactone and type I collagen can provide both a three-dimensional scaffold for hUC-MSCs exosomes to proliferate and mechanical support for infarcted myocardium, which, combined with the combined effect of TGF-β3 to inhibit myocardial fibrosis, greatly enhanced the therapeutic advantages of exosomes [184]. Bio-conductive polymer hydrogels generated using polypyrrole and chitosan can alleviate arrhythmias by re-synchronizing cardiac electrical transmission, which in combination with the beneficial effects of anti-apoptotic and pro-angiogenic effects of human endometrial mesenchymal stem cell-derived exosomes, provided yet another good method for post-infarction cardiac repair [185]. In conclusion, cell-free therapies based on exosomes of MSCs show broad application prospects in the field of CVD by virtue of their low immunogenicity and regulation of intercellular communication, etc. It was expected that exosomes optimized by different methods will be opened for clinical trials as soon as possible, providing a new option for repair therapy after MI [186].

Conclusion

MSCs played an important role in cardiac repair therapy after MI by virtue of their immunomodulatory ability, vascular and cardiomyocyte differentiation potential, and their efficacy in improving left ventricular ejection fraction, and reducing infarct size. The MSCs-based therapy has been demonstrated to make up for the shortcomings of traditional interventional and pharmacological therapies.

The implantation rate, survival rate, and ability to differentiate into myocardium and vasculature of genetically modified MSCs after transplantation into animal models of MI have been enhanced to a certain extent, and clinical trials have been conducted to screen for appropriate transplantation time, transplantation dose, and source of naive MSCs. The ability of MSCs to be used for cardiac repair after MI was further enhanced with the combination of techniques such as pharmacological intervention, tissue engineering, and nanoengineering. Pharmacological interventions optimized the transplanted myocardial microenvironment for MSCs, tissue processes provided MSCs with a spatial structure conducive to their growth and differentiation, and nano-engineering ameliorated the potential safety concerns of genetic modification by vectors such as viruses.

Future optimization pathways should continue to work on enhancing the survival of MSCs in the harsh microenvironment of infarcted myocardium, and in-depth exploration of the mechanisms of differentiation and migration of transplanted MSCs should be carried out to facilitate clinical translation while ensuring safety, with a view to bringing benefits to MI patients.

Abbreviations

MI	Myocardial infarction
MSCs	Mesenchymal stromal cells
CVD	Cardiovascular disease
BM-MSCs	Bone marrow derived mesenchymal stromal cells
AD-MSCs	Adipose-derived mesenchymal stromal cells
UC-MSCs	Umbilical cord derived mesenchymal stromal cells
VEGF	Vascular endothelial growth factor
Ang-1	Angiopoietin-1
IFN-γ	Interferon-γ
FGF-2	Fibroblast growth factor-2
IGF-1	Insulin-like growth factor-1
BMP-2	Bone morphogenetic protein-2
CMC	Cardiomyocyte

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TXL	Tongxinluo
SiRNA	Small interfering RNA
MiRNA	MicroRNA
MRNA	Messenger RNA
Akt1	Protein kinase Bα
Bax	BCL2-Associated X
Wnt11	Wnt Family Member 11
FAIM	Fas apoptosis inhibitory molecule
LUCAT1: Lung cancer-associated transcript 1;TPP1	Tripeptidyl peptidase 1
FoxC1	Forkhead box C1
FNDC5	Fibronectin type III domain-containing protein 5
IKKβ	IκB kinase β
MiR-155-5p	MicroRNA-155-5p
MiR-206	MicroRNA-206
HO-1	Haem oxygenase 1
MIF	Macrophage migration inhibitory factor
AAVs	Adeno-associated viruses
SFRP2	Secreted Frizzled-related protein 2
MK	Midkine
GATA-4	GATA binding protein 4
Bcl-xL	B-cell Lymphoma-extra-large
Bcl-2	B-cell lymphoma-2
ILK	Integrin-linked kinase
HMSCs	Human mesenchymal stromal cells
Fstl 1	Follistatin-like 1
ECM	Extracellular matrix
Oct4	Octamer-binding protein 4
BFGF	Basic fibroblast growth factor
JNK	C-Jun N-terminal kinase
ASK1	Apoptosis signal-regulated kinase 1
PI3K/Akt	Phosphoinositide 3-kinase/ Protein kinase B
SIRT3	Sirtuin 3
MiR-10a	MicroRNA-10a
ERBB4	Erb-B2 receptor tyrosine kinase 4
ERK	Extracellular signal-regulated kinase
ALKBH5	ALKB homologue 5
Ang1	Angiopoietin-1
AMI	Acute myocardial infarction
SDF-1α	Stromal cell-derived factor-1α
CXCR4	C-X-C motif chemokine receptor type 4
VEGF-A	Vascular endothelial growth factor-A
GSK	Glycogen synthase kinase
GCP-2	Granulocyte chemotactic protein-2
HGF	Hepatocyte growth factor
IL	Interleukin
Trx1	Thioredoxin-1
MiR-335	MicroRNA-335
Tbx20	T-Box Transcription Factor 20
PYGO2	Pygopus Family PHD Finger 2
HUC-MSCs	Human umbilical cord-derived mesenchymal stromal cells
MEK	Mitogen-activated extracellular signal-regulated kinase
INOS	Inducible nitric oxide synthase
IP7	5-Diphosphoinositol pentakisphosphate
IP6Ks	Inositol hexakisphosphate kinases
TNP	N2-(m-trifluorobenzyl)-N6-(p-nitrobenzyl) purine
ROS	Reactive oxygen species
RGD	Arginyl-glycyl-aspartic acid
HMONs	Hollow mesoporous organosilicon nanoparticles
PEI	Polyethyleneimine
3D	Three-dimensional
CS/SF	Chitosan/silk proteins
LBL	Layer-by-layer
QHREDGS	Glutamine-histidine-arginine-glutamic acid-aspartic acid-glycine-serine
DSAP	Designer self-assembling peptide
WJ-MSCs	Wharton's glial-derived MSCs
STEMI	ST-segment elevation myocardial infarction
IC	Intradermal injection
IV	Intravenous injection
HUCS-MSCs	Human umbilical cord-derived mesenchymal stromal cells
CABG	Coronary artery bypass grafting
EF	Ejection fractions
IL-6	Interleukin-6
IL-10	Interleukin-10
TGF-β	Transforming growth factor-β
NapFF	Naphthalene-conjugated short peptide

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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