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Stem Cell Therapy in Cardiovascular Diseases: The Reparative Mechanisms of Mesenchymal Stem Cells for Myocardial Infarction Treatment

Jin Han[1], **Jonghoon Choi**[2,3] **and Suk Ho Bhang**[1,*]

[1]*School of Chemical and Biological Engineering, Seoul National University, Seoul 151-744, Republic of Korea*

[2]*Department of Bionano Technology, Graduate School, Hanyang University, Seoul 133-791, Republic of Korea*

[3]*Department of Bionano Engineering, Hanyang University ERICA, Ansan 426-791, Republic of Korea*

[*]**Corresponding author:** Suk Ho Bhang, School of Chemical and Biological Engineering, Seoul National University, Seoul151-744, Republic of Korea, Tel : +82-2-880-1875; Fax: +82-02-2297-0838; E-mail: sukhobhang@gmail.com

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Abstract

Cell therapy, more specifically stem cell therapy, holds significant promise in the treatment of various diseases. Stem cells address a great therapeutic approach for tissue engineering in particular, as they are known to differentiate into various tissue lineages, including bone, cartilage, cardiac muscle, and even into the cells of the central nervous system. Another great strength of the stem cells is that autologous cell transplantation is available and the patients can be treated with their own cells. This greatly reduces the risk of host immune-related problems, and further enables more patient-friendly and patient-specific therapy. Recently, stem cell therapy shed some light on its paracrine mechanisms, in addition to the direct differentiation mechanism for disease treatment. Although a number of stem cell-based therapies are advancing, their reparative mechanism and therapeutic efficacy in disease treatment need further studies. Herein, we reviewed the major therapeutic approaches of the stem cells for cardiovascular diseases. In particular, we will focus on mesenchymal stem cells (MSCs) among various stem cell types, and discuss their reparative mechanisms in cardiac tissue regeneration.

Keywords: Cardiovascular diseases; Mesenchymal stem cells; Reparative mechanisms; Tissue regeneration

Introduction

Regenerative medicine in cardiovascular diseases, such as myocardial infarction (MI), is in great need to restore structural and electrophysiological function of the damaged heart. MI remains to be the leading cause of death in the western world; however, no treatment has been shown as the fundamental care for cardiac disease modulation [1]. MI occurs after the occlusion of coronary artery that supplies blood and nutrient to the heart. Reperfusion of this occluded artery greatly helps and salvages ischemic myocardium, regressing the cardiac remodeling [2]. Unfortunately, ischemic myocardium rapidly progresses apoptosis and necrosis of cardiomyocytes, causing dilation and remodeling of the left ventricle [3]. Treatment that helps regeneration of the damaged heart tissue has been regarded as the fundamental and ultimate strategy for MI repair. In such respect, therapeutic approaches associated with the stem cells address significant advances in cardiac tissue engineering because the stem cells can regenerate damaged cardiac tissues that have limited regenerative capacity [4]. Mesenchymal stem cells (MSCs) derived from patients' bone marrows or adipose tissues are being tested in a number of clinical trials today, and they have shown to repair myocardium damaged by myocardial infarction [5]. The use of stem cells for clinical trials has impacts in several aspects. Since the autologous stem cell transplantation is possible to the patient, there are no host immune problems after cell injection. Additionally, safe and efficient *in vitro* expansion of the patients' cells is readily available. Therefore, the acquisition of large number of cells that is required for clinical treatments can be resolved. A number of previous clinical trials, namely TOPCARE-AMI in 2002, BOOST in 2004, REPAIR in 2006 and FINCELL in 2008, demonstrated positive results showing improvements in cardiac function following stem cell (MSC) injection, and proved the safe and sound clinical impact of MSC treatment for cardiovascular diseases [5].

There are largely two reparative mechanisms of MSCs in MI treatment (Figure 1): 1) first mechanism suggests that MSCs directly differentiate into functional cardiac cells and replace damaged cells *in vivo* and 2) the second mechanism addresses MSCs secrete various trophic factors that help angiogenesis and cardiac tissue regeneration. The multipotency of MSCs to differentiate into various lineages have been studied previously [6], and their terminal cardiac differentiation *in vivo* has proposed a reliable reparative mechanism of how MSC could repair damaged myocardium [7,8]. Additionally, a number of studies showed MSCs secrete paracrine factors that help angiogenesis and immune modulation, which can further down regulate cardiac remodeling and progress tissue regeneration [3,9,10]. Taken together, MSCs take two pathways to repair damaged heart tissues and they certainly can serve as the fundamental therapeutic approach for cardiovascular diseases. Here, we demonstrate the therapeutic approach of adult stem cells for cardiovascular diseases, especially MI. We choose MSCs among various types of stem cells because they are the most actively utilized cell types in clinical trials. The roles and reparative mechanisms of MSCs in MI are summarized.

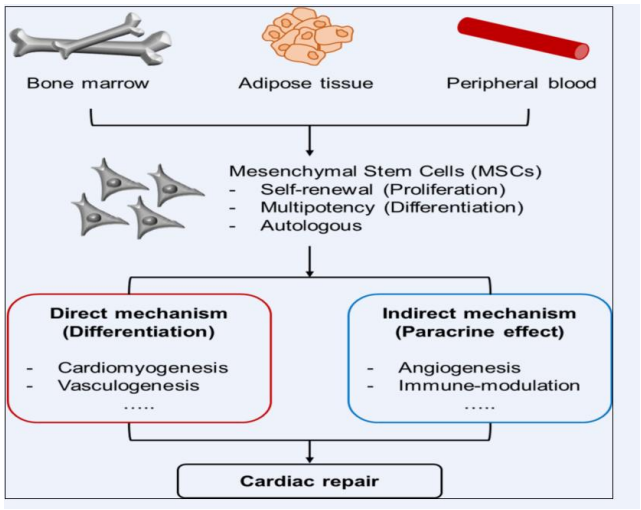

Figure 1: Sources, characteristics, and proposed therapeutic mechanisms of MSCs for cardiovascular disease. Direct differentiation of MSCs into functional cardiac cells and indirect paracrine molecule secretion from MSCs cooperatively affect cardiac repair

Reparative mechanisms of MSCs in MI repair

Transdifferentiation of MSCs into cardiomyocytes has originally been proposed as the major therapeutic mechanism of MSC therapy in MI repair [4,11]. Cardiomyocyte differentiation of MSCs *in vitro* has been studied by a number of studies by applying chemicals, proteins, small molecules, or co-culture method [12-18]. More recently, *in vivo* cardiomyocyte differentiation of MSCs and their functional engraftment into the myocardium was assessed [8]. However, no previous study has been able to induce MSC-derived cardiomyocytes that have electrophysiological phenotype of original cardiomyocytes [19,20]. Additionally, poor survival and engraftment ratio of the transplanted MSCs question the therapeutic efficacy of MSCs after transplantation *in vivo* [4]. Only recently the reparative paracrine signaling of MSCs was proposed as another major mechanism of the stem cell therapy for various diseases [3]. Especially for MI, extensive angiogenesis and immune modulation are required because a coronary artery occlusion rapidly blocks blood flow and activates monocytes. MSCs secrete numerous soluble factors that promote angiogenesis, prevent cardiac remodeling, activate endogenous cardiac cells, and regulate immune response [3,9,10]. MSC transplantation has been shown to be safe and effective for MI repair where transplanted MSCs take two major mechanisms of action to repair damaged cardiac tissue.

Transdifferentiation of MSCs

Cardiomyogenic differentiation of MSCs *in vitro* was first reported using exogenous chemical 5-azacytidine (5-AZA) [13]. After 24 hours of incubation with growth medium supplemented with 3 umol/L 5-AZA, MSCs showed morphological relevance to cardiomyocytes and expressed cardiomyogenic markers such as cardiac actin, cardiac troponin T (cTnT), and beta-myosin heavy chain (ß-MHC) [13]. Expression of sarcomere and adrenergic receptors were also observed from MSCs treated with 5-AZA. However, a generic protocol for 5-AZA treatment is not completed, and numerous studies have showed differential methods and results upon 5-AZA treatment; the concentration and treatment time vary in many cases. Additionally, 5-AZA is a demethylating agent that could be cytotoxic to the cells, hence limiting their application *in vivo*. Another strategy to induce cardiomyogenic differentiation of MSCs is related with proteins treatments [14,18]. Proteins, such as bone morphogenetic protein (BMP) and transforming growth factor (TGF) have been shown to induce cardiomyocyte differentiation of MSCs *in vitro*. Bone morphogenetic protein-2 (BMP-2) and transforming growth factor beta-3 (TGF-ß3) have been known to induce osteogenic and chondrogenic differentiation of MSCs, respectively [21,22]. Number of previous studies demonstrated that BMP or TGF-ß treatment could also work as cardiomyogenesis inducers [14,18]. It was shown that bone marrow derived MSCs treated with TGF-ß for 14 days reached similar levels of cardiac specific marker expression compared to those treated with 5-AZA, and showed significant increase of cardiac actin, cTnT, and myosin light chain (MLC) gene expression [14]. Treatment of BMP also enhanced the gene expression of Nkx2.5 and GATA4 in MSCs [14]. Besides the use of exogenous inducers, such as 5-AZA or proteins, co-culture with cardiac cells has also been studied for MSC cardiac differentiation [16,17]. Co-culture has long been the fundamental method of controlling lineage of the stem cells, and co-culture-based cardiac differentiation of the stem cells was studied using cardiomyocytes or cardiomyoblasts [16,17,23]. Previous studies of co-culturing MSCs with rat cardiomyocytes have showed that co-culture significantly upregulated the cardiac marker expression of MSCs, including cardiac troponin I, α-sarcomeric actinin, and myocyte enhancer factor-2C (MEF2C). Interestingly, many studies showed the enhancement in cardiac gene and protein expression was only significant when MSCs were co-cultured with cardiomyocytes directly, but not indirectly [17]. Additionally, co-culture with rat cardiomyoblast cell line H9C2 has also been shown to induce cardiac differentiation of endothelial progenitor cells (EPCs) [23]. More recently, small molecule has been proposed as an efficient inducer for cardiomyocyte differentiation of MSCs [15]. Previous study showed that MSCs treated with small molecule phorbol myristate acetate significantly up regulated the cardiomyogenic protein and electrophysiological phenotype expression [15]. Interestingly, when small molecule-treated MSCs were injected into MI-bearing rats, they restored not only the physiological function but also the electromechanical function of the heart. This result is particularly intriguing because MSCs were previously known to potentially induce electrophysiological abnormalities in the infarcted heart, and may cause cardiac arrhythmic risks [19,20].

Transdifferentiation of the transplanted MSCs into functional cardiac cells *in vivo* has been shown previously [4,7,11]. In most cases, MSCs were delivered directly into the myocardium rather than intravenously to enhance the engraftment of MSCs. Infarcted tissue is known to recruit MSCs for tissue regeneration, however it is not sufficient to repair relatively large infarcted region. In such respect, exogenous MSCs are injected directly to the peri-infarct. After intramyocardial injection of MSCs, they engraft and make contacts with native cardiomyocytes [7]. Cardiac microenvironment sends out signals and subsequently initiates cardiomyogenic differentiation of the transplanted MSCs. Previous studies showed that intramyocardial injection of MSCs successfully prevented remodeling of left ventricles, progressed regeneration of cardiac tissues and recovered cardiac function [4,7,11]. Reparative mechanism responsible for this beneficial effect of MSCs was further assessed by histochemistry. When green

fluorescent protein (GFP)-labeled MSCs were injected into the infarcted heart, GFP+ cells found at the injected peri-infarct showed cardiac structural marker alpha-myosin heavy chain (α-MHC) and cardiotin [24]. This result suggests that exogenously delivered MSCs can survive, differentiate and engraft at the peri-infarct for MI repair.

MSC's potential to differentiate into cardiac cells and regenerate infarcted tissue has intrigued the use of other cell types for MI repair [4]. Myoblasts are the progenitor cells of myocytes, and can differentiate into myotubes and muscles *in vivo* [4,11]. Similar to the MSC injection, myoblast injection also recovered structural function of the heart [4]. However, despite the enhancement in general cardiac function, transplanted myoblasts were unable to differentiate into cardiomyocytes and the cardiac specific marker expression was not observed [4]. Moreover, myoblast-transplanted groups showed arrhythmic risks and resulted in serious side effects [25]. This is due to the relatively lower expression of gap junction protein connexin 43 in the myoblasts compared to MSCs [25]. Connexin 43 is the major gap junction protein that is expressed in myocardium and accounts for electrophysiological function of the heart. Previous studies hence concluded that the absence of the key gap junction protein in the myoblasts limits their therapeutic approach. Taken together, MSC distinctively provides both structural and electrophysiological therapeutic approach for MI repair, and is regarded as a great source for cardiac regeneration. Major limitations of applying MSCs in clinical treatments are related with the low engraftment of MSCs in ischemic tissue, the poor cell survival, the use of exogenous proteins or chemicals for cardiac differentiation of MSCs, and the electrophysiological abnormalities of MSCs [19,26]. Despite such limitations, MSCs that are delivered to the damaged myocardium improved ejection fraction and fractional shortening to a significant extent in clinical trials, restoring normal cardiac function [5].

Paracrine mechanisms of MSCs

Despite the fact that MSCs can transdifferentiate into cardiac cells *in vitro* and *in vivo*, low survival and engraftment ratio of the transplanted MSCs questioned the general enhancement in cardiac function [9]. To further evaluate the reparative mechanism of MSCs, other than their direct differentiation into cardiac tissues, previous studies were focused on the indirect paracrine mechanisms of MSCs [3,9,10]. Stem cells are known to secrete a broad variety of trophic factors and growth factors to affect the cellular environments. MSCs in particular are known to release angiogenic and immune-modulatory paracrine molecules. Previous studies demonstrated that the conditioned medium of MSCs showed beneficial effects in various diseases [3,10]. Especially for the cardiovascular diseases, the infarcted heart treated with MSCs showed extensively increased protein expression levels of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF)-1 [4]. Interestingly, such beneficial effects were recapitulated with the administration of MSC conditioned medium [26]. In addition to the increased protein expression of the infarcted heart, MSC-treated, or MSC conditioned media-treated animal models demonstrated recovery of cardiac function. Beneficial effects of MSC conditioned media suggest the reparative effect of MSCs could be deduced not only from the transdifferentiation of MSCs after injection, but also from the paracrine molecules secreted from MSCs. In this respect, alterations in MSC culture condition were investigated to improve the indirect MSC paracrine mechanism [27-29]. Induced hypoxic culture conditions, or naturally generated mild hypoxia from MSC spheroids significantly upregulated the trophic factor secretion from MSCs and subsequently enhanced the therapeutic efficacy after cell therapy. Moreover, genetic modification of MSCs was also studied for enhanced paracrine molecule secretion [30,31]. When MSCs were genetically modified to overexpress Akt gene, MSCs exerted more cardiac protective and angiogenic proteins. This study further proved that the combinatorial approach of genetic modification of MSCs and hypoxic condition synergistically affected the secretion of trophic factors by assessing extensively up regulated secretion of VEGF, bFGF, HGF, and IGF [24]. Modifications in MSCs and MSC culture conditions both showed enhanced cardiac function recovery upon in vivo injection.

Trophic Factors Secreted from Stem Cells	Major Functions
Adrenomedullin	Cardioprotection
Angiogenin	Angiogenesis
Angiopoetin-1	Angiogenesis
Bone morphogenetic protein	Cell development
Endothelin	Cardioprotection
Fibroblast growth factor	Cell proliferation and migration
Hepatocyte growth factor	Cardioprotection and angiogenesis
Insulin-like growth factor	Cardioprotection
Interleukin-1	VEGF induction
Interleukin-6	VEGF induction
Macrophage migration inhibitory factor	Immune-modulatory
Platelet-derived growth factor	Cell proliferation
Thrombospondin-1	Cardiac remodeling prevention

Thymosin-b4	Cardioprotection
Transforming growth factor	Cell proliferation and angiogenesis
Tumor necrosis factor-a	Cell proliferation
Vascular endothelial growth factor	Angiogenesis

Table 1: Lists of paracrine molecules secreted from MSCs [3]

There are broad varieties of growth factors and cytokines secreted from MSCs [3], and these paracrine molecules in Table 1, function cohesively and synergistically to enhance MI repair. Trophic factors secreted from MSCs can induce angiogenesis, promote neovascularization, prevent cardiac remodeling, modulate immune response, and activate endogenous cardiac stem cells [3]. Proangiogenic factors, including VEGF, HGF, FGF, and IGF-1, are the major paracrine molecules secreted from MSCs and they collectively enhance proliferation of endothelial cells within remodeling collateral for arteriogenesis. Additionally, VEGF, FGF, and angiopoetin-1 secreted from MSCs further stimulate the sprouting of endothelial cells from the blood vessel, promoting angiogenesis at the infarcted heart. Beneficial effects of these trophic factors were also affective in cardiac hypertrophy prevention. As shown in the previous studies, paracrine molecules from MSCs salvaged cardiomyocytes under hypertrophy *in vitro*, and further prevented dilation of left ventricular and cardiac hypertrophy [9,26,27]. Another role of MSC's paracrine mechanism is that certain trophic factors from MSCs could recruit and activate endogenous quiescent stem cells [3]. MSCs secrete high level of stem cell-derived factor-1 (SDF-1), which is known to recruit endogenous MSCs and cardiac stem cells. Previous study has also showed that paracrine molecules secreted from MSCs can activate cardiac stem cells and consequently enhance their proliferation and differentiation into functional cardiac cells [32]. Collectively, MSCs can modulate the microenvironments not only by secreting trophic factors that can directly stimulate and enhance cardiac tissue regeneration, but also by recruiting and activating endogenous stem cells.

Conclusions

Only recently, the stem cell therapy has shed its light on cardiovascular disease treatment and clinical operations. MSC is an exceptionally attractive candidate for MI treatment, because MSCs have been shown to transdifferentiate into cardiomyocytes, and replace damaged cardiomyocytes. When MSCs were injected into the myocardium, fraction of these cells differentiated into cardiomyocytes and engrafted to the host tissue. Regardless of the low survival and engraftment ratio of these cells, significant reduction in cardiac remodeling along with increase in cardiac function underlines the beneficial effects of MSCs on MI treatment. More recently, when MSCs were pre-treated *in vitro* and differentiated into cardiomyogenic lineage, these MSC-derived cardiomyocytes displayed better electromechanical engraftment to the native myocardium compared with untreated MSCs. These results signify the importance of the MSC's cardiac lineage commitment and suggest the reparative mechanism of MSC treatment. In addition to the direct effect of MSC transdifferentiation into cardiomyocytes, innate paracrine molecules secreted from MSCs could further enhance the therapeutic efficacy by modulating cellular metabolisms at the peri-infarct. Previous studies reported that MSCs pretreated *in vitro* overexpressed angiogenic proteins resulting better therapeutic efficacy *in vivo*. These modified MSCs did not show any differences in the expression of cardiac specific markers, suggesting only the paracrine mechanism of the MSCs were modulated. Taken together, both direct mechanism (i.e. transdifferentiation of MSCs into functional cardiomyocytes) and indirect mechanism (i.e. secretion of trophic factors) work synergistically to enhance myocardial repair. Further studies that can embrace and combine these two crucial roles of MSCs may demonstrate a better therapeutic approach for MI and other cardiovascular diseases.

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