Review

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Stem Cell Therapy for Myocardial Infarction Recovery: Advances, Challenges, and Future Directions

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Abstract: Myocardial infarction (MI) is a leading cause of morbidity worldwide, resulting from ischemic damage and necrosis to cardiomyocytes. While the standard treatment regimen for MI can be successful in restoring coronary perfusion, it typically does not resolve myocardial damage, which can leave patients particularly vulnerable to complications such as heart failure or electrical conduction abnormalities. Stem cell therapies offer a promising novel approach aimed at restoring cardiac function and decreasing the incidence of functional complications after an MI. This review used a literature search to evaluate the current landscape of stem cell therapy for post-MI recovery and focuses on the stem cell candidates for MI recovery therapy, delivery methods of such treatment, and their effectiveness. Both preclinical and clinical trials have demonstrated the safety of stem cells, but have struggled with limited cell retention, inconsistent efficacy, and survival. Mechanisms employed by stem cells to promote regeneration such as paracrine signaling, angiogenesis, and structural remodeling in addition to the various stem cell delivery methods including intracoronary infusion, direct myocardial injection, and intravenous administration. Furthermore, some strategies to combat past challenges in this field are discussed, for instance, extracellular vesicles, bioengineered patches, hydrogels, gene editing, and bioprinting. This article will provide a framework for future research in stem cell therapies and highlight the current progress in the field.

Keywords: myocardial infarction; stem cell therapy; cardiac regeneration; regenerative medicine; cell-based therapy; tissue engineering

1. Introduction

Globally, ischemic coronary artery disease is a leading cause of death. Coronary artery disease frequently deteriorates to myocardial infarction (MI), wherein an occlusion of a coronary artery results in local ischemia causing extensive necrosis in the muscular myocardium, adverse ventricular remodeling, and fibrotic scar formation. [1]. Currently, reperfusion therapy is the standard of care for acute myocardial infarction, which consists of percutaneous coronary interventions, pharmaceutical thrombolytic therapy, and coronary artery bypass grafting. These interventions are all focused on swiftly restoring coronary circulation and preventing further tissue damage. However, this approach fails to foster longer-term regeneration of the recently damaged tissue, and complications in the years following a myocardial infarction still constitute a major source of mortality for these patients. [2].

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Mortality after MI highlights the pressing need for treatment modalities that can promote cardiac regeneration and approximate or completely restore pre-MI cardiac function.

Stem cell-based therapies including mesenchymal stem cells (MSCs), cardiac stem cells (CSCs), induced pluripotent stem cells (iPSCs) and bone marrow derived mononuclear cells (BMMCs) have been at the forefront of regenerative medicine in the treatment of many diseases [3] and have an acceptable safety profile, but their efficacy in cardiac regeneration is a topic of heated debate as cardiac cells are fully differentiated and upon damage are replaced by fibroblasts. Introduced stem cells, on the other hand, have the ability to differentiate into new cardiomyocytes [4] and can induce paracrine signaling pathways, angiogenesis, and immunomodulation. [5, 6]. Clinical and preclinical studies have demonstrated the safety of stem cells in addition to increases in left ventricular ejection fraction (LVEF) and reductions in scar tissue proliferation of infarct areas, although some studies have yet to be reproduced likely due to difficulty with lack of stem cell retainment and survival. [7].

Herein, this paper elaborates on the use of various stem cell therapies to induce cardiac regeneration and repair after the damage caused by MIs. There are many newly elucidated strategies that can help address the current issues with stem cells in regenerative cardiology such as extracellular vesicles, hydrogels, and special patches to allow stem cells to adhere to [8]. These methods, even if currently not particularly effective, still hold significant potential and will likely eventually be used in the definitive treatment of tissue damage after MI. This article will provide a framework for future research in stem cell therapies and highlight the current progress in the field.

2. Literature Review Methodology

A PubMed search was conducted to find articles relevant to the current landscape of stem cell therapy for post-myocardial infarction recovery using the following query: ((("myocardial infarction"[All Fields]) AND ("stem cells"[All Fields])) OR ("cardiac stem cells"[All Fields])) AND ("myocardial infarction"[All Fields]), applying filters for various study types, including clinical trials, comparative studies, experimental studies, and validation studies. The first 100 articles were screened and were selected based on relevance and content.

Based on findings in the selected articles, additional PubMed searches were conducted to explore future directions. The following queries were used: ("CRISPR" OR "gene editing") AND ("stem cells" OR "iPSCs") AND ("cardiac repair" OR "myocardial infarction"), as well as ("3D bioprinting" OR "bioprinted cardiac patches") AND ("stem cells" OR "myocardial infarction"). Relevant articles were screened and selected for their potential contributions to advancing myocardial infarction treatment strategies.

3. Types of Stem Cells Currently Researched for MI Recovery

The types of stem cells that have been widely researched for MI recovery therapy are varied. Many studies focus on investigation of obvious stem cell candidates for myocardium regeneration such as Cardiac Stem Cells (CSCs) [9, 10, 11], as well as the widely studied Mesenchymal Stem Cells (MSCs) [12, 13, 14, 15, 16] and Bone Marrow-derived Mononuclear Cells (BMMCs) [14, 17, 18, 19, 20, 21]. Fewer studies focus on other stem cell types, ranging from Induced Pluripotent Stem Cells (iPSCs) [22] and Adipose-derived Stem Cells (ASCs) [23], to Cortical Bone-derived Stem Cells (CBSCs) [24], Hematopoietic Stem Cells (HSCs) [13] and other progenitor cells.

Among these stem cell types, distinction is also made between the genetic origins of the cells, with the two clinical and preclinical classifications generally being autologous or allogeneic origin. Autologous stem cells cultured from patient/model-derived tissue generally have decreased risk of immune rejection, but face issues related to the time needed to expand ex vivo (usually resulting in an infusion time post-acute phase) and the decreased potency of stem cells with age or disease. Allogeneic stem cells, on the other hand, have the ability to be cultured and ready “off-the-shelf” for infusion in the acute or subacute phase of MI recovery and can be screened for the highest viability

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and/or potency, but run into aforementioned risks with Graft-vs-Host Disease (GVHD) and immune system inflammation [15, 16].

The exact mechanisms through which stem cells affect the repair of cardiac function and structure are unknown, though two main mechanistic routes are thought to be at play: direct cardiomyocyte differentiation and paracrine signaling [9]. While inherent challenges to stem cell engraftment in host heart tissue arise due to the non-static cardiac environment and the "washing away" of transplanted cells by blood flow, a few key stem cell lineages show enhanced ability to successfully traffic and differentiate to healthy cardiomyocytes [11, 22, 25]. As for paracrine effects, the most significant paracrine signaling pathways associated with stem cell-mediated cardiac repair involve direction of angiogenesis [11, 13, 22], as well as a reduction of fibrotic scarring.

The following sections contain a description of the most relevant types of stem/progenitor cells currently researched for cardiac repair:

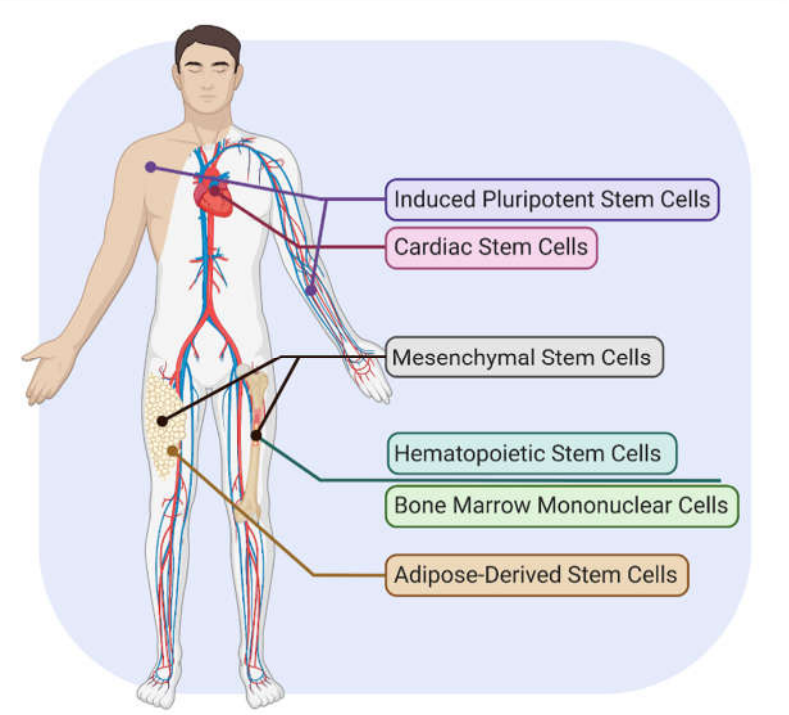

Figure 1. Overview of stem cell population origins for post-MI therapies. Created with Biorender.com.

3.1. Cardiac Stem Cells (CSCs)

Cardiac stem cells (CSCs) are a population of multipotent precursor cells (approximately 2% of total cardiac tissue) [26] within the heart that can differentiate into cardiomyocytes, endothelial cells, or smooth muscle cells. CSCs direct cardiogenesis during embryonic development as well as minorly contribute to cardiac repair. Due to the antiproliferative nature of the cardiac environment and their low numbers, CSCs in adult tissue are limited in their natural reparative ability.

Though not found in the heart in sufficient quantities to direct considerable repair, when isolated from heart tissue, CSC therapy involving *ex vivo* expansion can raise their numbers to an amount suitable for transplantation. Notably, due to the process by which heart tissue is isolated and prepared, autologous origins of these CSCs are not feasible, instead requiring the remains of heart transplant atria in humans [11] or minced whole donor hearts in *in vivo* models [27] for allogeneic transplantation. While this raises the potential for GVHD complications, studies investigating CSCs largely report no significant risk of Major Adverse Cardiac Events (MACE) post-transplantation [10].

Hong and colleagues' [9] exploration of c-kit+ cardiac stem cells found that only 5 minutes-post intracoronary injection in mice, less than 40% of the initially injected CSCs were present in the cardiac tissue, and 24 hours post-injection less than 6% of the initial dose were present. Despite these findings,

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MI-induced mice treated with the CSCs had significantly lower Left Ventricular Diastolic Volume (LVEDV) as well as a higher Left Ventricular Ejection Fraction (LVEF) indicating recovery towards pre-infarction heart function. This indicates that despite a lack of longevity in transplanted tissue, the paracrine effects of the CSCs significantly contribute to its ability to mediate cardiac repair.

Further exploration by Avolio and colleagues supported this mechanism, and found upregulated levels of VEGF, HGF, and FGF in CSC-transplanted murine models post-MI [11]. Interestingly, the study also indicated that a combinatorial treatment alongside Saphenous Vein-Derived Pericytes (SVPs) bolstered the treatments' overall efficacy, indicating possible synergistic modalities between CSCs and other progenitor/stem cells that future research could investigate.

3.2. Mesenchymal Stem Cells (MSCs)

By far one of the most heavily researched classifications of stem cells, Mesenchymal Stem Cells (MSCs) are multipotent stromal stem cells that can be isolated from a variety of tissues, including bone marrow, adipose tissue, and umbilical cord tissue [28]. MSCs also have the ability to differentiate into a wide range of lineages, ranging from chondrocytes, cardiomyocytes, and even neurons [28, 29].

Despite (or possibly due to) its differentiation abilities, MSCs' niche in myocardial repair likely lies more within its paracrine signaling abilities and/or ability to recruit endogenous stem cells for repair rather than direct MSC-to-cardiomyocyte differentiation [12]. Studies have implicated it in repair mechanisms independent of $CD34^+$ and $CD45^+$ markers, suggesting a more paracrine mode of action associated via decreased collagen deposition and angiogenesis [13]

Given their ubiquity throughout the body and persistence *ex vivo*, both autologous and allogeneic MSCs have been investigated for MI recovery and have similar levels of efficacy. Whether allogeneic or autologous, studies investigating their role in post-MI recovery indicated good safety outcomes [16], though it should be noted that MSCs do have an established tumorigenic risk [30].

3.3. Bone Marrow Mononuclear Cells (BMMCs)

Not technically a homogenous stem cell population, Bone Marrow Mononuclear Cells (BMMCs) are a population of progenitor/multipotent stem cells found in bone marrow. Its population broadly includes Hematopoietic Stem Cells (HSCs), Endothelial Progenitor Cells (EPCs), and Mesenchymal Stem Cells (MSCs) [31], among others. Despite being an amalgam of progenitor cells and not a unique stem cell type, it is one of the most studied types of cell treatment/therapy and thus warrants its own discussion.

Because of its varied cellular makeup, BMMCs exhibit a broad differentiation potential. They exhibit the ability to differentiate into all the lineages available to their constituent cells. Beyond this, they have some of the quickest turnaround times due to a lack of a need for significant *ex vivo* culturing, offering the rare possibility for autologous acute post-MI treatment [31].

Interestingly, and possibly due to its makeup being "dilute" with non-relevant progenitor cells, most studies which focused on functional markers of post-MI BMMC therapy found insignificant, if any, improvement in key markers such as LVEF, LVEDV, or LVESV, though it is important to mention a significant absence of MACE and other risk factors [17, 19, 20]. Despite this, BMMCs remain a promising candidate for stem cell therapy for MI recovery, as other studies indicate a synergistic effect of BMMCs in conjunction with homogenous stem cell populations such as MSCs [14] or when paired with Coronary Artery Bypass Grafts (CABGs) [21].

3.4. Induced Pluripotent Stem Cells (iPSCs)

Induced Pluripotent Stem Cells (iPSCs) are adult somatic cells that have been engineered back to an embryonic pluripotent state via forced gene expression and factor expression. They can be isolated from virtually any differentiated adult somatic tissue, though the most common sources are skin-derived fibroblasts or peripheral blood [32].

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Given their pluripotent nature, they are able to differentiate into all cellular lineages and hold the highest differentiative potential of any stem cell alongside Embryonic Stem Cells (ESCs). Their ability to minimize donor-specific variability also makes them promising for both autologous and allogeneic therapeutic applications [33].

However, the very pluripotency that makes iPSCs advantageous also presents challenges, notably the risk of teratoma formation following transplantation [33]. As such, utilization of iPSCs as a starting population for differentiation into CSCs or MSCs before transplantation has been proposed to maximize the benefits while minimizing risk.

Within the context of cardiac repair post-MI, iPSCs have shown unique advantages in preclinical settings. Yang and colleagues' transcriptome analysis of iPSC culturing in both a 2D and 3D environment clearly demonstrated successful differentiation into cardiomyocytes, as well as expression of paracrine signals to direct angiogenesis and recovery [22]. Should tumorigenic risk be mitigated, these preliminary studies indicate that iPSCs might be a strong candidate for a homogenous stem cell population therapeutic approach with the broadest potential effects.

3.5. Hematopoietic Stem Cells (HSCs)

Hematopoietic Stem Cells (HSCs) are a type of stem cell derived primarily from bone marrow and peripheral blood, which display multipotency in all blood lineages [34].

Hematopoietic stem cells (HSCs) can be safely obtained from both allogeneic and autologous sources, with annual therapeutic transplants being roughly evenly divided between the two origins (47% and 53% respectively) [34].

Due to their hematopoietic lineage commitment, while HSCs do not exhibit direct cardiomyocyte differentiation capability, preclinical data indicates that their overarching paracrine effects on the heart are considerable. Shalaby and colleagues' study in murine MI models found significant histopathological recovery associated with HSC treatment as indicated by decreased collagen deposition and improved cardiac tissue architecture, as well as a significant upregulation in key paracrine signaling markers. Furthermore, infarct size reduction was even greater with HSC therapy compared to MSC treatment [13].

3.6. Adipose-Derived Stem Cells (ASCs)

Adipose-derived stem cells (ASCs) are a subset of mesenchymal stem cells (MSCs) obtained from adipose tissue. Like other MSCs, they exhibit multipotency and can differentiate into various cell types, including osteogenic, chondrogenic, and adipogenic lineages. ASCs share many functional similarities with bone marrow-derived MSCs (BM-MSCs) but offer the advantage of being more readily accessible and available in higher quantities from fat tissue. While their regenerative potential and paracrine signaling effects largely overlap with other MSC populations, some studies suggest ASCs may have distinct immunomodulatory properties, making them a promising candidate for cell-based therapies [35].

Additionally, early studies on ASCs for MI recovery therapy have shown promising results in animal models, suggesting that their therapeutic potential is at least comparable to MSCs derived from other tissues [23].

3.7. Other Stem Cell Types

Other translationally relevant stem cell types within the current body of knowledge are Multilineage-Differentiation Stress-Enduring Cells (Muse Cells) and Cortical Bone-Derived Stem Cells (CBSCs).

Additionally, while Embryonic Stem Cells (ESCs) exist as a therapeutic avenue and have shown some preclinical promise, due to the ethical concerns regarding obtaining the cells, have not been investigated thoroughly or clinically [36].

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Muse Cells are endogenous pluripotent stem cells present in various tissues such as bone marrow. As opposed to iPSCs which must be artificially engineered to be pluripotent, Muse cells exist endogenously and exhibit similar pluripotency. Key preclinical studies implicated their ability for increased engraftment ability, immunomodulation, and angiogenesis at the level of or above that of traditional MSC or BMMC treatments [25]. However, clinical relevance is still unknown, and autologous therapeutic approaches are limited due to a long isolation and culturing timeline.

CBSCs are a novel somatic stem cell that in some preliminary *in vivo* and *in vitro* studies, has been implicated in cardiac repair and remodeling. They are derived from the cortical bone of donors prior to culturing, expansion, and transplantation [37]. Though exhibiting similar cell morphology to MSCs, CBSCs are unique in their WFA-binding glycan expression profile, evading glycan alterations that reduce differentiation abilities [24]. Moreover, the initial research indicates an immunomodulatory effect that reduces inflammation via promotion of regulatory T-Cells (Tregs).

A summary of the relevant stem cell types and important characteristics are listed in **table 1**.

Table 1. Summary of clinical and therapeutic characteristics of different stem cell types.

Stem Cell Type	Common Cell Origin	Possible Lineages	Therapeutic Concerns	Reference(s)
Cardiac Stem Cells (CSCs)	Heart tissue	Cardiomyogenic, Endothelial, Smooth Muscle	Potential for GVHD (allogeneic use), low engraftment	[9, 10, 11, 26, 27]
Mesenchymal Stem Cells (MSCs)	Bone marrow, adipose tissue, umbilical cord	Osteogenic, Chondrogenic, Adipogenic, Myogenic, Tenogenic, Neurogenic	Tumorigenic risk	[12, 13, 16, 27, 29, 30]
Bone Marrow Mononuclear Cells (BMMCs)	Bone marrow	Hematopoietic, Endothelial, Mesenchymal	Limited efficacy alone	[14, 17, 19, 20, 21, 31]
Induced Pluripotent Stem Cells (iPSCs)	Skin-derived fibroblasts, peripheral blood	Ectodermal, Mesodermal, Endodermal	Teratoma formation risk	[22, 32, 33]
Hematopoietic Stem Cells (HSCs)	Bone marrow	Myeloid, Lymphoid	Low engraftment	[13, 34]
Adipose-Derived Stem Cells (ASCs)	Adipose tissue	Osteogenic, Chondrogenic, Adipogenic, Myogenic, Neurogenic, Angiogenic.	Tumorigenic risk	[23, 35]
Muse Cells	Various tissues (bone marrow, etc.)	Mesodermal, Endodermal, Ectodermal	Limited clinical relevance, long isolation time	[25]
Cortical Bone-Derived Stem Cells (CBSCs)	Cortical bone	Osteogenic, Chondrogenic, Adipogenic, Angiogenics	Limited established research	[24, 37]
Embryonic Stem Cells (ESCs)	Embryos	Ectodermal, Mesodermal, Endodermal	Ethical concerns	[36]

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4. Role of Stem Cells in Cardiac Regeneration Post-Myocardial Infarction

MI is a major problem in the United States and other countries worldwide. Dealing with MI exhausts a lot of resources resulting in financial and logistical issues in the healthcare industry [38]. MI results in the death of cardiac myocytes and scar formation in the areas where myocyte death occurred [24]. With the emergence of stem cell therapy in the treatment of MI, they can contribute to cardiac regeneration by angiogenesis and paracrine signaling with extracellular vesicles (EVs) having a critical role in analyzing their treatment efficacy.

4.1. Restoration and Angiogenesis

Stem cell therapy holds great potential for cardiac regeneration, and restoration of cardiac tissue through angiogenesis is a key mechanism through which stem cells promote their regenerative effects. Angiogenesis is the proliferation of blood vessels from pre-existing vessels and is crucial to increasing blood flow, especially to ischemic tissue which needs more blood flow to survive. Neoangiogenesis, a specific type of angiogenesis, can improve the effectiveness of coronary circulation and can be triggered by myocardial infarction (MI), thereby reducing cardiomyocyte death and limiting the formation of non-contractile scar tissue [39]. MSC differentiation to cells such as myocytes, endothelial cells, and more could be a key contributor to angiogenesis. The induction of angiogenesis has been theorized to lead to more effective left ventricular function, a decrease in heart tissue damage, and the formation of new capillaries to help improve oxygen supply to cardiomyocytes (CMs) [16]. The main role of angiogenesis in cardiac regeneration post-MI could be the increased oxygen output to affected CMs. This could allow for the reduction in infarct size in the host heart and thereby promote better recovery of heart function. Also, studies show that an increase in angiogenesis is directly related to the reduction of myocardial damage or infarct size. Multiple types of stem cells have been shown to increase angiogenesis and the effect of angiogenesis on cardiac regeneration. Some of these stem cell types include BMMSCs, MSCs, HSCs, EPCs, iPSCs, CSCs, and more. The level of angiogenesis from each stem cell type could vary, which could mean that some stem cells are more suited for promoting restoration and angiogenesis. The way stem cells can exert angiogenesis is through secreting different proangiogenic factors. There are multiple proangiogenic factors, some of which include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), hepatocyte growth factor (HGF), IGF-1, tissue growth factor-β (TGF- β), and angiopoietin-1 [40]. Overall, angiogenesis is a key biological process important for heart restoration post-MI, and multiple factors contribute to promotion of angiogenesis that could be highlighted in future studies, such as the role of growth factors, proangiogenic factors, and different signaling pathways.

4.2. Extracellular and Paracrine Signaling

Once stem cells are implanted into the body, they exert their regenerative effects mainly through mechanisms like paracrine signaling rather than direct differentiation into new cardiac cells. Paracrine factors like chemokines, growth factors, and cytokines play a big part in heart regeneration through mechanisms such as regulating inflammatory responses, increasing the level of angiogenesis, attracting naturally present stem cells to the damaged area, and promoting cardiac cells to resume the cell cycle [41]. The paracrine hypothesis is a term used to describe paracrine effects compared to direct stem cell differentiation for stem cell therapy and their overall effectiveness on cardiac regeneration. The chemical signals that are released by implanted stem cells stimulate a multitude of regenerative mechanisms. This includes angiogenesis stimulation, lowering the level of tissue hypertrophy and apoptosis of nearby cardiac cells, extracellular matrix (ECM) remodeling, and the stimulation of CSCs [40, 41]. Paracrine factors like VEGF, IL-6, MCP-1, PGF, and the FGF family are key for angiogenesis stimulation. FGF21 and FGF23 are some of the specific genes from the FGF family that interact with receptors on CMs, playing an important role in prevention against hypertrophic remodeling and regulating cell proliferation, which are some of the mechanisms that

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contribute to cardiac damage post-MI. WNT signaling, a paracrine pathway that has shown potential in cardiac regeneration, plays an important role in the growth of the left ventricle and CM differentiation [22, 42]. TGF-β1 is another cytokine released from stem cells with a theorized strong paracrine effect once implanted. The cytokine stimulates the activation of fibroblasts, allowing them to potentially contribute to cardiac regeneration post-MI. Other paracrine factors contribute to the regeneration process by recruiting nearby cells in the host heart to the injury site, helping facilitate the repair process and potentially increasing the repair speed and efficiency [24]. Overall, paracrine signaling from stem cell therapy shows immense potential in the future to be a main contributor to cardiac regeneration.

4.3. Extracellular Vesicles (EVs) and Their Role in Cardiac Regeneration

Extracellular vesicles (EVs) are important in mediating stem-cell-based effects on cardiac regeneration and repair. EVs are cell-derived membrane vesicles that have differing diameters. They transport a variety of biomolecules such as membrane proteins, cytosolic proteins, metabolites and nucleic acids. Some of the important nucleic acids present in EVs are long RNAs that are non-coding, mRNAs, and microRNAs [43]. Based on these components present in EVs, the ones that are derived from stem cells likely have the function of gene expression regulation. There are three classifications of EVs, with the classification based on origin: apoptotic bodies that come from cells on the verge of death, microvesicles (MVs) that are formed by budding vesicles off the plasma membrane, and exosomes that are released from the endosomal pathway and multivesicular body fusion [44]. Exosomes could be the type of EV that shows the most potential in cardiac regeneration as they can come from a variety of stem cells and have a low chance of developing into harmful tumors. They also promote CM proliferation, angiogenesis, anti-inflammatory responses, lowering the infarct size, increasing stem cell activity of the native heart, reducing the level of apoptosis for local CMs, and metabolic regulation through gene expression modulation. Studies show positive effects from exosomes on cardiac function, especially those derived from CPCs, hiPSCs, and MSCs. The positive exosome effect is different for each of the stem cells mentioned. Ischemic preconditioning is also an important process that can increase the stimulation of exosome release and increase their levels in the myocardium, with the process in MSCs increasing the level of miRNAs (miR-21, miR-22, miR-199a-3p) that play a role in fibrosis and apoptosis reduction. Exosomes also show potential in CM survival and decreased inflammation after blood flow recovery. Exosomes have sustained reliability and low immune activation to the transplantation but also require multiple injections and specific cellular recognition to exert their effects on the heart. The exosomes injected may contain components other than the desired ones that may lead to unwanted effects other than cardiac regeneration [45]. Small extracellular vesicles (sEV) are also shown to play a role in cardiac repair and regeneration post-MI, with sEV derived from human embryonic stem cells (ESV) showing some of the best pro-angiogenic and scar-reducing properties. This is due to the fact that sEV from ESV are rich in fibroblast growth factor-2 (FGF-2), a molecule that promotes mitotic activity and angiogenic processes [43]. These mechanisms that EVs must contribute to cardiac regeneration further highlight the potential they have in MI treatment.

5. Methods of Delivery

Considerations for determining optimal delivery methods of stem cells include whether the patient will undergo open thoracic surgery, whether the patient will need cardiac catheterization, whether the patient has significant stenosis of coronary vessels, and whether the patient had recent myocardial infarction, which can produce homing signals for the stem cells. Another consideration would be whether there is an isolated area of interest for implanting the stem cells or specific coronary artery or venous territory, or whether the stem cells need to be directed towards multiple areas of interest.

Stem cell delivery method is important because it affects the retention rate of the stem cells, stem cell survival, stem cell integration into the host, and stem cell functionality.

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Several methods have been tried for the delivery of stem cells to myocardium. Each of them has their own advantages and disadvantages. These routes include:

5.1. Direct Intramyocardial Injection

In this method, the injection location is identified using nuclear imaging and echocardiography [46, 47]. Stem cells are then directly injected into the infarcted region of the heart during thoracotomy for open heart surgeries like coronary artery bypass graft [48] or as independent procedures, such as lateral mini thoracotomies [49].

The advantages of direct intramyocardial injection include higher cell retention and engraftment within the infarcted area. It targets the affected myocardium. Does not need mobilization and homing of the stem cells to the area of interest. This method has been shown to significantly improve left ventricular ejection fraction and improved cardiac dysfunction [14, 48, 50].

The key disadvantages are that it is a highly invasive procedure, requires a surgical approach which can be associated with higher procedural risks and complications, including arrhythmias, myocardial perforation and systemic embolization [47, 51, 52]. In addition, it is limited to specific areas of the myocardium and can potentially miss other affected regions. Also, this method has a prolonged recovery period and is not suitable for repeated use of the same individual. Implanted cells can also be lost from the site of injection [53].

5.2. Intravenous Infusion

This method is mainly used following acute myocardial infarction because the results depend on homing signals to include myocardium [54].

The advantages are that it is minimally invasive and easier to administer compared to direct myocardial injections. In cases of multiple infarcts, this method allows for targeting of multiple areas.

The disadvantages are the cells are often trapped in the lungs [55], leading to low delivery efficiency, low retention in the myocardium [56] and reduced therapeutic efficacy. This method shows less improvement in left ventricular ejection fraction compared to direct myocardial injection.

5.3. Intracoronary Infusion

This is done using standard balloon coronary catheterization catheters and can deliver stem cells through specific arteries of the coronary system [57]. The coronary catheter is used to cannulate the coronary artery of interest typically through a transfemoral approach. The stem cells are then injected and balloon occlusion done to minimize the cells from entering the systemic solution (stop flow conditions, [58] or injected with ongoing coronary blood flow (continuous flow conditions, [59]. Studies have shown improvement in left ventricular function, reduction in ventricular remodeling, reduction in infarct size, and improvement in clinical outcomes as well as quality of life [60, 61, 62].

The advantages are that stem cells can be directly infused into the area of interest and better cell retention in the myocardium compared to intravenous infusion. Also, this can be performed during routine cardiac catheterization procedures, which all interventional cardiologists are familiar with. It is also widely available. [62].

The disadvantages are that there is a potential for coronary artery damage, microvascular obstruction and embolization [63, 64], which limits the size and dose of stem cells delivered using this procedure [65]. It is difficult to deliver stem cells to areas that are not perfused well. Cell survival can also be affected by hypoxia and nutrient deprived conditions in the affected myocardium. Also, the stem cells can undergo myocardial trapping and redistribution in the pulmonary vasculature [66].

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5.4. Intramyocardial Administration Using Catheters

This method avoids dealing with obstructed coronary arteries and is therefore more commonly used in congestive heart failure secondary to ischemic heart disease. However, intramyocardial administration is associated with higher risk of ventricular arrhythmias than other delivery methods. There are two approaches, trans endocardial injection and trans coronary venous injection.

5.4.1. Intramyocardial Trans Endocardial Injection:

This technique was first used by Fuchs and colleagues in a swine model and showed improvement in cardiac function [67]. This process involves direct delivery of stem cells through catheter-based electromechanical mapping [67, 68]. Following the electromechanical mapping, the stem cells are injected into the border zone between necrotic and healthy endocardium [64, 67].

The advantages are that this method has demonstrated significant improvement in left ventricle ejection fraction and infarct size reduction in both clinical and preclinical studies [67, 68]. This method allows for precise delivery of cells to the infarcted area. There are also few significant adverse complications. This method has high efficacy in improving cardiac function and cell retention.

The disadvantages with this method are that specialized equipment and expertise is required. There are also procedural risks, including myocardial perforation, arrhythmias and inflammatory responses [69, 70].

5.4.2. Intramyocardial Trans Coronary venous Injection

This was first performed by Thompson and colleagues using intravascular ultrasound imaging in a swine model [71]. In this approach, the coronary veins are directly accessed, and the stem cells are injected

Advantages are that it allows for homogeneous distribution across the myocardium and increased retention of stem cells [72]. It is a minimally invasive procedure and can be performed percutaneously [71]. It allows for targeted delivery to specific areas of the myocardium [71, 73].

Disadvantages are that there is more variability in the coronary venous system and there may be difficulty in stem cell delivery to the correct coronary territory. The disadvantages also include arrhythmogenicity, inflammatory response, mechanical loss of the cells and pulmonary redistribution [69, 70].

5.5. Retrograde Coronary Venous Delivery System

In this method, stem cells are delivered to the area of interest by advancing a catheter through the coronary sinus. In this method, the catheter is passed through the femoral vein into the right atrium, followed by cannulation of the coronary sinus. The cardiac veins are accessed, stem cells injected, and balloon occlusion performed to prevent the stem cells from accessing the systemic circulation. [74].

Advantages are that it is beneficial in cases of coronary artery obstructions and in patients who are not good candidates for coronary artery bypass graft [74, 75]. There is also lower risk of coronary embolism compared to intracoronary injection. In a study where this technique was used for withdrawal infusion for ablation of refractory ventricular tachycardia, no complications related to coronary embolism were reported [76].

The disadvantages are that it may be difficult to navigate the venous system because of tortuosity. [77].There is also risk of damage to the coronary sinus, which can be difficult to repair [78].

6. Summary of Clinical and Preclinical Trials

Among the various stem cell therapies for myocardial infarction (MI) mesenchymal stem cells (MSCs) and autologous cardiosphere-derived cells (CDCs) showed the most promise. Intracoronary (IC) infusion of MSCs post-percutaneous coronary intervention increased LVEF by 8.8% at four months after injection, while the control increased LVEF by 4.8% (P = 0.031) [79]. A booster dose of

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Wharton's Jelly Mesenchymal Stromal Cells (WJ-MSCs improved LVEF function by 7.45%, while a single dose increased LVEF by 4.54% [13].

Additionally, IC CDC infusion significantly reduced scar size (−11.1%) and increased viable myocardium (22.6%) in the one year follow-up [80]. BM-MNCs delivered through graft vessels during Coronary Artery Bypass Grafting (CABG) enhanced left atrium function compared to sole usage of CABG [81]. Overall, there were no significant safety concerns or adverse events associated with the stem cell injections.

An overview of the key clinical and preclinical trials are listed in **table 2**

Table 2. Stem Cell Therapies for Cardiac Repair: Study Designs, Delivery Methods, and Outcomes.

Type of Stem Cell	Study Type	Delivery Route/Method	Dosage	Results	Reference
Wharton's Jelly Mesenchymal Stromal Cell (WJ-MSC)	Clinical, Single-blind, Randomized, Multicenter Trial	Intracoronary injection (once vs. twice)	Single dose 10^7 WJ-MSCs, Single (10^7) + Booster dose (10^7) = 20^7 cells	Baseline LVEF: 40% in all groups. Single MSC increased LVEF by 4.54±2% (one dose), Booster dose increased by 7.45±2% (P<0.001). Echocardiography: 6.71±2.4% (one dose), 10.71±2.5% (booster).	[38]
Bone Marrow Mononuclear Cell (BM-MNC)	Clinical, Phase 3 Randomized Trial (3-Year Follow-Up)	Intracoronary infusion	Single dose of 10^7 cells	Trial incomplete; expected outcome: evaluate prevention of HF post-AMI	[82]
Autologous Cardiosphere-Derived Cells (CDCs)	Clinical, Double-Blind, Placebo-Controlled Trial	Intracoronary (IC) injection	2.5×10^7 cells	IC infusion of CDCs (CAP-1002) was safe and feasible. No significant reduction in scar size at 6 or 12 months. LVEDV and LVESV reduced at 6 months, NT-proBNP decreased.	[83]
Bone Marrow-Derived Cells (BMCs) Autologous	Clinical, Randomized Controlled Trial (85 Patients, AMI)	Intracoronary infusion into infarct-related artery	19.8 x 10^7 cells	MACE incidence: BMCs (26.1%), Placebo (18%). No mortality, no significant difference in MI or revascularization between groups.	[80]
Bone Marrow Mesenchymal Stem Cells (BM-MSCs)	Clinical, Randomized, Single-Blind, Multicenter, Controlled Trial	Intracoronary infusion 15 days after PCI	3.31×10^6 cells	IC BM-MSCs did not improve LV function or myocardial viability at 12-month follow-up. Safe, no toxic events.	[84]
Bone Marrow Mesenchymal Stem Cells (BM-MSCs)	Clinical, Randomized, Open-Label, Multicenter Trial	Intracoronary administration into infarct-related artery (IRA) at one month	7.2×10^7 cells	LVEF by SPECT at 6 months: BM-MSC group (5.9%±8.5%) vs. Control (1.6%±7.0%, P=0.037). No significant LVEDV or LVESV differences.	[85]

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Bone Marrow Mesenchymal Stem Cells (BM-MSCs)	Clinical, Randomized, Single-Blind Trial	Intracoronary infusion 1 month post-PCI	7.2 × 10^7 cells	LVEF increased by 8.8±2.9% (BM-MSC) vs. 4.8±1.9% (control) at 4 months (P=0.031). No increased adverse events. Echocardiography showed sustained improvement at 12 months.	[42]
Allogeneic Human Cardiac Stem Cells (AlloCSC-01)	Clinical, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial	Intracoronary infusion at days 5-7 post-STEMI	3.5×10^7 cells	No deaths or MACE at 12 months. Infarct size reduction: -2.3% (95% CI, -6.5% to 1.9%). No differences in ventricular remodeling. Low immunogenicity.	[10]
Bone Marrow-Derived Progenitor Cells (BMCs)	Clinical, Randomized, Multicenter, Placebo-Controlled Trial	Intracoronary infusion post-STEMI	2.0 × 10^7 - 2.5 × 10^7 cells	At 12 months, BMC treatment effect on EF was 2.8% (P=0.26). In patients with EF ≤ 48.9%, BMCs improved EF (+6.6%, P=0.01), reduced EDV increase (P=0.02), and prevented ESV increase (P=0.01).	[79]
Mesenchymal Stem Cells (MSCs) vs. CD34+ Cells	Preclinical, Rat Model	Intravenous injection	2×10^6 cells	CD34+ cells showed superior efficacy over MSCs in infarct size reduction and angiogenesis markers (VEGF, VEGFR-2, Ang-1, Tie-2 upregulation). Both cell types improved myocardial tissue structure, but CD34+ had significantly better outcomes.	[86]
Mesenchymal Stem Cells (MSCs) vs. Bone Marrow Mononuclear Cells (BMMNC)	Preclinical, Porcine Model	Trans endocardial injection	10^7 autologous MSCs or BMMNCs	MSCs improved LVEF significantly over BMMNCs at 4 weeks post-injection. BMMNCs showed no significant LVEF improvement.	[87]
Mesenchymal Stem Cells (MSCs)	Preclinical, mouse model	Intracoronary infusion,	1.0 × 10^5 cells	Cardiac Stem Cell Hybrids Enhance Myocardial Repair. CCs improved left ventricular anterior wall thickness and increased capillary density.	[88]
Autologous Cardiosphere-Derived Cells (CDCs)	Clinical, Randomized, Controlled Trial	Intracoronary infusion	12.5 to 25 × 10^6 cells	CDC therapy led to reduced scar size, increased viable myocardium, and improved regional function at 1-year follow-up. No	[89]

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				significant safety concerns observed.	
Bone Marrow Mononuclear Cells (BMMNC)	Clinical, Randomized, Controlled Trial	Delivery through graft vessel during CABG	13.28 × 10^7 cells	CABG + BM MNC improved LA function more than CABG alone. LAGS, LVEF, and LAV significantly improved postoperatively. 2D strain imaging was a sensitive tool for LA function evaluation.	[90]
Mesenchymal Stem Cells (MSCs) (Autologous Bone Marrow-Derived Ex Vivo Expanded Mesenchymal Stem Cells)	Clinical, Randomized, Controlled Trial	Intramyocardial Injection	31 × 10^6 cells	Intramyocardial MSC injection in AMI patients was feasible and safe for up to 5-year follow-up. LV function improved, no significant differences compared to controls in event-free survival	[91]

7. Limitations in Cell Survival and Retention

Only a very small fraction, around 1% or less of transplanted stem cells survive long-term after transplantation. Ischemia, inflammation, and mechanical washout by the myocardium are the largest contributing factors to the substantial cell loss [16, 6]. Intracoronary or intravenous cell infusions have been known to suffer from rapid washout, which limits effective cell engraftment. Novel strategies such as direct intramyocardial injections, along with the usage of injectable hydrogels and epicardial patches have been developed to improve acute cell retention by creating a supportive extracellular matrix environment [41, 36]. Injectable hydrogels have shown up to 8-14x increased retention, while epicardial patches have shown up to 47-59x increased retention, compared to saline controls [41]. Due to difficulties trying to achieve high survival rates for implanted cells, multiple studies have advocated for the usage of cell derived exosomes (sEVs) as an alternative treatment option. Such vesicles can carry reparative signals, and avoid issues associated with cell viability [43].

7.1. Tumorigenicity Risks

Therapies that particularly involve pluripotent stem cells, such as ESCs and iPSCs pose inherent risks of uncontrolled cell proliferation and teratoma formation if undifferentiated cells are transplanted into unintended regions [92]. Even when properly transplanted towards a cardiac lineage, the presence of immature or incompletely differentiated cells may lead to arrhythmias or neoplastic lesions. Autologous BM-MSCs possess a lower risk of tumorigenicity because they are lineage-restricted, and that they possess a lower likelihood of forming teratomas. However, extensive in-vitro expansion may alter their phenotype, and potentially raise risks [93]. Usage of cell-derived exosomes are highlighted as a promising alternative to circumvent tumorigenic risks due to the fact that they are non-replicative, as they do not possess the appropriate cellular framework necessary for uncontrolled cell growth [43, 94]. Advances in gene editing, such as techniques like CRISPR/Cas9 in hPSC-derived cardiomyocytes can help reduce residual pluripotency and off-target mutations, hence lowering tumorigenic potential [95].

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7.2. Fibrosis and Adverse Remodeling

Following myocardial infarction, the loss of cardiomyocytes is replaced with fibrotic scar tissue, which leads to adverse ventricular remodeling and impaired function [93]. BM-MSCs and other stem cell therapies rely on paracrine signaling, as they secrete cytokines and growth factors such as VEGF and adrenomedullin that potentially mitigate fibrosis, and promote angiogenesis [96, 41]. In clinical settings, improvements in terms of reducing fibrotic scar or adverse remodeling have been modest at best [41]. Cardiac patches engineered from stem cells or biomaterials are currently being explored to provide structural support and reduce fibrosis by promoting increased cell-survival and organized tissue regeneration [93, 97]. ESC-derived exosomes demonstrate potent anti-fibrotic effects in-vitro, reducing markers such as collagen and α-SMA, and also in-vivo, by promoting angiogenesis and hence counteracting adverse remodeling. Though improvements in surrogate endpoints, such as LVEF (ex. 48-57% at 12 months) have been noted in certain trials, many studies have not yet demonstrated clear, consistent, and sustained reductions in adverse remodeling, measured by LVEDV, LVESV, and infarct size changes, highlighting the need for further research into cell therapy protocols [16].

8. Future Stem Cell Technologies/ Treatments

8.1. Gene Editing

The convergence of gene editing with stem cell technology has opened new avenues for cardiac regeneration. The following will be specific research directions and evaluation of the most viable approaches for stem cell therapy in cardiac applications.

Combining different stem cell types to create cardiac stem cell hybrids is an emerging strategy aimed at harnessing the complementary properties of each cell type to enhance myocardial repair. With Mesenchymal Stem Cells (MSCs) and Cardiomyocytes, hybrid constructs combining MSCs with cardiomyocytes have been developed to provide structural support and promote functional integration into the host tissue. With Endothelial Progenitor Cells (EPCs) and Cardiomyocytes, Co-culturing EPCs with cardiomyocytes can enhance vascularization of the engineered tissue, improving oxygen and nutrient delivery post-transplantation [95].

8.2. Small Extracellular Vesicles

Extracellular vesicles, particularly sEVs, emerge as mediators of intercellular communication. sEVs derived from iPSCs carry bioactive molecules such as proteins, lipids, and RNAs that can modulate recipient cell behavior. iPSC-derived sEVs have demonstrated potential in promoting cardiac repair by enhancing angiogenesis, reducing apoptosis, and modulating immune responses, and upregulate pro-angiogenic factors, facilitating the formation of new blood vessels in ischemic myocardial tissue. In addition, the bioactive cargo within these vesicles can inhibit cardiomyocyte apoptosis, thereby preserving cardiac function post-injury[44]. Many studies suggest that the therapeutic effects of stem cells are largely mediated by their secreted factors rather than direct differentiation into functional cardiac cells. sEVs act as carriers of bioactive molecules such as microRNAs, proteins, and lipids, which can influence recipient cell behavior and trigger regenerative responses in damaged myocardium. One major limitation of direct iPSC transplantation is the risk of teratoma formation, as iPSCs have unlimited proliferative capacity. Since sEVs are acellular vesicles, they do not carry the risk of tumor formation or uncontrolled differentiation, making them safer for clinical application. Examining the use of sEVs from iPSCs to promote cardiac repair could be a viable path due to their relative stability and comparatively easier storage to live cell [44, 94, 98].

8.3. Delivery Method

The efficacy of stem cell therapy for cardiac diseases is significantly influenced by the delivery method. Poor retention, immune rejection, and limited integration remain key challenges that

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optimized delivery methods aim to address. The harsh post-infarction environment—marked by inflammation, hypoxia, and mechanical stress—leads to significant loss of transplanted cells. Intramyocardial Injection, Intracoronary Infusion, Intravenous Administration works in specialized settings depending on the situation employed, but is limited by lack of research and specialized equipment [99, 100].

Delivery methods that improve cell engraftment and integration can significantly enhance the effectiveness of cardiac regeneration, which can be a viable direction for technology. Current market direction entails bioengineered scaffolds which support stem cell attachment, proliferation, and differentiation while providing a microenvironment that mimics native myocardium; 3D bioprinting for targeted cell placement, which enable precise cell deposition to create structured cardiac patches that enhance integration; and electrospun nanofibers as delivery vehicles, which provide a matrix that guides cell alignment and promotes electrical coupling between transplanted and native cardiomyocyte [98].

8.4. Feasibility Studies

Case studies that employ these methods demonstrate reactivity and feasibility. Mydicar exemplifies the potential of combining gene therapy with cardiac treatment. It involves delivering the SERCA2a gene to cardiomyocytes using an adeno-associated viral vector, aiming to enhance calcium handling and improve cardiac contractility. Clinical trials have demonstrated a 52% reduction in the risk of worsening heart failure among treated patients, highlighting the therapeutic potential of gene therapy in cardiac diseases. Human hepatocyte growth factor (HGF) possesses angiogenic and anti-apoptotic properties. Administering HGF plasmid DNA to ischemic cardiac tissue has shown promise in promoting angiogenesis and reducing adverse remodeling post-myocardial infarction. Clinical trials have indicated safety and potential efficacy, underscoring the viability of gene therapy approaches in cardiac regeneration [95, 101].

6. Conclusions

In this literature review, we identified that MSCs, BMMCs, CSCs, HSCs, iPSCs, and ASCs have been shown to increase paracrine signaling to straightforward acquisition. However, these therapies also face challenges such as low retention, tumorigenic risk, and immunologic complications. Among these, MSCs and CDCs demonstrate the most potential. Intramyocardial injection of MSCs is feasible and safe during five-year follow-up periods, resulting in improved LV function but showing no significant differences in event-free survival compared to controls. Likewise, CDCs administered via intracoronary infusion have also been found safe and feasible, showing reductions in LVEDV, LVESV, and NT-proBNP at six months. However, no significant decrease in scar size was observed at either six or twelve months. Additionally, BM-MNCs delivered through graft vessels during CABG enhanced left atrial function compared to CABG alone. Nevertheless, long-term survival of transplanted stem cells remains limited, typically at around 1% or less.

To address limitations, emerging areas of research should focus on (1) combination of gene cell therapies, (2) delivery methods to deliver pro-regenerative signals without the risks associated with whole-cell transplantation, and (3) advanced gene-editing tools to mitigate tumorigenicity and improve cardiomyocyte differentiation efficiency. Further optimization in cell sourcing, delivery methods, and genetic manipulation is necessary to achieve consistent and durable clinical benefits. Continued collaborative efforts across regenerative medicine, bioengineering, and clinical research are essential to refine these therapies and advance them toward broader clinical implementation.

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Abbreviations

The following abbreviations are used in this manuscript:

MI	Myocardial Infarction
MACE	Major Adverse Cardiac Events
LVEDV	Left Ventricular End-Diastolic Volume
LVESV	Left Ventricular End-Systolic Volume
CABGs	Coronary Artery Bypass Grafts
CABG	Coronary Artery Bypass Grafting
AMI	Acute Myocardial Infarction
STEMI	ST-Elevation Myocardial Infarction
SPECT	Single Photon Emission Computed Tomography
iPSCs	Induced Pluripotent Stem Cells
ASCs	Adipose-Derived Stem Cells
MSC	Mesenchymal Stem Cell
BMMSC	Bone Marrow Mesenchymal Stem Cell
HSC	Hematopoietic Stem Cell
EPC	Endothelial Progenitor Cell
CSC	Cardiac Stem Cell
ESCs	Embryonic Stem Cells
WJ-MSCs	Wharton's Jelly Mesenchymal Stromal Cells
CM	Cardiomyocyte
CPC	Cardiac Progenitor Cell
CDCs	Cardiosphere-Derived Cells
EVs	Extracellular Vesicles
MVs	Microvesicles
ESV	Embryonic Stem Cell-Derived Vesicles
sEV	Small Extracellular Vesicle
BMMCs	Bone Marrow-Derived Mononuclear Cells
BM-MNCs	Bone Marrow Mononuclear Cells
BMCs	Bone Marrow Cells
GVHD	Graft-versus-Host Disease
Muse Cells	Multilineage-Differentiation Stress-Enduring Cells
SVPs	Saphenous Vein-Derived Pericytes
ECM	Extracellular Matrix
HGF	Hepatocyte Growth Factor
hiPSC	Human Induced Pluripotent Stem Cell

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