Vascular Pharmacology 159 (2025) 107491

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Clinical translation of mesenchymal stem cells in ischemic heart failure: Challenges and future perspectives

Anqi Guan [a], Lisa Alibrandi [b], Elika Verma [a], Niketa Sareen [a], Qingdong Guan [c], Vincenzo Lionetti [b,d], Sanjiv Dhingra [a,*]

[a] Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Department of Physiology and Pathophysiology, Max Rady College of Medicine, Rady Faculty of Health Sciences, Biomedical Engineering Program, University of Manitoba, Winnipeg, Manitoba R2H 2A6, Canada
[b] TrancriLab, Laboratory of Basic and Applied Medical Sciences, Interdisciplinary Research Center "Health Science", Scuola Superiore Sant'Anna, Pisa, Italy.
[c] Manitoba Blood and Marrow Transplant Program, CancerCare Manitoba; Department of Immunology and Internal Medicina, University of Manitoba, Winnipeg, Canada.
[d] UOSVD Anesthesiology and Intensive Care, Fondazione Toscana G. Monasterio, Pisa, Italy

ARTICLE INFO

Keywords:
Mesenchymal stem cells
Heart failure
Ischemia
Myocardial infarction
Vascular pharmacology

ABSTRACT

Myocardial infarction (MI) with resulting congestive heart failure is one of the leading causes of death worldwide. Current therapies for treating MI, such as devices, traditional medicine, and surgeries, come with many limitations as patients in their final stages of heart failure have little chances of experiencing any reversible changes. In recent decades, Mesenchymal stem cell (MSC) based therapy has become one of the most popular and rapidly developing fields in treating MI. Their supremacy for clinical applications is partially due to their unique properties and encouraging pre-clinical outcomes in various animal disease models. However, the majority of clinical trials registered for MSC therapy for diverse human diseases, including MI, have fallen short of expectations. This review intends to discuss the recent advances in the clinical application of using MSCs for cardiac repair and discuss challenges facing the clinical translation of MSCs for cardiac regeneration such as restoration of endothelial-cardiomyocyte crosstalk, immunomodulation and immune rejection, poor homing and migration, as well as low retention and survival. Furthermore, we will discuss recent strategies being investigated to help overcome some of these challenges.

1. Introduction

Ischemic heart disease (IHD) is a life-threatening cardiac condition characterized by lowered blood and oxygen supply to the heart. Ischemic heart disease is a primary factor of cardiovascular diseases (CVD) and can lead to conditions like myocardial infarction (MI) and heart failure (HF) [1–3]. The life expectancy of patients with heart failure (HF) is low, with less than 50 % of patients surviving more than 5 years [4,5]. Myocardial infarction with resulting congestive heart failure is a primary cause of death worldwide [6–8]. Heart failure is particularly common and contributes significantly to the disease burden in industrialized first world countries, affecting between 3 and 5 % of the population, and has high diagnostic costs [9,10]. Furthermore, many therapies for treating MI, such as devices, medicine, blood replenishments, and surgeries show little remedial effects [9–11]. For instance, these therapies do not have the ability to induce regeneration and cannot restore the histological architecture of damaged cells [11]. As a result, these therapies come with many limitations as patients in their final stages of HF have little chances of experiencing any reversible changes [12].

Stem cell-based therapy which became popular in the late 1900s is being promoted as a promising field in regenerative medicine to help treat incurable diseases, including the reparation of cardiac damage after MI [13–15,16]. Following an ischemic injury, the heart has a very limited capacity to self-regenerate, hence, tissue regeneration using stem cell therapy is an actively investigated area of research [17]. Mesenchymal stem cells (MSCs) are viewed as a breakthrough therapy to help replenish lost cardiomyocytes, and are considered to be one of the

* Corresponding author at: Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Department of Physiology and Pathophysiology, Rady Faculty of Health Sciences, Max Rady College of Medicine, Biomedical Engineering Program, University of Manitoba, R-3028-2, 351 Tache Avenue, Winnipeg R2H2A6, Canada.
E-mail address: sdhingra@sbrc.ca (S. Dhingra).

https://doi.org/10.1016/j.vph.2025.107491
Received 15 December 2024; Received in revised form 12 March 2025; Accepted 17 March 2025
Available online 18 March 2025

most promising types of stem cells for tissue engineering, prevention, and treatment of different conditions [18]. These cells have remarkable clinical value and have been employed in many therapeutic applications, including cardiovascular diseases [19], and are now one of the most widely studied cell types for treating ischemic heart failure [20]. The success of MSCs in cardiac diseases has been a major intensity of research [21]. MSCs are recognized for their role in helping prevent inflammation and tissue damage, and function as an immunomodulator [22]. Additionally, they can regulate inflammatory responses by triggering anti-inflammatory subsets and through suppressing white blood cells [12]. Mesenchymal stem cell-based therapy can be used for fostering the expression of growth factors which supports the regeneration of the vascular network to help reconnect blood supply to affected tissues [22]. The vascular regeneration process is particularly important for restoring the endothelial-cardiomyocyte crosstalk, which is crucial for myocardial homeostasis but is disrupted in HF [23,24]. In a healthy heart, endothelial cells and cardiomyocytes communicate through the two-way release of paracrine factors, such as nitric oxide (NO) and neuregulin-1, ensuring the coordination of angiogenesis, metabolism, and contractility. In a failing heart, the endothelial cell-cardiomyocyte crosstalk is impaired, leading to endothelial dysfunction, cardiomyocyte apoptosis, interstitial fibrosis, and further deterioration of cardiac function. Mesenchymal stem cell-based therapies have demonstrated the potential to restore the endothelial-cardiomyocyte communication mainly through the secretion of factors like vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1) and extracellular vesicles, which stimulate endothelial cell proliferation, sprouting and tube formation while also promoting cardiomyocyte survival [22].

However, despite the rapid advancements in MSC therapy, significant obstacles remain that must be overcome to accelerate the approval and success of MSC products. Consequently, the clinical translation of MSCs in IHD/MI/HF have been disappointing and fallen short of expectations. This review will discuss the clinical application of MSCs for cardiac repair, focusing on the restoration of endothelial-cardiomyocyte crosstalk, the challenges faced in the cardiac repair process, as well as strategies to help overcome these challenges.

2. MSC characterization

MSCs were first identified from the bone marrow (BM) by Friedenstein and colleagues over 50 years ago [25]. They demonstrated that these cells were multi-potential, self-maintaining precursor cells that can differentiate into osteocytes, chondrocytes, and adipocytes in vitro [25,26]. However, the isolation and culturing of human bone marrow MSCs weren't reported until 1992 [27]. Today, they can also be isolated from many other sources such as adipose, umbilical cord, and myocardium, among many others [28,23,29]. Among these sources, BM-derived MSCs (BM-MSCs) and adipose-derived MSCs (ADSCs) are the most frequently tested and studied [30]. However it's important to note that even though MSCs have been reported to differentiate into osteoblasts, chondrocytes, and adipocytes, the cardiogenic potential of MSCs remains controversial [31,32].

MSCs, as described by The International Society for Cellular Therapy (ISCT), are a population of cells that (1) adhere to plastic in standard culture conditions; (2) expresses CD73, CD90, and CD105 and lack expression of CD34, CD45, CD14 or CD11beta, CD79alpha or CD19, and human leukocyte antigen-DR (HLA-DR) surface molecules; and (3) is able to differentiate into osteoblasts, adipocytes, and chondroblasts in vitro [15,33]. The above criteria for MSC characterization are still widely used and accepted today [34].

However, some researchers argue that these guidelines are ambiguous and can be applied to other cell types [17]. This is because MSCs possess species-specific characteristics which can vary depending on the cell source [35]. For instance, ADSCs are seen as superior to BM-MSCs in respect to their cell yield and ability to maintain proliferation [36]. The multipotentiality and self-renewability of MSCs, and their ease of isolation and expansion, has rapidly encouraged researchers to believe these cells to be promising therapeutic agents in regenerative medicine, making them a subject of intensive clinical research [37]. Although stem cells are classically defined by their self-renewal and multipotency, some researchers have challenged MSCs to be multipotent precursor cells rather than actual stem cells [15]. This may be due to MSCs isolated from different adult tissue sources expressing significantly different morphology, differentiation capacities, and gene expression.

3. Mesenchymal stem cells in cardiac repair

3.1. Clinical trials

As of 2020, over 1200 clinical trials exploring mesenchymal stem cells (MSCs) for various diseases have been registered at FDA.gov, with more than 350 of these trials having been completed. This includes, graft-versus-host disease (GvHD), Crohn's disease (CD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), myocardial infarction (MI), among others [38]. MSCs are typically delivered through intravenous infusion, catheter-based intracoronary infusion, or through intramyocardial injection in clinical trials [20]. While the current clinical successes using MSC therapies are encouraging, there are still many limitations as the predominating failures emphasize the difficulty in predicting their immunomodulatory and regenerative effects within human trials [38]. 956 patients with MI were enrolled into thirteen clinical trials, of which 468 patients received MSC infusion treatment [11,39]. These clinical trials showed MSC treatment increased left ventricular ejection fraction, tended to reduce scar mass and wall motion score index, and tended to reduce the incidence of mortality rate and re-hospitalization (Table 1). However, clinical trials of MSCs for HF/MI have fallen short of expectations, with most clinical-stage MSC therapies being unable to meet their primary efficacy endpoints [38]. For instance, the SCIENCE trial, a European multicenter phase II study, investigated the safety and efficacy of a single treatment with direct intramyocardial injections of adipose tissue-derived mesenchymal stromal cells (CSCC_ASCs) in patients with chronic ischemic heart failure with reduced ejection fraction (HFrEF). This double-blind, placebo-controlled trial aimed to determine whether the CSCC_ASC therapy could improve cardiac function in HFrEF patients [40]. Their study demonstrated that the intramyocardial allogeneic CSCC_ASC therapy was safe for patients with chronic HFrEF. However, the study found that while the MSC treatment was safe for these patients, it did not meet the predefined endpoints nor did it lead to improvements in cardiac function or clinical symptoms [40]. Similarly, the DREAM-HF (Double-Blind Randomized Assessment of Clinical Events with Allogeneic Mesenchymal Precursor Cells in Advanced Heart Failure) trial, a phase 3 study conducted by Perin and colleagues, assessed the efficacy and safety of mesenchymal precursor cells (MPCs) in patients with high-risk heart failure with reduced ejection fraction (HFrEF). This randomized, double- blind, multicenter study evaluated a single transendocardial administration of MPCs or sham-control in 565 patients with HFrEF receiving guideline-directed therapies. They found that both the primary and secondary pre-defined endpoints of the trial were negative, however, their post hoc exploratory analysis suggested MSCs to have potential in improving outcomes in patients, especially those with inflammatory conditions [41]. Overall, these clinical trials highlight that while MSC therapy may be safe, achieving meaningful benefits within the clinical setting still remains a major challenge.

4. Challenges of MSCs

MSCs have become one of the most used and sought after cellular therapies in clinical trials worldwide[52]. MSCs are the most used stem cells for myocardial injury as they have easy isolation, raise no ethical concerns, and cause no significant immune responses [53]. Many

Table 1
Large Animal Studies of MSC Therapy for Cardiac Repair.

Animal model	MSC Source	Delivery Method	Dose	Follow-up	Key Outcomes	Reference
Pig MI	Autologous BM-MSC	Intracoronary infusion	1×10^8 cells	3 months	Improved LVEF, reduced infarct size	Schuleri et al. 2009 [42]
Sheep MI	Allogeneic BM-MSC	Transendocardial injection	75×10^6 cells	8 weeks	Improved LVEF, increased vascular density	Hamamoto et al. 2009 [43]
Pig MI	Autologous BM-MSC	Intramyocardial injection	3×10^7 cells	1 and 4 weeks	Improved cardiac function, increased LVEF, reduced infarct size	Cai et al. 2016 [44]
Pig MI (porcine AMI)	Allogeneic UC-MSC	Intravenous injection	0.5×10^6 cells/kg or 1.5×10^6 cells/kg body weight	8 weeks	Preserves LV function, ameliorated myocardial remodeling	Lim et al. 2018 [45]
Sheep MI	Allogeneic BM-MSC and AT-MSC	Intraperitoneal injection	$1.25 \pm 0.30 \times 10^6$	7–9 days	Successful cell retention and localization, no immune response	Emmert et al. 2013 [46]
Sheep MI	Allogeneic BM-MSC	Intracardiac injection	3.33×10^7 cells	12 weeks	Reduced remodeling & strain, attenuated cardiomyocyte hypertrophy, reduced apoptosis & fibrosis, functional & structural improvements, cardiac apoptosis inhibition	Zhao et al. 2012 [47]
Pig MI	Allogeneic hUC-MSC	Intracoronary injection	5×10^5 hUC-MSCs/kg body weight	8 weeks	Improved Left-Ventricular Systolic Function, improved cardiac remodeling	Raposo et al. 2023 [48]
Sheep MI	Allogeneic hMSC	Intravenous injection	1×10^6 MSCs/ kg body weight	1 month	Improved Myocardial Perfusion, no Change in Ventricular Dimensions, no immune response	Dayan et al. 2016 [49]
Sheep MI	MSC	Intra-myocardial or intracoronary administration	10×10^6 cells)	5–7 days and 5–6 weeks	Perfusion and functional improvements,	Bailey et al. 2013 [50]
Dog chronic ischemia model	BM-MSC	Intramyocardial injections	100×10^6 MSCs/ 10 mL saline	60 days	Increased LVEF, trend towards reduced fibrosis and increased vascular density, successful MSC differentiation, improved vascularity and cardiac function.	Silva et al. 2005 [51]

preclinical animal studies have demonstrated satisfactory and promising results, such as MSCs effectively alleviating myocardial ischemic injuries, improving cardiac function, and reducing infarction size [20,54–57]. Of note, some study performed in swine model of myocardial infarction have failed to induce effective cardiac repair by myocardial transplantation of unmanipulated human MSCs [58] as previously observed in rodents by the same authors [59]. Besides limitations of animal model and route of administration, it is conceivable that myocardial transplantation of MSCs presents several challenges such as loss of immunomodulation, low engraftment, retention and survival, immune rejection, low nutrient, and oxygen as well as poor homing and migration. These bottlenecks may hamper potential beneficial effect of cell therapies for heart failure and acute myocardial infarction [60].

4.1. Loss of immunomodulation?

Preclinical trials using MSCs demonstrated improved cardiac function through immunomodulation [61]. Immunomodulation refers to the agent's ability to change the body's immune system by activating or suppressing its function. We cannot ignore that the endothelial-cardiomyocyte crosstalk may benefit from the paracrine crosstalk between infiltrated myeloid cells and a subset of cardiac endothelial cells which drives angiogenesis and tissue repair after myocardial infarction [62]. Although emerging evidence suggests that myeloid cells restore myocardial perfusion by secreting paracrine factors [63], it is unclear how the immunomodulatory effect of MSCs can determine the magnitude of cardiac recovery through regulation of infiltrated rather than resident macrophages activity. A major challenge that is still faced by researchers today is MSCs losing their immunomodulatory functions after transplantation, as studies have reported MSCs losing their immunosuppressive effects in vivo [59,64]. Initially, therapeutic efforts for MSCs were based on their multipotency, however, the discovery of their strong immunomodulatory, trophic characteristics, self-renewability, and readily engineerable enhancement of their immunomodulatory functions motivated researchers to harness MSCs as a therapy for various inflammatory and degenerative diseases [38,65,66]. Studies have demonstrated that in vitro expanded MSCs can promote repair and regeneration of damaged tissue through their immunomodulatory actions [67]. MSCs mainly exert their immunomodulatory functions through cell-to-cell contact and paracrine activity via the production of metabolites, cytokines, chemokines, growth factors, extracellular vesicles, apoptotic vesicles and T-cell death-mediated immune regulations [65,66,68]. Furthermore, MSCs interact with immune cells in both the innate and adaptive immune systems [1,2]. In the adaptive system, MSCs suppress T helper cells and cytotoxic T cell proliferation, inhibit dendritic and B cell maturation, and help prevent T-cell production of proinflammatory cytokines [69,70]. And in the innate system, MSCs work to reduce the stimulating receptors of natural killer cells [70].

The immunosuppressive activity of (MSCs) is well documented. However, the therapeutic benefit is completely unpredictable, thus raising concerns about MSC efficacy [71]. Although direct cell contact is also important for the immunosuppressive effects of MSCs, research has demonstrated that immunomodulators such as indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), transforming growth factor beta (TGF-B), interleukin-10 (IL-10), hepatocyte growth factor (HGF), histocompatibility locus antigen-G (HLA-G), CD39 and CD73, galectins, C—C motif chemokine ligand 2 (CCL2), programed cell death ligands 1 and 2 (PD-L1 and PD-L2), haem oxygenase 1 (HO-1), tumor necrosis factor-stimulated gene 6 (TSG6), interleukin-1 receptor antagonist (IL1RA) and complement system-related factors expressed by MSCs are more important [72]. Noteworthy, other MSC-derived immunomodulators, such as extracellular vesicles [73], can effectively suppress T cell activation and proliferation along with stimulation of macrophages shift from pro-inflammatory M1 to anti-inflammatory [74], which promote vascular reconstruction and myocardial repair by the release of additional anti-inflammatory factors [75].

4.2. Low retention and survival

The low retention (duration of localization of cells at target site) and survival of MSCs post-transplantation is a major limitation of the MSC

cardioprotective effects after intramyocardial injection [76]. It is now well established that MSCs have a high mortality rate after transplantation at the injury site regardless of delivery route [77]. Previous studies have demonstrated this challenge facing MSC transplants as cells reaching the target site were often found to be non-viable due to apoptosis and immune-mediated damage [78–80]. For instance, an in vivo rat study found that 2 days after local injection at the site of MI, there was an undetectable level of viable MSCs [81]. Similarly, a study by Toma and colleagues found that less than 0.44 % of MSCs survived past day 4 after engraftment in immunodeficient mouse hearts [82]. Accordingly, another study found that roughly 1 % of MSCs were detected 24 h post transplantation into the heart of a rat with experimental MI [83]. Clinical trials have also consistently demonstrated the low retention and survival of MSCs after transplantation into the infarcted heart. Hofmann et al., reported that in a small group of STEMI patients, intracoronary infusion of BM-MSCs showed between 1.3 and 2.6 % retention in the infarcted region when imaged using a PET scan at 50–75 min post injection [84]. Accordingly, more recent studies still demonstrate low retention and survival rates of intramyocardial injected MSCs with less than 50 % lost after three days and under 10 % on day seven, with almost all lost after two weeks [55]. The lack of retention has been attributed to cell death due to the harsh microenvironment created by MI and poor engraftment into the tissue [20,38]. This is because MI causes an abundance in the production of free radicals after ischemia or reperfusion injury, causes injured cells to release proinflammatory factors, and causes an infiltration of inflammatory cells, all of which are detrimental to cell survival [20]. Previous studies have suggested that preservation of endothelial-cardiomyocyte interaction may facilitate MSC homing. Indeed, the exposure of canine heart to focus ultrasound with microbubbles generates a local gradient of pro-angiogenic growth factors (i.e.: VEGF) and adhesion molecules increases retention of MSCs into ischemic heart [85].

4.3. Low oxygen and nutrient

Oxygen tension has been established to have a direct effect on cellular energy metabolism affecting cell survival and therapeutic efficacy [86]. Myocardial oxygen tension in a rodent's heart with arterial occlusion was shown to go from 2.6 % to 3.3 % down to 0.9 % pO_2 within the first 5 min, and reached near-anoxia (0.2 % PO_2) after 30 min of ischemia [87]. Small differences in oxygen tension such as 1 % vs 0.1 % can result in MSCs experiencing a cascade of metabolic and signaling pathways [86]. Many studies have demonstrated that ischemic conditions involving hypoxia and serum deprivation leads to MSC apoptosis and necrosis [88,89]. Cells must be roughly within 200 μm of the nearest blood vessel in order to retain sufficient nutrients and oxygen, however, cell death is prominent because it may take days for vascularization to reach the cells [90].

Oxygen deficiency triggers a “switch” from high-energy-yielding processes (glycolysis combined with OXPHOS) to low-energy-yielding processes of glycolysis. In the past, oxygen reduction was the primary cause of cell death in an ischemic environment. However, more recent studies have shown that the lack of nutrients, notably glucose, is the main reason behind cell death post transplantation [86,91]. Accordingly, a study showed that glucose supplementation of cell-containing constructs in vivo resulted in nearly a fivefold increase in cell survival [92]. These studies highlight that both the depletion of oxygen and nutrients following MSC implantation must be enhanced/overcome in order to improve the therapeutic outcome. Endothelial-cardiomyocyte crosstalk plays a crucial role in promoting the survival of MSC in ischemic tissue by creating a supportive microenvironment and enhancing the therapeutic potential of MSC [93]. The crosstalk may enhance metabolic adaptation in ischemic myocardium by promoting angiogenesis and improving local oxygen and nutrient supply. This reduces hypoxia and nutrient deprivation, key stressors that threaten MSC survival. Therefore, combined transplantation of MSC and endothelial colony-forming cells [94] or pharmacologically active microcarriers releasing VEGF [95] or biomaterials releasing nitric oxide [96] may enhance cardiac repair by MSC as the ischemic environment is reduced.

4.4. Immune rejection

Immune rejection is a major challenge faced in many MSC based clinical and preclinical trials that threatens MSC survival in vivo. The intrinsically low immunogenicity of MSCs, in addition to their immunosuppressive properties, results in reduced immune response after both autologous and allogeneic MSC transplants. However, some evidence suggests that MSCs are not as immune-privileged as previously reported. HLA antigen (also known as major histocompatibility complex [MHC] molecules) mismatches between the donor and recipient represent a significant immunological challenge in transplantation and can lead to severe complications, including engraftment failure, delayed rejection, and graft versus host disease (GVHD) [97]. MSCs however, possess important immunoprivileged/immunoevasive properties which renders them safe for allogeneic use [98]. MSCs are considered to be immune privileged due to low expression of human leukocyte antigen class I (HLA—I) molecules, and negligible expression of human leukocyte antigen class II (HLA-II) or costimulatory factors CD40, CD80 and CD86 [94,95,97,99,100]. When HLA-II molecules are expressed, they provide signals that alert the host immune system to initiate an immune response against transplanted cells [101,102,103–105]. Immune privilege allows for transplanted MSCs to remain undetected by the recipient's immune system and survive in the host [102]. Allogeneic MSC-based clinical trials constitute roughly 40 % of MSC transplantations and majority of these studies do not take into account if allogeneic donor MSCs and recipients are HLA-matched or HLA-mismatched, nor do they investigate if the MSCs induce immune responses and become rejected [97,106]. Hence, the potential that allogeneic MSCs may provide “off-the-shelf” cellular therapy that is readily available and accessible to a broad population of patients [98]. However, studies have shown that HLA-II can be re-expressed under inflammatory circumstances [97]. Therefore, a major limitation to allogeneic MSCs after transplantation is long-term survival as the cells experience an immune switch turning them from immunoprivileged to immunogenic which leads to immune rejection. Data from clinical and preclinical trials demonstrate that MSCs lose their immune privilege in long-term transplantations, and provoke an immune response in the recipient causing them to be rejected [97,99,100,103,107]. Moreover, the few studies that have controlled for MHC haplotype in both donors and recipients and examined immune responses following MSC injection suggest that adult MHC-mismatched MSCs are not immune privileged. In various animal models, bone marrow-derived MHC-mismatched MSCs triggered both cell-mediated and humoral immune responses in vivo, leading to their rejection [106,108–114]. For instance, it was found that allogeneic MSCs transplanted in a rat model of MI turned immunogenic and were rejected from the ischemic heart after only five weeks [115]. While these studies have offered important insights into the immune system's reaction to MHC-mismatched MSCs, the clinical consequences of MSC rejection by the recipient's immune system are still not fully understood [106].

5. Homing and migration

A major advantage of MSC-based therapy is their capability to migrate to inflamed and damaged tissues. MSCs are found to tend to migrate towards ischemic heart tissue through intravenous delivery and can provide cardioprotective effects. For the majority of MSC applications in basic and clinical studies, systemic delivery such as intravenous injections are preferred [20,116]. In systemic homing, systemically administered MSCs must undergo a multistep process to exit circulation and migrate to the site of injury to support functional recovery [69,116]. However, the mechanisms in which the MSCs migrate, and home are not

yet fully understood [116]. Although systemic delivery is generally preferred, it means that homing and migration of MSCs towards the target tissue is required [116]. Homing refers to the process by which cells travel to and integrate into specific tissues where they can survive and perform their intended local functions. Whereas, in non-systemic homing, MSCs are locally transplanted into the target tissue and subsequently directed to the injury site through a chemokine gradient [117]. Although in vivo MSC homing and migration has been achieved, the process is not highly efficacious [116]. Studies have shown that only few cells reach the target tissue and remain there after systemic administration, with many dying after injection while others become trapped in unwanted organs such as the lungs, liver, and spleen [20,116,118,119]. This has been attributed to the low expression levels of homing molecules, the loss in expression of these molecules during expansion, and the heterogeneity of MSCs in cultures and MSC culture protocols. Therefore, to overcome these restrictions and achieve significant numbers of therapeutic MSCs at the site of injury, it is essential to examine and improve the different strategies used to enhance MSC homing and migration. Combined intensive atorvastatin treatment, a cardioprotective lipid lowering pharmacological regimen, may increase therapeutic efficacy of MSC transplantation [120] by upregulating the release of exosomes delivering lncRNA H19 which mediates the activation of proangiogenic factor VEGF and intercellular adhesion molecule-1 promoting the endothelial cell function [121]. Indeed, the adhesion of circulating MSCs to the heart seems to depend on the endothelium and can be influenced by activators that target both MSCs and the endothelium.

BM-MSC: bone marrow-derived MSC; UC-MSC: umbilical cord-derived MSC; AD-MSC: adipose-derived MSC; MI: myocardial infarction; LVEF: left ventricular ejection fraction; LV: Left Ventricle.

6. Future directions/perspectives

Cutting-edge research in mesenchymal stem cell (MSC) therapy for cardiac applications is intensively focused on enhancing therapeutic efficacy, with scientists exploring innovative strategies to maximize the regenerative potential of these versatile cells. Strategies include genetic manipulation to increase engraftment potential (Table 2), preconditioning MSCs with hypoxia or pharmaceutical agents, and pretreatment with growth factors to boost paracrine properties [122]. Novel approaches involve using MSCs as microcapsules or incorporating them into scaffolds, which may improve their integration with host cardiac tissue. Additionally, combining MSCs with other cell types, such as endothelial progenitor cells, has shown synergistic effects in preclinical studies and is being explored in clinical trials (Table 2). Emerging trends also include utilizing MSC-derived exosomes, which can regulate gene expression and signaling pathways, potentially offering a new avenue for cardiovascular medicine. These advancements, along with optimizing cell delivery methods and recipient selection, hold promise for maximizing the regenerative potential of MSCs in treating cardiovascular diseases.

6.1. HLA matching

As previously mentioned, human MSCs in general do not express HLA class II, however, during cell expansion in vitro, the expression of this molecule may be significantly upregulated, which can cause an immunological reaction in vivo [97,133,134]. It was suggested that culture medium supplemented with growth factors, proinflammatory cytokines, oxygen conditions, or epigenetic modification, in both in vivo and in vitro conditions, may stimulate MHC/HLA molecule expressions on stem cells [133,135–137]. Studies showed that the expression of HLA class II molecules on MSCs can appear under proinflammatory environments of injured tissue and cell expansion [97], and in vivo animal studies have demonstrated that allogeneic MHC-mismatched bone marrow MSCs induced an immune response and got rejected [106].

Table 2
Studies Aimed at Increasing MSC Engraftment.

Approach	Model	Key Findings	Reference
Genetic modification (CXCR4 overexpression)	Rat MI	Enhanced MSC homing and survival, improved cardiac function	Cheng et al. 2008 [123]
Preconditioning with hypoxia	Pig MI	Increased MSC survival and angiogenic factor secretion	Hu et al. 2008 [124]
Biomaterial scaffold (fibrin patch)	Pig MI	Improved MSC retention and cardiac function	Xiong et al. 2011 [125]
Co-transplantation with endothelial progenitor cells	Rat MI	Enhanced MSC survival and cardiac repair	Suuronen et al. 2007 [126]
Magnetic targeting	Rat MI	Increased MSC retention in infarcted area	Cheng et al. 2010 [127]
Encapsulation in alginate microspheres	Rat MI	Prolonged MSC survival and paracrine effects	Levit et al. 2013 [128]
Akt gene modification	Rat MI	Enhanced MSC survival and cardiac function	Mangi et al. 2003 [129]
MSC injection on myocardial elasticity post MI	Rat MI	Reduced myocardial fibrosis, less left ventricular dilation, preservation of systolic and diastolic function, and reduced apoptosis	Berry et al. 2006 [130]
Genetic modification (chemokine receptors CCR1 overexpression)	Mouse MI	Enhanced migration, survival and engraftment, reduced infarct size, reduced cardiomyocytes apoptosis, prevented cardiac remodeling, and restored cardiac function 4 weeks after MI	Huang et al. 2010 [131]
Genetic modification (microRNA-1 Overexpression)	Mouse MI	Increased cardiomyocyte differentiation, improvement in cardiac function, MSC survival,	Huang et al. 2013 [132]

Immune rejection post allogeneic MSC treatment, might be a result of donor-recipient HLA-mismatching [106]. There is very limited data examining patients' sensitization post allogeneic MSC treatment, which showed that the immunogenicity of allogeneic MSC was noticed low in multiple clinical trials, however, donor specific anti-HLA antibody was detected in few patients post allogeneic MSC infusion. It was suggested that the level of detected donor specific anti-HLA antibodies might be correlated with the HLA mismatches between the donor and recipient, and the infusion times of allogeneic MSC [87]. Therefore, the presumption that MSCs do not cause an immunological conflict between the host and transplanted cells might be worthy to be re-evaluated for the efficacy of MSC therapy and the safety of patients, considering that allogeneic MSC-based clinical trials constitute almost half of the total clinical trials to date [97]. In the future, HLA typing might be considered not only for matching a donor and a recipient, but to also estimate the immunological risk of donor recognition, to improve the safety and efficacy of allogeneic MSC-based therapies and better transform MSCs into an “off-the-shelf” therapeutic. It may consider to use donors carrying the most common and homozygous haplotype to manufacture allogeneic MSC as the “off-the-shelf” product, for example the most common haplotype HLA-A*01:01-B*08:01-C*07:01-DRB1*03:01-DQB1*02:01 in Caucasian population, and HLA-A*30:01-B*42:01-C*17:01-DRB1*03:02-DQB1*04:02 haplotype in African American population and African populations [138]. These donor derived MSC product can be safely used to treat patients carrying these most common haplotypes even though the patients are carrying heterozygous haplotype, and it won't cause immune rejection post MSC infusion as the patient's immune system will treat these MSCs as self even if the expression of HLA class II on MSCs are induced under local inflammation condition.

6.2. Apoptotic MSCs

Different functional MSCs being efficacious for treating diseases have been a longstanding assumption by researchers [139]. Apoptotic MSCs (Apo-MSCs) have recently been an important prospective for new approaches in the development of cell-based therapies [71,140,141]. Apoptosis has long been considered to be a form of 'silent' cell death, however, this belief has changed as apoptosis has slowly been demonstrated to take part in the communication with neighboring cells to contribute to the remodeling of surrounding tissues as well as survival or apoptosis [142,143]. Apoptotic cell death is provoked by triggers ranging from developmental cues to cellular stressors or cytotoxic immune cells [144,145]. Apo-MSCs have been shown to deliver immunosuppression and tissue repair/homeostasis [71,146–148]. One recent study also shows Apo-MSCs could be cryopreserved without impairing efficacy compared to freshly prepared Apo-MSCs in suppressing an allergic murine inflammation, suggesting that cryopreserved Apo-MSCs could be a potential future off-the-shelf cellular product [149].

6.3. Immunomodulation

Programmed MSC cell death inhibits harmful immune responses and reduces persistent inflammation more effectively than viable MSCs. It was also demonstrated that the immune regulation mediated by MSCs can be achieved through apoptotic, metabolically dysfunctional, or fragmented MSCs [139,147]. Under phagocytosis, apo-MSCs induce monocytes/macrophages to develop immunosuppressive macrophages (M2 macrophages) that produce anti-inflammatory cytokines and growth factors, thereby suppressing inflammatory responses and enhancing tissue repair and homeostasis. M2 macrophages suppress T cell proliferation in the liver in a PGE2- and IL-10-dependent manner, inhibit the production of proinflammatory cytokines (IFN-γ and TNF-α) and profibrotic cytokines (TGF-β), and promote the expansion of regulatory T (Treg) cells, thereby inducing an immunosuppressive microenvironment in inflammatory tissues [139,150]. Apo-MSCs can regulate the role of immune cells and the large decrease in viable MSCs does not affect their immunosuppressive or therapeutic effects [139,147]. Furthermore, apo-MSC mediated immune regulation is similar to or even superior to mediation by viable MSCs, and the immunomodulatory effects of apo-MSCs are more predictable [139]. A study by Galleu et al. showed that it is a requirement for MSCs to experience extensive caspase activation and apoptosis after infusion in the presence of cytotoxic cells in order to achieve their immunosuppressive function [71]. They demonstrated the necessary role of MSCs experiencing in vivo apoptosis in order to achieve immunosuppression after infusion. Moreover, it was found that patients with GVHD displaying high cytotoxicity against MSC responded to MSC treatment whereas those who lack cytotoxic activity showed no improvements post MSC infusion. This suggests a patients ability to induce apoptosis in MSCs appears to be a necessity for MSCs therapeutic efficacy, and could be used as a potential biomarker to stratify patients for MSC infusions [71]. It also found that the Apo-MSC secretome inhibited human T cell proliferation and activation, and chemoattractant monocytes in vitro through PGE2/COX2 mediators [140]. Furthermore, it showed that both PGE2 and apoptosis of MSC were significantly associated with the clinical responses of Crohn's disease patients to MSC treatment.

6.4. Tissue repair

Besides educating phagocytes to become anti-inflammatory and restorative cells [145], apoptotic MSC may release caspase-dependent mitogenic factors which might trigger apoptosis-induced proliferation (AiP) process in surrounding cells, suggesting the role of apoptosis on tissue remodeling post injury. In a liver injury animal model, MSC can attenuate liver fibrosis in vivo by inducing a phenotypic switch in macrophages from profibrotic to proresolving via secreting anti fibrogenic-cytokines and activating apoptosis pathways [145,151]. MSC experienced severe apoptosis and released substantial apoptotic bodies in the fibrotic liver after infusion, which in turn were phagocytosed by restorative macrophages leading to MMP12 expression, and further contributing to the alleviation of liver fibrosis. Another study showed that MSC-derived extracellular vesicles promoted the phagocytic activities of macrophages and elicited the expression of amphiregulin in a phagocytosis-dependent manner, which mediated the function of MSC-primed macrophages to increase Treg cells and preserve corneal epithelial stem cells, suggesting the role of crosstalk between MSC and macrophages in maintaining tissue homeostasis [152]. These findings suggested that after undergoing apoptosis, MSC delivers signals to reprogram the negative inflammatory microenvironment to orchestrate tissue repair and homeostasis [145].

6.5. MSC-secretome

Rather than focusing solely on the direct engraftment of MSCs into damaged myocardium, researchers have discovered that MSCs secrete a diverse array of bioactive molecules, collectively referred to as the "secretome." This secretome encompasses soluble factors, extracellular vesicles (EVs), and apoptotic extracellular vesicles (Apo-EVs). These mediators play a pivotal role in myocardial repair by modulating key biological processes, including inflammation, angiogenesis, and cell survival, ultimately supporting the integrity of endothelial-cardiomyocyte crosstalk.

6.6. Soluble factors

The MSC secretome is a rich reservoir of soluble factors that are critical for facilitating myocardial repair. It comprises various growth factors and cytokines, including interleukin-1 (IL-1) and interleukin-6 (IL-6), which play essential roles in promoting angiogenesis and stimulating the expression of vascular endothelial growth factor (VEGF). These mechanisms enhance blood vessel formation and restore the vital crosstalk between endothelial cells and cardiomyocytes. This vascular-myocardial interaction is fundamental for sustaining survival and activity of MSC driving the repair of ischemic heart tissue.

MSC-derived hepatocyte growth factor (HGF) mobilizes cardiac progenitor cells, promoting cardiac repair, while transforming growth factor-beta (TGF-β1) secreted by MSCs modulates fibrosis to prevent excessive scarring. Placental growth factor (PLGF) and VEGF act synergistically to protect cardiomyocytes and endothelial cells from apoptosis, ensuring cell survival in the post-infarction environment [121]. Additionally, angiogenin, a secreted proangiogenic ribonuclease, hampers left ventricular remodeling through formation of new myocardial vessels, further contributing to cardiac recovery [153–155]. Matrix metalloproteinases (MMPs), including MMP-2, MMP-9, and MMP-14, play a critical role in extracellular matrix degradation, facilitating tissue repair while exhibiting antifibrotic effects [156,157]. Of note, survival of MSC due to higher expression of Akt1 is pivotal in counteracting hypoxic myocardial injury by promoting cardiomyocyte survival, reducing infarct size, and lowering apoptosis rates [158,159]. Moreover, the secretome of survived MSC even plays a pivotal role in stimulating endothelial cell proliferation and migration, processes essential for myocardial angiogenesis. Kinnaird et al. (2004) demonstrated that MSCs exert a paracrine effect, releasing growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) to stimulate angiogenesis without differentiating into endothelial cells. This angiogenic potential of MSCs extends beyond cardiac tissue, as evidenced by their ability to promote vascularization in non-cardiac ischemic models [160]. In a murine model of limb ischemia, MSC transplantation significantly improved perfusion, reduced tissue damage, and limited fibrosis, highlighting their therapeutic potential in restoring blood flow and supporting tissue repair. The paracrine modulation of endothelial-cardiomyocyte crosstalk by MSC-

derived factors is essential for effective cardiac repair. By promoting angiogenesis and preserving cardiomyocyte function, MSCs offer a promising therapeutic strategy for myocardial infarction. Further research into the mechanisms underlying MSC-mediated paracrine effects may lead to the development of novel therapies that harness the regenerative potential of the MSC secretome.

6.7. Extracellular vesicles (EV's)

MSCs release membrane-bound vesicles, including exosomes (size 40–100 nm) and microvesicles (size 100 nm-1 μm) [161]. Extracellular vesicles (EVs) are emerging as a captivating new frontier in cell-free next-generation therapies. Rather than directly utilizing the cells themselves, EVs, which are released by MSCs, carry the therapeutic potential of these cells. This innovative approach offers a promising avenue for treating various vital organs, opening up new possibilities in regenerative medicine [162]. The enthusiasm for EVs is on the rise because of their potential use in clinical settings [163]. EVs have immunomodulatory, regenerative, and anti-cancerous properties, and represent an interesting approach in the treatment of cardiovascular, nervous, immune system diseases, even in critical ill patients [164]. We cannot underestimate their potential as perioperative non-invasive liquid biopsy-based biomarkers, offering a tailored window into the complex process of cardiac recovery after surgery [165] and transplantation [166]. Their wide range of prospective therapeutic and diagnostic (theranostic) applications comes from their low immunogenicity and their ability to retain the function of protocells [167]. EVs offer significant advantages [167] as therapeutic agents due to their lack of self-replication and low risk of tumorigenicity, addressing key safety concerns associated with cell-based therapies. EVs also demonstrate reduced immunogenicity, enhanced ability to cross biological barriers, and improved stability during storage and handling. Furthermore, EVs can be engineered for targeted delivery and loaded with therapeutic cargo, making them versatile tools for various medical applications. [168,169]. In addition, EVs can be preserved for a prolonged period at -80 °C without deactivation even after repeated freeze thaw cycles [170,171]; (3) they have the potential to be used as a drug delivery platform, as they may be able to carry specific drugs and transport them to target cells due their encapsulation ability [172]; (4) they can transport DNAs, RNAs, miRNAs, proteins and many other important factors to target cells which act as messengers in intercellular communication [173]. Furthermore, EVs have been reported to have therapeutic efficacy in various preclinical models and have emerged as promising therapeutic agents that are proposed for testing in clinical trials [174–176]. For instance, a study by Amaro-Prellezo and colleagues aimed to investigate whether MSC-EVs could promote a pro-resolving environment in the heart by modulating macrophage populations. They found that MSC-EVs facilitated the differentiation of pro-inflammatory macrophages into a pro-resolving phenotype, as indicated by higher levels of M2 markers and reduced production of pro-inflammatory cytokines. Moreover, they found that in rats with acute MI, MSC-EV administration minimized the size of the infarcted area at 7 and 21 days post event. Additionally, they found that MSC-EV treatment decreased the number of pro-inflammatory macrophages in the infarcted region, aiding in the resolution of inflammation [177].

Studies have demonstrated that extracellular vesicles (EVs) derived from human bone marrow-derived mesenchymal stem cells (BM-MSCs) exhibit superior pro-angiogenic and anti-apoptotic properties compared to EVs released from patient-matched cardiac fibroblasts, making them particularly promising for post-myocardial infarction therapy [178,179]. However, cardioprotective effects mediated by EVs derived from patient-matched cardiac progenitor cells have been shown to be significantly more potent than those induced by BM-MSC-derived EVs [178,179]. This finding suggests that EVs released by progenitor/stem cells residing within the target tissue of therapy may exhibit greater therapeutic efficacy than those derived from circulating stem cells or progenitor/stem cells from other tissues. This enhanced effectiveness may be attributed to the fact that these vesicles carry bioactive molecules (including proteins, RNA, and microRNA) specifically tailored to the target tissue, optimizing regenerative and reparative processes in the myocardium. Moreover, their composition aligns with the functional requirements of the myocardial tissue, rendering them better suited to mediate localized beneficial effects. This understanding has significant implications for the development of cell-based therapies to mend the broken heart. It suggests that strategies aimed at harnessing the therapeutic potential of EVs should consider the source of the cells and the specific target tissue. By utilizing EVs derived from tissue-resident cells, it may be possible to achieve more targeted and effective therapies for a variety of diseases, including cardiovascular diseases. Phinney and Pittenger (2017) and Baglio et al. (2012) have revealed the heterogeneous molecular composition of MSC-derived EVs, which encompasses proteins, lipids, and nucleic acids [168,180]. Each of these components contributes significantly to cardiac repair. For example, certain proteins delivered by EVs can activate cell survival pathways, promoting the survival of damaged cardiomyocytes. Additionally, lipids present in EVs can facilitate interactions with target cell membranes, enhancing their uptake by target cells. This supports the potential use of EVs being an alternative to cell-based MSC therapies. However, for a better and full understanding, more data regarding their safety and efficacy is required through further research.

6.8. Apoptotic-extracellular vesicles (Apo-EVs)

Another form of EVs are apoptotic EVs (Apo-EVs), which researchers suggest to be another promising form of therapy. Apo-EVs have been shown to modulate the function of the immune system through T cells and macrophages and can improve tissue repair by regenerating the skin and protecting blood vessels [181–183]. An increasing pile of evidence has revealed that apo-EVs are key mediators of MSCs, and that administration of apo-EVs is a favorable strategy to achieve cell-free therapy [71,184]. Moreover, researchers found that in an MI model, transplanted MSCs were found to release apoptotic bodies that can enhance angiogenesis and improve cardiac functional recovery via the regulation of macroautophagy/autophagy in endothelial cells of the recipient [184]. Thus, researchers believe that the transplantation of MSC-derived apo-EVs are expected to treat various diseases, including but not limited to, MI, osteoporosis, colitis, and GvHD [139,184–188].

7. Conclusion

MSCs are promising cell therapy candidates with encouraging safety profiles, however, their controversial clinical efficacy limits their application in clinics. MSCs have been widely tested in the treatment of MI and other cardiovascular diseases, and shows promising results, such as migrating to infarcted myocardial tissue, reducing inflammation and fibrosis, and promoting formation of new blood vessels, which maintain endothelial-cardiomyocyte crosstalk. However, MSC therapy still faces many challenges, such as rejection, poor homing and migration, as well as low retention and survival. It also requires extensive studies of mechanisms responsible for therapeutic activity and reliable pharmacodynamics of MSCs. Key variables need to be considered too, including viable MSC vs Apo-MSC, MSC or MSC derived EV or Apo-EV, autologous MSC or allogeneic MSC, HLA matching or not, optimal dose, route of administration, and manufacturing parameters (Fig. 1). Administration of Apo-MSC into the local infarcted myocardial tissue may represent a path forward to mitigate the challenges of MSC therapy and to improve clinical success.

CRediT authorship contribution statement

Anqi Guan: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lisa Alibrandi:**

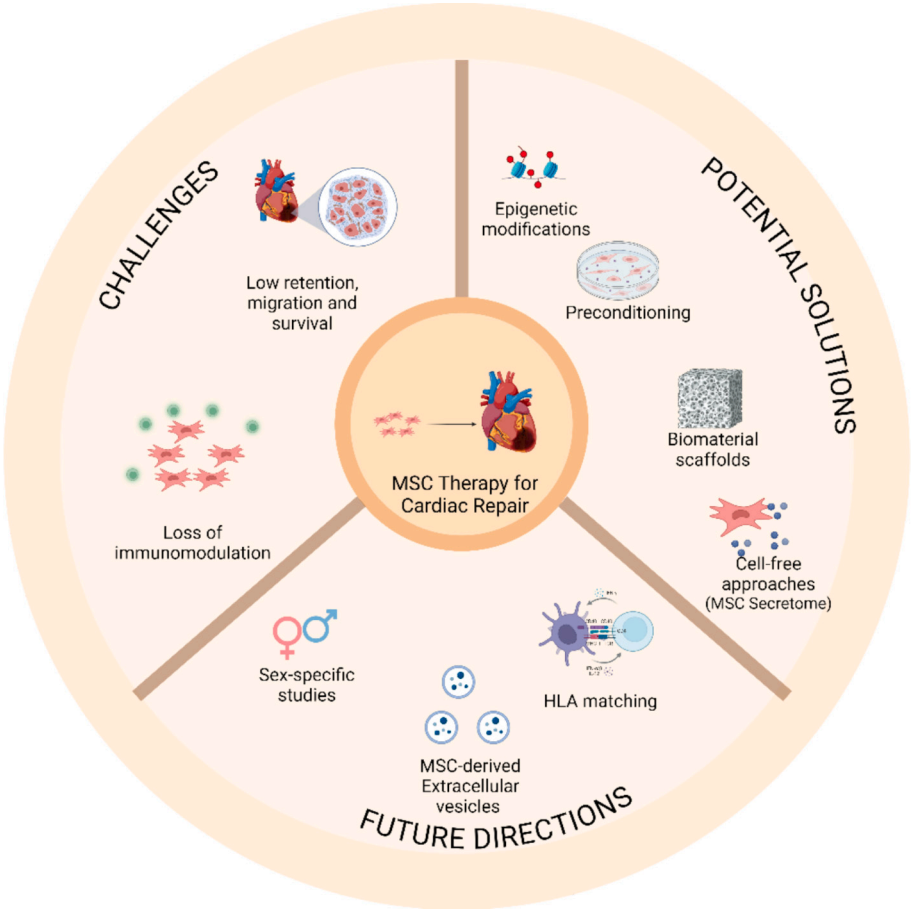

Fig. 1. The given figure illustrates the current landscape of Mesenchymal Stem Cell (MSC) therapy for cardiac repair. It highlights key challenges (e.g., low cell retention, immune rejection), potential solutions (genetic modification, biomaterial scaffolds), and future directions (HLA matching, extracellular vesicles), providing a concise roadmap for advancing MSC-based cardiac therapies.

Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Elika Verma:** Methodology, Investigation, Formal analysis, Data curation. **Niketa Sareen:** Methodology, Investigation, Data curation, Conceptualization. **Qingdong Guan:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vincenzo Lionetti:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sanjiv Dhingra:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Sanjiv Dhingra reports financial support was provided by Canadian Institutes of Health Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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