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Regenerative Therapy for Cardiomyopathies

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Abstract

Despite substantial advances in the development of medical and interventional strategies in ischemic and non-ischemic heart diseases, cardiovascular diseases (CVDs) remain the leading cause of mortality and morbidity worldwide. Stem cell therapy for heart disease has gained traction over the past 2 decades and is an emerging option for the treatment of myocardial dysfunction. In this review, we summarize the current literature on different types of stem cells and their potential usage in ischemic and non-ischemic heart diseases. We emphasize the clinical utility of stem cells to improve myocardial structural and function, promote microvascular angiogenesis, and diminish scar size and major adverse cardiovascular events. We also discuss the therapeutic potential of microvesicles, such as exosomes, in the treatment of CVDs, which may open novel avenues for further clinical studies.

Introduction

Cardiovascular diseases (CVDs) account for approximately 30% of global mortality, making them the leading cause of mortality worldwide (1). The histological damage associated with scar tissue and the irreversible loss of cardiomyocytes eventually leads to functional depression-heart failure (HF) (1)- and predisposes to malignant ventricular arrhythmias. Despite advances in medical and interventional therapies, none of the current clinical strategies are capable of restoring the loss of viable myocardial tissues (2). The adult heart innately lacks recuperative capacity, which ultimately limits the potential of conventional therapies (3). Heart transplantation can be utilized as a last resort to treat end-stage chronic HF, but the approach is expensive and candidacy is limited by common comorbidities and an insufficient supply of donor organs (3).

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The basic properties of stem cells are self-renewing capacity and pluripotency, i.e., the potential to differentiate into various functional cell types, such as cardiomyocytes (4), endothelial cells (5) or smooth muscle cells (6). Stem cell therapy for heart disease has gained extensive attention over the past 2 decades and has become a new option for the treatment of the damaged myocardial tissue. The rationale of stem cell therapy is that infused stem cells might contribute to the regeneration of injured cardiac tissues, thereby restoring myocardial contractility and perfusion and improving heart function, exercise capacity, etc. (7, 8). Variable types of stem cells have been investigated as promising therapeutic agents, including multipotent stem cells, embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSC), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), cardiac stem cells (CSCs), and bone marrow mononuclear cells (BMMNCs). A number of small scale clinical trials have demonstrated mild to moderate benefit in restoring left ventricular ejection fraction (LVEF) in patients with HF (9, 10). However, the clinical use of stem cells in CVDs is hampered by the incomplete understanding of cardiac tissue repair process, limited differentiation of stem cells into host cell types (11), and constrained therapeutic effects and cell viability under the harsh environment of damaged heart tissue (12).

In this review, we summarize the current literature on different types of stem cells and their potential usage in ischemic and non-ischemic heart diseases. Emphasis will be put on the clinical utility of stem cells on myocardial structural and functional change, microvascular angiogenesis, scar size and major adverse cardiovascular events. We will also consider the evolving therapeutic potential of microvesicles, such as exosomes, in the treatment of CVDs, which may open novel avenues for further clinical studies.

Stem cell therapy for ischemic cardiomyopathy

The loss of viable myocardial tissues, inadequate perfusion leading to ischemia, and subsequent tissue remodeling are the key issues in ischemic cardiomyopathy. Stem cell-based therapy has been demonstrated to have the capability of cardiac tissue repair in basic research studies (2, 13). Clinical trials have traditionally focused on the ability of stem cells to improve cardiac function, remodeling, and exercise capacity. Contemporary research is focused on timing of stem cell therapy to optimally salvage the area at risk and assessing the benefits of stem cell therapy on scar size, microvascular obstruction and intramural hemorrhage.

Various types of stem cells

Different kinds of stem cells have their advantages in the treatment of ischemic cardiomyopathy (ICM). In trials focused on this area, bone marrow-derived stem cells were commonly applied in an attempt to regenerate the infarcted myocardium using multipotent stem cells, MSCs or BMMNCs. The majority of clinical trials successfully demonstrated their safety, feasibility and effectiveness in improving LVEF to a mild-to-moderate extent (commonly 3–5% LVEF increase). Amelioration of left ventricular remodeling and infarct size reduction was also observed (14–16). EPCs were also extensively investigated over the past 2 decades with regard to repairing damaged heart and found to improve cardiac systolic

function post-myocardial infarction. In addition, ESC-derived cardiomyocytes transplanted into the injured heart were suggested to contract synchronously with host cardiomyocytes and protect against arrhythmias, and to enhance the ejection fraction (17). Multiple preclinical studies reported this phenomenon, despite the controversy surrounding the capability of EPCs to promote angiogenesis (18, 19). Additionally, CSCs, isolated from heart tissue, have been observed in a phase 1 clinical trial (Stem Cell Infusion in Patients with Ischemic cardiomyopathy [SCIPIO]) for the treatment of heart failure resulting from ischemic heart disease to preserve heart function, reduce infarct size and attenuate adverse myocardial remodeling (9). Recently, iPSCs have emerged as a promising cell source in cardiac regeneration (20) associated with their robust differentiation into cardiomyocytes coupled with the low risk of immune rejection (21). Currently, stem cell therapy is considered to be an alternative clinical approach with the possibility to reduce the incidence of death, recurrent MI, ventricular arrhythmia, and cerebrovascular accident during follow-up in the first 12 months (22).

Genetic modifications of stem cells

Genetic modifications of stem cells has the potential to enhance efficiency of cell therapy. Overexpression of cytoprotective genes, a strategy directed towards increasing the survival of transplanted cells, has been applied to different types of stem cells, especially MSCs (13). Researchers reported that upregulated expression of Akt in transplanted MSCs blunted ischemic-induced cardiomyocyte injury, collagen deposition, inflammation, infarction size and ventricular remodeling (23–25). Moreover, Aonuma et al. demonstrated that APE1 overexpression in Cardiac progenitor cells (CPCs) improved LVEF (APE1-CPC: $11.2 \pm 4.0\%$, control-CPC: $3.1 \pm 6.7\%$ vs control-medium: $23.5 \pm 5.3\%$; $p < 0.01$) while reducing cardiac inflammation and fibrosis in the ischemic heart through TAK1-NF- κ B pathway activation, serving as a novel strategy to improve cardiac cell therapy (26).

Overexpression of other cytoprotective proteins, such as heme oxygenase-1 and silent mating type information regulation 2 homolog 1, as well as pro-angiogenic factors, was also demonstrated to produce therapeutic benefit. Continuous advances of techniques for delivering the target genes will likely further improve the outcome of therapy with the genetically engineered stem cells.

Combined multi-cell therapy

Combining different types of stem cells has been hypothesized to lead to superior outcome in eliciting cardiac repair. Groups led by Karantalis have separately reported that injection of MSCs and CSCs together could achieve greater scar size reduction (MSCs: $-44.1 \pm 6.8\%$; CSC combined with MSC $-37.2 \pm 5.4\%$; control $-12.9 \pm 4.2\%$; $p < 0.0001$) (27) and William's demonstrated that combining MSCs and CSCs achieved better left ventricular chamber compliance (end-diastolic pressure-volume relationship; P work and dP/dtmax; $P < 0.05$) than either cell therapy alone in swine models, establishing the safety of autologous cell combination strategies (28). Also, Avolio et al. showed that combinational therapy with human saphenous vein-derived pericytes and cardiac stem cells via intramyocardial delivery potentiated cardiac repair in a myocardial infarction model (29). Furthermore, CardioChimeras formed by fusion of CPCs and MSCs exhibited enhanced heart reparative

capability compared with individual stem cells or combined cell injection, indicating CardioChimeras are a novel cell therapy that might improve on combinational cell approaches to support myocardial regeneration (30). These promising results suggest that combining multitype stem cells could enhance therapeutic efficacy through cell–cell complementary and synergistic effects.

Effect of stem cells on improving exercise capacity

Exercise capacity is a comprehensive and reproducible physiological endpoint to assess cardiovascular function (31) which correlates closely with the severity of chronic ischemic heart failure. The most widely reported parameters are exercise time and walking distance. Reduced exercise time and peak O₂ uptake are powerful markers of worse prognosis in chronic heart failure patients (32, 33). In patients with post-infarct heart failure, intracoronary infusion of bone marrow-derived progenitor cells produced a trend towards improved exercise time by 16.8s ($p=0.073$) at 3 months' follow-up compared with baseline (34). A systematic review of stem cell therapy in patients with acute myocardial infarction reported improvements in diastolic function and exercise capacity (14.29-minute increase in exercise time), and a clinically significant decrease in the ventilation/CO₂ production (VE/VCO₂ slope) at 1 year of follow-up) (8).

Effects of stem cells on left ventricular remodeling

ESCs, MSCs, BMMNCs, and iPSCs are considered to be promising therapeutic candidate stem cells given their self-renewal capacity and potential to differentiate into multiple cell types, including cardiomyocytes (35–38). The administration of these stem cells has resulted in improvements in cardiac systolic and diastolic function and attenuation of left ventricular remodeling in animal studies and in humans (39, 40). Strauer et al. carried out the first clinical trial of BMMNCs in AMI in 2002, demonstrating that BMMNCs were safe and effective at improving global and regional left ventricular dysfunction and myocardial perfusion (41). Manginas et al. observed that intracoronary administration of CD133+ or CD34+ cells into post-infarction zones with non-viable myocardium produced a sustained improvement in regional perfusion and a decrease in LV end-diastolic and end-systolic volumes ($P=0.008$ and $P=0.002$, respectively) (42). MSCs, which have the potential to differentiate into a variety of cell types such as chondrocytes, adipocytes, and osteocytes, tendons, as well as cardiomyocyte-like cells, vascular smooth muscle cells and endothelial-like cells, may be particularly effective at reducing myocardial remodeling. Infusion of autologous/allogeneic MSCs in heart failure patients not only prevented ventricular remodeling but also improved the functional capacity, 6-minute walk test, exercise peak VO₂, Minnesota Living with Heart Failure Questionnaire, and New York Heart Association classification (10). Finally, BMMNCs and CSCs were consistently suggested to curtail LV dysfunction and vascular remodeling while promoting cardiac tissue regeneration (43–45).

Effects of stem cells on angiogenesis, scar size, microvascular obstruction and intramuscular hemorrhage

Favorable effects of stem cells on perfusion and myocardial blood flow have been reported in a number of trials of cell therapy (46–48). Enhanced myocardial angiogenesis surrounding infarcted myocardium was detected after administration of CD133+ bone

marrow cells into patients with ischemic cardiomyopathy treated with coronary artery bypass grafting (CABG)(44). Also, Tang et al. showed that intravenously infused c-kit⁺ CSCs stimulated angiogenesis and improved LV function (21). EPCs derived from bone marrow were reported to mobilize into circulation and home toward ischemic regions, where they participate in neovascularization of the injured tissue in a paracrine manner (49).

As for scar size and microvascular obstruction (MVO), Meneveau et al. reported that presence of endothelial colony-forming cells was associated with reduced infarct size ($12.8 \pm 24\%$) and MVO ($3.2 \pm 5\%$) at 6 months post infarction (50). Moreover, transplanted stem cells have been reported to reside in para-infarction sites, in association with reduced MVO and preservation of microvascular integrity (51). The change in MVO predicted improvement in LVEF in the randomized, placebo-controlled double-blind SCAMI trial; improvement in LVEF up to 3 years was higher in BMC-treated patients without MVO compared with those with MVO (52). On the other hand, some types of stem cells, such as MSC, have innate procoagulant activity and potentially could aggravate microvascular obstruction following intracoronary delivery (53, 54). Heparin, which can reduce MSC-associated thrombosis, was reported to ameliorate MVO associated with MSC therapy (55).

Effects of stem cells on major adverse cardiovascular events

Major adverse cardiovascular events (MACEs), such as all-cause death, heart failure, myocardial re-infarction, requirement for re-operation, and arrhythmia, are robust outcome measures in patients treated with stem cells. Some systematic reviews and clinical trials have shown that the incidence of MACEs was lower in patients with AMI subjected to selected bone marrow-derived stem cell therapy compared with controls, with a trend toward reduced incidences of heart failure and arrhythmia, albeit not statistically significant (56, 57). Conversely, in a meta-analysis of individual patient data from randomized trials in patients with recent AMI, Gyongyosi M. et al. reported that cell therapy did not reduce key MACEs [adverse cardiac and cerebrovascular events (14.0% versus 16.3%, $p=0.289$), death (1.4% versus 2.1%, $p=0.499$), or death/AMI recurrence/stroke (2.9% versus 4.7%, $p=0.088$)] in comparison with controls, and the authors concluded that intracoronary cell therapy provided no benefits against MACEs (58). Larger scale trials with longer follow-up terms are called for to resolve this controversy.

Effects of stem cells therapy are summarized in Table 1 [(10, 14, 18–21, 35, 39–42, 50–54, 56, 59–64)]

Optimal infusion dose and timing

There has been a gap between basic and clinical research in terms of cell injection timing and dose. Recently, our group has performed a meta-analysis examining the dosage and timing of MSC transplantation in patients with AMI (65). The data suggest that injection of no more than 10^7 MSCs within 1 week after AMI treated with percutaneous coronary intervention might be optimal to improve left ventricular systolic function and prognosis (65). These findings are consistent with randomized trials showing that the most benefit was achieved when administering cell therapy between 4 and 7 days after AMI (16).

Mechanisms of benefit of stem cells

Although the transplanted stem cells have been found to be able to differentiate into cardiomyocytes, vascular smooth muscle and endothelial cells, most studies report that the paracrine effects of stem cells represent the dominant mechanism leading to enhanced survival of existing myocytes, recruitment of progenitor cells, reduction of fibrosis and scar formation, and eventually preservation of heart function (66–68). In addition, other mechanisms, such as simulation of native cardiac stem cells (69), immune modulation (70) and inflammatory control (71, 72), enhanced cell homing (73), and stimulation of cell-cell communications (70) have also been suggested to contribute to myocardial recovery.

Extracellular vesicles secreted from stem cells

Notably, it has recently been reported that extracellular vesicles secreted from stem cells may play a major role in repairing and regenerating the damaged myocardium (74–77). Stem cell-derived extracellular vesicles have potent cytoprotective, regenerative, anti-fibrotic and angiogenic properties, and they can enhance cardiomyocyte differentiation (77–79). Exosomes are a type of lipid bilayer extracellular vesicles of 30–150nm in size (ExoCarta.org). The major components of Exosomes are lipid entries (about 1,116), proteins entries (about 41,860), mRNA entries (about 4,946), miRNA (about 2,838) from about 286 studies. Long non-coding RNA and CircRNA were discovered in exosomes, which are important mediators of intercellular communication (80). Exosome are released from stem cells during stress or pathological conditions, contain a variety of miRNA and small molecules that can augment endogenous CPC survival, proliferation and function (75). These exosomes are implicated in stem cell survival (81), proliferation, migration (82), and differentiation into cardiomyocyte lineage (83, 84). MiRNAs derived from ESCs, EPCs, MSCs, iPSCs, may be involved in the modulation of myocardial regeneration in ischemic heart tissue (75, 85). More research is needed to further validate stem cell-derived exosomes as a therapeutic tool in the treatment of CVDs.

Stem cell therapy for non-ischemic cardiomyopathy

Non-ischemic cardiomyopathy (NICM), studied much less than its ischemic counterpart (86), has supplanted ICM as the leading cause of heart transplantation in adults (87), outlining the necessity of developing alternative therapies for this entity. The majority of clinical studies in this area were from non-ischemic dilated cardiomyopathy (NIDCM) and hypertrophic cardiomyopathy (HCM).

Non-ischemic dilated cardiomyopathy

Although current therapeutic approaches to NIDCM improve symptoms and prolong life, they are palliative in that they cannot directly address the fundamental problem of the loss of cardiac tissue and function. It is for this reason that stem cells have sparked intense interest, though the evidence for the therapeutic potential of autologous stem cells for NIDCM has been scarce.

In 2009, Fischer-rasokat et al. evaluated for the first time the effects of BMC for the treatment of NIDCM in a clinical trial and demonstrated the safety and feasibility of stem

cell therapy, which produced a small but significant improvement of LVEF (from $30.2 \pm 10.9\%$ to $33.4 \pm 11.5\%$, Pindex (from 1.53 ± 0.63 to 1.32 ± 0.61 mmHg·s/cm, $P=0.002$) after 3 months of BMC infusion, and a decrease in N-terminal probrain natriuretic peptide serum levels (from 1610 ± 993 to 1473 ± 1147 pg/ml, $P=0.038$) after 12 months (88). Recently, the results of a few small-scale randomized trials reported that intracoronary stem cell transplantation might contribute to the improvement of cardiac systolic function, exercise tolerance, and long-term survival without improvement in left ventricular end-diastolic volume (89–91), suggesting that stem cells do not cause any change in the remodeling process but improve myocardial cell function and quality of life measures. However, not all clinical trials demonstrated the same beneficial effects (92, 93). More recently, a systematic review addressed this issue and showed that bone marrow-derived stem cell therapy exhibited a significant reduction in mortality rate (19.7% in the cell group vs. 27.1% in the control group; 95% confidence interval (CI) -0.16 to -0.00 , $I^2=52\%$, $p=0.04$). Bone marrow-derived stem cell therapy also significantly improved LVEF after mid-term (6–12 months) follow-up (3.53% increase; 95% CI 0.76 to 6.29 , $I^2=88\%$, $p=0.01$) but produced no significant benefit in the 6 minutes walking test ($p=0.18$) (94).

Hypertrophic cardiomyopathy

HCM is another genetic NICM with an incidence of 1:500 in general population that is best known for its associated risk of sudden cardiac death in athletes (95, 96). Current medications, devices and surgery can significantly improve symptoms, but no specific strategies have been directed towards the underlying disease pathogenesis. Stem cell research may lead to novel approaches in the treatment of HCM, but the field is just now emerging. In 2014, Han et al. developed a patient-specific iPSC-derived cardiomyocytes (iPSC-CMs) model *in vitro* to evaluate therapeutic benefits of pharmaceutical agents, and demonstrated the potential of using iPSC-CMs for future development of personalized therapeutic strategies (97). At present, however, insufficient data are available to draw solid conclusions regarding the potential for stem cell therapy in HCM.

Limitations and potential risks of stem cell therapy

Despite the promising aspects of stem cell therapy in CVDs, the associated limitations of cell-infusion therapy must be recognized, indicating the need for proceeding with improvement, for example, the donor cell survival and engraftment are important issues determining the long term beneficial effect of stem cell therapy, over 85% of donor cells were lost 24hrs post cell transplantation (98). Immune rejection of iPSCs, difficulty in controlling stem cell behavior *in vivo*, risks of obstructing the microvessels (54, 99), and tumor-like formation (100) are issues that merit particular consideration. For example, stem cells infused immediately after AMI might cause excessive obstruction and dysfunction in the microvascular bed, thereby creating a hostile environment due to inflammation of the myocardium, potentially limiting cell retention and engraftment (101). The potential of stem cell therapy for cardiac repair may be influenced not only by cell dosage but also by patient status, such as the level of baseline ejection fraction, as well as patient's age, gender and diabetic status (102). Therefore, more preclinical and clinical trials are required to

demonstrate the most suitable therapy strategy depending on the underlying clinical process and individual patient variables.

Future perspective

In the absence of specific target-oriented therapy, stem cell-based therapy has been emerged as a viable option for cardiac tissue repair in clinical trials. Cell transplantation at the time of acute myocardial infarction or at later times may attenuate severity of cardiac tissue damage and accelerate the regeneration process. Emerging approaches including genetic modification, stem cell-derived exosomes and tissue engineering in combination with biomaterials have been applied to improve the efficacy of stem cell therapy. New clinical markers beyond traditional volumetric indices have transformed quantification of efficacy from primarily morphological to evaluation of tissue characteristics. The combination of clinical evaluation methods has improved our understanding of both the pros and cons of stem cell therapy.

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Table 1

Stem Cell Therapy in Ischemic Cardiomyopathy.

	ESCs	MSCs	HSCs	EPCs	CSCs	iPSCs	BMMNCs
Ventricular function improvement	Y (35)	Y (14)	Y (60)	Y (18, 19)	Y (21)	Y (20)	Y (40)
Exercise capacity improvement	Y (59)	Y (60)	NR	Y (61)	Y (63)	NR	Y (61)
Myocardial remodeling inhibition	Y (35, 59)	Y (14)	Y (42)	Y (62)	Y (21, 63)	Y (39, 64)	Y (40, 41)
Scar size reduction	Y (35, 59)	Y (14)	Y (42)	Y (62)	Y (21, 63)	Y (39, 64)	Y (40, 41)
Microvascular obstruction improvement	NR	Y (54, 56)	Y (52)	Y (50, 53)	Y (51)	NR	NR

ESCs, embryonic stem cells; MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells, EPCs, endothelial progenitor cells; CSCs, cardiac stem cells; iPSCs, induced pluripotent stem cells; BMMNCs, bone marrow mononuclear cells. Y: Yes; N; No; NR: not reported