

## Translational research of adult stem cell therapy

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### Abstract

Congestive heart failure (CHF) secondary to chronic coronary artery disease is a major cause of morbidity and mortality world-wide. Its prevalence is increasing despite advances in medical and device therapies. Cell based therapies generating new cardiomyocytes

and vessels have emerged as a promising treatment to reverse functional deterioration and prevent the progression to CHF. Functional efficacy of progenitor cells isolated from the bone marrow and the heart have been evaluated in preclinical large animal models. Furthermore, several clinical trials using autologous and allogeneic stem cells and progenitor cells have demonstrated their safety in humans yet their clinical relevance is inconclusive. This review will discuss the clinical therapeutic applications of three specific adult stem cells that have shown particularly promising regenerative effects in preclinical studies, bone marrow derived mesenchymal stem cell, heart derived cardiosphere-derived cell and cardiac stem cell. We will also discuss future therapeutic approaches.

**Key words:** Congestive heart failure; Adult stem cells; Mesenchymal stem cell; Cardiosphere-derived cell; Cardiac stem cell

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**Core tip:** Cell-based therapy emerged as a new approach to restore damaged heart function. Although cell therapy in experimental animal models is promising, beneficial effects in clinical trials are variable. This review summarizes recent preclinical and clinical applications on three specific adult stem cells (bone marrow derived mesenchymal stem cell, heart derived cardiosphere-derived cells and cardiac stem cell) and discuss about future approaches.

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### INTRODUCTION

The prevalence of congestive heart failure secondary to chronic coronary artery disease is increasing in spite of

**Table 1 Clinical Trials of mesenchymal stem cells, cardiosphere-derived cells and cardiac stem cells in heart disease**

Trial name	Study design	No. of patients	Delivery method	Cell dose	End point evaluation	Follow-up period	Outcome
<b>MSCs</b>							
Chen <i>et al</i> <sup>[10]</sup>	Randomized, controlled study	MSC <i>n</i> = 34 Control <i>n</i> = 35	Intracoronary	48-60 × 10 <sup>9</sup> cells	Echocardiography	3 and 6 mo	LVEF↑
POSEIDON <sup>[28]</sup>	Randomized, Pilot study	MSC <i>n</i> = 30 Auto <i>vs</i> Allo	Intramyocardial (transendocardial)	20, 100, 200 × 10 <sup>6</sup> cells	Cardiac CT	12 mo	LVEF↔ LVEDV↓
PROMETHEUS <sup>[29]</sup>	Randomized, Pilot study	MSC <i>n</i> = 6 No control	Intramyocardial (transepical)	20, 200 × 10 <sup>6</sup> cells	MRI	18 mo	LVEF↑ Scar size↓
C-CURE <sup>[30]</sup>	Randomized, controlled study	MSC <i>n</i> = 21 Control <i>n</i> = 15	Intramyocardial (transendocardial)	7 × 10 <sup>6</sup> cells	Echocardiography	6 and 24 mo	LVEF↑ LVESV↓
<b>CDCs</b>							
CADUCEUS <sup>[36,37]</sup>	Randomized, controlled study	CDC <i>n</i> = 17 Control <i>n</i> = 8	Intracoronary	12.5-25 × 10 <sup>6</sup> cells	MRI	6 and 12 mo	LVEF↔ Scar size↓
ALCADIA	Pilot study	CDC <i>n</i> = 6 No control	Intracoronary	25-30 × 10 <sup>6</sup> cells	MRI	12 mo	LVEF↑ Scar size↓
TICAP <sup>[38]</sup>	Randomized, controlled study	CDC <i>n</i> = 7 Control <i>n</i> = 7	Intracoronary	2-3 × 10 <sup>6</sup> cells	MRI	18 mo	LVEF↑
<b>CSCs</b>							
SCIPIO <sup>[50]</sup>	Randomized, controlled study	CSC <i>n</i> = 20 Control <i>n</i> = 13	Intracoronary	1 × 10 <sup>6</sup> cells	Echocardiography MRI	12 mo	LVEF↑ Scar size↓

Auto: Autologous; Allo: Allogeneic; MSCs: Mesenchymal stem cells; CSCs: Cardiac stem cells; CDCs: Cardiosphere-derived cells; CT: Computed tomography; MRI: Magnetic resonance imaging.

recent advances in medical and device therapies that delay the progression of disease<sup>[1]</sup>. Currently available medical interventions attenuate neurohormonal activation (*e.g.*, renin-angiotensin-aldosterone system, sympathetic nervous system, and arginine vasopressin), reducing myocyte apoptotic cell death, reducing interstitial connective tissue proliferation and attenuating the progression of myocyte cellular hypertrophy. However, none of the current therapies are effective in reversing myocyte loss and cellular abnormalities associated with myocyte contractile performance which are impaired in the failing heart. Recent investigations have demonstrated that there is an endogenous cardiac repair system that arises from resident cardiac stem cells regulating cardiac engraftment by maintaining a low level of myocyte proliferation, regeneration and cell death<sup>[2]</sup>. Nevertheless, the regenerative capacity of this endogenous stem cell pool is limited.

Expansion of adult stem cells *ex vivo* can stimulate the heart to induce endogenous or exogenous cell based repair. Cell-based therapy has emerged as a promising therapy to regenerate the failing heart through its potential to repair dead myocardium and improve left ventricle (LV) function<sup>[3-5]</sup>. Although clinical trials have demonstrated the safety and feasibility of using bone marrow-derived stem cells [Bone marrow mononuclear cells (MNCs) or mesenchymal stem cells (MSCs)] or heart-derived stem cells [cardiac stem cells (CSCs) or cardiosphere-derived cells (CDCs)] in humans with MI who do not have severe heart failure, the long term clinical efficacy of this approach is variable with a small improvement in LV function<sup>[6-8]</sup>. Although the biological action of adult stem cells *in vivo* is still controversial, for now, the beneficial effects of adult stem cells are

considered to be associated with the secretion of paracrine factors rather than direct differentiation of *de novo* cardiac cells<sup>[9]</sup>. Accordingly, stem cells secrete multiple growth factors and cytokines which reduce scar volume and myocyte apoptosis, increase myocyte proliferation and activate endogenous CSCs to produce new myocytes. Therefore, current research using adult stem cells has focused on optimizing cell based therapy that effectively improves LV function and decreases disease progression. This would have a major impact on the survival and quality of life in patients with ischemic heart disease as well as reduce healthcare expenditures related to recurrent hospitalizations from advanced disease. In this review we will discuss three types of adult stem cells, MSCs, CDCs and CSCs, which are involved in the early phase of clinical trials (Table 1) and address current problems and future directions (Table 2).

## MSCS IN ISCHEMIC CARDIOMYOPATHY

MSCs arise from a small proportion of bone marrow mononuclear cells (0.001%-0.01% of nucleated cells in the bone marrow). Although it has been reported that MSCs can be differentiated into cardiomyocytes and vascular-like structures<sup>[10-14]</sup>, actual *in vivo* differentiation is infrequent. Moreover, current approaches using direct myocardial injection or intracoronary infusion of cells in the infarcted region result in a low myocardial retention of stem cells<sup>[15]</sup>. Thus, most of the beneficial effects derived from MSCs are considered to be related to a paracrine mechanism. MSCs produce a wide variety of cytokines, chemokines and growth factors, and many are involved in restoring cardiac function or regenerating myocardial tissue. Factors such as basic fibroblast

**Table 2 Alternative strategies of stem cell therapy**

Enhancement of cell survival, mobilization and paracrine secretion
Pharmacology (Statins, <i>etc.</i> )
Genetic modification (Akt and Ang1, VEGF and SDF-1, HO-1, bFGF/IGF-1/BMP2)
Preconditioning (Hypoxia, TLR3 stimulation)
Combination of different cell types or delivery approaches
MSCs and CSCs
Stop-flow (infarct area) and global intracoronary infusion (viable area)
Others
Cell infusion immediate after revascularization (allogeneic MSCs, CDCs, <i>etc.</i> )
Repeated cell infusion
Stimulation of exosome release
Direct exosome (or microRNAs) injection
Cell therapy in hypertrophied myocardium or dysfunction due to congenital heart disease

MSCs: Mesenchymal stem cells; CSCs: Cardiac stem cells; CDCs: Cardiosphere-derived cells; VEGF: Vascular endothelial growth factor; SDF: Stromal cell-derived factor; bFGF: Basic fibroblast growth factor; IGF: Insulin-like growth factor; BMP2: Bone morphogenetic protein 2; HO-1: Heme-oxygenase 1; Ang1: Angiopoietin 1.

growth factor (bFGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), transforming growth factor (TGF)- $\beta$ , and stromal cell-derived factor (SDF)-1 inhibit LV remodeling<sup>[16]</sup> and apoptosis, stimulate proliferation of endogenous myocytes and angiogenesis, activate endogenous CSCs<sup>[4]</sup> and mobilize bone marrow progenitor cells to the heart<sup>[17]</sup>. Importantly, MSC are immunoprivileged because they do not express MHC class II molecules therefore they escape immune-rejection, release immunomodulatory factors and inhibit T-cell proliferation. Allogeneic cells can be expanded *ex vivo* and stored to use in patients<sup>[18,19]</sup>. This would allow for "off-the-shelf" treatment of patients with severe LV dysfunction, without the need to wait for cell processing and expansion<sup>[19]</sup>.

A large number of preclinical investigations have been performed using MSCs, and demonstrate a significant beneficial effect on cardiac structure and function<sup>[13,20-23]</sup>. In a large animal model, Quevedo *et al*<sup>[18]</sup> demonstrated that administration of allogeneic MSCs to a swine model of chronically infarcted myocardium resulted in improvements in regional contractility and myocardial blood flow, as well as engraftment, differentiation and enhanced survival. Williams *et al*<sup>[24]</sup> assessed serial cardiac MRI in animals with post-MI LV remodeling and showed progressive scar size reductions, improvements in ejection fraction (EF) and reverse LV chamber remodeling in animals receiving allogeneic MSCs as compared to controls<sup>[24]</sup>. Mesenchymal precursor cells (MPCs) are subpopulation of MSCs expressing the STRO-3 cell surface marker. MPCs are highly proliferative and secrete abundant paracrine factors. Houtgraaf *et al*<sup>[25]</sup> demonstrated that slow infusion of allogeneic MPCs (12.5 to 37.5 million cells) to an bovine model with acute MI improved

regional and global function and reduced scar volume and LV remodeling. Interestingly, MPC infusion in the infarct-related coronary artery caused myocyte cell size reduction in the infarcted and remote regions. Based on these data a clinical trial is currently ongoing (NCT01781390, phase II) that investigates the safety of MPCs in patients with *de novo* anterior MI.

We have demonstrated that slow infusion of allogeneic MSCs into the three major coronary arteries in swine with hibernating myocardium increased regional cardiac function in both the ischemic left anterior descending (LAD) artery and remote regions (wall thickening: LAD: 24% to 43%, Remote: 60% to 85%,  $P < 0.05$ )<sup>[17]</sup>. Intracoronary MSCs (icMSCs) significantly increased cKit+/CD133 positive cells (or bone marrow-derived progenitor cells) in the bone marrow and circulation corresponding to the increase in myocardial localization of cardiac progenitor cells (cKit+/GATA4 or Nkx2.5+). icMSCs also induced myocytes to enter the cell cycle and increased the production of small cardiac myocytes indicating the presence of cardiac regeneration. Although some laboratories have identified rare myocytes arising from MSCs in swine<sup>[18]</sup>, our own studies using multiple reporter genes could not identify cardiac myocytes differentiating from labeled MSCs<sup>[26]</sup>. Thus, cardiac regeneration after icMSCs is related to a bone marrow-derived progenitor cell mediated endogenous cardiac repair mechanism.

Chen *et al*<sup>[10]</sup> administered 48-60 billion bone marrow derived MSCs by intracoronary injection into 34 patients and reported a 13% increase in EF compared to placebo groups at 3-6 mo follow-up. The Percutaneous Stem Cell Injection Delivery Effects on neo-myogenesis (POSEIDON) trial, by Hare's group, tested the ability of autologous and allogeneic MSCs (20, 100 and 200 million cells) in patients with ischemic cardiomyopathy to promote cardiac recovery following transendocardial stem cell injection<sup>[27,28]</sup>. Using multidetector computed tomography and biplane left ventriculography, this study reported a 32% reduction in scar size in allogeneic MSCs group vs a 35% reduction in autologous MSCs groups without improvement of LV EF. Subgroup analysis demonstrated that 20 million MSCs improvement in LV EF and LVEDV. Furthermore, autologous MSCs showed improvement in the 6 min walk test and allogeneic MSCs reduced LVEDV. Additionally, allogeneic MSCs did not stimulate a donor specific alloimmune reaction. Thus, this study clearly demonstrates the importance of cell injection site and the safety of using allogeneic MSCs in patients. The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial investigated injection of autologous MSCs (20-200 million cells) into akinetic or hypokinetic areas in hearts that were unsuitable for surgical revascularization during coronary artery bypass graft surgery (CABG)<sup>[29]</sup>. Cardiac MRI analysis demonstrated that MSC injection increased EF by 9.4% as well as increased scar reduction by 48%

and contractile improvement in dysfunctional areas where surgical reperfusion was not performed<sup>[29]</sup>. Although this study lacked a placebo control group and had a limited patient number (6 patients), it demonstrates the potential benefits of injection of MSCs directly into non-revascularized myocardium. The Cardiopoietic stem Cell therapy in heart failure (C-CURE) trial tested the ability of a "cardiogenic cocktail" to enhance the therapeutic benefits of autologous MSCs<sup>[30]</sup>. Bartunek *et al*<sup>[30]</sup> pretreated MSCs with growth factors to enhance their cardioprotective functions. Twenty-one patients with class 2 or 3 heart failure received over 700 million cardiogenic cocktail treated MSCs by electromechanically guided endomyocardial injections. No adverse events or systemic toxicity was observed. Moreover, in LV EF, end-systolic volume and the 6-min walking test were significantly improved. Subsequently, the Safety and Efficacy of Autologous Cardiopoietic Cells for Treatment of Ischemic Heart Failure (CHART-1) trial is currently ongoing. This study is investigating the efficacy and safety of Bone Marrow-derived Mesenchymal Cardiopoietic Cells for the Treatment of Chronic Advanced Ischemic Heart Failure. The safety and efficacy of MSCs and modified MSCs in patients have been confirmed. In the future, randomized controlled trials involving a large population of patients are anticipated.

## CDCS IN ISCHEMIC CARDIOMYOPATHY

Smith *et al*<sup>[31]</sup> expanded in culture tissue from percutaneous myocardial biopsies to form cardiospheres as the basis for cardiac stem cell expansion. They selected floating cardiospheres (out-growing cells) for culture and expanded them in a monolayer to isolate what is termed CDCs. Cardiospheres and CDCs express antigens specific for stem cells (cKit, CD90, CD105 and the absence of CD34 and CD45) as well as proteins vital for cardiac contractile (Nkx2.5, GATA4) and electrical function (Cx43)<sup>[32]</sup>. This defines cardiospheres and CDCs as a population of cardiac progenitor cells. Cardiospheres are heterogeneous groups of cells that contain not only adult CSCs, which are capable of long-term self-renewal and cardiomyocyte differentiation, but also vascular cells and differentiated progenitor cells<sup>[33]</sup>. Preclinical investigations were exclusively reported from Marban's group, they demonstrated that administration of CDCs in an experimental acute MI model reduced LV remodeling, improved contractility and reduced the infarct size without improvement in cardiac function<sup>[5]</sup>. Specifically they show that injection of 10 million of autologous CDCs to a swine model of infarcted myocardium resulted in a significant reduction in infarction size (approximately 5%) compared to a 2.4% reduction in placebo with no change in global function<sup>[5]</sup>. Malliaras *et al*<sup>[34]</sup> showed that injection of 12.5 million of allogeneic CDCs significantly reduced scar size (3.6%) and preserved EF in a swine model of MI compared to no reduction in scar size (0.4%) and deterioration of EF (approximately

9.9%) in placebo. Lee *et al*<sup>[33]</sup> compared the effects of CDCs and their precursor cells, cardiospheres, in a swine MI model. They found that the effects on infarct reduction and preservation of EF were similar in both CDCs and cardiospheres whereas there was improved hemodynamics and regional function and preservation of LV chamber remodeling (all quantified by serial cardiac MRI) in animals receiving cardiospheres.

We previously demonstrated that slow infusion of CDCs into the three major coronary arteries (total dose 30 million CDCs) in swine with hibernating myocardium improved regional function in ischemic LAD (wall thickening: 23% to 51%,  $P < 0.05$ ) as well as in the normal right coronary artery (RCA) regions (68% to 107%,  $P < 0.05$ ) and global function (EF: 54% to 71%,  $P < 0.05$ )<sup>[35]</sup>. Quantitative histochemical analysis demonstrated that CDCs increased myocyte nuclear density and significantly reduced myocyte cellular hypertrophy in hibernating LAD and normal RCA regions indicating viable myocardium is a main therapeutic target.

The cardiosphere-derived autologous stem cells to reverse ventricular dysfunction (CADUCEUS) involved 25 patients who were given 12.5-25 million autologous CDCs<sup>[36]</sup> after successful percutaneous coronary intervention. The CDCs were expanded for approximately 36 d in culture from right ventricular endomyocardial biopsies taken 2-4 wk after acute MI. After expansion CDCs were injected into the previously stented coronary artery between 6-12 wk after heart attack. Despite the lack of improvement in left ventricular EF or patient reported outcomes, the scar reduction was 28% and 46% at 6 and 12 mo respectively and regional wall thickening was significantly improved in treated patients by 7.7%<sup>[37]</sup>. Serious adverse events were also reported to be three times higher in the treated group, however due to the relatively small number of patients enrolled, this trial cannot ascertain to the safety of CDCs. The autologous human cardiac-derived stem cell to treat ischemic cardiomyopathy (ALCADIA) trial investigated CDCs expanded from cardiac (endomyocardial) tissue isolated during CABG. This trial combined the use of stem cells, bioengineered scaffolds and biologics to create a hybrid therapy. CDCs were cultured for 1 mo before intracoronary injection followed by placement of a gelatin sheet containing bFGF over the injection site. Six months after therapy, cardiac MRI indicated a 12.1% increase in EF, a 3.3% reduction in infarct size and a significant improvement in wall motion as well as maximum aerobic exercise capacity. Since this study enrolled only 6 subjects, study is anticipated to enroll larger patients.

The transcatheter Infusion of Cardiac Progenitor Cells in Patients with Single Ventricle Physiology trial involved in 14 patients who had hypoplastic left heart syndrome. Tissue was isolated from the right atrium of patients receiving stage 2 (Glenn) or stage 3 (Fontan) surgeries<sup>[38]</sup>. Cardiospheres were expanded from this right atrium tissue for 2-3 wk in culture. CDCs (2-3

million autologous cells,  $n = 7$ ) were injected into the 3 major coronary arteries 1 mo after surgery<sup>[38]</sup>. At 18 mo post injection, cardiac echo and MRI indicated an increase in right ventricular EF from 46.9% to 54.0% ( $P = 0.0004$ ) compared to no change in EF (46.7% to 48.7%,  $P$ -ns) in control. This was a small study (only 7 patients received CDCs) but indicates that viable and dysfunctional myocardium can be treated with autologous CDCs. Although CDCs are beneficial in patients with heart disease, CDCs have many characteristics that overlap with MSCs<sup>[39]</sup>. Therefore, it is necessary to identify the similarities and differences in biological responses of both MSCs and CDCs prior to further proceeding with clinical applications.

### CSCS IN ISCHEMIC CARDIOMYOPATHY

Several investigators have demonstrated the presence of small clusters of Sca-1+, cKit+ or a side population cells (multipotent stem cells identified by the ability to efflux Hoechst dye) in the cardiac atria and apex<sup>[40-42]</sup>. These cells were named CSCs and are most abundant during postnatal cardiac development after birth. Progeny of CSCs acquire a cardiomyocyte phenotype therefore resident CSCs are optimal candidates for cardiac regeneration studies. CSCs are self-renewing, can replace senescent and apoptotic CSCs *via* mobilization of BM-derived stem cells, and participate in maintaining the CSC pool in the heart<sup>[43-45]</sup>. In adulthood, the cells are quiescent and reside within the heart. Following ischemic injury, activation by paracrine signals induces CSCs to divide. Nevertheless, their proliferative potential is limited and the extent of the myocardial injury (*e.g.*, necrosis and fibrosis following MI) is frequently too large to be compensated by new cardiomyocytes formed from dividing resident CSCs<sup>[40]</sup>. In the normal organism the heart retains a pool of CSCs that regulate cardiac homeostasis by maintaining a low level of myocyte proliferation, regeneration and cell death<sup>[2]</sup>. It is well known that CSCs are a rare population in the myocardium making their isolation and cultivation difficult and time-consuming. Since these cells are located in the heart and are primed for cardiac repair, protocols to enhance their endogenous activity or expand these cells *in vitro* before re-implanting them in the heart are currently being tested. A limited number of animal studies indicate that the administration of CSCs can slow left ventricular remodeling and cardiac improve function after ischemic injury<sup>[40,46,47]</sup>. Welt *et al*<sup>[48]</sup> demonstrated that intramyocardial injection of autologous CSCs in a canine infarct model with permanent LAD occlusion resulted in the preservation of global function (31% to 33%) and reduced LV remodeling compared to functional deterioration (35% to 26%,  $P < 0.05$ ) and LV remodeling in vehicle animals<sup>[48]</sup>. Bolli *et al*<sup>[49]</sup> demonstrated that administration of autologous CSCs to a swine model of chronically infarcted myocardium

resulted in improvements in regional and global contractility (45.4% to 51.7%,  $P < 0.05$ ) as well as engraftment and differentiation of injected CSCs<sup>[49]</sup>.

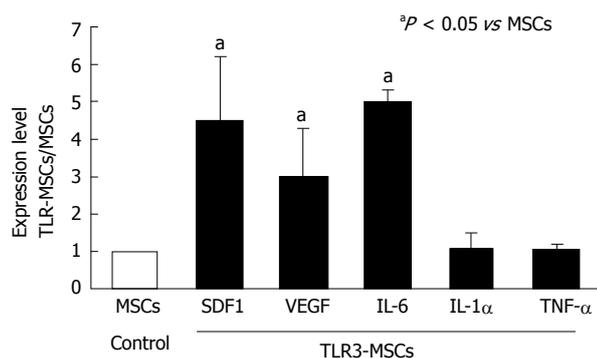
The stem cell infusion in patients with ischemic cardiomyopathy (SCIPIO) trial isolated autologous CSCs during CABG<sup>[50]</sup>. SCIPIO involved 23 patients who had experienced MI in the past and exhibited an EF of under 40%. One million of cKit positive and lineage negative CSCs were isolated with magnetic beads from cultures of right atrial appendage tissue and administered *via* intracoronary infusion 1 mo after CABG. Twelve months after the treatment, infarct size was decreased by 30.2%, regional wall thickening was increased by 18% and left ventricular EF was increased by 8.2%. The benefits of treatment continued to increase and left ventricular EF was increased by 12% after 2 years<sup>[51]</sup>. Although studies have shown the beneficial effects of CSCs on the infarcted myocardium, their biological actions in the heart are still controversial<sup>[52]</sup>. Further studies are necessary to clarify the significance of CSCs in clinical applications.

### FUTURE DIRECTIONS

Based on current achievements in experimental large animal studies and clinical trials of cell-based therapies, it is evident that cell therapies still require significant progress to be registered in the daily practice of modern medical therapies. The following strategies are solutions to overcome current limitation of cell-based therapies.

### PRECONDITIONED MSCS

Since the safety and efficacy of MSCs has been demonstrated by clinical work, there has been an increasing interest on enhancing the benefits of MSC therapy. For example, combining MSC and pharmacotherapy<sup>[53]</sup>, genetically modifying MSCs<sup>[54-56]</sup> and pre-conditioning MSCs<sup>[57]</sup> are approaches that are being explored to augment MSC-mediated cardiac repair. MSCs transfected to overexpress Akt or cell survival protein promoted myocardial protective function<sup>[16,55]</sup>. Furthermore, MSCs engineered to express combinations of gene products such as Akt and angiopoietin-1 (Ang1) have also shown functional benefits in experimental animal models<sup>[58]</sup>. MSCs overexpressing VEGF and SDF-1 improved cardiac function by activating Akt pathway<sup>[54]</sup>. MSCs transfected to express hemoxygenase 1 (HO-1), an enzyme that improves MSC tolerance to hypoxia, infused into a cardiac ischemia-reperfusion model improve EF and lower end systolic volume compared to controls<sup>[59]</sup>. MSCs pretreated with growth factors, bFGF, IGF-1 and bone morphogenetic protein 2 (BMP2), improved myocardial repair in a rat model of MI<sup>[60]</sup>. Those preconditioned MSCs improved engraftment and survival of transplanted cells. Although data are promising, the safety of these cells must be carefully evaluated before use in humans.



**Figure 1 Toll-like receptor 3-mesenchymal stem cells enhance to secrete paracrine factors.** RNA mimetic polyinosinic-polycytidylic acid [poly(I:C)] stimulated TLR3 system on MSCs. TLR3-MSCs secreted a variety of paracrine factors. RT-PCR detected significant upregulation of SDF1, VEGF and IL6 while inflammation related cytokines (IL-1 $\alpha$ , TNF $\alpha$ ) were downregulated. Injection of TLR3-MSCs in cardiomyopathy model improved cardiac function more than standard MSCs in association with increasing myocyte proliferation, reducing fibrosis and myocyte apoptosis. TLR3: Toll-like receptor 3; MSCs: Mesenchymal stem cells; SDF1: Stromal cell-derived factor-1; VEGF: Vascular endothelial growth factor; IL: Interleukin; TNF: Tumor necrosis factor.

## PRECONDITIONED MSCS WITHOUT GENETIC MODIFICATION

As mentioned above, the currently used approaches to enhance stem cells are mostly through genetic modification. Thus, modified cells are not considered as a clinically relevant approach because genetically engineered stem cells may have increased unwanted long-term side-effects. We demonstrated that stimulation of toll-like receptor 3 (TLR3) produced many trophic factors without induction of inflammatory-related cytokines<sup>[26]</sup>. Poly (I:C) is structurally similar to double-stranded RNA and is known to interact with TLR3, which is expressed on the membrane of B-cells, macrophages, dendritic cells, MSCs and CDCs. Poly (I:C) directly reacts with the TLR3 receptor on the surface of MSCs/CDCs. Thus, after washing and collecting MSCs/CDCs after stimulation, poly (I:C) does not reside within the cells and does not affect the heart environment after injection of cells. Interaction of Poly (I:C) with TLR3 on MSCs causes secretion of the growth factors VEGF and the cytokine IL-6 without up-regulation of the inflammatory cytokines IL-1 and TNF $\alpha$  (Figure 1). Injection of TLR3 activated MSCs (TLR3-MSCs) in a non-ischemic cardiomyopathy model improved cardiac function more than standard MSCs in association with increasing myocyte proliferation, reducing fibrosis and myocyte apoptosis<sup>[61]</sup>. Activation of TLR3 on CDCs (TLR3-CDCs) stimulated the secretion of HGF, IGF1 and IL-6 without up-regulation of inflammatory cytokines. TLR3-MSCs or TLR3-CDCs are safe and feasible to use in the human heart. Further investigation is necessary to confirm the safety and feasibility to use in the heart.

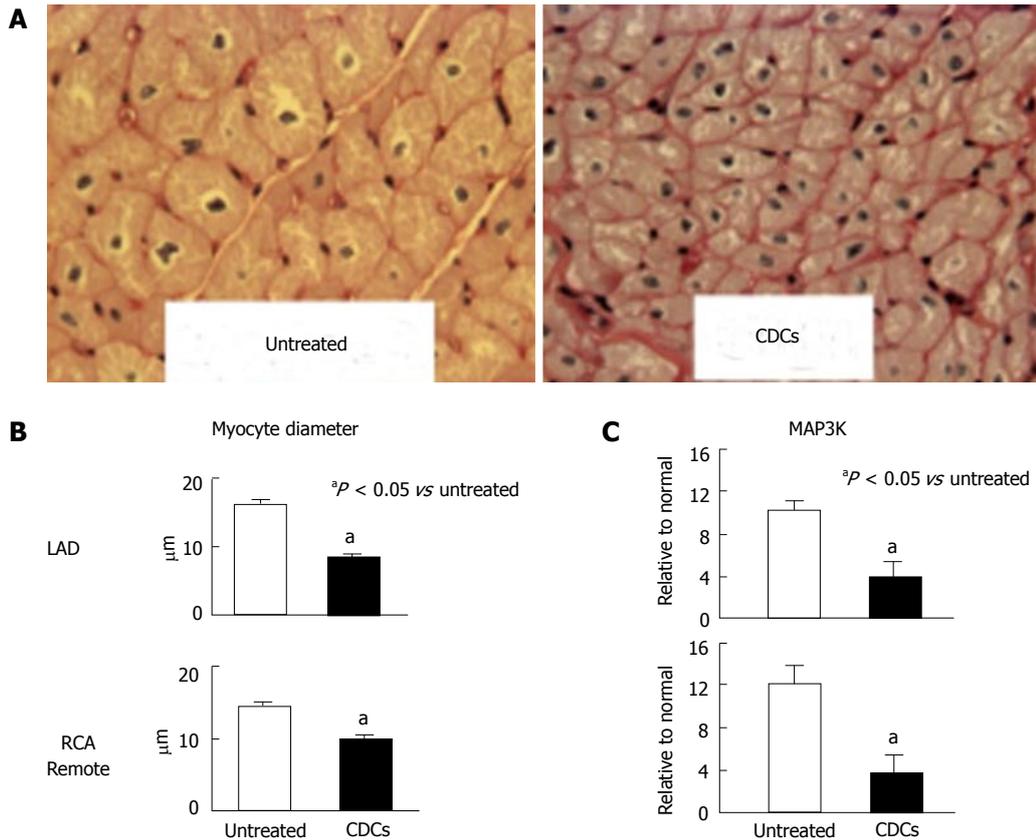
## MSCS AND CSCS

Combining MSC and CSC in post-MI treatment may

further enhance the therapeutic effects of each cell type. Recent work by Williams *et al*<sup>[62]</sup> demonstrated that the combined use of 1 million human CSCs with 200 million human MSCs provided greater recovery, almost to baseline, in a swine model of anterior wall MI<sup>[62]</sup>. While all stem cell treated animals demonstrated improved LV EF compared to placebo controls, notably, animals receiving dual cell therapy had a 2-fold greater reduction in scar size (21.1% for CSC/MSC vs 10.4% for CSC alone or 9.9% for MSC alone) and had improved rates of pressure change during diastole. Overall left ventricular chamber dynamics were improved in both the dual therapy and CSC or MSC alone treated groups. Interestingly, CSC alone treated animals demonstrated better isovolumic relaxation as compared to controls, while MSC alone treated animals exhibited improved diastolic compliance, indicating that the enhanced effect of dual therapy on both systolic and diastolic function may be due to a synergistic effect between CSC and MSC targeted mechanisms.

## REGIONAL INFUSION WITH STOP-FLOW VS GLOBAL INFUSION WITH SLOW INFUSION

Clinically applied techniques for cell delivery include endomyocardial injection using an injection needle or infusion of cells into a coronary artery supplying the infarcted region using a stop coronary flow technique. Although both approaches elicit significant improvements in cardiac function, they increase the risk of endomyocardial hemorrhage and MIs caused by stem cells plugs in the capillaries which could potentially limit the beneficial effects of cell-therapy. We previously demonstrated that slow infusion of MSCs into the three major coronary arteries without stop flow technique (global infusion) did not cause microembolization and stimulated prominent cardiac regeneration in ischemic as well as normally perfused RCA regions in swine with hibernating myocardium<sup>[17]</sup>. Likewise, intracoronary injection of autologous CDCs<sup>[35]</sup> without a stop-flow technique in swine with hibernating myocardium stimulated myocyte proliferation and regeneration in an ischemic LAD region as well as the normally perfused RCA regions. Subsequently, we applied the global infusion approach in an acute MI model, CDC infusion significantly improved cardiac function despite no changes in the size of infarction area. These results indicate that scar reduction and functional improvement are independent phenomenon<sup>[63]</sup>. Accordingly, the approach of stem cell injection in the entire heart is safe and feasible to improve LV dysfunction and our results indicate that normally perfused and viable myocardium could be the target for regenerative therapy. Alternatively, combining stop-flow infusion in the infarcted area with slow flow infusion into the viable myocardium may be a method to enhance therapeutic efficacy.



**Figure 2** The effect of cardiosphere-derived cells on myocyte cell size and MAP kinase in the dysfunctional left anterior descending vs remote regions. A: Images (PAS staining) demonstrate that hypertrophied myocytes in untreated hibernating LAD became smaller after CDCs. Myofibrils were condensed indicating the production of healthy myocytes; B: Myocyte diameter was significantly reduced in hibernating LAD and remote regions; C: Corresponding to the morphological change, protein level of MAP3K was downregulated in LAD and remote regions. Data indicates CDCs induced myocyte regeneration and hypertrophy regression. CDCs: Cardiosphere-derived cells; LAD: Left anterior descending; RCA: Right coronary artery.

## ALLOGENEIC CDCS INFUSION IMMEDIATE AFTER REPERFUSION

Allogeneic CDCs can escape direct recognition of helper T cells due to the lack of expression of MHC class II antigen (SLA class II on pig)<sup>[34,64]</sup> and therefore are immunoprivileged. Based on these observations, a recent clinical trial was initiated using allogeneic human CDC treatment in patients with chronic myocardial infarction (ALLSTAR trial). These allogeneic cells can be expanded *ex vivo* and stored for use at a future time<sup>[18]</sup>. This "off-the-shelf" treatment for patients with AMI immediately after revascularization is unique in that *ex vivo* expanded cells are available immediately for treatment and the patient does not need to wait for cell processing and expansion<sup>[19]</sup>. Recently, administration of CDCs immediately after reperfusion demonstrated the protective effects in swine with acute myocardial infarction<sup>[65]</sup>. Thirty minutes after ischemia-reperfusion, CDCs were injected into the infarct-related coronary artery and reduced the size of the infarct area and myocyte apoptosis in the border region. Although data were collected 48 h post CDCs injection, we recently demonstrated that functional improvement and myocyte regeneration were maintained up to 1-mo follow-up. These data indicate that the cardioprotective

effects at early times were maintained. Previously bone marrow cell and endothelial progenitor cells injection in patients were performed within 7 d after AMI and demonstrated superiority to cell injection within 24 h<sup>[66,67]</sup>. Since stem cell homing factors (mobilization, migration and adhesion) are maximized between day 3 and day 7<sup>[68]</sup>, these therapies are effective for stem cell homing. However, the inflammation caused by MI is already developed and the potential cardioprotective effects (*i.e.*, *via* anti-apoptotic effects or modulation of the inflammatory response) are limited when cells are delivered. Since CDCs secrete multiple cytokines (SDF-1, Akt)<sup>[69]</sup>, growth factors (HGF, IGF-1, VEGF)<sup>[69,70]</sup> and exosomes<sup>[71,72]</sup>, CDCs early after reperfusion might reduce the inflammatory response and protect the heart from functional deterioration due to reperfusion injury.

## REPEATED INJECTION OF STEM CELLS

Since single injection of CDCs improved regional function and reduced scar volume<sup>[36,37]</sup>, repeated injection of stem cells has been considered a more effective approach to regenerate myocardial tissue<sup>[73,74]</sup>. However, the initial infusion of cells activates and enhances the immune response<sup>[34,64]</sup> and the subsequent injected cells are quickly eliminated and ineffective. This quick

reaction is mainly associated with acquired/adaptive rather than innate immunity. Repeated infusion of autologous/allogeneic CDCs may overcome the limited functional recovery from a single injection<sup>[73,74]</sup>. However, the extent of immune activation caused by repeated injections is unclear and optimal immunosuppressive therapy is still undetermined. Development of efficacious CDC platforms administered with optimal immune suppression would circumvent barriers related to multiple injections of stem cells and allow the widespread application of “off-the-shelf” cell therapy to treat the large number of patients in need<sup>[64,75,76]</sup>.

## EXOSOME ACTIVATION AND MICRORNAS

The beneficial effects of adult stem cells are mainly associated with the secretion of paracrine factors rather than direct differentiation of *de novo* cardiac cells<sup>[9]</sup>. They secrete multiple growth factors and cytokines which reduce scar volume and myocyte apoptosis, increase myocyte proliferation and activate endogenous CSCs to produce new myocytes. Recently, it was reported that CDCs secrete exosomes and they play important roles for cardiac regeneration<sup>[71]</sup>. Exosomes transfer microRNAs from cell to cell and they inhibit inflammation and apoptosis and increase angiogenesis and myocyte proliferation. Therefore, a new method of treatment may focus on how to effectively stimulate secretion of exosomes from stem cells or may be directly injecting exosomes in the infarcted myocardium.

## ANTI-HYPERTROPHIC EFFECT

Besides their regeneration potential, adult stem cells have other beneficial effects such as anti-apoptosis, anti-inflammation, extracellular matrix reduction, contractile alternation and anti-hypertrophy. Pathological cardiac hypertrophy in post MI remodeling is a major cause of mortality and morbidity including the risk of sudden cardiac death and heart failure in patients<sup>[77-81]</sup>. It is associated with increased interstitial fibrosis, cell death and cardiac dysfunction. LV assist devices used in heart failure patients as a bridge to heart transplantation not only improved peripheral circulation but also reversed the geometric remodeling of the heart and restored the function of the heart<sup>[82-85]</sup>.

We demonstrated that global infusion of CDCs into hearts with chronically ischemic myocardium's improved myocardial function in the ischemic and remote regions<sup>[86]</sup>. CDCs significantly increased newly formed small myocytes. Interestingly, CDCs also reduced the cell size of pre-existing myocytes and hypertrophic signaling (mitogen activated kinases) in the ischemic and remote regions. Data indicate that CDCs have the potential to reverse cardiac hypertrophy (Figure 2). Future studies are necessary to determine whether hypertrophy regression is primary or secondary to

myocardial regeneration and functional improvement.

## CONCLUSION

Promising data derived from experimental models indicate the potential success of using cell based therapy in clinical applications. To overcome the current limitations in the field, development of new methods to enhance cardiac repair is necessary. In light of their proven safety profiles, MSC, CDC and CSC are prime candidates for cell based therapies. Recently, it was reported that a combination of CSCs and MSCs may be more effective than either one alone, and this approach is under investigation. Similarly, pre-conditioning MSC and CDCs are also promising approaches, and further investigation is anticipated. Optimizing the dose and method of delivery, as well as the timing for delivery are important variables that should be studied. It is anticipated that cell based therapies will become a mainstream treatment for heart diseases due to their potential ability to improve functional outcomes and decrease mortality.

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